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### Authors

Christoph, Mary J  
Allison, Matthew A  
Pankow, James S  
[et al.](#)

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## Impact of Adiposity on Cellular Adhesion: The Multi-Ethnic Study of Atherosclerosis (MESA) Study

Mary J. Christoph<sup>1</sup>, Matthew A. Allison<sup>2</sup>, James S. Pankow<sup>3</sup>, Paul A. Decker<sup>4</sup>, Phillip S. Kirsch<sup>4</sup>, Michael Y. Tsai<sup>5</sup>, Michele M. Sale<sup>6</sup>, Mariza de Andrade<sup>4</sup>, Hugues Sicotte<sup>4</sup>, Weihong Tang<sup>3</sup>, Naomi Q. Hanson<sup>5</sup>, Cecilia Berardi<sup>4,7</sup>, Christina L. Wassel<sup>8</sup>, Nicholas B. Larson<sup>4</sup>, and Suzette J. Bielinski<sup>4</sup>

<sup>1</sup>Department of Kinesiology and Community Health, University of Illinois at Urbana-Champaign, Urbana, IL, USA

<sup>2</sup>Department of Family and Preventive Medicine, University of California, San Diego, La Jolla, CA, USA

<sup>3</sup>Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, MN, USA

<sup>4</sup>Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA

<sup>5</sup>Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN, USA

<sup>6</sup>Center for Public Health Genomics, University of Virginia, VA, USA

<sup>7</sup>Montefiore Medical Center, Bronx, NY, USA

<sup>8</sup>Department of Epidemiology, University of Pittsburgh, PA, USA

### Abstract

**Objective**—At the cellular level, how excess adiposity promotes atherogenesis is not fully understood. One pathway involves secretion of adipokines that stimulate endothelial dysfunction through increased expression of the adhesion molecules. However, the relationship of adiposity to adhesion molecules that promote atherosclerosis is largely unknown.

**Methods**—Linear regression models were used to assess the sex-specific associations of soluble cellular adhesion molecules (sP- and sL-selectin, sICAM-1, sVCAM-1, and sHGF) and adiposity in 5,974 adults examined as part of the Multi-Ethnic Study of Atherosclerosis (MESA). Adiposity measures included body mass index (BMI), waist-to-hip-ratio (WHR), and, computed tomography measures of subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT).

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Correspondence: Dr. Suzette J. Bielinski; Mayo Clinic, Division of Epidemiology, Department of Health Sciences Research, Harwick Building 6-56, 200 First Street SW, Rochester, MN 55905. Telephone: (507) 538-4914; Fax: (507)284-1516; bielinski.suzette@mayo.edu.

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**Author contributions:** MJC, CLW, NBL and SJB designed the research; MJC and SJB conducted the research; MJC, PAD and PSK analyzed data and performed the statistical analyses; MJC, JSP, PAD, MMS, MdA, HS, WT, CB, CLW and NBL contributed in the conception, design, data analysis, drafting and revising of the manuscript and MAA, MYT, NQH and SJB contributed in data collection, interpretation of results, writing and reviewing of the manuscript.

Additional Supporting Information may be found in the online version of this article.

**Results**—The mean age was 64 years and 52% were female. In multivariable models adjusting for traditional cardiovascular risk factors, sHGF was positively associated with BMI, WHR, and VAT in both males and females, and sP-selectin with WHR and VAT in males. sVCAM-1 was inversely associated with VAT in females only.

**Conclusions**—Our results showed the relation of adiposity to soluble cellular adhesion proteins was similar across adiposity measures and for both sexes. However, the relationship between adiposity and sVCAM-1 and P-selectin may be modified by sex and the measure used to assess adiposity.

### Keywords

adiposity; L-selectin; P-selectin; VCAM-1; ICAM-1; HGF

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### Introduction

Almost 35% of United States adults are obese, a condition associated with diabetes, atherosclerosis, and inflammation (1). How excess adiposity promotes atherogenesis is not fully understood. However, one mechanism involves secretion of the pro-inflammatory cytokines (i.e., adipokines) by adipose tissue and the macrophages in the interstitial tissue around adipocytes. Adipokines can stimulate endothelial dysfunction and subsequent atherogenesis by increasing endothelial permeability and leukocyte recruitment through increased expression of adhesion proteins including intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and P-selectin (2).

Adhesion proteins are integral to fatty streak formation in the first stage of atherosclerosis, and are responsible for recruiting leukocytes, binding them to the endothelium, and aiding in transmigration across the endothelium (3). Therefore, these proteins are potentially early predictors of atherosclerosis, and have been linked to adiposity. Soluble ICAM-1 (sICAM-1) levels are elevated in individuals with obesity, insulin resistance, and diabetes (4). The relationship of soluble VCAM-1 (sVCAM-1) with excess adiposity is less clear. That is, higher sVCAM-1 levels are associated with cardiovascular disease (CVD) and type 2 diabetes, but not body mass index (BMI) (5). Soluble L-selectin (sL-selectin) levels are negatively associated with obesity and weight loss surgery has been found to increase L-selectin expression (6). Soluble P-selectin (sP-selectin) has been associated with adiposity and both clinical and sub-clinical atherosclerosis (7), and has been shown to predict atherosclerosis independent of BMI and other CVD risk factors. In addition, soluble hepatocyte growth factor (sHGF) is positively associated with subclinical heart disease (8) and visceral adipose tissue (VAT) (9) with decreasing levels observed with weight loss (10). However, few studies have investigated the relation of various measures of adiposity to adhesion molecules.

Assessing the relationship between adiposity, adhesion proteins, and subsequent CVD risk is challenging due to the use of different measures to assess adiposity. In addition, it is rare for these studies to account for regional fat deposition. Large epidemiologic cohort studies show that higher BMI (11), waist circumference (WC) (12), and waist-to-hip-ratio (WHR) (13) are associated with increased risk of CVD. However, anthropometric measures such as BMI

may result in misclassification with respect to adipose tissue types and do not accurately or adequately reflect the distribution, location, and complex biology of adipose tissue (14,15). This despite the fact that central adiposity confers significant metabolic risk but lower-body (gluteofemoral) fat (16) and larger hip circumference are associated with better metabolic and cardiovascular outcomes. Differences in regional fat deposition could be the distinguishing characteristics between metabolically healthy and unhealthy obesity (16). Therefore, regional measures of adiposity may provide a more refined representation of adiposity in chronic diseases and how adiposity contributes to CVD and diabetes risk profiles (14). Furthermore, there are recognized race/ethnicity differences in fat distribution that affects risk for metabolic diseases (17). Regional ectopic fat depots including subcutaneous adipose tissue (SAT) and VAT, measured via computed tomography (CT), appears to be better indicators of disease risk. In this regard, VAT contains a greater number of macrophages compared to SAT, is metabolically active, and associated with inflammation and adhesion proteins (18–21).

Our aim was to investigate how adiposity, measured by BMI, WHR, SAT, and VAT, are associated with soluble adhesion proteins (sP- and sL-selectin, sICAM-1, sVCAM-1, and sHGF) in a large, ethnically diverse population and assess effect modification by sex and race/ethnicity. We hypothesized that higher adiposity would be associated with higher adhesion protein levels in a dose-dependent manner independent of age, sex, and race/ethnicity.

## Methods

### Population

The Multi-Ethnic Study of Atherosclerosis (MESA) consists of 6,814 adults aged 45–84 years old. MESA participants underwent five examinations between 2000–2012 at six field centers located in Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; Northern Manhattan, NY; and Saint Paul, MN and include 38% non-Hispanic white, 28% African, 22% Hispanic, and 12% Chinese Americans. The design of the cohort has been previously described(22).

For this study, results from two MESA ancillary studies were used; Multiscale Biology of Atherosclerosis in the Cellular Adhesion Pathway (HL98077, PI: Bielinski) and Abdominal Body Composition, Inflammation, and Cardiovascular disease (HL088451, PI: Allison). Of those who participated in Exam 2 (2002–2004), 6,108 had plasma and serum samples eligible for adhesion protein measurement. We excluded a total of 134 samples, 2 Chinese and 3 Hispanic Americans from field centers that did not actively recruit these two ethnic groups, 77 participants with CVD events prior to Exam 2, 44 participants with BMI < 18, 7 sample failures, and 1 participant who did not complete Exam 2 or subsequent exams due to cognitive impairment. The final sample size included 5,974 participants including 1,623 African, 681 Chinese, 2,370 non-Hispanic white, and 1,300 Hispanic Americans. This study was conducted according to the principles of the Declaration of Helsinki, and informed consent was obtained from all participants. Institutional review boards at each research center approved the study.

### Adiposity measurements

Anthropometric protocols were standard across sites. Participants wore light clothing and no shoes. Height was measured to the nearest 0.1 cm using an Accu-Hite stadiometer (Seca, Hanover, MD, USA), and weight was measured to the nearest pound using a Detecto Platform Balance Scale (Webb City, MO, USA). Waist and hip circumferences were measured to the nearest 0.1 cm using Gulick II 150-cm anthropometric tape measures (Country Technology Inc., Gays Mills, WI, USA), with the tape (standard 4 oz. tension) in the horizontal plane and participants standing. Waist circumference was measured at the umbilicus, and hip circumference around the widest circumference of the buttocks. Circumference measurements were either taken around either light tight-fitting clothing or no clothing. BMI was calculated as weight (kg)/height<sup>2</sup> (m<sup>2</sup>). WHR was calculated from waist and hip circumferences.

A random subset of MESA subjects underwent CT scanning of the abdomen at Exam 2 or 3 (23,24). These scans were used to measure areas of visceral and subcutaneous adiposity at three different vertebral levels. Data collection methods are described elsewhere(23). In brief, 6 mm thick slices were used, with two each at the L2–L3, L3–L4 and L4–L5 disc spaces. Fat tissue was classified as  $-190$  fat pixel  $-30$  Hounsfield Units. Two analysts from a centralized reading center (UCSD, La Jolla, CA) independently assessed each scan; intraclass correlations were 0.92–0.99 for different body composition measures. Due to its high correlation with total abdominal volume and lower standard error of estimates, VAT and SAT were defined (in cm<sup>2</sup>) as the average of two slices from L2–L3, and adjusted for height.

### Adhesion protein measurements

sP-selectin levels were measured on 5,974 participants and the other adhesion proteins on a subset of 2,372. Figure 1 shows the sample sizes and exclusions for each protein. sP-selectin was measured in plasma by a quantitative sandwich enzyme-linked immunosorbent assay using the Human Soluble P-selectin/CD62P Immunoassay Kit (R&D Systems, Minneapolis, MN). Two independent groups of samples were assayed. A different lot of ELISA reagent and different human control pool was used for each group. The inter-assay CV for group 1 was 6.7% at a control concentration of 182 mg/dL; the inter-assay CV for group 2 was 9.7% at a control concentration of 79 mg/dL. The minimum detectable level was 0.5 ng/mL for both assay groups.

sL-selectin was measured in serum on using the Human soluble L-selectin/CD62L Immunoassay Kit, a quantitative sandwich enzyme-linked immunosorbent assay (R&D Systems); minimum detectable level was 0.3 ng/mL, inter-assay CV was 6.7% at a mean control concentration of 943 ng/mL. sICAM-1 was measured in serum using the Human sICAM-1 Instant ELISA (Bender MedSystems GmbH, Vienna, Austria) with a minimum detectable level of 2.17 ng/mL; the inter-assay CV was 9.1% at a mean concentration of 261 ng/mL. Of importance, this assay is not affected by variant rs5491 in the *ICAM1* gene, which is common in African Americans and blocks the detection of soluble ICAM-1 by antibodies used in some ELISA assays. sVCAM-1 was measured using a human Quantikine ELISA Kit (R&D Systems); the minimum detectable level was 0.6 ng/mL, and the inter-

assay CV was 3.6% at a mean concentration of 564 ng/mL. sHGF was measured in serum using the Quantikine Human HGF Immunoassay kit (R&D Systems), with a lower limit of detection of 40 pg/mL and inter-assay CV of 6.2% at a mean concentration of 946 pg/mL.

### Other measurements

A combination of self-administered and interview-administered questionnaires was used to collect data such as smoking history, alcohol intake, and medication use. Resting seated blood pressure was measured three times using an automated oscillometric method (Dinamap), and the average of the second and third readings are used in analyses. Hypertension was defined as systolic blood pressure (SBP) of  $\geq 140$  mm Hg, diastolic blood pressure (DBP) of  $\geq 90$  mm Hg, or taking antihypertensive medication. Diabetes was defined as any participant who self-reported a physician diagnosis, used diabetic medication, or had a fasting glucose  $\geq 126$  mg/dL (i.e., 7 mmol/L). Serum glucose was assayed by a hexokinase/glucose-6-phosphate dehydrogenase method, and triglycerides and cholesterol were assayed by enzymatic methods. HDL cholesterol was measured after precipitation of non-HDL-cholesterol with magnesium/dextran and LDL was calculated via the Friedewald equation. Hemoglobin A<sub>1c</sub> was assayed using an automated high performance liquid chromatography methods (Tosoh HPLC Glycohemoglobin Analyzer, Tosoh Bioscience, Inc., San Francisco, CA, USA). Measurements from Exam 2 for all of these variables were used.

### Statistical analysis

Outliers were excluded as appropriate ( $n = 14$  for sHGF  $n = 48$  for sP-selectin). Participant characteristics were compared across groups using analysis of variance (Kruskal-Wallis) and chi-square (exact) tests as appropriate. Regression models were used to compare demographic and traditional cardiovascular risk factors by sex adjusting for race. Primary endpoints include soluble adhesion protein levels: sL-selectin, sP-selectin, sICAM-1, sVCAM-1, and sHGF. To address differences in sP-selectin levels across groups, we obtained residuals from a linear regression model using log-transformed raw sP-selectin values as a response and group status as a predictor. All references of sP-selectin levels heretofore refer to these residual values. Linear regression was performed to quantify the relationship between BMI, WHR, VAT, and SAT and adhesion proteins controlling for age and race/ethnicity. In a subsequent model, total cholesterol, HDL cholesterol, systolic blood pressure, hypertension treatment, current smoking, and diabetes status were added as covariates. We assessed effect modification by sex and race/ethnicity. Assumptions of linearity for each were evaluated using generalized additive models with cubic B-splines. From these, there were no indications of major departures from linearity. We used a Bonferroni correction to account for multiple comparisons ( $0.05/5$  proteins  $\times 2$  sexes = 0.005). Given that adiposity measurements are highly correlated (some as high as 80% in our sample), additional Bonferroni correction by measurement type would produce overly conservative results due to dependence on the test statistics, reducing the effective number of tests.

## Results

Characteristics of the MESA participants are listed in Table 1. Pairwise plots of adhesion molecules versus obesity measures by sex are included in Figures S1–S5. Significant differences by sex were observed for all clinical and CT adiposity measures as well as for sP- and sL-selectin and sHGF (Table 2). Compared to men, women had lower mean sP-selectin levels ( $P < 0.001$ ), but higher mean sL-selectin ( $P < 0.001$ ) and HGF ( $P = 0.001$ ) levels. These differences were largely consistent within race/ethnic strata (Table S1); further, no interaction between race/ethnicity and the association between adiposity and adhesion proteins was found. Therefore we present results stratified by sex, but not race/ethnicity.

BMI, WHR, and VAT were associated with higher levels of HGF in both males and females (Table 3, Tables S2, S3, and S4). The magnitude of association was consistently higher in males compared to females for every measure of adiposity investigated (sex interaction for BMI,  $P = 0.022$ ; WHR,  $P = 0.001$ . and VAT  $P = 0.29$ ). For example, each 1-unit increase in WHR was associated with an increase of 1,094 pg/ml in HGF levels for males and 658 pg/ml for females. Likewise, increased adiposity was associated with higher levels of sP-selectin in both males and females (Table 3). The associations were attenuated with adjustment for additional risk factors but remained significant in males for WHR and VAT (sex-interaction  $P = 0.0063$  and  $0.13$ , respectively). Higher VAT was inversely associated with sVCAM-1 in females only (sex interaction  $P = 0.09$ ). For each 1-unit increase in VAT, sVCAM-1 levels decreased by 203 ng/ml in females, but only 40 ng/ml (not significant) in males. Neither sL-selectin nor sICAM-1 were significantly associated with any of the measures of adiposity after accounting for CVD risk factors. None of the adhesion proteins were significantly associated with levels of SAT.

## Discussion

Extending previous findings, we assessed the relationship between measures of adiposity and soluble cellular adhesion proteins in a large multi-ethnic population. We observed that increased levels of sHGF and sP-selectin were associated with greater adiposity. sHGF was positively associated with all the clinical measures of adiposity whereas, for CT measures, the association was exclusive to VAT. Furthermore, we found evidence of a sex-interaction between sP-selectin levels and adiposity. We propose that the effect of adiposity on adhesion proteins and even endothelial dysfunction and subsequent atherosclerosis may be somewhat modified by the measure used to assess adiposity, and perhaps by sex for some proteins.

The relationship between sHGF and adiposity has been previously documented. In a sample of 65 lean and subjects with obesity, Rehman et al. (8) showed that serum HGF was, on average, more than three times higher in subjects with obesity versus their lean counterparts. Corroborating these results in larger populations, Faber et al. reported that serum HGF significantly increased with greater adiposity as assessed by both BMI and VAT (9). However, neither of these studies reported sex-specific analyses. Sex-specific associations of adiposity and HGF were investigated in 1,806 Framingham Heart Study participants,

where it was observed that the association of VAT and serum HGF was stronger in females (25). In contrast, we report that the association was greater in magnitude for males. These conflicting results could be due to differences in the population composition as MESA is more ethnically diverse and older (mean age of 64 vs. 45 years old) with higher average BMI. Similar to previous studies, the association in MESA was highly significant and consistent by sex and independent of other risk factors, as well as the measure used to assess adiposity. These results suggest that sHGF could serve as an important marker of chronic disease risk due to its strong correlation with excess adiposity and putative participation in atherosclerotic lesions (26) and type 2 diabetes (27).

sP-selectin was associated with WHR and VAT but not BMI. This pattern may indicate that the relationship of sP-selectin to adiposity is dependent on measures that account for central adiposity and regional fat deposition. Prior reports have reported mixed results. P-selectin was significantly related to VAT and SAT independent of CVD risk factors, but not independent of BMI/waist circumference (28) and P-selectin significantly correlated with pericardial and intrathoracic fat after adjusting for age and sex, but not in multivariable models (29), in the Framingham Heart Study population. In contrast, P-selectin and BMI or WHR were neither correlated after adjusting for just age, sex, and smoking, nor in multivariable models accounting for CVD risk factors (30). These studies, with ours, suggest that P-selectin may not be related to BMI after accounting for other factors, but P-selectin is likely related to VAT, although this may not be independent of BMI, and may be stronger for males than for females. That there was a sex-specific interaction is not particularly surprising given that males and females often differ in fat distribution, and sex-specific interactions have been reported in some of the very adipokines associated with adiposity that promote atherosclerosis, including leptin (31) and adiponectin (32).

In contrast to Pou et al. (28), we did not include BMI, WC, and VAT in the same model as they were highly correlated in our sample. Our results indicate that WHR may be more strongly related to certain fat depots and adhesion protein levels than BMI. Thus, sP-selectin may serve as one instance where simply measuring adiposity via BMI may be insufficient. As noted previously, BMI may lead to the mischaracterization of health since it cannot adequately account for the variability in fat deposition or muscle that is related to metabolic risk or subclinical indicators of CVD (18–21). The mechanism behind this likely deals with the different characteristics of each fat depot; while abdominal adipose tissues exhibit higher lipid turnover and more rapid storage of diet-derived fat, gluteofemoral tissue has lower triglyceride turnover, less sensitivity to stress-stimulated lipolysis, and stores a higher proportion of fatty acids that have been recirculated (16). Since sP-selectin levels have been associated with both clinical and sub-clinical atherosclerosis (7), future studies should further investigate how P-selectin may be related to fat distribution, particularly noting sex-specific differences.

sVCAM-1 was negatively associated with VAT in females in the MESA sample. Previous investigations on adiposity and sVCAM-1 are limited in number with mixed results. Two larger studies have shown that VCAM-1 was not associated with BMI (5) or WHR (30). In contrast, Bosanska et al. (33) reported increased VCAM-1 mRNA expression with higher VAT (33). Likewise, increased sVCAM-1 correlated with BMI (34) (35). It is important to



note that neither of these latter two studies accounted for CVD risk factors. Our results suggest that sex may modify the relationship between adiposity and sVCAM-1, and that only using measures that account for fat deposition and composition may truly elucidate this relationship.

We found that sICAM-1 was associated with greater adiposity; however, this relationship was not independent of traditional CVD risk factors. Our results concur with those reported by Miller and Cappuccio, who found that although WHR correlated with sICAM-1, the relationship was not independent of traditional CVD risk factors (30). In contrast, increased levels of sICAM-1 correlated with VAT and SAT independent of CVD risk factors (28). The discrepancy could be due to differences in modeling; whereas Pou et al. (28) adjusted for age, sex, menopausal status and hormone replacement therapy, and behavioral characteristics including smoking, aspirin, alcohol intake, and physical activity index, we adjusted for traditional CVD risk factors. Although sICAM-1 appears to be related to adiposity, the conflicting studies make it difficult to definitively report whether this result is independent of other CVD risk factors.

No measures of adiposity were associated with sL-selectin in MESA. Two prior studies reported conflicting results; one found lower levels of sL-selectin in patients with severe obesity compared to normal weight individuals (6). In contrast, Ponthiux et al. (36) reported that sL-selectin levels were uncorrelated with BMI after adjustment for age and sex. The relationship of sL-selectin as a risk factor for CVD is questionable as prior investigations in MESA did not find sL-selection levels to increase risk of atherosclerosis (37).

Our study had several advantages, first we assessed adiposity using 4 different measures, which have varying levels of precision and association with atherosclerosis risk, in contrast to prior studies that used a single clinical measure of adiposity (5,30,34). While the impact of VAT on cardiometabolic risk is well-established (38,39), few have investigated how central adiposity is related to soluble adhesion protein levels. Contrary to other studies, we reported sex-specific results due to significant interactions between both sex and adhesion protein levels and adiposity measures. Limitations of our study include the cross-sectional design precluding observing adiposity and adhesion protein levels over time, and the relatively small sample size for the CT measures of adiposity may have precluded our ability to detect effect modification by sex and race/ethnicity. Furthermore, only frozen samples were available for measurement of soluble adhesion proteins, therefore, we have no measures the cellular expression of the membrane bound proteins (e.g., ICAM-1, VCAM-1, and L-selectin) as this type of sample is not suitable for flow cytometry.

## Conclusions

Our results showed the relation of adiposity to adhesion proteins may be modified by both sex and the measure used to assess adiposity for some proteins. When assessing cardiovascular risk in overweight and patients with obesity, instead of simply relying on BMI and traditional cardiovascular risk factors such as cholesterol levels and blood pressure, it may be more reflective of risk to measure adiposity with WHR or CT scans that account

for regional fat deposition. Further, because adhesion proteins are directly related to the development and instability of atherosclerotic plaques, adding these measures may improve patient outcomes by providing more targeted therapy. Future studies examining the relationship between adiposity and adhesion proteins should ideally use multiple measures of adiposity, and especially measures that account for regional fat deposition; furthermore, studies must examine these relationships in light of possible sex-specific effects.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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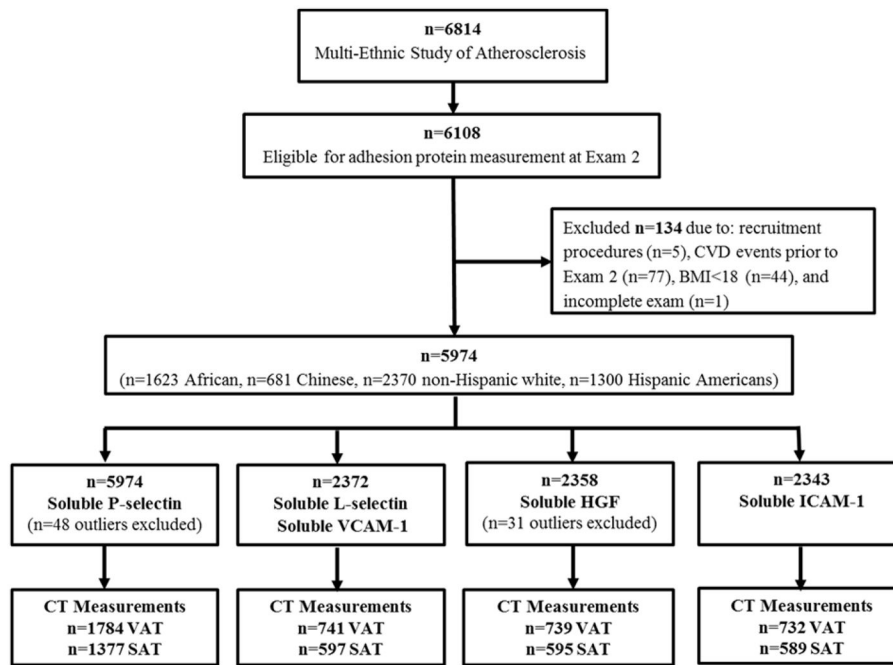
### Study Importance Questions

**What is already known about this subject? Please remember to also include this between the title page and structure abstract in your paper**

- Soluble cellular adhesion pathway proteins are associated with traditional measures of adiposity such as body mass index in predominantly white populations.
- Regional measures of adiposity may provide a more refined representation of adiposity in chronic diseases as opposed to a single clinical measure of adiposity.

**What does this study add? Please remember to also include between the title page and structured abstract in your paper**

- In a large multi-ethnic cohort, we observed that increased levels of hepatocyte growth factor and P-selectin were associated with greater adiposity and found evidence of a sex-interaction between P-selectin levels and adiposity.
- The effect of adiposity on adhesion pathway proteins may be somewhat modified by the measure used to assess adiposity.



**Figure 1.**  
Study design.

**TABLE 1**

Exam 2 characteristics by race/ethnicity, mean (standard deviation) or percent

Characteristics	European American	Chinese American	African American	Hispanic American
<b>N</b>	2,622	803	1,893	1,496
<b>Age, years</b>	63 (10)	62 (10)	62 (10)	61 (10)
<b>Sex, % female</b>	52	51	56	52
<b>Body mass index, kg/m<sup>2</sup></b>	28 (5.1)	24 (3.3)	30 (5.9)	29 (5.1)
<b>Waist to hip ratio</b>	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	1.0 (0.1)
<b>Systolic blood pressure, mmHg</b>	124 (20)	125 (22)	132 (22)	127 (22)
<b>Diastolic blood pressure, mmHg</b>	70 (10)	72 (10)	75 (10)	72 (10)
<b>Hypertension, % yes</b>	39	38	60	42
<b>Antihypertensive therapy, % yes</b>	33	29	50	33
<b>Hypertension categories, %</b>				
<b>Normotensive, SBP &lt; 140 and DBP &lt; 90 mm Hg</b>	62	63	41	59
<b>Controlled hypertensive, SBP &lt; 140 and DBP &lt; 90 mm Hg</b>	28	26	48	30
<b>Uncontrolled hypertensive, SBP 140 or DBP 90 mm Hg</b>	11	12	12	12
<b>Diabetes mellitus, % yes</b>	6	13	18	18
<b>Hemoglobin A1c</b>	5.4 (0.6)	5.8 (0.9)	5.9 (1.1)	5.9 (1.2)
<b>Total cholesterol, mg/dL</b>	196 (35)	193 (32)	190 (36)	198 (38)
<b>HDL cholesterol, mg/dL</b>	52 (16)	50 (13)	52 (15)	48 (13)
<b>LDL cholesterol, mg/dL</b>	117 (30)	115 (29)	117 (33)	120 (33)
<b>Triglycerides, mg/dL</b>	133 (90)	143 (85)	105 (69)	157 (101)
<b>Any antilipidemic therapy, % yes</b>	18	14	16	13
<b>Statin use, % yes</b>	17	13	15	12
<b>Current smoker, % yes</b>	12	5.6	18	14
<b>Smoking status, %</b>				
<b>Never</b>	44	75	45	54
<b>Former</b>	44	19	37	33
<b>Current</b>	12	5.6	18	14
<b>Current use of alcohol, % yes</b>	72	31	49	47

SBP, systolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

**TABLE 2**

Measures of adiposity and levels of soluble adhesion proteins by sex-adjusted for race/ethnicity measured at Exam 2 unless otherwise specified, mean (standard deviation) or percentage

Characteristics	Females	Males	<i>P</i> -value <sup>a</sup>
Age, years	64 (10)	64 (10)	0.74
Body mass index, kg/m <sup>2</sup>	29 (6)	28 (4)	<0.001
Waist circumference, cm	97 (16)	100 (12)	<0.001
Waist to hip ratio, %			<0.001
Men 0.95, women 0.80	12	41	
Men 0.96–1.0, women 0.81–0.85	16	34	
Men > 1.0, women > 0.85	71	25	
<b>CT measures of fat, Exam 2/3</b>			
VAT, cm <sup>2</sup>	0.54 (0.16)	0.64 (0.14)	<0.001
SAT, cm <sup>2</sup>	0.95 (0.03)	0.91 (0.04)	<0.001
<b>Soluble Adhesion Proteins</b>			
sP-selectin, ng/mL (n = 5,974)	35 (12)	39 (13)	<0.001
sL-selectin, ng/mL (n = 2,372)	931 (200)	847 (190)	<0.001
sVCAM-1, ng/mL (n = 2,372)	730 (225)	746 (235)	0.2
sICAM-1, ng/mL (n = 2,343)	255 (87)	251 (86)	0.56
sHGF, ng/mL (n = 2,358)	1,002 (234)	965 (226)	0.001

<sup>a</sup>Sex comparisons from regression models adjusting for race/ethnicity.

CT, computed tomography; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; VCAM-1, vascular cell adhesion molecule-1; ICAM-1, intercellular adhesion molecule; HGF, hepatocyte growth factor.



**TABLE 3**

Adjusted associations of soluble adhesion protein levels and adiposity, stratified by sex

	sP-selectin			sL-selectin ng/mL (SD = 200)			sICAM-1 ng/mL (SD = 87)			sVCAM-1 ng/mL (SD = 232)			sHGF pg/mL (SD = 234)			
	Females	Males		Females	Males		Females	Males		Females	Males		Females	Males		
	Beta (S.E.)	P-value	Beta (S.E.)	P-value	Beta (S.E.)	P-value	Beta (S.E.)	P-value	Beta (S.E.)	P-value	Beta (S.E.)	P-value	Beta (S.E.)	P-value	Beta (S.E.)	
<i>Clinical Measures of Adiposity</i>																
Body mass index, kg/m <sup>2</sup> (Exam 2)	n=3,129		n=2,845		n=1,119		n=1,253		n=1,104		n=1,253		n=1,119		n=1,245	
Model 1	0.005 (0.001)	<0.0001	0.007 (0.001)	<0.0001	1.3 (1.4)	0.039	2.1 (1.0)	0.039	1.2 (0.63)	0.053	1.2 (1.1)	0.26	0.68 (1.6)	0.68	11 (1.1)	<0.0001
Model 2	0.002 (0.001)	0.027	0.004 (0.002)	0.009	-0.29 (1.5)	0.85	1.9 (1.1)	0.09	-0.04 (0.69)	0.95	-0.45 (1.2)	0.71	-1.6 (1.8)	0.38	8.9 (1.2)	<0.0001
Waist-to-hip ratio (Exam 2)	n=3,126		n=2,845		n=1,119		n=1,252		n=1,104		n=1,252		n=1,119		n=1,244	
Model 1	0.42 (0.07)	<0.001	0.87 (0.10)	<0.0001	-2.2 (100)	0.46	55 (75)	0.46	182 (46)	<0.0001	-18 (83)	0.83	273 (119)	0.022	658 (81)	<0.0001
Model 2	0.24 (0.08)	0.002	0.65 (0.11)	<0.0001	6.3 (108)	0.38	72 (82)	0.38	113 (49)	0.021	-142 (90)	0.11	263 (127)	0.038	424 (86)	<0.0001
<i>CT Measures of Adiposity</i>																
Visceral adipose tissue (Exam 2) <sup>f</sup> , cm <sup>2</sup>	n=911		n=873		n=363		n=378		n=359		n=378		n=363		n=376	
Model 1	0.27 (0.06)	<0.0001	0.37 (0.08)	<0.0001	78 (70)	0.27	-119 (62)	0.056	3.6 (38)	0.45	-203 (64)	0.002	-40 (79)	0.61	277 (68)	<0.0001
Model 2	0.17 (0.07)	0.016	0.32 (0.09)	0.0002	-13.4 (76)	0.86	-171 (67)	0.011	43 (39)	0.31	-253 (70)	0.0003	-79 (85)	0.35	200 (72)	0.006
Subcutaneous adipose tissue (Exam 2/3) <sup>f</sup> cm <sup>2</sup>	n=720		n=656		n=286		n=310		n=282		n=310		n=286		n=308	
Model 1	0.36 (0.34)	0.28	0.40 (0.31)	0.2	346 (237)	0.14	281 (331)	0.40	52 (129)	0.69	248 (334)	0.46	329 (267)	0.22	145 (347)	0.68
Model 2	0.60 (0.35)	0.082	0.44 (0.33)	0.18	437 (248)	0.08	264 (340)	0.44	12 (133)	0.93	307 (351)	0.38	382 (282)	0.18	535 (347)	0.12

Model 1 = adjusted for age and race/ethnicity.

Model 2 = adjusted for model 1 + total cholesterol, HDL cholesterol, systolic blood pressure, hypertension treatment, current smoking, diabetes status.

<sup>f</sup> CT Adiposity Measures also adjusted for height.

CT, computed tomography; VCAM-1, vascular cell adhesion molecule-1; ICAM-1, intercellular adhesion molecule; HGF, hepatocyte growth factor.