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Coronary atherosclerotic plaque burden and composition by CT angiography in Caucasian and South Asian patients with stable chest pain

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Corresponding Author:	Francesca Pugliese, MD, PhD, FESC NIHR Cardiovascular Biomedical Research Unit at Barts London, UNITED KINGDOM
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	NIHR Cardiovascular Biomedical Research Unit at Barts
Corresponding Author's Secondary Institution:	
First Author:	Francesca Pugliese, MD, PhD, FESC
First Author Secondary Information:	
Order of Authors:	Francesca Pugliese, MD, PhD, FESC
	Peter Ryom Villadsen
	Steffen Erhard Petersen
	Damini Dey
	Lu Zou
	Shivali Patel
	Hafiz Naderi
	Katarzyna Gruszczynska
	Jan Baron
	Lewis Ceri Davies
	Andrew Wragg
	Hans Erik Bøtker
Order of Authors Secondary Information:	
Abstract:	*Aims South Asian (SA) patients are known to have an increased incidence of acute cardiovascular events compared to Caucasians. The aim of this observational study was to compare the prevalence of coronary stenoses, the amount and composition of coronary atherosclerosis in a cohort of Caucasian and SA patients with stable chest pain in non-acute settings. *Methods and Results The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. In 963 consecutive Caucasian and SA patients undergoing coronary computed tomography angiography atherosclerotic plaques were quantified using a semi-automated algorithm. The vessel percent diameter and area stenosis were measured. Plaque composition was examined from measurement of calcified, non-

	calcified and total plaque burden. There were 420 Caucasian (238 males) and 543 SA (297 males) patients. Caucasian patients were older than SA (54.39±11.65 vs. 49.83±11.03 years), had lower prevalence of diabetes (13.13% vs. 32.41%) and hyperlipidemia (56.90% vs. 68.51%) (all p-values<0.001). After adjusting for differences in cardiovascular risk factors, there were no differences in percent diameter and area stenosis, and no difference in the proportions of patients with one-, two- or three-vessel disease. There was no difference in total plaque burden, however the percent non-calcified plaque composition was lower in Caucasians compared to SA (80.95% vs. 90.42%; p-value<0.001). *Conclusion This study conducted in non-acute settings showed an ethnic difference in composition of coronary atherosclerotic plaque with lower non-calcified composition in Caucasian patients compared to SA, which was independent of age, diabetes, hyperlipidemia and the other available cardiovascular risk factors.

Cover Letter

Prof G Maurer, Editor in Chief

European Heart Journal - Cardiovascular Imaging

Dr F Pugliese

Centre for Advanced Cardiovascular Imaging,

St Bartholomew's Hospital

West Smithfield, London EC1A 7BE

United Kingdom

London, 24 February 2016

Dear Editor,

Please find attached the revised version of our manuscript, No. EHJCI-D-15-01415-R1, entitled:

"Coronary atherosclerotic plaque burden and composition by CT angiography in Caucasian and South Asian patients with stable chest pain".

We have revised according to yours and the reviewers' advice. We enclose in a separate file point-to-point responses to the comments made.

Please, consider that reported on the title page as the intended order of Authors.

We hope that this paper is now suitable for the Journal.

With kind regards,

Dr Francesca Pugliese, MD PhD FESC

Title Page (include all author information)

Coronary atherosclerotic plaque burden and composition by CT angiography in Caucasian and South Asian patients with stable chest pain

Peter R Villadsen, BMedSci (1,2)
Steffen E Petersen, MD DPhil MPH FESC FACC (1)
Damini Dey, PhD (3)
Lu Zou, PhD (4)
Shivali Patel, BMedSci (1)
Hafiz Naderi, MBBS (1)
Katarzyna Gruszczynska, MD PhD (1,5)
Jan Baron, MD PhD (4)
L Ceri Davies, MD FRCP (1)
Andrew Wragg, PhD FRCP (1)
Hans Erik Bøtker, MD DPhil FESC FACC (2)
Francesca Pugliese, MD PhD FESC (1,2)

(1) Centre for Advanced Cardiovascular Imaging, NIHR Cardiovascular Biomedical Research Unit at Barts, William Harvey Research Institute, Barts and The London School of Medicine, Queen Mary University of London and St Bartholomew's Hospital, London, UK *(Institution where the work was carried out)*

(2) Department of Cardiology, Arhus University Hospital, Arhus, DK

(3) Cedars-Sinai Medical Centre, Los Angeles, CA

(4) Experimental Medicine and Rheumatology, William Harvey Research Institute, Barts and The London School of Medicine, Queen Mary University of London

(5) Department of Radiology and Nuclear Medicine, Medical University of Silesia, Katowice, Poland

Type of manuscript: Original paper

Keywords: atherosclerosis; coronary circulation; coronary artery disease (CAD); computed tomography; computed tomography angiography; ethnicity.

Corresponding Author:
Dr Francesca Pugliese, MD PhD FESC
Centre for Advanced Cardiovascular Imaging / NIHR Cardiovascular Biomedical Research Unit at Barts
Cardiac Imaging, 2nd floor, King George V building
St Bartholomew's Hospital
West Smithfield
London EC1A 7BE (United Kingdom)
Phone: +44 (0)20 7882 6906 / Fax: n.a.
Email: f.pugliese@qmul.ac.uk

Coronary atherosclerotic plaque burden and composition by CT angiography in Caucasian and South Asian patients with stable chest pain

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Abstract
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Aims

South Asian (SA) patients are known to have an increased incidence of acute cardiovascular events compared to Caucasians. The aim of this observational study was to compare the prevalence of coronary stenoses, the amount and composition of coronary atherosclerosis in a cohort of Caucasian and SA patients with stable chest pain in non-acute settings.

Methods and Results

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. In 963 consecutive Caucasian and SA patients undergoing coronary computed tomography angiography atherosclerotic plaques were quantified using a semi-automated algorithm. The vessel percent diameter and area stenosis were measured. Plaque composition was examined from measurement of calcified, non-calcified and total plaque burden.

There were 420 Caucasian (238 males) and 543 SA (297 males) patients. Caucasian patients were older than SA (54.39±11.65 vs. 49.83±11.03 years), had lower prevalence of diabetes (13.13% vs. 32.41%) and hyperlipidemia (56.90% vs. 68.51%) (all p-values<0.001). After adjusting for differences in cardiovascular risk factors, there were no differences in percent diameter and area stenosis, and no difference in the proportions of patients with one-, two- or three-vessel disease. There was no difference in total plaque burden, however the percent non-calcified plaque composition was lower in Caucasians compared to SA (80.95% vs. 90.42%; p-value<0.001).

Conclusion

This study conducted in non-acute settings showed an ethnic difference in composition of coronary atherosclerotic plaque with lower non-calcified composition in Caucasian patients compared to SA, which was independent of age, diabetes, hyperlipidemia and the other available cardiovascular risk factors.

Keywords: atherosclerosis; coronary circulation; coronary artery disease (CAD); computed tomography; computed tomography angiography; ethnicity.

List of abbreviations

CAD = coronary artery disease

CI = confidence interval

CT = computed tomography

CTA = computed tomography angiography

ECG = electrocardiogram

eGFR = estimated glomerular filtration rate

IQR = interquartile range

LM = left main coronary artery

MLR = multivariable linear regression

PS = propensity score

RI = remodeling index

SA = South Asian

SD = standard deviation

SE = standard error

SIS = segment involvement score

Introduction

People of South Asian (SA) ethnicity constitute a quarter of the world's population and face an increased risk of premature coronary artery disease (CAD), a pattern recorded among Indians in urban India and among SA migrants in other countries (1-4). In SA people there is greater incidence of early myocardial infarction, cardiovascular mortality and a higher number of traditional cardiovascular risk factors compared to other ethnicities (5, 6). Whether cardiovascular risk factors can adequately explain this high number of events is controversial (7, 8).

Evidence that plaque characteristics such as total plaque burden and composition as well as coronary stenosis may yield independent incremental prognostic value in both symptomatic and asymptomatic subjects is becoming increasingly available (9-12). Ethnic differences in the prevalence of coronary stenoses, atherosclerotic plaque burden and composition could have implications for understanding the mechanism behind the increased risk of developing acute events in SA people, which may not be fully explained by differences in classical cardiovascular risk factors. Data in the SA ethnicity are lacking (10).

Coronary computed tomography angiography (CTA) has emerged as a non-invasive technique for the detection of CAD. The feasibility of CTA as a method to detect early coronary atherosclerosis and assess plaque composition in stable and unstable patients has been previously reported (13, 14). Available semi-automated software tools to quantitatively measure coronary plaques have shown good accuracy and reproducibility (15-19).

The purpose of this observational study was to determine whether the prevalence of coronary stenoses, the burden and composition of coronary atherosclerotic plaque were associated with SA ethnicity and if any difference persisted after adjustment for cardiovascular risk factors in a cohort of patients with stable, non-acute chest pain.

Methods

Study population

All patients underwent physician-referred coronary computed tomography angiography (CTA) and gave written informed consent to the use of the data for research purposes (20). The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and received approval by the local Research Ethics Committee.

We screened 2,635 consecutive patients who had coronary CTA between 2010 and 2012 in a tertiary hospital in the borough of Tower Hamlets, East London, United Kingdom. Inclusion criteria were stable chest pain due to suspected coronary artery disease (CAD) and Caucasian or South Asian (SA) ethnicity (first generation migrants). Exclusion criteria were contraindications to coronary CTA such as impaired kidney function (eGFR <30ml/min), suspected or known allergy to iodinated contrast and inability to lay flat. Pregnant women were also excluded. Also not included were patients with known CAD, previous acute myocardial infarction (AMI), previous percutaneous coronary angioplasty (PCI) or coronary artery bypass graft (CABG) surgery, patients being evaluated prior to valve replacement procedures and with cardiomyopathies (**Appendix II; Figure 1**). Both ethnic groups lived in the same borough in East London and patients were evaluated at a single, public National Health Service (NHS) tertiary hospital with standardized care protocols and pathways.

Cardiovascular risk factors and type of chest pain

Data on cardiovascular risk factors were obtained through standardized patient questionnaires administered prior to the scans and were checked with information held in the hospital's electronic medical records. The type of chest pain was classified as typical, atypical, or non-anginal (21) (definitions given in the **Appendix II**)**.** Data fields that could not be observed or obtained from the medical records were coded as missing.

Coronary CTA acquisition and analysis

A second-generation dual-source CT scanner (Somatom Definition Flash, Siemens, Forchheim, Germany) was used. First, the Agatston calcium score was measured on a commercially available workstation (Syngo MultiModality Workplace VE25A, Siemens, Forchheim, Germany) by a single experienced observer using dedicated software (Syngo Calcium Score). No patients were excluded from the study due to a high calcium score. Then, image quality of coronary CTA was graded as good, adequate or poor (details in **Appendix II**). Datasets with good or adequate image quality were included for plaque quantification using a validated semi-automated software tool (Autoplaq, version 8.9, Cedars-Sinai Medical Centre, Los Angeles, CA) (16). A single independent, blinded observer inspected all coronary segments with a diameter above 1.5mm according to a modified 18-segment anatomical model (22). Segments with visually detectable coronary plaque were further analysed with semi-

automated software (**Figure 2**). Atherosclerotic plaque was defined as any clearly discernible structure greater than 1 mm^2 in diameter that could be assigned to the coronary wall on at least two consecutive sections (23).

The segment involvement score (SIS) was defined as the number of coronary segments containing any plaque. The percent area stenosis and diameter stenosis in each coronary segment were calculated using a simplified method (24) (**Appendix II**). Coronary artery diameter stenosis was reported using a 5-grade ordinal scale; 0: no stenosis, 1: 1-24% stenosis, 2: 25-49% stenosis, 3: 50-69% stenosis, 4: 70-89% stenosis, 5: ≥90% stenosis (25). The severity of disease on a patient level was reported as the maximum stenosis per patient and the number of vessels with at least one ≥50% diameter stenosis (one, two, three-vessel disease, left main (LM)-disease).

The remodeling index (RI) was calculated as the ratio between the total cross-sectional vessel area (including both plaque and vessel lumen) at the site of worst percent area stenosis and the mean cross-sectional vessel area between the proximal and distal reference sites (26).

Non-calcified plaque and calcified plaque were distinguished based on a scan-specific threshold level based algorithm. The procedure of semi-automatic plaque measurement is further described in the Appendix II and detailed in a previous publication (16). Low density non-calcified plaque (a sub-type of non-calcified plaque with particularly low attenuation) was defined as non-calcified plaque with attenuation values lower than 30 Hounsfield Units, in keeping with previously published data (27). To measure the atherosclerotic plaque burden, first the segmental non-calcified, calcified and total plaque volumes were measured within the same patient and were summed to derive per-patient non-calcified, calcified and total plaque volumes. Non-calcified plaque burden, calcified plaque burden and total plaque burden were calculated as 100*(plaque volume/vessel volume). The vessel volume in the denominator included both the vessel wall (including any plaque in it) and lumen. The plaque volume is a measured plaque parameter, where the plaque burden is normalised to the patient's individual coronary vessel volume, and was used in the analyses. Percent non-calcified plaque composition was derived as 100*(non-calcified plaque volume/total plaque volume).

Statistical methods

Categorical data were summarized as frequencies and percentages, and compared using χ^2 test or Fisher's Exact test when Chi-square approximation could be incorrect. Continuous variables were presented by both mean with standard deviation (SD) and median with interquartile range (IQR). Variables were compared using Mann-Whitney U test without assuming the normal distribution. To confirm the suitability of nonparametric testing, Shapiro Wilk test was used to test for normality of continuous variables. Most of the continuous variables were not normally distributed by Shapiro Wilk

test, including percent coronary diameter stenosis, no. vessels with ≥50% diameter stenosis, minimal luminal diameter and area, percent area stenosis, RI, SIS, Agatston calcium score and plaque burden. All p-values were <0.001.

To assess the effect of the exposure variable ethnicity on continuous outcome variables of plaque characteristics, we applied propensity score (PS) matching and weighting to adjust for potential confounders available in our retrospective database (28). Potential confounders included in the model were age, gender, hypertension, hyperlipidemia/cholesterol lowering medication, diabetes, smoking status, type of chest pain and family history. The propensity score was produced using logistic regression, and then propensity score weighting was applied to Mann-Whitney regression without assuming the normality of residual distribution (29). For comparison, we also applied general multiple linear regression (MLR) adjusting for the same baseline confounders used to produce propensity scores. The drawback here is that the normality assumption on the residuals may not be met.

Statistical analyses were performed using R for Windows, (open-source) version 3.2.2, with a p-value<0.05 considered to indicate statistical significance.

Results

The inclusion procedure is shown in Figure 1. Of 1,067 patients (464 Caucasians and 603 SA), good or adequate image quality on coronary CTA was found in 963/1067 (90.25%) patients. Patients with poor image quality (104/1067; 9.75%) were excluded from further analysis (**Figure 1)**.

Baseline characteristics

The study population consisted of 963 patients of whom 420 were Caucasian and 543 were SA. Between Caucasians and SA there were no significant differences in gender distribution (p-value=0.586), prevalence of hypertension (p-value=0.562) and the type of chest pain (p-value=0.630) (**Table 1**). On average Caucasians were older than SA (54.39 ± 11.65 vs. 49.83 ± 11.03 years; p-value<0.001), with a lower prevalence of diabetes (13.13% vs. 32.41%; p-value<0.001) and hyperlipidemia (56.90% vs. 68.51%; p-value=0.001). Caucasians had a higher prevalence of smoking than SA (50.24% vs. 30.94%; p-value<0.001) (**Table 1**).

Coronary CTA

Between Caucasians and SA, we observed no difference in the SIS (p-value=0.208) and in the number of vessels with ≥50% diameter stenosis, i.e. one, two, three-vessel disease and/or LM disease (p-value=0.559) (**Table 2**)**.** Similarly, there was no significant difference in coronary minimal luminal diameter (p-value=0.216), minimal luminal area (p-value=0.290) and percent area stenosis (p-value=0.342) (**Table 2**).

Caucasians had slightly higher Agatston score than SA (121.80 vs. 56.65; p-value=0.002), higher calcified plaque burden (2.89% vs. 1.40%; p-value<0.001) and lower non-calcified plaque burden (13.43% vs. 14.69%; p-value=0.002)**.** Despite these differences there was no significant difference in total plaque burden (p-value=0.889) and RI (p-value=0.792) (**Table 2**). In patients with atherosclerotic plaque, the percent non-calcified plaque composition was lower in Caucasians compared to SA (80.95% vs. 90.42%; p-value<0.001) (**Table 2**).

In the sub-analysis by diabetes (**Table 3**), non-calcified and calcified plaque burden, as well as non-calcified plaque composition remained different between Caucasian and SA patients, regardless of whether or not the patients had diabetes. In this subanalysis, not adjusted by age nor by any of the other cardiovascular risk factors, differences between ethnic groups in percent coronary diameter stenosis (p=0.033), percent area stenosis (p=0.006), RI (p=0.017), SIS (p=0.001) and Agatston calcium score (p<0.001) were seen in the non-diabetic group, but not in the diabetic group.

After propensity score matching, there were no significant differences in covariates between ethnic groups (**Table 4**). A significant association between Caucasian ethnicity and Agatston calcium score, calcified plaque burden as well as calcified plaque composition remained, as shown by propensity score matching, propensity score weighting and MLR (**Table 5, Figure 3**).

The association between SA ethnicity and non-calcified plaque burden remained by propensity score weighting, but not by the other two approaches. Both of these variables were not normally distributed according to Shapiro Wilk test, thus using MLR may have caused bias. Propensity score exact matching, on the other hand, despite a more rigorous adjustment for confounders, reduced the power of testing using a much smaller sample size. SA ethnicity, however, remained associated with non-calcified plaque composition by all three approaches.

Discussion

In a cohort of consecutive symptomatic patients with stable chest pain undergoing coronary CTA we observed ethnic differences between Caucasians and SA in the composition of atherosclerotic plaque that were not fully explained by available, classical cardiovascular risk factors. SA patients presented with chest pain at a younger age and had higher rate of diabetes, which was roughly 2.5 times the rate in Caucasians. A similar difference in age and prevalence of diabetes was found previously between SA and Caucasian patients receiving percutaneous revascularization in the setting of an acute coronary syndrome (30). We found no difference in the severity of coronary atherosclerosis expressed as either the percent area stenosis, or the number of vessels with at least one ≥50% diameter stenosis (one, two, three-vessel disease, LM-disease). However, the percent non-calcified plaque composition was lower in Caucasians compared to SA. Caucasians had slightly higher calcified plaque burden than SA, although this difference was small.

Our study has two important features. Firstly, we included a large group of SA subjects lacking in many of the previous studies. Secondly, the majority of previous studies evaluated coronary calcification on non-contrast electron-beam computed tomography (EBCT). We used coronary CTA to evaluate quantitatively calcified as well as non-calcified plaque burden together with coronary artery stenosis. We report on coronary plaque phenotype (quantity of plaque, composition, stenosis) in Caucasians and SA with stable chest pain. Evidence that plaque characteristics such as plaque burden and composition as well as coronary stenosis may yield incremental prognostic value both in symptomatic and asymptomatic subjects is becoming increasingly available, and may gain increasing importance for patient management, especially in populations at higher risk (9-12).

In the population-based Multi-Ethnic Study of Atherosclerosis (MESA) (31), the amount of coronary calcifications measured with non-contrast EBCT was higher in Caucasian subjects compared to other ethnicities such as Chinese, Hispanic and African-American subjects.

Similarly, in another non-contrast EBCT study of asymptomatic individuals referred by their physician for cardiovascular risk assessment, Caucasians had a higher relative risk of having coronary calcification compared to Hispanic and African-American subjects (32).

A study by Kanaya et al. (MASALA study) (33) looked at a prospective community-based cohort of asymptomatic SA individuals in the United States and compared the coronary artery calcium score to that of the other ethnic groups included in the MESA study. In this study, the SA group was younger and had higher prevalence of diabetes, hyperlipidemia and lower prevalence of cigarette smoking compared to Caucasian, in exact agreement with our findings. The crude prevalence of coronary calcification (any detectable calcium score vs. zero calcium score) was higher in Caucasians compared to SA. After adjusting for age and covariates, Caucasian and SA subjects had similar calcium scores.

This is not in contrast with our study where the difference in calcified plaque burden between Caucasian and SA patients was statistically significant but small.

However, not all coronary plaques are calcified and calcification may lead to underestimation of the total amount of coronary atheroma (23). In our study coronary CTA allowed the assessment of non-calcified and calcified components as well as total atherosclerotic plaque.

We found a ~10% higher non-calcified plaque composition in SA compared to Caucasians. However, we also observed a younger age and a higher rate of diabetes in SA. The amount of coronary calcification is known to increase with age (34). This baseline difference was also observed in SA and Caucasian patients receiving revascularization in the context of acute coronary syndromes (30). The same pattern was also observed in the study by Kanaya et al. (33) looking at a prospective, community-based cohort of asymptomatic subjects without known coronary artery disease. A higher proportion of non-calcified plaque in diabetic patients compared to non-diabetics was reported using invasive (35) and non-invasive (36, 37) imaging techniques. It could be argued that the higher non-calcified plaque composition in the SA group may be related to younger age and higher prevalence of diabetes. However, following adjustment for diabetes, age and classical cardiovascular risk factors, a difference in plaque composition remained, not fully explained by available cardiovascular risk factors.

A study by Roos et al. (38) using coronary CTA included 240 Caucasian and SA asymptomatic patients all with diabetes. In this study, where all patients were diabetic and were matched by age, gender and duration of diabetes, the Authors found that SA had more advanced atherosclerosis with a higher number of vessels with ≥50% diameter stenosis compared to Caucasians. Although non-calcified plaque was not evaluated in this study, findings suggested that ethnicity and not only differences in risk factors might have an effect on the atherosclerotic process, in keeping with our findings.

Another study by Koulaouzidis et al. (39) looked at 101 Caucasian and SA symptomatic patients matched for age, gender and presence of diabetes. In this cohort coronary atherosclerosis was much more advanced than in our study and this was particularly in SA compared to Caucasians: 26% of SA and 6% of Caucasian patients had three-vessel disease, 14% of SA and 28% of Caucasians had one-vessel disease. SA patients had more calcified as well as non-calcified plaques (visually assessed) compared to Caucasians. Since patients were matched for age, gender and presence of diabetes, the Authors excluded conventional risk factors as an explanation for these differences, again suggesting a role for ethnicity.

Due to inherent limitations in spatial resolution, the analysis of plaque characteristics by coronary CTA is rather crude. Firstly, the visual impression of coronary calcifications on CTA images is affected by the ‘blooming effect’ that exaggerates the size of calcifications. Because this is a known challenge, in this study we used a scan-specific, threshold level based software tool to quantify and classify coronary plaques as calcified or non-calcified. Secondly, the fibrous tissue component and lipid-rich (or necrotic)

core of a coronary plaque cannot always be distinguished hence both will contribute to the non-calcified plaque volume detected on coronary CTA. The percent non-calcified plaque composition found in our study likely reflects the sum of a larger fibrous tissue component and a smaller lipid-rich component, in good agreement with histology data (40). The ability to identify selectively and accurately low density non-calcified plaques associated with a thin fibrous cap (a histopathological entity called thin-cap fibroatheroma) could provide a more sophisticated parameter to identify patients at higher risk of acute coronary events. However, this task appears rather unrealistic with current non-invasive imaging technology.

Despite these limitations, the clinical value of straightforward plaque characteristics such as estimated quantity of plaque (plaque burden) and composition, as well as coronary stenoses, has been previously shown for evaluating plaque progression/regression and refining prognostication (9, 12). The magnitude of the plaque burden expressed as the number of plaques or the number of diseased segments (SIS) in combination with stenosis severity scores were also reported as directly associated with worse prognosis in both non-diabetic and diabetic patients (11, 41).

We acknowledge a few study limitations. Firstly, this is a cross-sectional study. Clinical outcome data were not available. Given that a small proportion of these stable patients had ≥50% coronary stenosis, long follow-up times will be necessary to collect meaningful numbers of hard events (death, myocardial infarction). The observational data included in this study however offer an insight into earlier, non-acute stages of coronary atherosclerosis. Secondly, there may be residual confounding factors such as incomplete adjustment for physical activity levels, inflammatory biomarkers, vitamin D levels, cultural factors (consumption of high salt and high glycemic index foods) and socio-economic status (income and education). After propensity score exact matching, the power of testing was reduced using a much smaller sample size. Thirdly, the physician's knowledge of SA patients being at higher risk for acute coronary events at younger ages might as well induce an earlier referral to diagnostic testing compared to Caucasians, adding some selection bias. However, both ethnic groups lived in a single borough in East London and were evaluated at a single, public National Health Service (NHS) tertiary hospital with standardized care protocols and pathways. Nevertheless, we acknowledge that generalizability of our results may be limited given that we used data from a single tertiary centre in the UK.

In conclusion, this observational study carried out in non-acute settings showed a difference in composition of coronary atherosclerotic plaque between Caucasian and SA patients not entirely explained by cardiovascular risk factors. SA patients had higher percent non-calcified plaque composition compared to Caucasians. Further longitudinal research is warranted to evaluate the mechanistic and clinical significance of this difference in phenotype, which may be related to ethnicity or to more complex interactions between ethnicity and risk factors.

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Appendix I

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Appendix II

Study population

The ethnicity recorded was that declared by the patient. SA ethnicity describes patients of Indian, Pakistani, Bangladeshi, Sri Lankan or Nepalese origin, as previously described (42). The SA people included in this study were first generation migrants living in the borough of Tower Hamlets (London, United Kingdom) (43). This study did not aim to perform comparison among first, second and third generation migrants because this mix is not observed in our practice based in East London, United Kingdom.

Cardiovascular risk factors and type of chest pain

Diabetes was defined as a fasting blood glucose level above 126mg/dl (7mmol/l) or requirement for insulin or oral hypoglycemic drugs. Hyperlipidemia was defined as a total cholesterol level above 200mg/dl (5.18mmol/l). Use of cholesterol lowering medication was dichotomized into on treatment and not on treatment. Hypertension was defined as blood pressure above 140/90mmHg or use of anti-hypertensive medication. Smoking was dichotomized into never smokers and smokers (current and former). Family history of coronary heart disease was defined as having first- or second- degree relatives with premature CAD (age <50 years for men, <55 years for women). Typical chest pain was defined as having (i) substernal chest pain or discomfort, that is (ii) provoked by exertion or emotional stress and (iii) relieved by rest and/or nitroglycerine (21). Atypical chest pain was defined as having two of the before-mentioned criteria. When one or none of the criteria was present, the patient was classified as having non-anginal chest pain.

Coronary CTA acquisition

Patients with resting heart rates >65 beats per minute (beats/min) and no contraindications were given 5-35mg i.v. metoprolol until a desired heart rate of ≤65beats/min was reached. All patients underwent a non-enhanced calcium scoring scan using a prospectively ECG-triggered high pitch spiral technique with the following parameters: 2x64x0.6mm collimation, 280msec gantry rotation time, a pitch of 3.4, 120kV tube voltage, 150mA tube current. Images were reconstructed with a 3mm slice thickness and an increment of 1.5mm. Coronary CTA was performed with a sequential, prospectively ECG-triggered (step-and-shoot) protocol with the following parameters: 2x64x0.6mm collimation with z-flying focal spot for both detectors, 280ms gantry rotation time, tube voltage of 100/120kV (<90kg/≥90kg) and a maximum tube current of 370mAs. The imaging window was set at 70% of the R-R interval for heart rates <70beats/min and was prolonged to include 40-70% of the R-R interval for heart rates ≥70beats/min. The optimal scan delay was determined by injection of 15ml of iodinated contrast

(300mgI/ml, Omnipaque, GE Healthcare, UK) with an injection rate of 7.0ml/s. Scan time was 6-8 s with this protocol. A volume of 60 ml of contrast was injected followed by 40 ml saline chaser with the same injection rate to ensure consistent intra-coronary attenuation across the scan range. Coronary CTA images were reconstructed at the best mid-to-end diastolic phase (and systolic phase when available) with a 0.75mm slice thickness and a 0.4mm increment using a dedicated (B26f) convolution filter. The median (interquartile range) dose length product (DLP) associated with the protocol was 202 (115-402) mGy*cm.

Coronary CTA analysis

Image quality of coronary CTA datasets was graded as good, adequate or poor. Good image quality was defined as a clear delineation of the coronary arteries without motion artifacts. Adequate image quality was defined as mild motion artifacts and blurring of the vessel wall. Poor image quality was defined as severe motions artifacts, severely blurred vessels and/or poor signal-to-noise-ratio.

Datasets with good or adequate image quality were analysed using a validated semi-automated software tool (Autoplaq, version 8.9, Cedars-Sinai Medical Centre, Los Angeles, CA) (16) that applies a scan-specific threshold level-based quantification method. A single independent, blinded observer inspected all coronary segments with a diameter above 1.5mm according to an 18-segment anatomical model (22). Segments with visually detectable coronary plaque were further analysed with semi-automated software (**Figure 2**). Atherosclerotic plaque was defined as any clearly discernible structure greater than 1 mm^2 in diameter that could be assigned to the coronary wall on at least two consecutive sections (23).

First a 1-cm^2 region of interest was placed in the aorta to define blood pool attenuation. Using the most representative longitudinal image of the coronary vessel of interest, two points were placed in the vessel marking the proximal and distal vessel reference points. Then the vessel centerline was manually drawn between these points and the plaque characteristics were quantified as described below with the vessel wall edited if necessary.

Because the intra-arterial injection of iodinated contrast results in enhancement of the arterial lumen as well as significant enhancement of the vessel wall and atherosclerotic plaque (44, 45), plaque attenuation may vary with intracoronary attenuation. Cademartiri et al. (46) also demonstrated that plaque attenuation varied significantly with the reconstruction kernel. The approach used here used scan-specific attenuation thresholds for non-calcified plaque and calcified plaque components, which were automatically determined from luminal attenuation. In addition to the CTA data, the algorithm required as input a region of interest in the aorta defining the normal blood pool, five to seven control points in the arterial lumen along the plaque, from which luminal centrelines were derived, and two points marking the start and the end of the artery to be analysed. To calculate scan-specific thresholds

for non-calcified and calcified plaque, previously published algorithms (47) for non-contrast cardiac CT were implemented, adding specific consideration to the scan-specific variation in contrast distribution through the coronary arteries. Non-calcified and calcified plaque components were automatically classified within the arterial wall by an iterative, recursive 3D region-growing algorithm, which expanded from a starting seed voxel similar to an expanding 3D balloon. The seed voxel was first localized from the cross-sectional plane with the greatest luminal stenosis. The classified voxels were displayed with color-coded overlay and volumetric percentages provided in the analysis output. The analysis procedure and mathematical algorithm were previously described in full detail (16).

This algorithm was previously validated showing robust inter-observer agreement, expressed by r=0.83 for total plaque, r=0.90 for calcified plaque, 0.93 for non-calcified plaque and 0.96 for non-calcified plaque composition (15). Inter-observer mean percent differences were 0.3% for calcified plaque and 0.1% for non-calcified plaque (18). Intra-observer agreement was also proven robust with r= 0.97 for both total plaque and calcified plaque, and r=0.96 for both non-calcified plaque and non-calcified plaque composition (15). Intra-observer mean percent differences were 0.4% for calcified plaque and 0.3% for non-calcified plaque (18). Variability in estimating plaque burden, however, would have equally impacted on both ethnicities, without impairing the between-cohorts comparison reported in this study.

The percent area stenosis and diameter stenosis in each coronary segment were calculated using a simplified method that estimates the normal tapering of the coronary artery (24). This method requires measurement of the following: reference luminal area proximal to stenosis (Aprox); reference luminal area distal to stenosis (Adis); minimal luminal area at the site of stenosis (Asten); distance between proximal reference site and distal reference site (X1), and distance between proximal reference site and minimal luminal diameter (X2). The percent area stenosis was derived as {1 - [Asten] / [Aprox - (X1/X2) * (Aprox - Adist)]}.

Table 1: Baseline characteristics

	Caucasians (n=420)	South Asians (n=543)	p-value[2]	Proportion of data available[3]
Age, years, mean (SD[1])	54.39 (11.65)	49.83 (11.03)	<0.001	99.79%
Gender (Male), n (%)	238 (56.67)	297 (54.70)	0.586	100%
Hypertension, n (%)	164 (39.05)	225 (41.44)	0.562	97.61%
Diabetes, n (%)	56 (13.13)	176 (32.41)	<0.001	99.07%
Hyperlipidaemia, n (%)	239 (56.90)	372 (68.51)	0.001	95.85%
Smoking, n (%)	211 (50.24)	168 (30.94)	<0.001	97.09%
Family history of CAD, n (%)	168 (40.00)	182 (33.52)	0.035	96.05%
Type of chest pain, n (%)				
Typical	38 (9.05)	41 (7.55)	0.630	100%
Atypical	191 (45.48)	259 (47.70)		
Non-anginal	191 (45.48)	243 (44.75)		

[1] sd=standard deviation;
[2] Chi-square test for categorical variables and two-tailed student's t test for continuous variables;
[3] Deviation from the total number of patients in each group is explained by missing values in this retrospective analysis.
Data on Body Mass Index (BMI) were available in 60.11% of the study population. BMI was 27.10 (4.10) in Caucasian and 26.66 (5.90) in SA patients (p=0.54). Due to missing data, this variable was excluded from further analyses.

Table 2: Coronary CTA findings

		Caucasians (n=420)	South Asians (n=543)	p-value
Percent coronary diameter stenosis class (most severe lesion per patient), n (%)				
None		188 (44.76)	264 (48.62)	
1-24%		116 (27.62)	125 (23.02)	
25-49%		62 (14.76)	95 (17.50)	
50-69%		22 (5.24)	28 (5.16)	0.114 [1]
70-89%		18 (4.29)	10 (1.84)	
≥90%		14 (3.33)	21 (3.87)	
No. vessels with ≥50% diameter stenosis, n (%)				
None		356 (84.76)	460 (84.71)	
1-vessel disease		45 (10.71)	53 (9.76)	
2-vessel disease		10 (2.38)	22 (4.05)	0.559 [1]
3-vessel disease		8 (1.90)	7 (1.29)	
LM disease		1 (0.24)	1 (0.18)	
Minimal luminal diameter (mm)	Mean (SD)	2.32 (1.02)	2.23 (0.97)	0.216 [2]
	Median (IQR)	2.35 (1.60-3.00)	2.20 (1.60-2.90)	
Minimal luminal area (mm^2)	Mean (SD)	4.54 (3.59)	4.26 (3.62)	0.290 [2]
	Median (IQR)	3.75 (1.70-6.70)	3.45 (1.60-6.00)	
Percent area stenosis (%)	Mean (SD)	27.43 (32.54)	26.24 (32.54)	0.342 [2]
	Median (IQR)	13.10 (0-47.53)	0.60 (0-50.88)	
RI. maximum segmental	Mean (SD)	1.48 (2.42)	1.87 (9.43)	0.792 [2]
	Median (IQR)	1.1 (1.0-1.6)	1.1 (1.0-1.6)	
SIS (%)				
None		186 (44.29)	263 (48.43)	
1-3 segments		150 (35.71)	199 (36.65)	
4-6 segments		59 (14.05)	58 (10.68)	0.208 [1]
≥7 segments		25 (5.95)	23 (4.24)	
Agatston calcium score	Mean (SD)	121.80 (435.58)	56.65 (213.93)	0.002 [2]
	Median (IQR)	0 (0-49.98)	0 (0-14.90)	
Plaque burden *				
Total plaque burden	Mean (SD)	15.89 (5.82)	16.06 (6.03)	0.889 [2]
	Median (IQR)	15.17 (12.08-19.34)	15.28 (12.07-19.93)	
Non-calcified plaque burden	Mean (SD)	13.43 (8.66)	14.69 (6.16)	0.002 [2]
	Median (IQR)	12.24 (9.17-15.72)	13.83 (10.37-18.68)	
Low-density non-calcified plaque burden	Mean (SD)	2.04 (1.45)	2.27 (1.59)	0.110 [2]
	Median (IQR)	1.76 (1.00-2.66)	1.90 (1.18-3.05)	
Calcified plaque burden	Mean (SD)	2.89 (3.23)	1.40 (2.05)	<0.001 [2]
	Median (IQR)	2.09 (0.29-4.27)	0.49 (0-2.15)	
Non-calcified plaque composition**	Mean (SD)	80.95 (18.05)	90.42 (13.23)	<0.001 [2]
	Median (IQR)	83.87 (69.43-97.82)	96.52 (83.31-100)	

[1] Chi square test, or Fisher's test when Chi-square approximation may be incorrect.
[2] Mann-Whitney U test used for continuous variables without assuming the normality of distributions.
* Plaque burden=100*(plaque volume/vessel volume).
** Non-calcified plaque composition=100*(non-calcified plaque volume/total plaque volume).

Table 3: Coronary CTA findings by diabetes

		Diabetic (n=232)		p-value*	Non diabetic (n=722)		p-value*
Percent coronary diameter stenosis class (most severe lesion per patient), n (%)		**Caucasians (n=56)**	**South Asians (n=176)**		**Caucasians (n=360)**	**South Asians (n=362)**	
None		20 (35.71)	58 (32.95)	0.164	166 (46.11)	203 (56.08)	0.033
1-24%		22 (39.29)	45 (25.57)		92 (25.56)	80 (22.10)	
25-49%		7 (12.50)	45 (25.57)		55 (15.28)	48 (13.26)	
50-69%		2 (3.57)	13 (7.39)		20 (5.56)	15 (4.14)	
70-89%		3 (5.36)	6 (3.41)		15 (4.17)	4 (1.10)	
≥90%		2 (3.57)	9 (5.11)		12 (3.33)	12 (3.31)	
No. vessels with ≥50% diameter stenosis, n (%)							
None		44 (78.57)	133 (75.57)	0.543	308 (85.56)	322 (88.95)	0.149
1-vessel disease		8 (14.29)	27 (15.34)		37 (10.28)	26 (7.18)	
2-vessel disease		2 (3.57)	11 (6.25)		8 (2.22)	11 (3.04)	
3-vessel disease		1 (1.79)	5 (2.84)		7 (1.94)	2 (0.55)	
LM disease		1 (1.79)	0 (0)		0 (0)	1 (0.28)	
Minimal luminal diameter (mm)	Mean (SD)	2.26 (0.91)	2.14 (0.96)[	0.268	2.31 (1.04)	2.29 (0.97)	0.812
	Median (IQR)	2.30 (1.70-3.03)	2.10 (1.55-2.80)		2.30 (1.60-3.00)	2.30 (1.80-2.90)	
Minimal luminal area (mm^2)	Mean (SD)	4.50 (2.97)	3.78 (3.48)	0.091	4.53 (3.69)	4.62 (3.70)	0.654
	median (IQR)	4.25 (1.98-7.28)	2.60 (1.40-5.15)		3.70 (1.70-6.63)	3.80 (1.75-6.45)	
Percent area stenosis (%)	Mean (SD)	30.13 (31.77)	35.64 (34.52)	0.328	27.23 (32.78)	21.71 (30.61)	0.006
	median (IQR)	23.20 (0-46.25)	31.95 (0-62.15)		11.30 (0-49.15)	0 (0-42.00)	
Remodelling index segmental maximum	Mean (SD)	1.36 (0.43)	1.49 (0.51)	0.132	1.49 (2.61)	2.06 (11.55)	0.017
	median (IQR)	1.2 (1.0-1.7)	1.4 (1.0-1.8)		1.1 (1.0-1.6)	1.0 (1.0-1.5)	
SIS (%)							
None		20 (35.71)	57 (32.39)	0.749	164 (45.56)	203 (56.08)	0.001
1-3 segments		21 (37.50)	71 (40.34)		127 (35.28)	126 (34.81)	
4-6 segments		9 (16.07)	35 (19.89)		50 (13.89)	23 (6.35)	
≥7 segments		6 (10.71)	13 (7.39)		19 (5.28)	10 (2.76)	
Agatston calcium score	Mean (SD)	248.03 (763.36)	80.78 (182.64)	0.377	102.59 (359.25)	45.67 (228.24)	<0.001
	Median (IQR)	4.50 (0-122.38)	0.95 (0-71.00)		0 (0-39.75)	0 (0-4.00)	

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Plaque burden (%)							
Total plaque burden	Mean (SD)	16.65 (7.50)	15.56 (5.21)	0.739	15.80 (5.47)	16.38 (6.58)	0.790
	Median (IQR)	15.39 (13.13-18.95)	15.50 (12.35-19.09)		15.18 (12.06)-19.37)	15.04 (12.06-20.37)	
Non-calcified plaque burden	Mean (SD)	12.82 (7.18)	14.00 (4.99)	0.038	13.59 (8.94)	15.16 (6.88)	0.013
	Median (IQR)	11.67 (8.76-14.58)	13.83 (10.41-17.73)		12.43 (9.37-16.42)	13.76 (10.31-19.29)	
Low-density non-calcified plaque burden	Mean (SD)	1.93 (1.43)	2.18 (1.51)	0.298	2.07 (1.46)	2.32 (1.66)	0.229
	Median (IQR)	1.66 (1.14-2.28)	1.90 (1.17-3.11)		1.82 (0.99-2.84)	1.87 (1.19-3.00)	
Calcified plaque burden	Mean (SD)	3.85 (3.90)	1.56 (1.97)	0.001	2.71 (3.07)	1.27 (2.12)	<0.001
	Median (IQR)	3.01 (0.81-5.04)	0.72 (0-2.66)		1.96 (0.20-4.13)	0.33 (0-1.86)	
Non-calcified plaque composition (%)	Mean (SD)	77.59 (17.05)	89.76 (12.02)	<0.001	81.60 (18.22)	90.84 (14.14)	<0.001
	Median (IQR)	77.84 (67.72-91.17)	94.46 (80.83-100)		85.06 (69.97-98.40)	98.18 (86.38-100)	

* Chi-square/Fisher test is used for categorical variables and Mann-Whitney U test is used for continous variables without assuming the normality of distributions.

Table 4: Summary of confounders on the matched cases by propensity score (n=109)

	Caucasians (n=53)		South Asians (n=56)		p-value*
	Mean	**SD**	**Mean**	**SD**	
Age	49.40	8.92	49.25	8.77	0.915
	n	**%**	**n**	**%**	
Gender (male)	35	66	36	64	>0.999
Hypertension	10	19	11	20	>0.999
Diabetes	3	6	4	7	>0.999
Hyperlipidaemia	36	68	40	71	0.850
Smoking	20	38	21	38	>0.999
Family history of CAD	15	28	16	29	>0.999
Type of chest pain					
Typical	1	2	1	2	
Atypical	28	53	29	52	>0.999
Non-anginal	24	45	26	46	

* Two-sided t test and Wilcoxon rank sum test for continuous variables; Chi-square/Fisher's test for contingency tables.

Table 5: Ethnicity difference (Caucasian vs. South Asian) using propensity score matching and weighting, and multivariate analysis

Dependent variable	Propensity score matching (n=109)					Propensity score weighting (n=902)					Multivariate linear regression (n=963)*		
	Caucasian (n=53)		South Asians (n=56)		Mann Whitney p-value	Caucasian (n=390)		South Asians (n=512)		Mann Whitney p-value	Estimate	SE	p-value
	Mean	SD	Mean	SD		Mean	SD	Mean	SD				
Percent coronary diameter stenosis	14.14	23.51	14.01	23.83	0.992	18.22	26.03	17.30	25.39	0.909	-1.93	1.74	0.267
No. vessels with ≥50% diameter stenosis	0.09	0.30	0.09	0.35	0.694	0.23	0.62	0.23	0.60	0.847	-0.05	0.04	0.239
Minimal luminal diameter	2.19	1.04	2.43	1.29	0.714	2.30	1.02	2.23	0.97	0.662	0.14	0.10	0.139
Minimal luminal area	3.69	3.16	5.58	6.21	0.356	4.49	3.60	4.26	3.63	0.426	0.52	0.36	0.148
pvaluePercent area stenosis	24.34	31.42	22.44	31.67	0.729	28.52	32.74	26.63	32.64	0.663	-2.77	2.16	0.200
Remodelling index, segmental max	2.12	6.02	1.25	0.34	0.712	1.50	2.51	1.82	9.55	0.589	-0.33	0.53	0.542
SIS	1.40	2.13	1.07	1.37	0.890	1.77	2.31	1.51	2.06	0.742	-0.07	0.14	0.608
Agatston calcium score	64.03	174.68	21.70	53.46	0.376	128.96	450.84	50.95	172.97	0.037	37.66	21.74	0.084
Plaque burden (%)													
Total plaque burden	14.11	4.35	16.53	6.64	0.186	15.94	5.78	16.03	6.07	0.929	-0.16	0.60	0.792
Non-calcified plaque burden	15.23	20.43	15.17	7.27	0.060	13.45	8.71	14.73	6.21	0.009	-0.99	0.73	0.176
Low density non-calcified plaque burden	1.95	1.98	2.37	1.80	0.192	2.07	1.46	2.28	1.61	0.214	-0.15	0.15	0.340
Calcified plaque burden	2.81	2.75	1.38	2.00	0.033	2.94	3.27	1.33	1.93	0.000	1.18	0.24	0.000
Non-calcified plaque composition	79.18	17.10	90.04	17.50	0.009	80.86	17.98	90.72	12.92	0.000	-7.35	1.46	0.000

* Multivariate linear regression (MLR) includes independent variables: Caucasian and all the variables (see Table 4) involved in propensity score calculation. The limitation of MLR is that the assumption of normality of response variable may not be met.

Figure 1. Inclusion procedure.

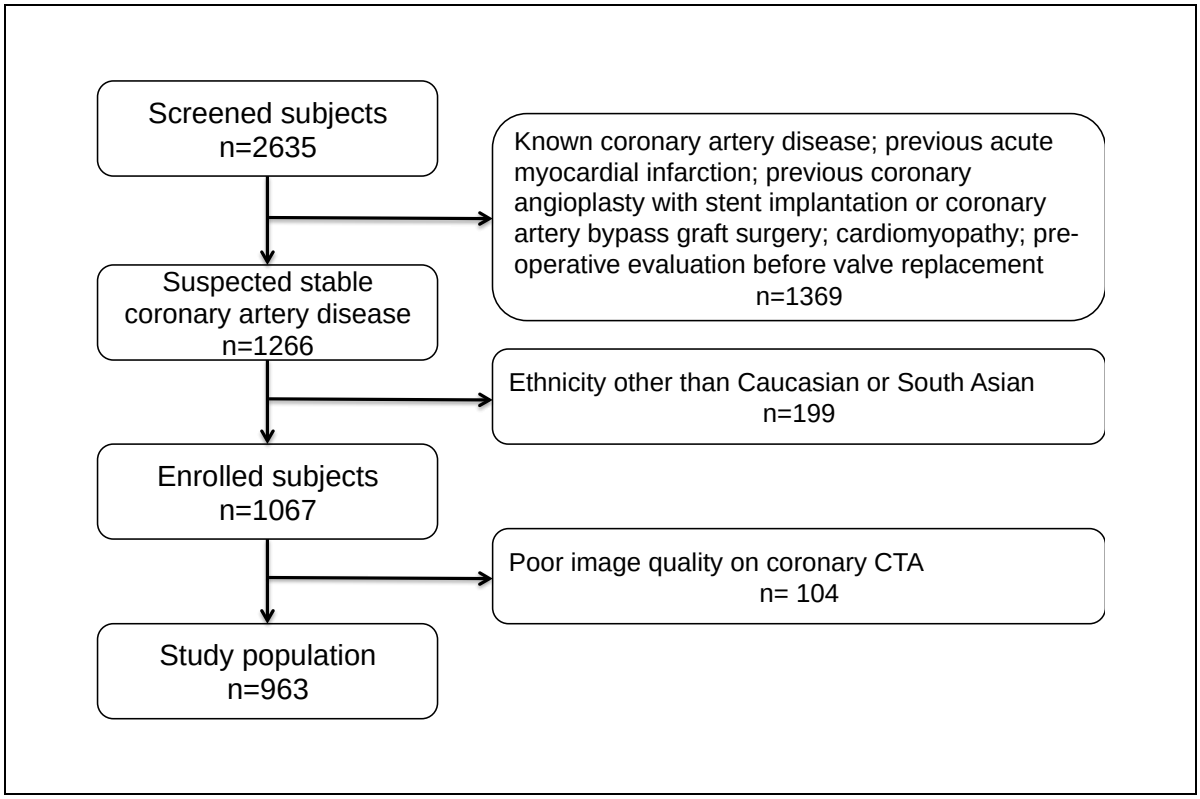


Figure 2. Semi-automated analysis procedure.

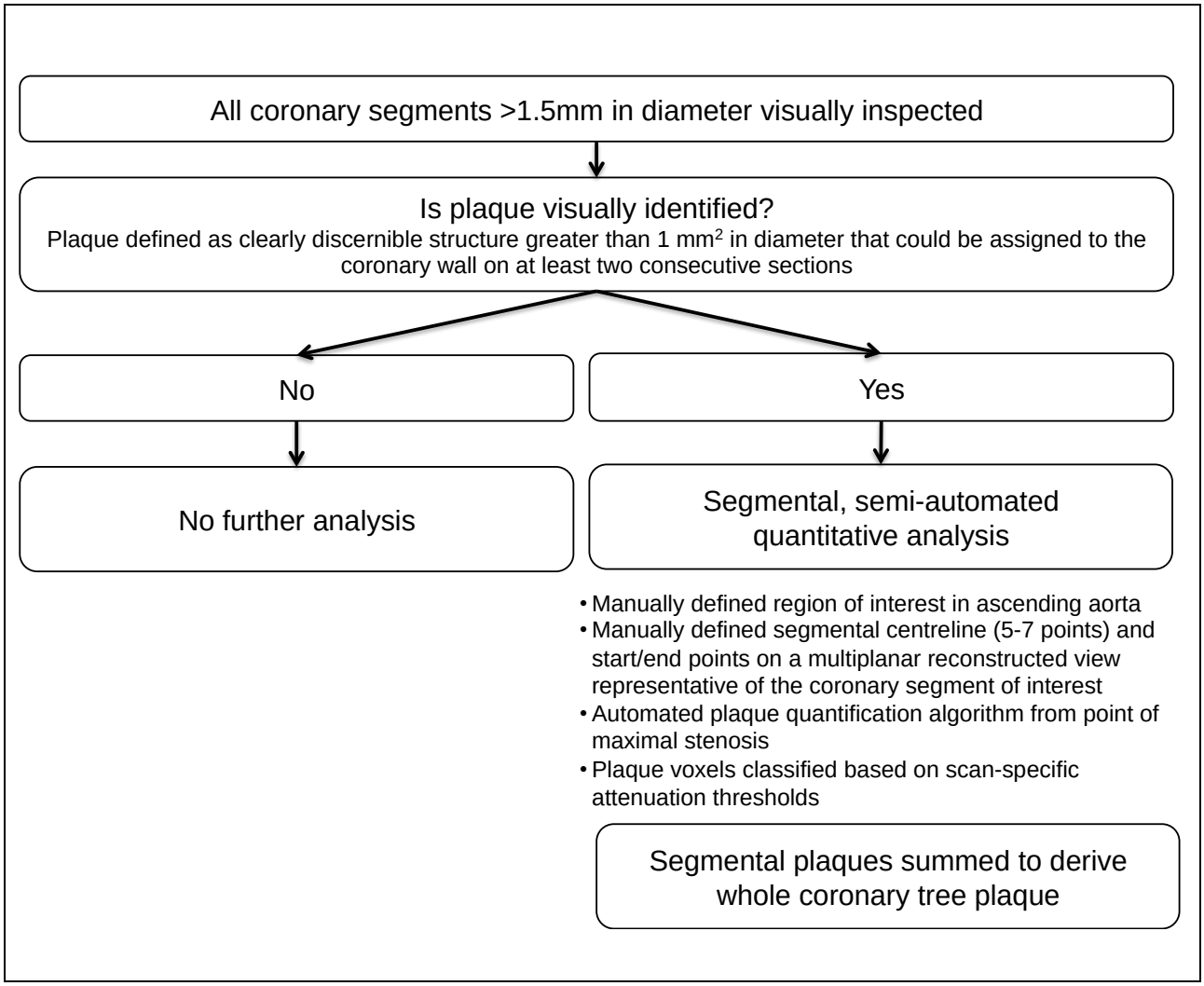
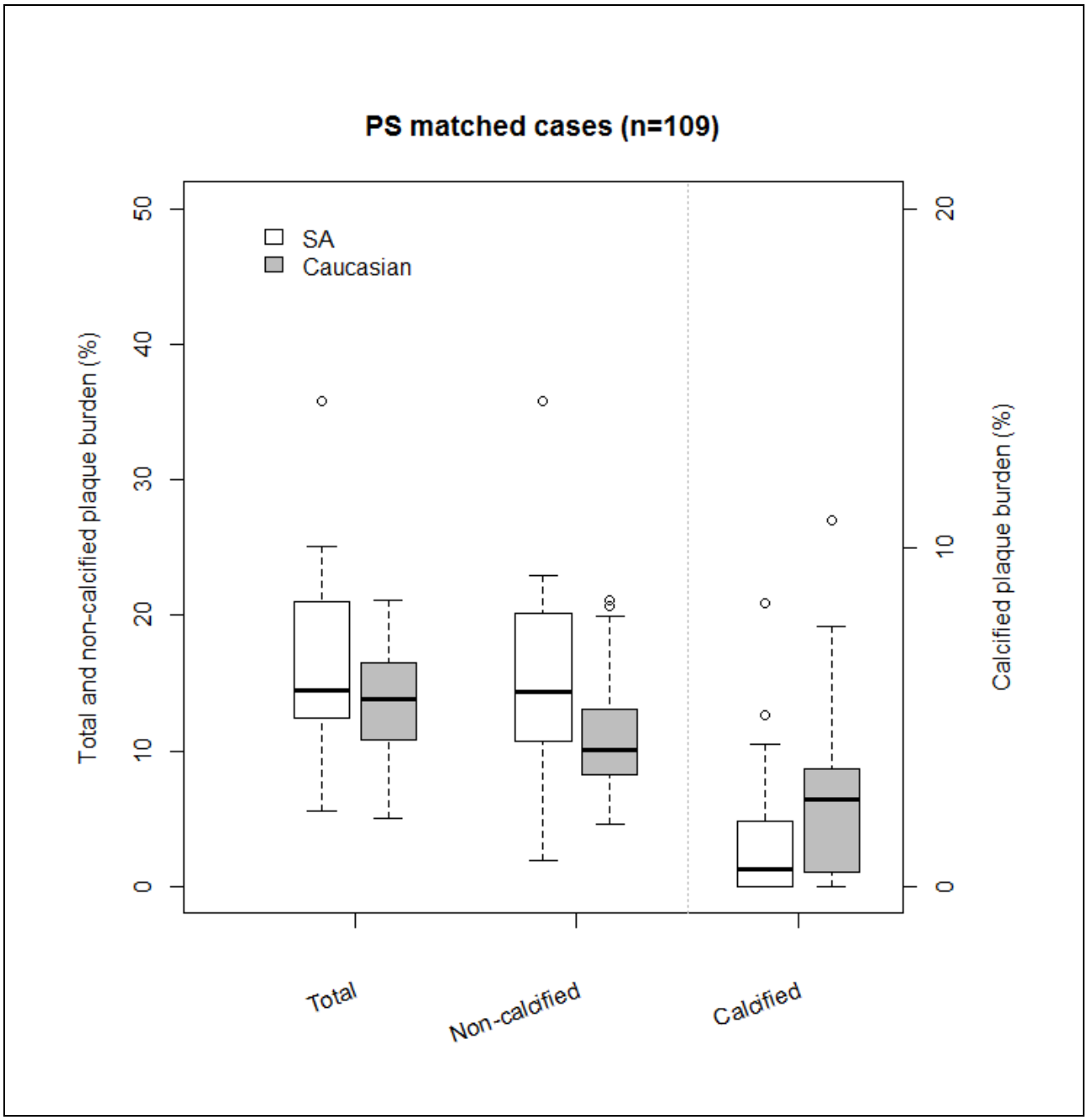


Figure 3. Plaque burden according to ethnicity using propensity score (PS) matched cases (n=109).

Although there was no overall difference in total plaque burden between ethnicities, Caucasian patients had significantly lower non-calcified plaque burden and higher calcified plaque burden compared to South Asians.



Coronary atherosclerotic plaque burden and composition by CT angiography in Caucasian and South Asian patients with stable chest pain

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