ORIGINAL RESEARCH

Ectopic Fat Depots and Coronary Artery Calcium in South Asians Compared With Other Racial/Ethnic Groups

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***Background*—**South Asians have a low body mass index and high prevalence of cardiovascular disease (CVD) relative to other racial/ethnic groups. Radiographically detected ectopic fat distribution is better associated with CVD than body mass index. We assessed whether differences in ectopic fat depots explained differences in the prevalence/severity of coronary artery calcium (CAC), a predictor of incident CVD events, among South Asians compared with other racial/ethnic groups.

***Methods and Results*—**We examined the associations of radiographically detected visceral, intermuscular, intrahepatic, and pericardial fat with CAC among adults without baseline CVD. We compared 803 South Asians in the Mediators of Atherosclerosis in South Asians Living in America to 4 racial/ethnic groups in the Multi-Ethnic Study of Atherosclerosis: 2622 whites, 1893 blacks, 1496 Latinos, and 803 Chinese Americans. We adjusted for body mass index and known CVD risk factors. South Asians had the highest intrahepatic fat and lowest pericardial fat volume (PFV). There was a positive graded association between ectopic fat and higher CAC scores in all the groups with the strongest associations observed with PFV. PFV was independently associated with CAC severity in South Asians (P=0.01) and blacks (P=0.05) and borderline in whites (P=0.06). PFV partially explained the higher CAC burden in South Asians compared with blacks, but not the other racial/ethnic groups.

***Conclusions*—**Differences in PFV explain a small fraction of the higher CAC burden in South Asians. Our findings suggest that ectopic fat depots may not explain the elevated CAC risk in South Asians. **(*J Am Heart Assoc*. 2016;5:e004257 doi: 10.1161/JAHA.116.004257)**

Key Words: adipose tissue • coronary artery calcification • ethnicity • MESA (Multi-Ethnic Study of Atherosclerosis) • pericardial fat • South Asian

South Asians—individuals with ancestry from India, Pakistan, Bangladesh, Nepal, or Sri Lanka—are a rapidly growing minority group in the United States[1] and have a high prevalence of cardiovascular disease (CVD) that is not explained by traditional risk factors.[2,3] Radiographically detected coronary artery calcium (CAC) is a strong predictor of incident CVD events.[4] South Asian men in the United States have a high burden of CAC (similar to whites, but higher than black, Latinos, and Chinese Americans) independent of traditional CVD risk factors.[5–7] The underlying factors explaining racial/ethnic variations in CAC prevalence are not completely understood and not well studied in South Asians.

Several CVD and metabolic risk factors linked to obesity have been implicated in the pathophysiology of CAC development, including dyslipidemia, diabetes mellitus, and hypertension.[8,9] However, South Asians more frequently develop CVD and these associated metabolic conditions at a lower relative body mass index (BMI), younger ages, and even before development of obesity.[10,11] South Asians have lower average BMIs than other racial/ethnic groups in the United States, yet they have more body fat for a given BMI level.[12] Several professional organizations have recommended a lower BMI cutpoint for Asians populations to trigger preventative CVD screening.[13,14]

Obesity is commonly approximated using BMI and/or other anthropometric measurements like waist circumference.[15,16] However, these measurements are imperfect surrogates for total body adiposity and do not fully capture the heterogeneity

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An accompanying Table S1 is available at http://jaha.ahajournals.org/content/5/11/e004257/DC1/embed/inline-supplementary-material-1.pdf

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in function and complexity of various regional fat depots,[9,17–21] nor the variation in body composition between different racial/ethnic groups.[22–24] Computed tomography (CT) has been used to separate subcutaneous adipose tissue from smaller and physiologically detrimental depots of fat that are less likely to be reflected in BMI. These "ectopic fat depots" surround specific organs and accumulate in various body compartments, such as the liver (intrahepatic fat), heart (pericardial fat), abdominal viscera, kidney, neck, muscles tissues, and blood vessels (perivascular).[9,25] Ectopic fat depots are thought to promote CVD through (1) impairment of insulin sensitivity, lipid metabolism, and vascular resistance; (2) systemic mediators like oxidative stress, inflammation, and adipocytokines; and (3) local paracrine effects on the heart and blood vessels.[9,17,25–27]

We sought to compare the association of four ectopic fat depots—visceral abdominal, intermuscular abdominal, intrahepatic, and pericardial—with CAC in a community-based sample of asymptomatic South Asians in the United States compared with other racial/ethnic groups. We used baseline data from 2 cohorts: (1) MESA (Multi-Ethnic Study of Atherosclerosis) and (2) the MASALA Study (Mediators of Atherosclerosis in South Asians Living in America) that was modeled on MESA with similar protocols to allow for efficient cross-ethnic comparisons. We hypothesized that (1) all 4 measured ectopic fat depots would be associated with CAC in South Asians, and (2) differences in ectopic fat depots would explain differences in the prevalence and severity of the CAC burden in South Asians compared with other racial/ethnic groups.

Methods

We performed an analysis of cross-sectional data that were collected in the United States from 2 distinct community-based prospective cohorts: MASALA and MESA. The study design, eligibility, and methods for both studies have been previously published.[28,29] Institutional review boards of all clinical centers and steering committees for both studies approved our protocol, and all enrolled subjects gave informed consent.

The MASALA Study was modeled on the MESA Study and included 906 adults of South Asian ethnicity without known CVD at baseline (recruitment period: 2010–2013). To have a similar age range of participants from both studies, MASALA participants younger than 45 years were excluded, leaving 803 South Asians for this analysis. Data from the MESA baseline exam (2000–2002) included individuals without known CVD from 4 racial/ethnic groups: 2622 whites, 1893 blacks, 803 Chinese Americans, and 1496 Hispanics/Latinos. Pericardial fat volume (PFV) and intrahepatic fat volume (measured radiographically with hepatic fat attenuation) were measured at baseline in MESA. Abdominal fat area measurements—visceral, intermuscular, and subcutaneous—were measured from Exam 2 (2002–2004) and Exam 3 (2004–2005) with a random sample of participants in each of the 4 racial/ethnic groups: 785 whites, 407 blacks, 251 Chinese Americans, and 501 Latinos.

Participant exclusion criteria for both the MASALA and MESA studies were identical. Briefly, both studies excluded those with a physician-diagnosed myocardial infarction, stroke or transient ischemic attack, heart failure, angina, nitroglycerin use, history of cardiovascular procedures or any surgery on the heart or arteries, current atrial fibrillation, active treatment for a malignancy, weight above 136 kg (300 pounds), shortened life expectancy (attributed to a serious medical illness), impaired cognitive ability, and current or pending occupancy in a nursing home.

MASALA Study Methods

Study participants were recruited from 2 clinical sites: (1) the San Francisco Bay Area at the University of California San Francisco (San Francisco, CA) and (2) the greater Chicago area at Northwestern University (Chicago, IL).[29] All MASALA participants self-reported South Asian ethnicity, were aged 40 to 84 years and could speak and/or read English, Hindi, or Urdu languages. To be included in the MASALA Study, participants were required to report that 3 of 4 grandparents were born in 1 of the following countries: India, Pakistan, Bangladesh, Nepal, or Sri Lanka.

Bilingual study staff help participants complete a detailed questionnaire to obtain demographic information, family health history, medication use, medical history (including hypertension and diabetes mellitus), and health-related behaviors, including tobacco and alcohol use. A positive family history of heart disease in a first-degree relative was defined by self-report of a heart attack in a child or sibling or parent. Physical activity was assessed using the Typical Week's Physical Activity Questionnaire.[30] Seated resting blood pressure was measured using an automated blood pressure monitor with the average of the last 2 of 3 total readings used for the analysis. Diabetes mellitus was defined by use of a glucose-lowering medication or a fasting glucose $\geq$126 mg/dL. Hypertension was defined by the use of an antihypertensive medication, systolic blood pressure $\geq$140 mm Hg, or diastolic blood pressure $\geq$90 mm Hg. Blood samples were obtained after a 12-hour fast. Low-density lipoprotein cholesterol was calculated after standard measurement of cholesterol using enzymatic methods.

Body composition measurements

To calculate BMI, participant height was measured with a stadiometer and weight was measured using a balance-beam

scale or digital weighting. To measure subcutaneous, visceral, and total intermuscular ectopic fat areas (cm^2) in the abdominal cavity, a single-slice CT scan was obtained between the fourth and fifth lumbar vertebral levels. Trained radiology technicians used lateral scout images of the spine to establish correct positioning for the abdominal CT.[29] The abdominal fat measures were conducted at the University of California San Diego body composition reading center using the Medical Image Processing, Analysis, and Visualization (MIPAV) software.[31] The subcutaneous compartment was defined as tissue outside the visceral cavity but within the body contour. Visceral fat was defined as tissue within the contour of the visceral cavity with pixels in the appropriate Hounsfield Unit (HU) range. Muscle segmentation was done as previously described.[32] We calculated total intermuscular fat area by combining extramyocellular fat around the oblique, rectus abdominus, paraspinus, and psoas muscle groups.

To measure both PFV (cm^3) and intrahepatic fat, noncontrast cardiac CT images were obtained using a cardiac-gated CT scanner. Intrahepatic fat was measured by quantifying radiographical hepatic fat attenuation, with lower attenuation indicating more liver fat. CT images were also interrogated using MIPAV at the T12 to L1 vertebral level. Nine regions of interest within homogenous portions of the liver at 2 levels were read, avoiding any vascular structures or other liver pathology. Measurement methods matched those in MESA[33,34] and were also conducted under the supervision of Dr Jeffrey Carr. For PFV, the CT scan range encompassed the entire heart and provided information on a 45-mm *z*-axis (15 mm above and 30 mm below) of adipose tissue encasing the proximal coronary arteries. We used volume analysis software (GE Healthcare, Waukesha, WI) to separate adipose tissue from other tissue using a threshold HU range of −190 to −30. Because of the challenges of visualizing the pericardium, PFV in our study included epicardial fat within the pericardium and paracardial fat superficial to the pericardium. The technician segmented the heart from the thorax by removing tissues beyond the lung using a deformable model-based edge detection method, such as active contours or live wires, to detect the boundary between the lung and fat around the heart.[35–37]

CAC measurements

Noncontrast cardiac CT scans were used as described above and detailed methods have been previously described.[7] Briefly, participants were examined in the supine position with both arms raised above the head. All scans were examined by the CT reading center at Harbor-University of California Los Angeles using Rephot Imaging Software. Phantom-adjusted CAC Agatston scores were reported for each of 4 major coronary arteries and summed for this analysis.

MESA Methods

MESA investigated the prevalence, correlates, and progression of subclinical cardiovascular disease from 6 urban US communities in the 4 aforementioned racial/ethnic groups.[28] As described above for the MASALA Study, MESA used identical questionnaires for assessing participant demographic information, medical history, and heath behaviors, as well as identical protocols for seated blood pressure, anthropometry, and abdominal and cardiac CT scanning. Both studies also used the same reading centers and protocols for measuring CAC, abdominal body composition, PFV, and intrahepatic fat.

Statistical Analysis

Baseline characteristics, ectopic fat measures, and CAC scores for each racial/ethnic group in the MASALA Study and MESA were standardized using within-group SDs and compared using ANOVA and chi-squared tests. Baseline CAC scores were reported using ordinal categories of 0, 1 to 100, and >100. Across these 3 CAC groups, we performed tests for linear trend of the mean for each ectopic fat measure within each racial/ethnic group. Analyses were repeated after only BMI-adjustment of ectopic fat variables. An additional analysis was performed to compare the baseline characteristics of participants with and without visceral fat measures (Table S1); we concluded there were no consistent differences.

Further analyses assessed the independent associations of ectopic fat measures with CAC. To determine statistical significance, we used an alpha-threshold of less than or equal to 0.05. Because CAC scores cannot be transformed to meet the assumptions of any single generalized linear model, we used a 2-step procedure to assess these associations with 2 complementary CAC outcomes: (1) a logistic model for the prevalence of any CAC and (2) a linear model for log-transformed CAC scores among participants with nonzero scores. The residuals of the linear model were normally distributed. We adjusted for known CVD risk factors: age, sex, BMI, family history of heart disease, exercise, alcohol use, current smoking, hypertension, cholesterol medication use, low-density lipoprotein cholesterol, and diabetes mellitus. Independent associations of ectopic fat measures with any CAC and log-transformed positive CAC scores were captured using adjusted risk differences (RDs) and regression (β) coefficients, respectively. We separately examined the entire cohort (combining all racial/ethnic groups) and the MASALA cohort of South Asians alone.

We then used newer methods[38] implemented by the *medeff* command in STATA[39] to assess whether differences in PFV explained differences in CAC between South Asians and each of the 4 MESA groups, again using a logistic model for any CAC and a linear model for CAC levels among those with any CAC. Using *medeff*, we estimated the adjusted associations of racial/ethnic group with these 2 measures of CAC before and after further adjustment for PFV. In a final step, *medeff* calculates the proportion of the effect of racial/ethnicity explained as the percentage difference between estimates before and after adjustment for PFV. All analyses were conducted using SAS (version 9.4; SAS Institute, Inc., Cary, NC) and STATA software (version 14.1; STATA Corporation, College Station, TX).

Results

There were 7617 participants between ages 45 to 84 years for the analysis of intrahepatic and PFV, including 803 South Asians from the MASALA Study and 6814 participants in MESA (2622 white; 1893 black; 1496 Latino; 803 Chinese American). There were fewer participants (N=2747) for the analysis of abdominal fat measurements: 803 South Asians, 785 whites, 407 blacks, 251 Chinese Americans, and 501 Latinos. Table 1 shows the baseline characteristics, CAC scores, and ectopic adiposity for all 5 groups. A total of 3857 (51%) participants had zero CAC scores. There was significant heterogeneity in ectopic fat measurements across groups. South Asians and Chinese Americans had lower mean BMIs and subcutaneous fat areas. South Asians had the lowest

Table 1. Baseline Characteristics of MASALA and MESA Participants by Racial/Ethnic Group

	South Asian N=803	Whites N=2622	Black N=1893	Latino N=1496	Chinese American N=803	*P* Value*
Age, y	57±9	63±10	62±10	61±10	62±10	<0.001
Male sex (%)	424 (53)	1259 (48)	843 (45)	721 (48)	390 (49)	0.002
Medical history (%)						
Diabetes mellitus	168 (21)	158 (6)	332 (18)	264 (18)	105 (13)	<0.001
Hypertension	347 (43)	1010 (39)	1126 (59)	621 (42)	301 (37)	<0.001
Current smoker	26 (3)	301 (12)	338 (18)	203 (14)	45 (6)	<0.001
Alcohol use (≥1 drinks/wk)	260 (32)	1667 (64)	961 (52)	697 (47)	171 (21)	<0.001
Heart disease in first-degree relative	373 (47)	377 (14)	298 (16)	252 (17)	52 (7)	<0.001
Cholesterol medication use	242 (30)	460 (18)	312 (16)	211 (14)	118 (15)	<0.001
BMI, kg/m^2	26±4	28±5	30±6	29±5	24±3	<0.001
LDL-cholesterol, mmol/L	111±32	117±30	116±33	120±33	115±29	<0.001
Exercise (MET-min/wk), IQR	945 (315–1838)	1853 (870–3360)	1654 (630–3570)	1200 (428–2730)	1230 (593–2423)	<0.001
CAC score						
Median in those with CAC >0, IQR	80 (25–275)	117 (26–374)	73 (20–261)	72 (19–254)	65 (22–200)	<0.001
Ordinal category	—	—	—	—	—	<0.001
CAC=0 (%)	441 (55)	1127 (43)	1072 (57)	818 (55)	399 (50)	N/A
CAC 1 to 100 (%)	193 (24)	701 (27)	464 (25)	393 (26)	236 (29)	N/A
CAC >100 (%)	169 (21)	794 (30)	357 (19)	285 (19)	168 (21)	N/A
Radiographically detected adiposity						
Subcutaneous abdominal, cm^2	236±95	253±115	298±132	264±108	177±72	<0.001
Visceral abdominal, cm^2	137±57	159±75	128±60	164±65	114±49	<0.001
Total intermuscular abdominal, cm^2	22±9	28±12	21±12	26±12	19±8	<0.001
Intrahepatic fat (HU of attenuation)†	55±11	61±12	63±12	59±14	62±12	<0.001
Pericardial, cm^3	60±30	85±46	67±35	88±44	74±31	<0.001

BMI indicates body mass index; CAC, coronary artery calcium; HU, Hounsfield unit; IQR, interquartile range; LDL, low-density lipoprotein; MASALA, Mediators of Atherosclerosis in South Asians Living in America; MESA, Multi-Ethnic Study of Atherosclerosis; MET, metabolic equivalent of task.

*Multiway *P* value for homogeneity using ANOVA for continuous variables or chi-squared tests for categorical variable.

†Radiographically measured hepatic fat attenuation (in HU) is inversely correlated with intrahepatic fat (ie, lower HU=more fat).

mean PFV and hepatic fat attenuation (highest intrahepatic fat).

Table 2 displays the average levels of each ectopic fat depot by CAC category for each group both before and after adjustment for BMI (but no other variables). In South Asians, higher CAC scores were associated with increasing levels of all of 4 ectopic fat depots (Table S1). With the exception of intrahepatic fat, similar trends were also observed in the MESA groups. South Asians had the lowest mean PFV in each CAC category compared with the other groups. After BMI adjustment, blacks had the lowest PFV and Chinese Americans had the highest.

Table 3 shows that PFV, when compared with the 3 other ectopic fat measures, was more strongly associated with CAC after adjustment in both South Asians and the pooled cohort. Visceral abdominal and total intermuscular abdominal fat depots were not independently associated with either CAC prevalence or severity in the pooled and South Asian cohorts. Intrahepatic and pericardial fat depots were associated with CAC prevalence in the pooled cohort ($P \leq 0.01$), but not in South Asians. PFV was independently associated with CAC severity in the pooled cohort ($P<0.01$) and in South Asians ($P=0.01$). Given the strength of associations for PFV relative to other ectopic fat depots, we report in Table 4 a stratified evaluation of the association of PFV with CAC by race/ethnicity. In the logistic models for any CAC, PFV was independently associated with any CAC among only whites (RD per SD, 2.93%; $P=0.01$). However, in participants with positive CAC scores, PFV was independently associated with ln(CAC) in South Asians ($\beta=0.25$; $P=0.01$) and blacks ($\beta=0.13$; $P=0.05$), and borderline in whites ($\beta=0.10$; $P=0.06$).

Table 2. Ectopic Fat Depots and CAC Score by Race/Ethnicity

Racial/Ethnic Group	CAC=0	CAC 1 to 100	CAC >100	*P* Value for Trend*	Adjusted for BMI†
Visceral abdominal fat (cm^2), N=2747					
South Asian	124±51	146±61	157±58	<0.001	<0.001
White	143±70	170±78	173±75	<0.001	<0.001
Black	122±56	133±69	141±58	0.03	0.05
Latino	150±60	177±65	185±72	<0.001	<0.001
Chinese American	108±51	115±46	130±44	0.03	0.07
Total intermuscular abdominal fat (cm^2), N=2747					
South Asian	21±8	23±10	23±9	<0.001	0.03
White	26±12	29±13	29±12	0.003	0.009
Black	21±12	21±10	25±14	0.006	0.008
Latino	24±11	28±13	29±14	<0.001	<0.001
Chinese American	17±6	19±7	23±9	<0.001	0.001
Intrahepatic fat (HU of attenuation)‡, N=7617					
South Asian	56±11	54±11	54±8	0.03	0.05
White	62±12	60±13	61±12	0.03	0.18
Black	63±12	62±11	63±13	0.40	0.31
Latino	59±15	60±13	60±13	0.51	0.47
Chinese American	62±12	62±11	62±14	0.97	0.60
Pericardial fat (cm^3), N=7617					
South Asian	53±27	61±28	76±33	<0.001	<0.001
White	71±37	88±45	102±52	<0.001	<0.001
Black	62±31	70±33	81±43	<0.001	<0.001
Latino	80±40	96±44	103±48	<0.001	<0.001
Chinese American	67±28	79±33	83±33	<0.001	<0.001

BMI indicates body mass index; CAC, coronary artery calcium; HU, Hounsfield unit.
*Testing for a linear association of ectopic fat depots and CAC tertile, specific to race/ethnicity.
†Testing for a linear association of BMI-adjusted ectopic fat depots and CAC tertile, specific to race/ethnicity.
‡Hepatic fat attenuation (in HU) is inversely correlated with intrahepatic fat (ie, lower HU=intrahepatic fat).

Table 3. Adjusted Associations of Ectopic Fat Depots and CAC Across All Racial/Ethnic Groups and in South Asians Alone*

Any CAC Models, All Participants						
	Across All Racial/Ethnic Groups			In South Asians Only		
Ectopic Fat Depot	N	Risk Difference Per SD % (95% CI)	*P* Value	N	Risk Difference Per SD % (95% CI)	*P* Value
Visceral abdominal	2645	1.1 (−1.0 to 3.2)	0.32	765	−0.1 (−3.8 to 3.6)	0.94
Total intermuscular abdominal	2604	0.1 (−0.1 to 0.3)	0.39	746	−0.1 (−0.5 to 0.3)	0.58
Intrahepatic	7313	−1.5 (−2.5 to −0.5)	<0.01	776	0.1 (−3.1 to 3.2)	0.97
Pericardial	7363	1.8 (0.5 to 3.1)	0.01	779	−1.8 (−5.3 to 1.8)	0.32
Ln(CAC) Models, Participants With CAC>0						
Ectopic Fat Depot	N	β Per SD	*P* Value	N	β Per SD	*P* Value
Visceral abdominal	1261	−0.05 (−0.15 to 0.06)	0.38	343	−0.02 (−0.21 to 0.18)	0.85
Total intermuscular abdominal	1240	0.00 (−0.01 to 0.01)	0.55	332	−0.02 (−0.04 to 0.00)	0.13
Intrahepatic	3605	0.02 (−0.04 to 0.08)	0.49	349	0.12 (−0.09 to 0.34)	0.27
Pericardial	3634	0.12 (0.05 to 0.18)	<0.01	349	0.25 (0.06, 0.44)	0.01

CAC indicates coronary artery calcium.
*Covariates in the adjusted model include: body mass index, age, sex, heart disease in first-degree relative, exercise, alcohol use, current smoking, hypertension, cholesterol medication use, low-density lipoprotein, and diabetes mellitus.

In Table 4, we further assessed whether PFV explained differences in prevalence of CAC between South Asians and each of the 4 MESA groups. In the above analyses, we demonstrated that racial/ethnic group is associated with PFV (Table 2) and that PFV is associated with CAC after multivariable adjustment (Table 4). Table 5 then quantifies the relative difference in estimates of the effect of racial/ethnic group (with South Asians as referent) on CAC before and after adjustment for PFV and then expresses this difference as a proportion of the estimate before adjustment. In logistic models for any CAC, whites were at a modest 4% higher risk of having any CAC compared with South Asians, which decreased to 3.3% after adjustment for PFV, explaining 19% (95% CI, 9 to 102) of the effect of race/ethnicity. Though the adjusted differences in prevalence of any CAC between South Asians and blacks was greater, PFV explained only 5% (95% CI, 4 to 7) of this difference. In the linear models for log-transformed CAC among participants with positive scores, there was no difference in adjusted positive CAC scores between whites and South Asians before or after the addition of PFV. However, PFV explained 8% (95% CI, 5 to 20) of the lower adjusted CAC scores observed in blacks compared with South Asians. Also, differences in CAC in Latinos compared with South Asians became larger after adjusting for PFV in both models.

Table 4. Adjusted Associations of PFV and CAC Within Racial/Ethnic Groups*

Any CAC Models, All Participants			
Racial/Ethnic Group	N	Risk Difference Per SD % (95% CI)	*P* Value
South Asian	779	−1.8 (−5.3 to 1.8)	0.32
White	2534	2.9 (0.6 to 5.3)	0.01
Black	1824	2.2 (−0.3 to 4.7)	0.09
Latino	1450	0.6 (−2.2 to 3.4)	0.68
Chinese American	776	0.5 (−3.8 to 4.8)	0.83
Ln(CAC) Models, Participants With CAC >0			
Racial/Ethnic Group	N	β Per SD	*P* Value
South Asian	349	0.25 (0.06 to 0.44)	0.01
White	1441	0.10 (0.00 to 0.21)	0.06
Black	796	0.13 (0.00 to 0.26)	0.05
Latino	657	0.05 (−0.11 to 0.20)	0.56
Chinese American	391	0.08 (−0.12 to 0.27)	0.44

CAC indicates coronary artery calcium; PFV, pericardial fat volume.
*Covariates in the adjusted model include: body mass index, age, sex, heart disease in first-degree relative, exercise, alcohol use, current smoking, hypertension, cholesterol medication use, low-density lipoprotein, and diabetes mellitus.

Discussion

Given that BMI may not adequately reflect the unique body composition of South Asians, we examined whether or not ectopic fat depots help to further explain the differences in CAC scores we observe in South Asians compared with 4 other racial/ethnic groups in the United States: whites, blacks, Latinos, and Chinese Americans. We detected higher amounts of 4 measured ectopic fat depots—visceral

Table 5. Proportion of the Difference in CAC between South Asians and Each of the 4 MESA Racial/Ethnic Groups Groups Explained by PFV*

		Effect of Racial/Ethnic Group Before PFV Adjustment†	Effect of Racial/Ethnic Group After PFV Adjustment†	Proportion of the Effect Explained (PE %)‡
Any CAC Models, All Participants				
Racial/Ethnic Group	N	Risk Difference % (95% CI)	Risk Difference % (95% CI)	PE % (95% CI)
South Asian (referent)	779	—	—	—
White	2534	4.0 (0.2 to 7.7)	3.3 (−0.5 to 6.9)	19 (9 to 102)
Black	1824	−11.7 (−15.5 to −8.0)	−11.2 (−15.0 to −7.3)	5 (4 to 7)
Latino	1450	−7.3 (−11.2 to −3.5)	−7.9 (−11.7 to −4.0)	−8 (−16 to −5)
Chinese American	776	1.5 (−2.9 to 5.7)	0.6 (−3.8 to 4.9)	61 (−503 to 793)
Ln(CAC) Models, Participants With CAC >0				
Racial/Ethnic Group	N	ß (95% CI)	ß (95% CI)	PE % (95% CI)
South Asian (referent)	349	—	—	—
White	1441	0.02 (−0.19 to 0.23)	−0.03 (−0.25 to 0.17)	270 (−1014 to 691)
Black	796	−0.38 (−0.61 to −0.16)	−0.35 (−0.58 to −0.13)	8 (5 to 20)
Latino	657	−0.34 (−0.57 to −0.12)	−0.38 (−0.61 to −0.16)	−11 (−32 to −7)
Chinese American	391	−0.25 (−0.50 to −0.01)	−0.32 (−0.56 to −0.07)	−26 (−167 to −12)

CAC indicates coronary artery calcium; MESA, Multi-Ethnic Study of Atherosclerosis; PFV, pericardial fat volume.
*All models adjusted for body mass index, age, sex, heart disease in first-degree relative, exercise, alcohol use, current smoking, hypertension, cholesterol medication use, low-density lipoprotein, and diabetes mellitus.
†For the presence of "Any CAC," effects are shown as risk differences on the proportion scale, shown in percentage points. For effects on CAC severity, effects are shown as adjusted differences in average ln(CAC), or betas, between each comparison group and South Asians.
‡The proportion of the effect explained (PE) is calculated as the percent difference between the residual adjusted association of race/ethnicity with presence or severity of CAC after adjustment for PFV, and the overall adjusted association, before adjustment for PFV. Note that PE may be negative, if the direct effect is larger than the overall effect; it can also exceed 100% if the direct and overall effects have opposite signs. Please note that for PE estimates, 95% CIs were obtained as the 25th and 95th percentiles of PE estimates based on 1000 simulations of unobserved potential outcomes and therefore may not be symmetric about the point estimate.

abdominal, intermuscular abdominal, intrehepatic, and pericardial—in South Asians with higher CAC scores, but only PFV was significantly associated with CAC after adjustment. Although South Asians had less PFV compared with the other groups, higher amounts of pericardial fat in South Asians may still be harmful. In multivariate analyses, the addition of PFV partially explained the difference in CAC scores between black and South Asians, but not between South Asians and other racial/ethnic groups.

In the United States, South Asians have among the highest rates of CVD,[2,3] some of which is likely to be explained by lower exercise levels, dietary patterns, and an adverse metabolic risk profile, including high rates of both diabetes mellitus and hypertension.[7,40,41] Despite this, South Asians have lower BMIs[10,12] with important differences in the distribution of their total body and regional adiposity compared with other racial/ethnic groups[42] that may uniquely impact their metabolic and cardiovascular risk.[9] In our study, for example, blacks replaced South Asians as having the lowest PFV when BMI was taken into consideration, suggesting that South Asians have more PFV at each BMI level than blacks. In contrast, Chinese Americans have similarly low BMIs as South Asians, but had even more PFV than South Asians at a given BMI level. Despite this latter difference, PFV was more strongly associated with CAC in South Asians than in Chinese Americans. Several mechanisms for the effects of ectopic fat on vascular disease have been proposed, including systemic pathways such as oxidative stress, inflammation, impaired glucose and lipid metabolism, and renin angiotensin system activation, as well as local vascular and toxic effects.[9] It is possible that such mechanisms may play stronger or weaker roles on the effect of ectopic fat presence in a given racial/ethnic group.

In our study, we used CAC as a subclinical marker of atherosclerosis and future CVD risk to understand how the amount and location ectopic fat might further our understanding of the unique CVD risk in South Asians. Our results suggest that PFV is strongly associated with CAC in South Asians, whites, and blacks. However, the strength and significance of these associations varied with the CAC modeling approach. This variability may be explained, in part, by real differences and, in part, attributed to statistical differences in sample size (lower for South Asians) or the number of nonzero CAC scores (highest in whites). That is, the

fully adjusted association of PFV with CAC was stronger and more significant in South Asians than all other racial/ethnic groups when only participants with nonzero CAC scores were considered (in comparison to models of CAC prevalence only). One possible explanation for this discrepancy may be that the underlying biology is different in individuals who have more CAC compared with those with very little (but detectable) CAC. In the context of our study, we speculate that having fat in these ectopic depots may be either a marker of, or causally related to, more metabolic and/or inflammatory perturbation, hence more CAC. Not surprisingly, adjustment with potentially mediating cardiometabolic variables related to impaired glucose tolerance, lipid metabolism, and hypertension attenuated, but did not fully eliminate, this association, bolstering support that the implicated pathophysiological pathways for PFV may be locally mediated.[43]

Several previous studies have found an association between PFV and CAC presence and severity. A seminal study by Rosito et al of 1155 men and women in the Framingham cohort found that pericardial fat within the pericardium (ie, epicardial fat) was associated with CAC (odds ratio, 1.21; P=0.004) after adjusting for BMI, demographic, and CVD risk factors.[44] Our study was more ethnically diverse and broadly defined PFV to include fat both superficial to and within the pericardium. Different physiological pathways for atherosclerosis have been proposed for pericardial fat within the pericardium as opposed to outside the pericardial sac.[9,45] In a previous MESA study, McClain et al reported significant pooled associations after multivariable adjustment of both CAC prevalence (N=6727) and severity (N=3262) per SD increase in PFV, but, unlike our study, did not detect heterogeneity in these associations by racial/ethnic group.[46] Moreover, the previous MESA study demonstrated stronger associations between PFV and CAC compared with our study results, but we additionally adjusted for metabolic covariates, such as hypertension, diabetes mellitus, and cholesterol medication use that may have further attenuated the effect.[9] Several other studies have similarly found associations between pericardial fat (often measured differently in each study) and CAC.[45,47–49] A study by Wassel et al found stronger associations of intrathoracic fat (fat between the external pericardium and marked mediastinal structures) with CAC compared with fat depots within the pericardial sac.

In comparison to PFV, other ectopic fat depots were not as strongly associated with CAC. Traditional cardiovascular and metabolic pathways (which were adjusted for in our analysis) may have accounted for most of the mechanistic explanation of their effects on CAC. Whereas South Asians had the most intrahepatic fat in our study, previously suggested systemic pathways involving excess hepatic fat, such as insulin resistance and disrupted lipid metabolism, may have been accounted for in our multivariable models given that South Asians had higher baseline prevalence of diabetes mellitus and cholesterol medication use in our cohort. Another explanation is that our measurement of visceral and intermuscular fat areas were not sensitive enough to detect an association with CAC given that they were measured using a single-level CT slice of the abdomen and represented fewer MESA participants. A recent study by Alvey et al of the Framingham cohort measured visceral and subcutaneous fat volumes using multislice CT scans and found that both were significantly associated with CAC after multivariable adjustment.[50]

For effective health prevention, it is important to understand how we can reduce development and progression of coronary atherosclerosis. For South Asians, it is important to understand the unique factors that explain their increased CVD risk beyond traditional CVD risk factors and metabolic conditions. Our findings warrant further study into the role and mechanisms of regional and ectopic fat depots in the incidence of CVD and, specifically, for pericardial fat. A recent systematic review suggests that epicardial fat burdens may be reduced through lifestyle modification and weight loss.[51] Though distant and still theoretical, there is also the promise of depot-specific targets in the design of therapeutic interventions.

There are several limitations of our study that warrant consideration. First, there were some differences in the CT equipment used, and the years of data collection between the MASALA and MESA studies though the protocol and reading centers were identical. We believe these differences were unlikely to meaningfully affect the results. Second, we are unable to generalize our results to the entire US population (or globally) given that catchment geographies for participants were limited number to selected geographical areas, and the participants enrolled in both of these studies did not have known CVD. Third, measurement of 2 ectopic fat depots of the abdomen (visceral, total intermuscular) were limited to a single spinal level as mentioned above. Fourth, our inferences of statistical significance may be overstated given that no statistical adjustment was made for examining multiple endpoints. This adjustment was not performed because (1) the relevant number of tests is not clearly defined for a more-complicated observational analysis like our study, and (2) Bonferroni adjustment would be overly conservative given that many of the outcomes are correlated and the number of tests is large. Fifth, race/ethnicity in the MASALA Study was determined using self-reported information. However, given that 98% of MASALA participants were immigrants to the United States, mixed race/ethnicity is much less likely. Finally, our study was cross-sectional in design and therefore causality cannot be determined.

In conclusion, we detected a positive graded association between ectopic fat depots and higher CAC scores in all the studied racial/ethnic groups. South Asians have less PFV than other groups, but the association of PFV with CAC

severity in participants with prevalent CAC remained significant after adjusting for known CVD risk factors. However, PFV only partially explained differences in the CAC scores observed in South Asians compared with blacks, but not other groups. We conclude that the higher risk of CVD (measured using CAC as a surrogate marker in our study) in South Asians may not be explained by greater ectopic adiposity among South Asians. Future research, including follow-up data from the MASALA and MESA studies, should attempt to clarify how the radiographical measurement of ectopic adiposity can further our understanding of the racial/ethnic variation in body composition and its association with incident CVD.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Comparison of baseline characteristics of participants with and without visceral fat measurements (page 1 of 2)*

	South Asian		White		African American	
	Without	**With**	**Without**	**With**	**Without**	**With**
	N = 19	**N = 784**	**N = 1851**	**N = 771**	**N = 1488**	**N=405**
Age (years)	57 ± 7	57 ± 9	63 ± 10	63 ± 10	62 ± 10	62 ± 10
Male sex	14 (74%)	410 (52%)	856 (46%)	403 (52%)*	664 (45%)	179 (44%)
Medical history						
Diabetes	7 (37%)	161 (21%)	114 (6%)	44 (6%)	266 (18%)	66 (16%)
Hypertension	11 (58%)	336 (43%)	688 (37%)	322 (42%)*	889 (60%)	237 (59%)
Current smoker	0 (0%)	26 (3%)	206 (11%)	95 (12%)	263 (18%)	75 (19%)
Alcohol use (≥ 1 drinks/week)	5 (26%)	255 (33%)	1163 (64%)	504 (66%)	766 (53%)	195 (49%)
Heart disease in 1st-degree relative	4 (21%)	369 (47%)*	255 (14%)	122 (16%)	245 (16%)	53 (13%)
Cholesterol medication use	5 (26%)	237 (30%)	320 (17%)	140 (18%)	260 (17%)	52 (13%)*
BMI (kg/m^2)	28 ± 6	26 ± 4*	28 ± 5	28 ± 5	30 ± 6	30 ± 5*
LDL-cholesterol (mmol/L)	111 ± 31	111 ± 32	117 ± 30	117 ± 29	116 ± 33	118 ± 31
Exercise (MET-min/week), interquartile range (IQR)	750 (315, 1470)	945 (315, 1838)	1800 (870, 3360)	1950 (900, 3338)	1650 (630, 3570)	1680 (720, 3570)
CAC score						
Median in those with CAC>0, IQR	166 (77, 566)	79 (24, 270)	125 (24, 400)	104 (28, 327)	72 (21, 259)	85 (17, 265)
Ordinal category	-	-	-	-	-	-

CAC=0	10 (53%)	431 (55%)	785 (42%)	342 (44%)	823 (55%)	249 (61%)*
CAC 1-100	4 (21%)	189 (24%)	490 (26%)	211 (27%)	377 (25%)	87 (21%)
CAC>100	5 (26%)	164 (21%)	576 (31%)	218 (28%)	288 (19%)	69 (17%)
Radiographically detected adiposity						
Subcutaneous abdominal (cm^2)	227 ± 72	236 ± 95	N/A	253 ± 115	N/A	298 ± 132
Visceral abdominal (cm^2)	N/A	137 ± 57	N/A	159 ± 75	N/A	128 ± 60
Total intermuscular abdominal (cm^2)	31 ± .	22 ± 9	44 ± 14	28 ± 12	N/A	21 ± 12
Intrahepatic fat (HU of attenuation) #	53 ± 9	55 ± 11	61 ± 12	62 ± 13	62 ± 12	66 ± 10*
Pericardial (cm^3)	75 ± 41	59 ± 29*	84 ± 46	87 ± 46	68 ± 35	65 ± 32

* p value<0.05; Overall test for equality/heterogeneity performed for each variable comparing participants with and without visceral fat measurements for each race/ethnic group. An overall test for heterogeneity was also performed using ANOVA or chi-squared tests. Abbreviations: Coronary artery calcium (CAC); body mass index (BMI); metabolic equivalent of task (MET); Hounsfield unit (HU).

Table S1. Comparison of baseline characteristics of participants with and without visceral fat measurements (page 2 of 2)*

	Hispanic		Chinese American		Overall
	Without	**With**	**Without**	**With**	**P-value**
	N = 999	**N = 497**	**N = 553**	**N = 250**	
Age (years)	61 ± 11	61 ± 10	62 ± 10	62 ± 10	<0.001
Male sex	471 (47%)	250 (50%)	258 (47%)	132 (53%)	<0.001
Medical history					
Diabetes	186 (19%)	78 (16%)	79 (14%)	26 (10%)	<0.001
Hypertension	407 (41%)	214 (43%)	203 (37%)	98 (39%)	<0.001
Current smoker	138 (14%)	65 (13%)	32 (6%)	13 (5%)	<0.001
Alcohol use (≥ 1 drinks/week)	454 (46%)	243 (49%)	115 (21%)	56 (23%)	<0.001
Heart disease in 1st-degree relative	164 (16%)	88 (18%)	35 (6%)	17 (7%)	<0.001
Cholesterol medication use	137 (14%)	75 (15%)	78 (14%)	40 (16%)	<0.001
BMI (kg/m^2)	29 ± 5	29 ± 5	24 ± 3	24 ± 3	<0.001
LDL-cholesterol (mmol/L)	1119 ± 33	121 ± 32	115 ± 29	116 ± 28	<0.001
Exercise (MET-min/week), interquartile range (IQR)	1125 (368, 2700)	1290 (540, 2925)*	1193 (548, 2213)	1331 (630, 2745)	<0.001
CAC score					
Median in those with CAC>0, IQR	73 (18, 269)	70 (19, 247)	66 (21, 215)	58 (22, 184)	<0.001
Ordinal category	-	-	-	-	<0.001
CAC=0	556 (56%)	262 (53%)	273 (49%)	126 (50%)	N/A

CAC 1-100	256 (26%)	137 (28%)	162 (29%)	74 (30%)	N/A
CAC>100	187 (19%)	98 (20%)	118 (21%)	50 (20%)	N/A
Radiographically detected adiposity					
Subcutaneous abdominal (cm^2)	N/A	264 ± 108	N/A	177 ± 72	<0.001
Visceral abdominal (cm^2)	N/A	164 ± 65	N/A	114 ± 49	<0.001
Total intermuscular abdominal (cm^2)	27 ± .	26 ± 12	25 ± .	19 ± 8	<0.001
Intrahepatic fat (HU of attenuation) [#]	59 ± 14	60 ± 14	62 ± 12	62 ± 12	<0.001
Pericardial (cm^3)	89 ± 44	88 ± 43	74 ± 32	74 ± 30	<0.001

[*] p value<0.05; A test for equality/heterogeneity was performed for each variable comparing participants with and without visceral fat measurements for each race/ethnic group. An overall test for heterogeneity was also performed using ANOVA or chi-squared tests. Abbreviations: Coronary artery calcium (CAC); body mass index (BMI); metabolic equivalent of task (MET); Hounsfield unit (HU).