Relation of Ectopic Fat with Atherosclerotic Cardiovascular Disease Risk Score in South Asians Living in the United States (from the Mediators of Atherosclerosis in South Asians Living in America [MASALA] Study)

Morgana Mongraw-Chaffin, PhD, Unjali P. Gujral, PhD, Alka M. Kanaya, MD, Namratha R. Kandula, MD, John Jeffrey Carr, MD, and Cheryl A.M. Anderson, PhD

Few studies have investigated the association between ectopic fat from different depots and cardiovascular risk scores and their components in the same population, and none have investigated these relations in South Asians. In a cross-sectional analysis of 796 participants in the Mediators of Atherosclerosis in South Asians Living in America (MASALA) study who had measurements of visceral, subcutaneous, pericardial, hepatic, and intermuscular fat from abdominal and cardiac computed tomography scans, we used linear regression to determine the associations of 1 standard deviation difference in each ectopic fat depot with pooled cohort risk score and its components. Pericardial and visceral fat were more strongly associated with the pooled cohort risk score (3.1%, 95% confidence interval [CI] 2.5 to 3.7, and 2.7%, 95% CI 2.1 to 3.3, respectively) and components than intermuscular fat (2.3%, 95% CI 1.7 to 3.0); subcutaneous fat was inversely associated with the pooled cohort risk score (−2.6%, 95% CI −3.2 to 1.9) and hepatic fat attenuation was not linearly associated with the pooled cohort risk score when mutually adjusted (−0.3%, 95% CI −0.9 to 0.4). Associations for risk factor components differed by fat depot. In conclusion, subcutaneous and hepatic fat may have different functions than fat stored in other depots in South Asians. Determining whether these relations are heterogeneous by race may help elucidate the mechanisms underlying CVD disparities. © 2017 Elsevier Inc. All rights reserved. (Am J Cardiol 2017; ■■: ■■ – ■■)

Visceral fat is associated with cardiovascular disease (CVD) risk and mortality, where subcutaneous fat has even been suggested to play a protective role in cardiometabolic risk. The growing understanding that the function and effects of fat are heterogeneous highlights the need to understand the role of ectopic fat stored in different depots, such as pericardial, hepatic, and intermuscular fat. Importantly, because so few studies have temporally concordant measurements from multiple fat compartments beyond visceral and subcutaneous fat, the mutual relation of these fat stores with CVD risk remains unknown. Determining which of these scenarios is best supported by the evidence is particularly important for the cardiometabolic health of South Asians. A pathway of increased CVD risk has been outlined for this group through higher levels of visceral fat. To address these issues, we hypothesized that fat from different ectopic depots would be differentially associated with the American College of Cardiology/American Heart Association Atherosclerotic Cardiovascular Disease Pooled Cohort (ASCVD) Risk Score and its components in a cross-sectional analysis of the Mediators of Atherosclerosis in South Asians Living in America (MASALA) study. Specifically, we hypothesized that subcutaneous fat would be inversely associated with CVD risk, but fat from all other depots would be positively associated with the pooled cohort risk score.
Methods

MASALA is a 2-site longitudinal cohort study of 906 self-identified South Asians in the United States, free of CVD, who weighed ≤300 lb and were enrolled from 2010 to 2013. After excluding those with any missing ectopic fat measurements (n = 97) and those with missing CVD risk factors needed to calculate the pooled cohort risk score (n = 13), we included 796 participants in this analysis. All participants provided written informed consent and MASALA protocols were approved by review boards at each participating institution.

To measure ectopic fat depots, trained radiology technicians conducted standardized abdominal computed tomography (CT) protocols. Lateral scout image of the spine was used to establish the position between the L4 and L5 vertebrae for measurement of visceral, subcutaneous, and intermuscular fat mass using the Medical Image Processing, Analysis, and Visualization software. Visceral fat was defined by the area on the slice within the body cavity and appropriate density in Hounsfield units. Subcutaneous fat was defined as the area outside the body cavity, and intermuscular fat was calculated by combining extramyocardial fat from the muscles in the abdomen. Noncontrast cardiac-gated CT scans were used to measure pericardial fat volume and hepatic fat attenuation. Pericardial fat was also distinguished by density from the entire heart using volume analysis software (GE Healthcare, Waukesha, WI), and included epicardial and paracardial fat in and around the pericardium. Higher hepatic fat was quantified as the inverse of the hepatic fat attenuation.

The pooled cohort risk score was calculated from 11 components measured using a standardized protocol. Age, gender, smoking status, education level, family income, medical history, and medication use were self-reported at the enrollment interview. Body mass index (BMI) was calculated from weight and height measured with a balance-beam scale and a stadiometer, respectively. Blood pressure, total and high-density lipoprotein (HDL) cholesterol, and fasting glucose were measured using standardized measurements and protocols.

We categorized the pooled cohort risk score into 3 groups: < 7.5%, 7.5% to 10%, and ≥10%. We then described the MASALA participants by calculating means and standard errors for baseline characteristics for each of the 3 groups, and used the Cuzick nonparametric test for trend across the groups. We calculated Pearson correlations between risk scores, ectopic fat measurements, BMI, and waist circumference.

We used multivariable linear regression to determine the associations between each ectopic fat depot and the pooled cohort risk score. We used likelihood ratio tests and R² values to investigate best-fitting models, including quadratic terms to assess nonlinearity. To compare the strength of associations for different depots and to assess whether mutual adjustment of different fat depots produces different results, specifically focusing on mutual adjustment for visceral and subcutaneous fat, we estimated the difference in risk score specifically to determine whether ectopic fat depots provide additional explanatory value beyond the use of anthropometric measurements. All analyses were conducted using Stata 14 (StataCorp, College Station, Texas).

Results

Participants with higher pooled cohort risk scores were more likely to be older and male, to have income below $75,000, to be current smokers, drink alcohol, and to have lower subcutaneous fat, but higher waist circumference and visceral, pericardial, hepatic, and intermuscular fat (Table 1). The following sets of variables were highly correlated: visceral fat and pericardial fat with waist circumference; and BMI with subcutaneous fat (Supplementary Table S1).

All fat depots were significantly associated with the pooled cohort risk score (Table 2), with the strongest association for pericardial fat, followed closely by visceral fat, and then by intermuscular fat. Subcutaneous fat was inversely associated with risk, and hepatic fat attenuation estimates were reduced and became nonsignificant when mutually adjusted for other depots. Hepatic fat also explained ≤1% of the variance in risk and was the only fat depot with a nonsignificant likelihood ratio test. The full model with all 5 fat depots explained 18% of the variance in the pooled cohort risk score. Although the distribution of risk scores was approximately log normal, results using log transformation produced nearly identical results (data not shown).

No fat depots exhibited evidence of nonlinearity in their relation with pooled cohort risk score (p < 0.10), except for hepatic fat (p < 0.001). The inverted U-shape seen for hepatic fat attenuation in Figure 1 is unusual in biologic relations, and this specific relation may explain why hepatic fat is inversely associated with pooled cohort risk score in the linear model and nonsignificant when adjusted for other fat depots in Table 2. When the curvature for hepatic fat is accounted for, the estimate for hepatic fat is inverse and greatly increased (∼6.30%, −9.88 to −2.73), and the estimates for nonlinearity and model fit are also significant (p < 0.001). The inflection point of the curve is close to the cut-point for fatty liver (hepatic attenuation <40 HU), but including fatty liver in the model did not significantly improve the model fit (p = 0.20). Including alcohol consumption in the model did not alter the results (not shown).
Sensitivity analyses investigating further adjustments for potential confounders found relatively similar results (Supplementary Table S2). Including BMI in the model resulted in an inverse and significant estimate for BMI (−0.34 kg/m², −0.54 to −0.15) and a significant likelihood ratio test for its inclusion (p < 0.001) with all ectopic fat depots, except hepatic fat, remaining significant at the p < 0.005 level. The inclusion of waist circumference (0.06 cm, −0.03 to 0.15) strongly attenuated the estimate for visceral fat, but the estimates for the other depots were similar and the likelihood ratio test for the inclusion of waist circumference was not statistically significant (p = 0.20). Although the relation differed significantly by age only for pericardial and hepatic fat, estimates were generally attenuated for the older age group with the exception of a much stronger relation for hepatic fat (Supplementary Table S2). Estimates were weaker overall in the subgroup analysis by gender, but with significantly stronger relations for subcutaneous and intermuscular fat for men. Pericardial fat had the strongest estimates overall for risk factor components (Figure 2), followed by visceral fat and subcutaneous fat, 0.1038 for pericardial, 0.0074 for hepatic, and 0.0595 for intermuscular fat. Adjusted R² for the full model is 0.1805.
Figure 1. Lowess curves for ASCVD Risk Score by 1 standard deviation difference in ectopic fat depot in 796 MASALA participants. (A) Visceral, subcutaneous, and intermuscular fat. (B) Pericardial fat. (C) Hepatic fat. Hepatic fat values have been inverted so high Hounsfield units indicate higher levels of fat in the liver. Standard deviations for each fat depot are 56 cm² (visceral fat), 94 cm² (subcutaneous fat), 30 cm³ (pericardial fat), 11 HU (hepatic fat), and 9 cm² (intermuscular fat).
Figure 2. Association of ASCVD Risk Score components (odds ratios and 95% confidence intervals) by 1 standard deviation of ectopic fat. (A) Univariate. (B) Mutually adjusted for other fat depots. Hepatic fat values have been inverted so high Hounsfield units indicate higher levels of fat in the liver. Standard deviations for each fat depot are 56 cm² (visceral fat), 94 cm² (subcutaneous fat), 30 cm³ (pericardial fat), 11 HU (hepatic fat), and 9 cm² (intermuscular fat). For (A), all odds ratios are statistically significant at a p value of <0.05 except for hepatic and intermuscular fat with high cholesterol. For (B), only the following estimates are statistically significant: hypertension with pericardial and intermuscular fat; diabetes with pericardial and hepatic fat; high cholesterol with pericardial fat and hepatic fat; and low HDL with pericardial, visceral, hepatic, and subcutaneous fat.
but with mutual adjustment remained significant for total cholesterol and HDL cholesterol.

Discussion

Among a South Asian sample, higher pericardial fat volume, visceral fat area, and intermuscular fat area were significantly associated with higher pooled cohort risk score, whereas higher subcutaneous fat was significantly associated with lower risk. The relation with hepatic fat was nonlinear. Associations for ectopic fat differed by each CVD risk factor component in the pooled cohort risk score.

Excess adiposity stored centrally has long been known to be a more specific predictor of cardiometabolic risk compared with fat stored peripherally; however, the relative contributions of fat from different depots to cardiometabolic risk remains unknown. Mutual adjustment of fat from multiple depots is rare because few studies have ectopic fat measured from multiple depots at the same time point in the same participants. Our findings are generally consistent with previous literature showing that visceral fat is positively associated with CVD risk independent of BMI. Our results are also generally consistent with previous evidence about the association between pericardial fat and CVD risk; however, the relative contribution of pericardial and visceral fat in our results adds to inconsistent previous evidence. Whether pericardial fat has a stronger association with CVD risk than visceral fat may depend on factors yet to be fully investigated, including the relative quantities of fat in these depots, their relative contributions to the development of type 2 diabetes, and the population being studied.

It has been suggested that subcutaneous fat may be protective against CVD, which is consistent with our results; however, most studies of CVD events have shown no association with subcutaneous fat. One promising theory is that subcutaneous capacity allows for the benign storage of excess adiposity, and only when this capacity is exceeded and fat is placed in other depots does this excess becomes pathologic. This concept has been used specifically to explain higher CVD risk in South Asians compared with other groups, suggesting that this ethnic group has lower subcutaneous capacity and therefore develops higher levels of ectopic fat at a lower BMI. New methods to appropriately test this theory of subcutaneous capacity are needed, and it is possible that, with further study, we will need to reconceptualize subcutaneous fat.

Our results show that hepatic fat is either nonlinearly related or not an independent risk factor for CVD. Additional evidence and biologic justification that this is the true shape of the association between hepatic fat and CVD risk is needed before concluding that these estimates are valid. Although there is growing interest in using hepatic fat to predict CVD risk, very few studies have investigated hepatic and visceral fat together. Hepatic fat may also play a different role in CVD risk than other ectopic fat, given the high level of within-person variability of hepatic fat in the short term. Compared with the relative stability of ectopic fat in other depots over time, the high variability of hepatic fat may also indicate a less direct association with CVD risk. Although fat in all ectopic compartments may increase CVD risk, this may be due to differential impacts on risk score components, with hepatic fat contributing disproportionately to diabetes risk, pericardial fat to hypertension, and visceral and subcutaneous fat to HDL.

One important finding from our work is that estimates for all fat depots are independent from BMI. As a surrogate measurement of total fat mass, BMI may account for variance orthogonal from fat stored in ectopic depots. Waist circumference is believed to be a more specific marker of ectopic fat and visceral fat explicitly. Our results showing that estimates for visceral fat are attenuated by the inclusion of waist circumference agree with this premise, indicating that waist circumference may be a decent proxy for visceral fat in South Asian populations when the use of CT scans is impractical.

The present study has a number of limitations. First, CVD outcomes are not yet available, and the pooled cohort risk score has not been validated in the South Asian American population and therefore may not appropriately account for differences observed in this group. Second, the MASALA study excluded participants with a body weight of ≥300 lb because of CT scanner weight limitations, thereby limiting the ability to assess pathology from the highest levels of obesity. Lastly, the inclusion of age and gender in the risk score definitions limits the analytic options for investigating heterogeneity, and the present study is not powered to detect interaction. The present study also has a number of strengths. The primary strength is the direct measurement with CT of ectopic fat from a comprehensive group of fat depots measured concurrently. This unique resource allowed us to compare and mutually adjust for fat in different depots. The MASALA study also offers the opportunity to study a unique population. Given the current concern that groups from Asia may have higher cardiometabolic risk at the same level of BMI than non-Hispanic whites, the ability to assess the associations between directly measured ectopic fat and atherosclerotic CVD risk in South Asians offers novel insight into this topic.

Higher visceral, pericardial, and intermuscular fat are strongly and significantly associated with a higher pooled cohort risk score in South Asian Americans. Subcutaneous fat is inversely associated with risk, but more work is needed to determine if subcutaneous fat is itself protective or if another theory such as subcutaneous capacity is better supported. The relation between hepatic fat and CVD risk may differ from fat stored in other compartments; these discrepancies might be ascribed to differences in either measurement or function. The present study provides early evidence for a more comprehensive understanding of the role ectopic fat plays in the development of atherosclerotic CVD risk.

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Disclosures

The authors have no conflicts of interest to disclose.

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ajmcard.2017.10.026.


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