


ORIGINAL RESEARCH

# Cardiovascular Biomarkers of Obesity and Overlap With Cardiometabolic Dysfunction

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**BACKGROUND:** Obesity may be associated with a range of cardiometabolic manifestations. We hypothesized that proteomic profiling may provide insights into the biological pathways that contribute to various obesity-associated cardiometabolic traits. We sought to identify proteomic signatures of obesity and examine overlap with related cardiometabolic traits, including abdominal adiposity, insulin resistance, and adipose depots.

**METHODS AND RESULTS:** We measured 71 circulating cardiovascular disease protein biomarkers in 6981 participants (54% women; mean age, 49 years). We examined the associations of obesity, computed tomography measures of adiposity, cardiometabolic traits, and incident metabolic syndrome with biomarkers using multivariable regression models. Of the 71 biomarkers examined, 45 were significantly associated with obesity, of which 32 were positively associated and 13 were negatively associated with obesity (false discovery rate  $q < 0.05$  for all). There was significant overlap of biomarker profiles of obesity and cardiometabolic traits, but 23 biomarkers, including melanoma cell adhesion molecule (MCAM), growth differentiation factor-15 (GDF15), and lipoprotein(a) (LPA) were unique to metabolic traits only. Using hierarchical clustering, we found that the protein biomarkers clustered along 3 main trait axes: adipose, metabolic, and lipid traits. In longitudinal analyses, 6 biomarkers were significantly associated with incident metabolic syndrome: apolipoprotein B (apoB), insulin-like growth factor-binding protein 2 (IGFBP2), plasma kallikrein (KLKB1), complement C2 (C2), fibrinogen (FBN), and N-terminal pro-B-type natriuretic peptide (NT-proBNP); false discovery rate  $q < 0.05$  for all.

**CONCLUSIONS:** We found that the proteomic architecture of obesity overlaps considerably with associated cardiometabolic traits, implying shared pathways. Despite overlap, hierarchical clustering of proteomic profiles identified 3 distinct clusters of cardiometabolic traits: adipose, metabolic, and lipid. Further exploration of these novel protein targets and associated pathways may provide insight into the mechanisms responsible for the progression from obesity to cardiometabolic disease.

**Key Words:** biomarkers ■ cardiometabolic disease ■ obesity

The prevalence of obesity has increased in recent decades, reaching >30% in the US population.<sup>1</sup> Obesity is associated with several metabolic abnormalities, including insulin resistance, hyperlipidemia, hypertension, and metabolic syndrome (MetS). Both obesity and MetS have been linked to increased cardiovascular disease (CVD) morbidity and mortality.<sup>2,3</sup> Investigations into proteomic signatures of obesity and metabolic dysfunction have yielded important

insights into the biological pathways that drive cardiometabolic disease. Previous work has implicated the insulin growth factor axis and inflammation in the regulation of obesity and insulin resistance.<sup>4-6</sup>

In this context, we sought to investigate proteomic signatures of cardiometabolic disease, including obesity, different adipose depots, and related clinical traits. We hypothesized that distinct aspects of cardiometabolic dysfunction would be associated with

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## CLINICAL PERSPECTIVE

### What Is New?

- In an analysis of 71 circulating cardiovascular disease–related protein biomarkers ascertained in 6981 participants free of cardiovascular disease, we demonstrate abundant associations of biomarkers with obesity, cardiometabolic traits, and computed tomography measures of regional adiposity.
- Although all biomarkers significantly associated with obesity were also associated with 1 or more cardiometabolic traits, several biomarkers were unique to metabolic traits only.
- Clustering based on biomarker profiles revealed 3 distinct groups of traits: (1) adipose, (2) metabolic, and (3) lipid. The biomarkers apoB (apolipoprotein B), KLKB1 (plasma kallikrein), C2 (complement C2), and FBN (fibrinogen) were associated with an increased risk of future metabolic syndrome, whereas the biomarkers IGFBP2 (insulin-like growth factor-binding protein 2) and NT-proBNP (N-terminal pro-B-type natriuretic peptide) were associated with a lower risk of incident metabolic syndrome.

### What Are the Clinical Implications?

- There are many biological pathways that are shared between obesity and cardiometabolic disease.
- Examining proteomic profiles that are unique to cardiometabolic disease may offer insights into the mechanistic drivers of the transition from obesity to metabolic syndrome.

## Nonstandard Abbreviations and Acronyms

<b>ADM</b>	Adrenomedullin
<b>AGP1</b>	Alpha-1 acid glycoprotein
<b>ANGPTL3</b>	Angiotensin-like 3
<b>apoB</b>	apolipoprotein B
<b>B2M</b>	Beta-2-microglobulin
<b>BCHE</b>	Butyrylcholine esterase
<b>BIKUNIN</b>	AMBIP-bikunin
<b>C2</b>	Complement C2
<b>CD14</b>	Monocyte differentiation antigen
<b>CD163</b>	Cluster of differentiation 163
<b>CD40L</b>	Soluble CD40 ligand
<b>CD56 or NCAM</b>	Neural cell adhesion molecule
<b>CD5L</b>	CD5 antigen-like
<b>CNTN1</b>	Contactin 1
<b>CRP</b>	C-reactive protein

<b>CXCL16</b>	Chemokine (C-X-C motif) ligand 16
<b>DM</b>	diabetes mellitus
<b>EFEMP1</b>	EGF containing fibulin-like extracellular matrix protein 1
<b>FBN</b>	Fibrinogen
<b>FG</b>	fasting glucose
<b>FHS</b>	Framingham Heart Study
<b>GDF15</b>	growth differentiation factor-15
<b>GMP140</b>	Granule membrane protein 140
<b>HOMA-IR</b>	Homeostatic Model Assessment of Insulin Resistance
<b>IGF-1</b>	Insulin-like growth factor 1
<b>IGFBP1</b>	Insulin-like growth factor binding protein 1
<b>IGFBP2</b>	Insulin-like growth factor binding protein 2
<b>KLKB1</b>	Plasma kallikrein
<b>LPA</b>	lipoprotein(a)
<b>MCAM</b>	melanoma cell adhesion molecule
<b>MCP1</b>	Monocyte chemoattractant molecule 1
<b>MetS</b>	metabolic syndrome
<b>MMP8</b>	Matrix metalloproteinase 8
<b>MMP9</b>	Matrix metalloproteinase 9
<b>MPO</b>	Myeloperoxidase
<b>NT-proBNP</b>	N-terminal pro-B-type natriuretic peptide
<b>OSTEO</b>	Osteocalcin
<b>PAI1</b>	Plasminogen activator inhibitor 1
<b>PC1</b>	principal component 1
<b>PC2</b>	principal component 2
<b>REG1A</b>	Lithostathine-1-alpha
<b>SAA1</b>	Serum amyloid A1
<b>SAT</b>	subcutaneous adipose tissue
<b>SDF1</b>	Stromal cell-derived factor 1
<b>sICAM1</b>	Intercellular adhesion molecule 1
<b>SRAGE</b>	Receptor for advanced glycation endproducts
<b>TIMP1</b>	Tissue inhibitor of metalloproteinases 1
<b>UCMGP</b>	Uncarboxylated matrix Gla protein
<b>VAT</b>	visceral adipose tissue
<b>VEGF</b>	Vascular endothelial growth factor
<b>WC</b>	waist circumference

different characteristic proteins. We leveraged cardiovascular biomarkers ascertained as part of the National Heart, Lung, and Blood Institute's Systems Approach to Biomarker Research in Cardiovascular Disease Initiative, which used high-throughput technologies to identify novel circulating biomarkers in participants in the FHS (Framingham Heart Study).<sup>7</sup>

Using the Systems Approach to Biomarker Research in Cardiovascular Disease platform, we examined the associations of 71 protein biomarkers with cardiometabolic traits including traditional metabolic risk factors such as hypertension, dyslipidemia, and obesity as well as regional adiposity. We aimed to ascertain pathophysiological pathways that contribute to both obesity and metabolic disease, with the ultimate goal of identifying promising targets for the prevention and treatment of cardiometabolic disease.

## METHODS

### Data Sharing

The data supporting the study findings will be made available on reasonable request. FHS data are made publicly available and can be accessed through the National Institutes of Health database of genotypes and phenotypes (<https://www.ncbi.nlm.nih.gov/gap/>).

### Study Population

We examined proteomic profiles of participants in the Systems Approach to Biomarker Research in Cardiovascular Disease initiative of the FHS, a prospective longitudinal community-based observational cohort study. Cross-sectional analyses included all FHS Offspring cohort participants who attended examination 7 (1998–2001,  $n=3539$ ) and FHS Generation 3 cohort participants who attended examination 1 (2002–2005,  $n=4095$ ). Individuals with prevalent myocardial infarction ( $n=173$ ), prevalent heart failure ( $n=24$ ), end-stage renal disease ( $n=24$ ), missing covariates ( $n=288$ ), and incomplete biomarker profiles ( $n=144$ ) were excluded. The final cross-sectional sample included 6981 individuals. For analyses involving computed tomography (CT) measures of adiposity, individuals with missing CT measures were further excluded (visceral adipose tissue [VAT]/subcutaneous adipose tissue [SAT],  $n=3840$ ; pericardial/intrathoracic fat,  $n=3809$ ; liver fat,  $n=3981$ ). For longitudinal analyses, we included all FHS Offspring cohort participants who attended both examinations 7 and 8 and FHS Generation 3 cohort participants who attended both examinations 1 and 2, with a final sample of 4662 participants. Study protocols were approved by the appropriate institutional review boards, and all participants provided informed consent.

### Clinical Assessment

Comprehensive medical histories, physical exams, and sample collections were obtained at each examination cycle. We defined obesity as body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup>. Hypertension was defined as systolic blood pressure  $\geq 130$  mm Hg, diastolic blood pressure  $\geq 85$  mm Hg, or current antihypertensive use.

Diabetes mellitus (DM) was defined as fasting glucose (FG)  $\geq 126$  mg/dL, use of medication for DM, or reported history of DM. MetS was determined based on the National Cholesterol Education Program definition, which includes  $\geq 3$  of the following metabolic risk factors: abdominal obesity defined as waist circumference (WC)  $\geq 88$  cm for women and  $\geq 102$  cm for men, high triglyceride levels ( $\geq 150$  mg/dL), low high-density lipoprotein (HDL) levels ( $< 50$  mg/dL for women or  $< 40$  mg/dL for men), elevated blood pressure, high FG ( $\geq 100$  mg/dL or current use of glucose-lowering medications). Alcohol use was defined as  $\geq 14$  and  $\geq 7$  alcoholic drinks per week for men and women, respectively.

### Intrathoracic, Pericardial, and Abdominal Fat Volume Measurements

Protocols for quantification of intrathoracic, pericardial, and abdominal fat have been described.<sup>8,9</sup> Quantification of all fat volumes involved measurement of fat-containing pixels in a predefined image display setting based on Hounsfield units on a dedicated offline workstation (Aquarius 3D Workstation; TeraRecon Inc., San Mateo, CA). VAT and SAT were quantified by manually tracing the abdominal wall separating VAT and SAT. The interclass correlations of VAT and SAT were 0.992 and 0.997, respectively. Pericardial and intrathoracic fat volumes were determined using a semiautomatic segmentation technique. Pericardial fat volume was defined as adipose tissue within the pericardial sac. Total thoracic fat volume was defined as adipose tissue located within the thorax (from the level of the right pulmonary artery to the diaphragm and the chest wall to the descending aorta). Intrathoracic fat was derived from subtracting pericardial fat from total thoracic fat. The interclass correlation coefficients were 0.98 for total thoracic fat and 0.95 for pericardial fat. Liver fat content was quantified as the ratio of liver fat attenuation relative to a control (the liver phantom ratio). A total of 3 measures of at least 100 mm<sup>2</sup> in the liver, avoiding hepatic blood vessels, were performed. A calibration control (phantom) with CT-Water and calcium hydroxyapatite was placed under each subject and used to standardize all liver measurements. The liver phantom ratio was calculated by dividing the mean of the 3 liver measures by the single phantom measure. Intrareader and interreader class correlation coefficients for the liver phantom ratios were 0.99 and 0.99, respectively.

### Measurement of Circulating Biomarkers

Plasma concentrations of 85 candidate protein biomarkers were measured in the FHS Systems Approach to Biomarker Research in Cardiovascular

Disease initiative. Candidate biomarkers were selected based on the association with atherosclerotic CVD, gene expression profiling, published genome-wide associations studies of myocardial infarction and coronary heart disease, and discovery proteomics. Among the 85 biomarkers, 14 had few individuals above the lower limit of detection and were excluded, leaving 71 biomarkers for this analysis. Plasma proteins were quantified using a modified ELISA sandwich approach and Luminex xMAP platform (Sigma-Aldrich, St. Louis, MO). Protocols for assay development have been previously presented. The assays demonstrated acceptable coefficients of variation from 2.0% to 9.5%. Assay characteristics are presented in Table S1.

### Statistical Analysis

Baseline characteristics for the Offspring and Generation 3 cohort participants were summarized separately for the overall sample used in cross-sectional analyses and for the sample included in the longitudinal analysis of incident MetS. Because of the skewed distributions of some proteins, values were rank normalized across all biomarkers. To assess the associations of single biomarker concentrations with metabolic traits, we performed linear regression analyses in an age-adjusted and sex-adjusted model and then a multivariable model additionally adjusting for systolic blood pressure, hypertension treatment, HDL, total cholesterol, DM, smoking, BMI, and log triglycerides. Liver fat analyses were also adjusted for alcohol use. Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) analyses further excluded participants with DM. To account for multiple testing in single biomarker models, a false discovery rate (FDR)  $q$  value  $<0.05$  was set.<sup>10</sup> For incident MetS, a logistic regression was performed where all prevalent cases were excluded from the analysis data set. Age and sex models were performed first, followed by a multivariable model additionally adjusting for systolic blood pressure, WC, hypertension treatment, FG, HDL, and log triglycerides. Statistical analyses for single biomarker analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

To better understand the association of cardiometabolic traits with potentially correlated protein biomarkers, we used hierarchical clustering and principal component analysis. Traits were grouped into discrete clusters based on biomarker profiles using hierarchical clustering (hclustvar function, ClustOfVar package, R). The optimal number of clusters was determined by maximizing average silhouette width (Fviz\_nblust package in R). Next, we performed principal component analysis to reduce the dimensionality of the 71 biomarkers. We examined the associations of each of the 13 traits with the first 2 principal component terms

(principal component 1 [PC1] and principal component 2 [PC2]). To visualize the associations of cardiometabolic traits with biomarker profiles, the  $\beta$  coefficients for each trait were projected onto the first 2 principal components (PC1 and PC2) to produce a vector plot. Inclusion of PC1 and PC2 explained up to 50% of the overall variance. Each trait vector demonstrates the directionality of each trait along the first 2 principal component terms (PC1 and PC2).

## RESULTS

A total of 6981 participants were included in the analysis (mean age 49 years; 54% women) with clinical characteristics displayed in Table 1. A total of 26% were obese (BMI  $\geq 30$  kg/m<sup>2</sup>), with a mean BMI of 27.4 $\pm$ 5.5 kg/m<sup>2</sup> and WC of 96 $\pm$ 15 cm. The prevalences of hypertension, DM, and MetS were 35%, 6%, and 33%, respectively.

**Table 1. Baseline Demographic and Clinical Characteristics**

	Total	Offspring	Generation 3
	N=6981	N=3048	N=3933
Age, y	49 (14)	61 (9)	40 (9)
Women	3773 (54)	1678 (55)	2095 (53)
Body mass index, kg/m <sup>2</sup>	27.4 $\pm$ 5.5	28.0 $\pm$ 5.3	26.9 $\pm$ 5.6
Waist circumference, cm	96 $\pm$ 15	100 $\pm$ 14	93 $\pm$ 15
Fasting glucose, mg/dL	99 $\pm$ 22	104 $\pm$ 26	95 $\pm$ 18
Systolic blood pressure, mm Hg	121 $\pm$ 17	127 $\pm$ 19	117 $\pm$ 14
Diastolic blood pressure, mm Hg	75 $\pm$ 10	74 $\pm$ 10	75 $\pm$ 10
Hypertension treatment	1303 (19)	982 (32)	321 (8)
Triglycerides, mg/dL	119 (109–130)	124 (114–137)	115 (107–124)
Total cholesterol, mg/dL	194 $\pm$ 36	201 $\pm$ 36	189 $\pm$ 36
HDL cholesterol, mg/dL	54 $\pm$ 17	54 $\pm$ 17	54 $\pm$ 16
Diabetes mellitus	390 (6)	316 (10)	74 (2)
Metabolic syndrome	2319 (33)	1444 (47)	875 (22)
HOMA-IR, mg IU/dL:mL	6.1 $\pm$ 5.5	4.0 $\pm$ 3.5	7.7 $\pm$ 6.2
Current smoker	997 (14)	396 (13)	601 (15)
CT measures of adiposity			
Liver fat	0.36 $\pm$ 0.05	0.35 $\pm$ 0.05	0.36 $\pm$ 0.05
VAT, cm <sup>3</sup>	1789 $\pm$ 1015	2081 $\pm$ 1086	1602 $\pm$ 920
Intrathoracic fat, cm <sup>3</sup>	98 $\pm$ 62	114 $\pm$ 62	88 $\pm$ 59
Pericardial fat, cm <sup>3</sup>	112 $\pm$ 44	123 $\pm$ 49	105 $\pm$ 39
SAT, cm <sup>3</sup>	2874 $\pm$ 1388	3013 $\pm$ 1333	2785 $\pm$ 1415
VAT/SAT ratio	0.68 $\pm$ 0.39	0.76 $\pm$ 0.44	0.63 $\pm$ 0.34

Values are presented as number (percentage), mean $\pm$ SD, or median (interquartile range). The following are the total sample sizes for CT measures of adiposity: liver fat, N=3000; VAT, N=3141; intrathoracic fat, N=3172; pericardial fat, N=3172; VAT/SAT ratio, N=3141. CT indicates computed tomography; HDL, high-density lipoprotein; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; SAT, subcutaneous adipose tissue; and VAT, visceral adipose tissue.



Mean visceral and subcutaneous adipose volumes were  $1789 \pm 1015 \text{ cm}^3$  and  $2874 \pm 1388 \text{ cm}^3$ , with a mean VAT/SAT ratio of  $0.68 \pm 0.39$ . Mean intrathoracic and pericardial fat volumes were  $98 \pm 62$  and  $112 \pm 44 \text{ cm}^3$ . Over a median follow-up of 6.3 years, 888 of 4662 (19%) participants free of MetS at baseline developed incident MetS.

### Multiple Biomarkers Associated With Obesity and Cardiometabolic Traits

Of the 71 biomarkers analyzed, 45 were significantly associated with obesity (multivariable-adjusted FDR  $q$  value  $< 0.05$  for all listed in Table 2; full results are presented in Table S2). Among these 45 biomarkers, 32 were positively associated with obesity, with the largest associations observed for leptin, CRP (C-reactive protein), and plasminogen activator inhibitor 1 (PAI1). A 1-SD higher leptin level was associated with a near 7-fold increased odds of obesity (odds ratio [OR], 6.99; 95% CI, 6.23–7.85;  $P = 1.11 \times 10^{-237}$ ). By contrast, 13 biomarkers were negatively associated with obesity, insulin-like growth factor-binding protein 1 (including IGFBP1) and insulin-like growth factor-binding protein 2 (IGFBP2). Higher levels of IGFBP1 and IGFBP2 were both associated with significantly lower odds of obesity (IGFBP1: OR, 0.37 [95% CI, 0.34–0.40],  $P = 3.30 \times 10^{-134}$ ; IGFBP2: OR, 0.49 [95% CI, 0.45–0.52],  $P = 2.55 \times 10^{-81}$ ).

We next examined the associations of circulating biomarkers with 13 cardiometabolic traits including triglyceride level, insulin resistance as measured by HOMA-IR, and CT measures of adiposity including SAT, VAT, pericardial, and intrathoracic fat depots as well as liver fat. We similarly found that numerous proteins were significantly associated with each of these cardiometabolic traits (Figure 1; full results are presented in Table S3). Of 71 biomarkers, 68 were significantly associated with 1 or more of the 13 examined cardiometabolic traits in multivariable adjusted analyses (FDR  $q$  value  $< 0.05$  for all). We observed the greatest number of biomarker associations with triglyceride levels. Specifically, 53 of the 71 biomarkers were significantly associated with triglyceride levels (FDR  $q$  value  $< 0.05$  for all;  $P$  value range  $1.40 \times 10^{-1179}$  to 0.024). Among those 53 biomarkers, 38 were positively associated with triglycerides, including apoA1 (apolipoprotein A1) and KLKB1, whereas 15 were negatively associated with triglycerides, including IGFBP2 and tetranectin. A 1-SD higher apoA1 level was associated with 0.19 SD higher log triglyceride levels ( $\beta$ , 0.19; SE, 0.01;  $P = 1.48 \times 10^{-63}$ ), whereas a 1-SD higher IGFBP2 level was associated with 0.23-SD lower log triglyceride levels ( $\beta$ ,  $-0.23$ ; SE, 0.01;  $P = 1.40 \times 10^{-119}$ ).

Protein biomarkers significantly associated with CT measures of regional adiposity, including SAT, VAT, pericardial, intrathoracic, and liver fat (Figure 1). In multivariable-adjusted analyses, 22 biomarkers were associated with VAT, 16 with SAT, 15 with pericardial fat, 17 with intrathoracic fat, and 26 with liver fat (FDR  $q$  value  $< 0.05$  for all;  $P$  value range 0.01 to  $1.82 \times 10^{-40}$ ). Of the 22 biomarkers significantly associated with VAT, higher concentrations of 8 biomarkers, including PAI1, AGP1 (alpha-1 acid glycoprotein), and leptin, were associated with higher VAT levels, whereas higher levels of the remaining 14 biomarkers were associated with lower levels of VAT, including IGFBP1, IGFBP2, and CNTN1 (contactin 1). A 1-SD higher PAI1 level was associated with a 0.11 unit higher VAT ( $\beta$ , 0.11; SE, 0.01;  $P$  value  $2.21 \times 10^{-18}$ ), whereas a 1-SD higher IGFBP2 level was associated with a 0.13 unit lower VAT ( $\beta$ ,  $-0.13$ ; SE, 0.01;  $P$  value  $7.57 \times 10^{-24}$ ).

### Overlapping Versus Distinct Proteins of Obesity and Cardiometabolic Disease

We observed significant overlaps of biomarker profiles of obesity, cardiometabolic clinical traits, and measures of regional adiposity (Figure 2). When superimposing biomarker profiles of obesity and metabolic traits (triglycerides, FG, liver fat, and HOMA-IR), we found that all 45 biomarkers associated with obesity were also associated with 1 or more metabolic traits and 7 biomarkers (butyrylcholine esterase (BCHE), intercellular adhesion molecule 1 (sICAM1), PAI1, IGFBP1, granule membrane protein 140 (GMP140), B-type natriuretic peptide (NT-proBNP), IGFBP2) were shared by all 4 traits (Figure 2A). We also examined the overlap of obesity with CT measures of adiposity (Figure 2B). Specifically, 4 biomarkers (leptin, PAI1, AGP1, CNTN1) were common to obesity and all measures of regional adiposity. VAT, intrathoracic fat, and pericardial fat shared similar proteomic signatures. Of the 22 biomarkers associated with VAT, 13 were also associated with pericardial fat and 10 were associated with intrathoracic fat. Although SAT also shared similar proteomic profiles with VAT, intrathoracic fat, and pericardial fat, 6 biomarkers (ceruloplasmin, complement C2 (C2), Cystatin C, FBN, adipsin, and adrenomedullin (ADM)) were uniquely associated with obesity and SAT. Results were similar when restricting the analyses to participants with available CT measures of adiposity only (Table S4 and Figure S1).

### Biomarker Profiles Identify Cardiometabolic Trait Clusters

Despite significant overlap in some proteins across cardiometabolic traits, we recognized that distinct

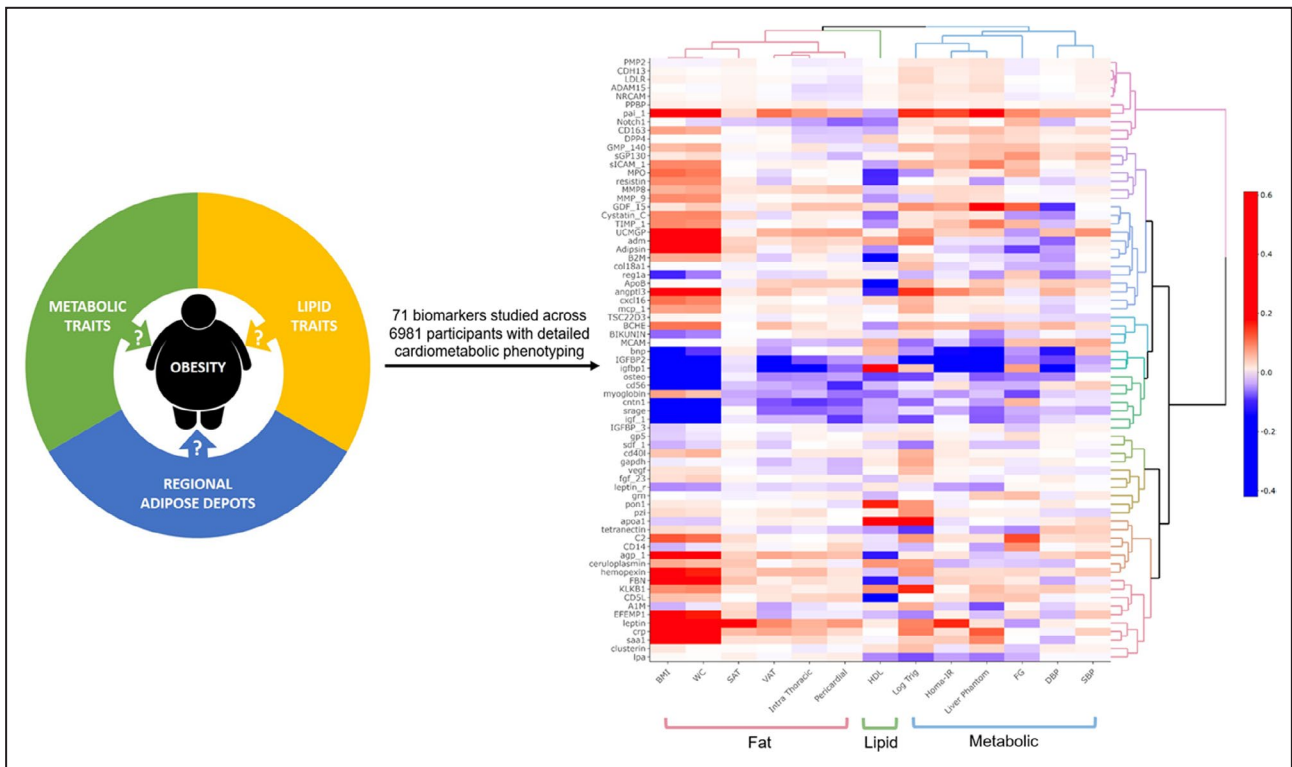
**Table 2. Protein Biomarkers With Significant Associations With Obesity**

Biomarker	OR (95% CI)	P Value	Biomarker	OR (95% CI)	P Value
Positive Association			Negative Association		
Leptin	6.99 (6.23–7.85)	1.11E-237	IGFBP1	0.37 (0.34–0.40)	3.30E-134
CRP	2.21 (2.05–2.37)	7.05E-104	IGFBP2	0.49 (0.45–0.52)	2.55E-81
PAI1	2.06 (1.91–2.21)	2.58E-83	SRAGE	0.69 (0.64–0.73)	9.40E-34
ADM	1.82 (1.69–1.96)	5.42E-55	CNTN1	0.69 (0.65–0.74)	9.43E-30
SAA1	1.81 (1.70–1.94)	2.67E-68	CD56 or NCAM	0.69 (0.65–0.74)	1.05E-27
ANGPTL3	1.77 (1.65–1.91)	2.30E-56	OSTEO	0.73 (0.69–0.78)	6.84E-23
UCMGP	1.69 (1.57–1.81)	1.51E-46	IGF-1	0.75 (0.71–0.80)	1.79E-17
Adipsin	1.63 (1.52–1.75)	2.71E-43	NT-proBNP	0.82 (0.77–0.88)	1.61E-08
AGP1	1.52 (1.42–1.62)	4.18E-37	REG1A	0.82 (0.79–0.89)	1.10E-09
FBN	1.49 (1.39–1.59)	7.48E-33	BIKUNIN	0.84 (0.79–0.89)	1.71E-08
EFEMP1	1.45 (1.35–1.56)	8.19E-24	Leptin Receptor	0.89 (0.84–0.94)	0.0001
Hemopexin	1.41 (1.32–1.51)	3.65E-25	SDF1	0.90 (0.85–0.95)	0.0003
C2	1.28 (1.20–1.36)	1.43E-14	CD14	0.93 (0.88–0.99)	0.025
CXCL16	1.25 (1.18–1.33)	4.03E-13			
MPO	1.25 (1.18–1.33)	3.68E-13			
TIMP1	1.25 (1.16–1.34)	6.71E-10			
Cystatin C	1.24 (1.16–1.33)	1.50E-09			
BCHE	1.23 (1.15–1.31)	1.80E-10			
sICAM1	1.22 (1.15–1.30)	2.39E-10			
Resistin	1.22 (1.15–1.30)	8.22E-11			
MMP9	1.20 (1.13–1.28)	4.15E-09			
CD163	1.19 (1.12–1.26)	1.60E-08			
KLKB1	1.18 (1.11–1.26)	3.73E-07			
Ceruloplasmin	1.17 (1.10–1.26)	3.75E-06			
MCP1	1.17 (1.10–1.24)	1.02E-06			
B2M	1.16 (1.08–1.25)	2.16E-05			
MMP8	1.15 (1.08–1.22)	7.45E-06			
Myoglobin	1.13 (1.06–1.21)	0.0004			
GMP140	1.11 (1.04–1.18)	0.0001			
VEGF	1.09 (1.03–1.16)	0.003			
CD5L	1.09 (1.02–1.15)	0.007			
CD40L	1.08 (1.01–1.14)	0.02			

Multivariable model adjusts for age, sex, smoking status, HDL, total cholesterol, hypertension treatment, log triglycerides, SBP, and diabetes. ADM, Adrenomedullin; AGP1, Alpha-1 acid glycoprotein; ANGPTL3, Angiotensin-like 3; B2M, Beta-2-microglobulin; BCHE, Butyrylcholinesterase; BIKUNIN, AMBP-bikunin; C2, Complement C2; CD14, Monocyte differentiation antigen; CD163, Cluster of differentiation 163; CD40L, Soluble CD40 ligand; CD56 or NCAM, Neural cell adhesion molecule; CD5L, CD5 antigen-like; CNTN1, Contactin 1; CRP, C-reactive protein; CXCL16, Chemokine (C-X-C motif) ligand 16; EFEMP1, EGF containing fibulin-like extracellular matrix protein 1; FBN, Fibrinogen; GMP140, Granule membrane protein 140; HDL, indicated high-density lipoprotein; IGF-1, Insulin-like growth factor 1; IGFBP1, Insulin-like growth factor binding protein 1; IGFBP2, Insulin-like growth factor binding protein 2; KLKB1, Plasma kallikrein; MCP1, Monocyte chemoattractant molecule 1; MMP8, Matrix metalloproteinase 8; MMP9, Matrix metalloproteinase 9; MPO, Myeloperoxidase; NT-proBNP, N-terminal pro-hormone of brain natriuretic peptide; OR, odds ratio per 1-SD increase in rank normalized biomarker; OSTEO, Osteocalcin; PAI1, Plasminogen activator inhibitor 1; REG1A, Lithostathine-1-alpha; SAA1, Serum amyloid A1; SBP, systolic blood pressure; SDF1, Stromal cell-derived factor 1; sICAM1, Intercellular adhesion molecule 1; SRAGE, Receptor for advanced glycation endproducts; TIMP1, Tissue inhibitor of metalloproteinases 1; UCMGP, Uncarboxylated matrix Gla protein; VEGF, Vascular endothelial growth factor.

traits also displayed differences. We sought to identify clusters of traits based on proteomic signatures. In hierarchical clustering analyses, we identified 3 unique cardiometabolic trait clusters with distinct biomarker profiles: (1) adipose traits, (2) metabolic traits, and (3) lipid traits (Figure 1). Adipose traits included BMI, WC, SAT, VAT, intrathoracic fat, and pericardial fat.

Metabolic traits included triglycerides, HOMA-IR, liver fat, FG, diastolic blood pressure, and systolic blood pressure, and lipid traits included HDL. In a complementary analysis using principal component analysis, we similarly found that distinct cardiometabolic traits displayed different proteomic architecture. Based on the first and second principal component terms,



**Figure 1. Proteomic signatures of obesity and related cardiometabolic traits.**

Heatmap of associations of single biomarkers with cardiometabolic traits. Color coding represents standardized  $\beta$  coefficient in multivariable-adjusted analyses (X-SD change in trait per 1-SD change in biomarker). Clustering based on biomarker correlations (rows) and traits (columns). BMI indicates body mass index; DBP, diastolic blood pressure; FG, fasting glucose; HDL, high-density lipoprotein; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; SAT, subcutaneous adipose tissue; SBP, systolic blood pressure; trig, triglycerides; VAT, visceral adipose tissue; and WC, waist circumference. For abbreviations of biomarkers, please see Table S1.

traits separated along the following vector directions based on biomarker profiles (Figure 3): BMI and WC separated along the same vector direction, and SAT followed a parallel but opposite vector direction, suggesting close alignment in biomarker profiles for these 3 traits. HDL and triglycerides separated along a vector that was orthogonal to BMI, WC, and SAT, which suggests that the biomarker profiles of lipid traits (HDL and triglycerides) were uniquely different from the proteomic signature of fat traits (BMI, WC, and SAT).

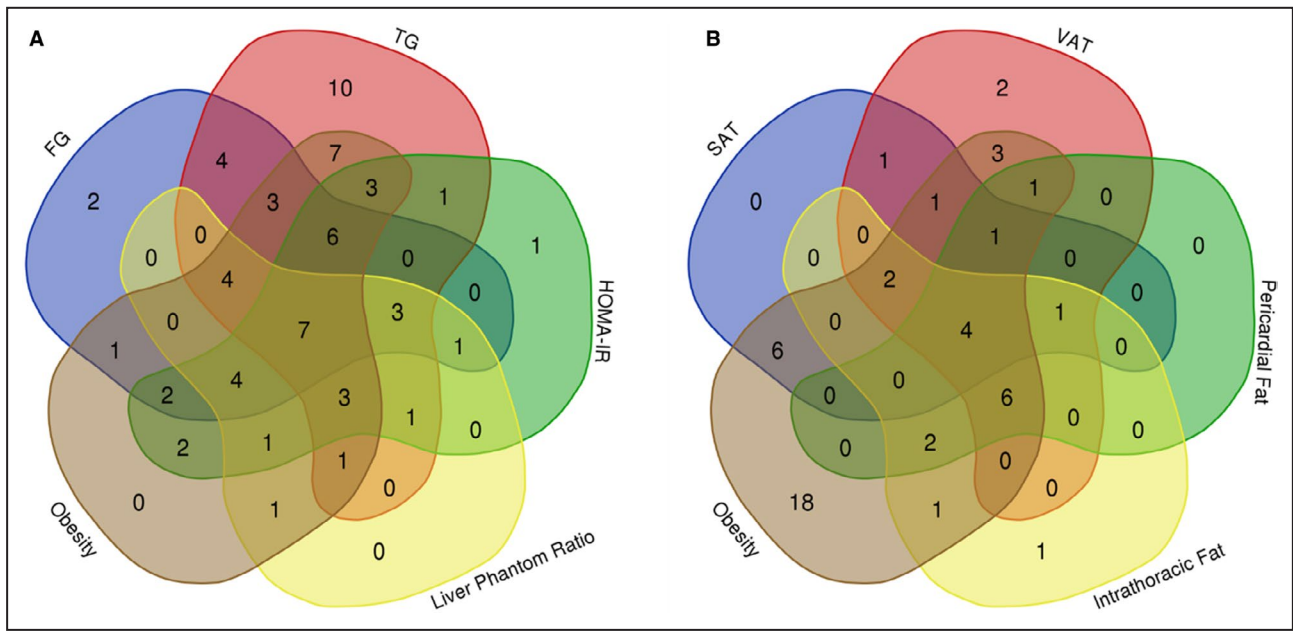
### Biomarkers Predict Incident MetS

Finally, we evaluated the association of protein biomarkers with incident MetS in age- and sex-adjusted models and a multivariable-adjusted model (Figure 4; full results are presented in Table S5 through S6). Of 71 biomarkers, 30 were significantly associated with incident MetS in age-adjusted and sex-adjusted models (FDR  $q$  value  $<0.05$ ). Among these 30 biomarkers, 21 biomarkers were associated with an increased odds of developing MetS, including apoB (apolipoprotein B), leptin, and CRP, whereas 9 were associated with a decreased odds of incident MetS, including

IGFBP1, IGFBP2, and NT-proBNP. Of the 30 biomarkers, 6 remained significant after multivariable adjustment, including apoB, IGFBP2, KLKB1, C2, FBN, and NT-proBNP. IGFBP2 and NT-proBNP were associated with a decreased odds of incident MetS. A 1-SD higher IGFBP2 concentration was associated with a 0.83 decreased odds of future MetS (OR, 0.83; 95% CI, 0.75–0.92;  $P$  value 0.0005). Conversely, apoB, KLKB1, C2, and FBN were associated with an increased odds of future MetS; a 1-SD higher apoB concentration was associated with a 1.50 increased odds of incident MetS (OR, 1.50; 95% CI, 1.36–1.66;  $P$  value  $4.97 \times 10^{-13}$ ).

## DISCUSSION

We examined the proteomic profiles of obesity and associated cardiometabolic traits, including specific adipose depots in a community-based sample of adults free of CVD. Our findings are 4-fold: (1) numerous CVD-related protein biomarkers are associated with obesity, cardiometabolic clinical traits, and CT measures of regional adiposity; (2) the proteomic architecture of obesity overlaps considerably with associated



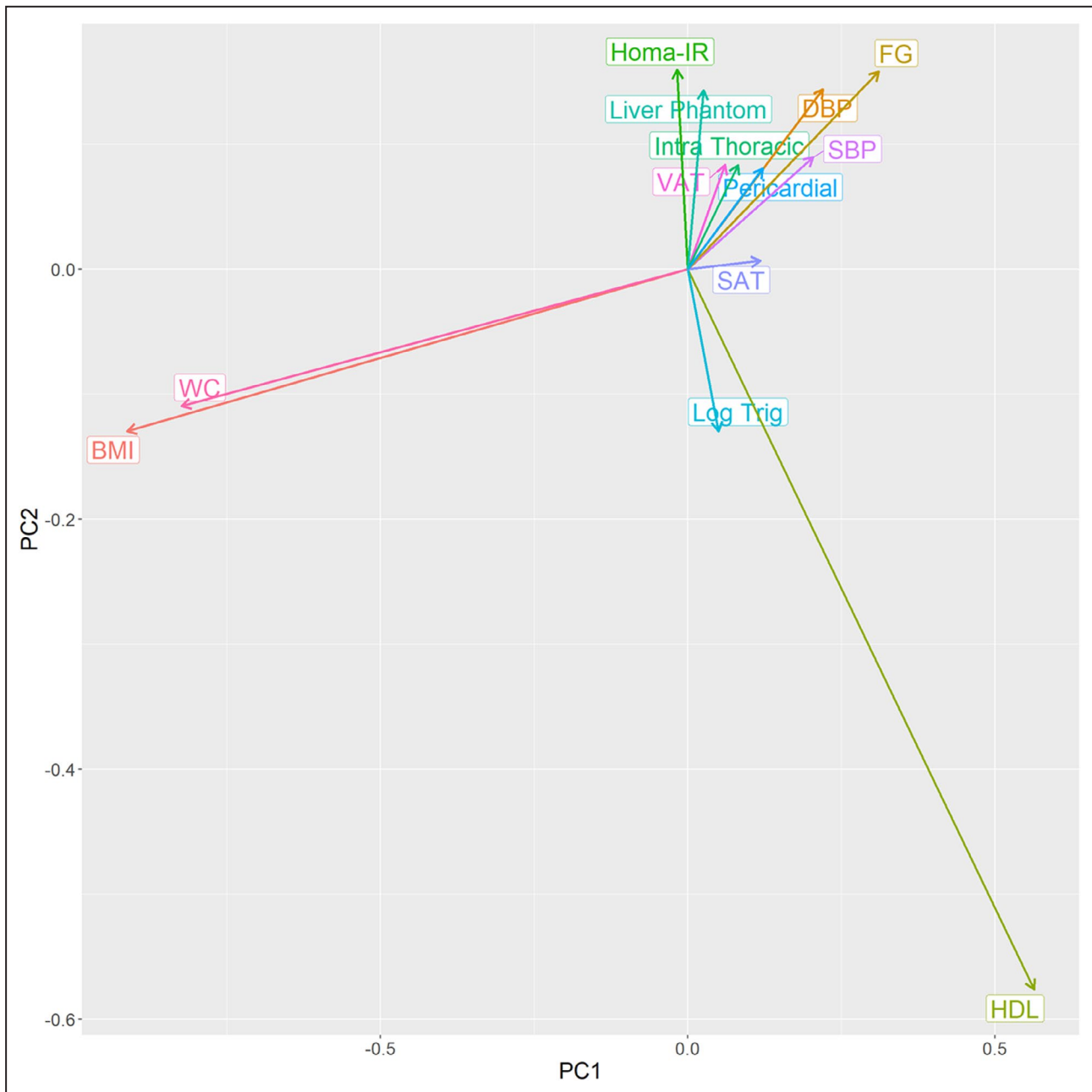
cardiometabolic traits, implying shared pathways; (3) despite overlap, hierarchical clustering of proteomic profiles identified 3 distinct clusters of cardiometabolic traits (adipose, metabolic, and lipid traits); and (4) 6 protein biomarkers were associated with a future risk of MetS. Collectively, our findings highlight new associations of CVD biomarkers with obesity, cardiometabolic traits, and CT measures of adiposity and suggest that proteomic profiles may refine our phenotypic characterization of obesity and cardiometabolic disease by elucidating both unique and shared biological pathways.

Although the link between obesity and cardiometabolic disease is well established, biological pathways involved in the pathogenesis of obesity-related diseases are complex and incompletely understood. Previously established biomarkers for obesity are implicated in pathways of inflammation, adipogenesis, and cell proliferation.<sup>4,11</sup> Small-scale proteomic-targeted approaches have sought to better understand the mechanistic pathways that link obesity with cardiometabolic disease. A study of 56 healthy middle-aged overweight subjects examined the association of 124 plasma proteins with BMI and plasma insulin.<sup>6</sup> The authors identified 3 clusters of plasma proteins associated with BMI and 4 protein clusters associated with insulin. Proteins strongly associated with both BMI and insulin included complement 3, CRP, serum amyloid protein, and VEGF (vascular endothelial growth factor), highlighting the importance of inflammation

in the pathogenesis of both obesity and DM. We extend these findings and demonstrate novel biomarkers shared among obesity and cardiometabolic traits. Our observations corroborate existing data: higher levels of adipokines leptin, adiponectin, adipisin, and CRP, and lower levels of IGF-1 (insulin-like growth factor 1), IGFBP1, IGFBP2, and insulin-like growth factor-binding protein 3 (IGFBP3) were significantly associated with obesity and several cardiometabolic traits. We also show that other markers of inflammation, fibrosis, and angiopoietins were among the protein biomarkers with the strongest associations with obesity. For instance, higher levels of PAI1, a physiologic inhibitor of plasminogen activators, and ANGPTL3, an angiopoietin involved in angiogenesis and the regulation of circulating HDL and triglyceride levels, were both significantly associated with obesity and numerous cardiometabolic traits.

An important novelty of our study is the examination of protein biomarker associations with regional adiposity measures. Although traditional metrics of obesity (BMI and WC) are well correlated with cardiometabolic risk, they do not accurately capture the differential contributions of different fat compartments to metabolic risk. Previous work has demonstrated that VAT, SAT, pericardial fat, and intrathoracic fat are all variably associated with metabolic risk, with VAT being the most strongly predictive of cardiometabolic risk and CVD.<sup>8,12-14</sup> In a study of 1583 participants from the FHS, biomarkers secreted by adipose



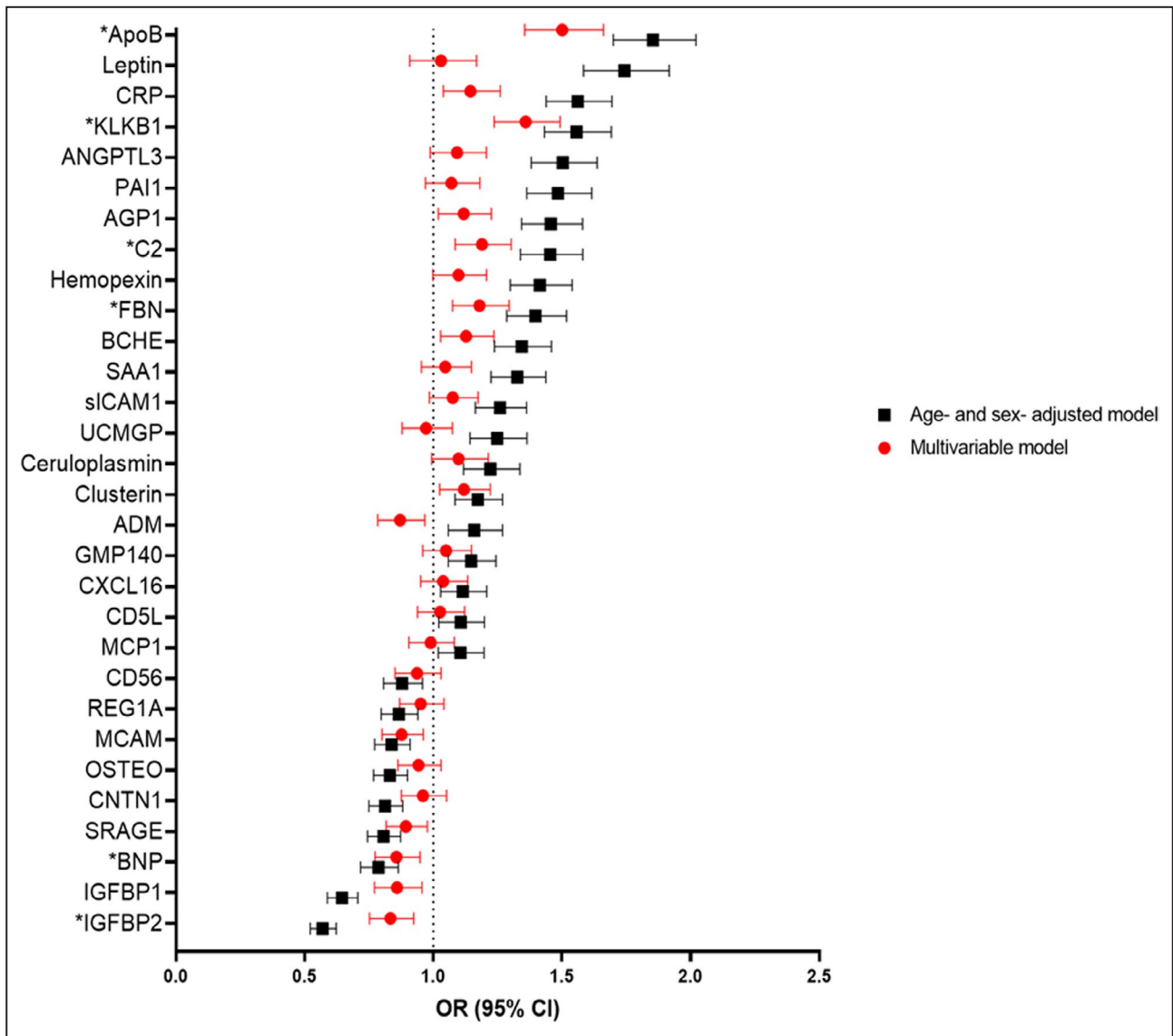


**Figure 3. Vector map of PC1 and PC2 calculated using principal components analysis.**

BMI indicates body mass index; DBP, diastolic blood pressure; FG, fasting glucose; HDL, high-density lipoprotein; PC1, principal component 1; PC2, principal component 2; SAT, subcutaneous adipose tissue; SBP, systolic blood pressure; Trig, triglycerides; VAT, visceral adipose tissue; and WC, waist circumference.

tissue (adiponectin, leptin, leptin receptor, and fatty acid-binding protein 4) and those secreted by both adipose tissue and the liver (fetuin-A and retinol binding protein 4) were significantly associated with SAT and VAT.<sup>15</sup> In our analysis, 4 biomarkers were significantly associated with all 4 measures of adiposity and obesity: leptin, PAI1, AGP1 (positively associated), and CNTN1 (negatively associated). Although the associations of leptin and PAI-1 with obesity have been described,<sup>16,17</sup> little is known about the associations of

AGP1 and CNTN1 with cardiometabolic disease. In obese mice, AGP1 expression was induced by metabolic and inflammatory signals in adipose tissue and was protective against the deleterious effects of severe inflammation.<sup>18</sup> In a study of 64 obese individuals undergoing weight reduction surgery, circulating levels of AGP1 were associated with BMI, leptin, fasting insulin, HOMA-IR, and CRP. There were no differences in protein AGP1 expression between VAT and SAT.<sup>19</sup> CNTN1 is a neuronal membrane protein required for



**Figure 4. Association of single biomarkers with incident metabolic syndrome. Biomarkers shown were statistically significant in age-adjusted and sex-adjusted models (false discovery rate  $q$  value  $<0.05$ ).**

\*Biomarkers that were statistically significant in multivariable adjusted models (false discovery rate  $q$  value  $<0.05$ ). ORs displayed per 1-SD increase in biomarker concentration. Black represents the age-adjusted and sex-adjusted model. Red represents the multivariable model. Multivariable model adjusts for age, sex, waist circumference, high-density lipoprotein, log triglycerides, systolic blood pressure, hypertension treatment, fasting glucose, and statin therapy. OR indicates odds ratio. For biomarker abbreviations, please see Table S1.

axonal growth and maturation. In one study examining regional differences in subcutaneous adipose tissue gene expression, CNTN1 was differentially expressed in the lower abdomen compared with the flank.<sup>20</sup> Interestingly, the biomarker profiles of VAT, pericardial fat, and intrathoracic fat were closely aligned, whereas SAT appeared to carry a unique proteomic profile. Emerging data suggest that visceral adiposity, rather than subcutaneous fat, is associated with increased metabolic risk.<sup>15,21</sup> Of note, the insulin growth factor axis demonstrated strong inverse correlations with VAT, pericardial and intrathoracic fat, but not with SAT.

The insulin growth factor axis is an important regulator of obesity and metabolic risk; its lack of association with SAT may explain in part why SAT only conveys minimal cardiometabolic risk compared with other fat compartments.

Although we observed many shared protein biomarker associations between obesity and multiple cardiometabolic traits, there were additional biomarkers that were uniquely associated with 1 or more cardiometabolic clinical traits. For example, melanoma cell adhesion molecule (MCAM), growth differentiation factor 15 (GDF15), and lipoprotein(a) (LPA)

were significantly associated with FG, HOMA-IR, triglycerides, and liver fat, but not with obesity. The notion that distinct proteomic profiles exist was further corroborated by clustering analyses and principal component analysis, which identified 3 distinct clusters of cardiometabolic traits: adipose, metabolic, and lipid. These findings suggest that in addition to shared biology, there may be pathways that are related to metabolic dysfunction independent of generalized adiposity. These may represent a precursor phenotype to obesity and its related diseases. This assertion is supported by the concept of obesity without MetS or the metabolically healthy obesity phenotype.<sup>22</sup> In a study of 6809 participants from the Multi-Ethnic Study of Atherosclerosis, investigators found that the risk of incident CVD was not increased in participants with the metabolically healthy obesity phenotype, although nearly 50% of individuals with the metabolically healthy obesity phenotype at baseline eventually developed MetS with a subsequent increased risk of CVD.<sup>23</sup> Ascertaining which biologic pathways are activated in cardiometabolic disease may refine our understanding of the mechanistic drivers of the transition from metabolically healthy obesity to MetS. For instance, GDF15 and lipoprotein(a) have both been associated with cardiometabolic risk, and further exploration of their associated pathways may offer insights into that transition.<sup>24,25</sup> Moreover, duration of obesity may influence proteomic profiles as well as the development of cardiometabolic disease. Future longitudinal investigations examining the association of time-dependent changes in biomarkers with cardiometabolic traits in obesity may also provide biomarker targets for further study and potential intervention.

Finally, we identified 6 unique protein biomarkers with significant associations with incident MetS in multivariable analyses. Higher levels of IGFBP2 and NT-proBNP were associated with a lower risk of future MetS, whereas increased levels of apoB, KLKB1, C2, and FBN were associated with a higher risk of future MetS. IGFBP2 levels are consistently lower among patients with MetS, and lower levels are associated with unfavorable metabolic risk factors such as higher BMI, lower insulin sensitivity, and less favorable lipid profiles.<sup>26–28</sup> Experimental evidence suggests that after fetal development, IGFBP2 inhibits adipogenesis, improves insulin sensitivity, and significantly attenuates the risk of developing DM.<sup>29–31</sup> NT-proBNP was also protective against risk of MetS, even after adjustment for BMI. It is well known that natriuretic peptide levels are inversely related to BMI and obesity.<sup>32–34</sup> Given the strong negative association of natriuretic peptides with obesity, the relationship between NT-proBNP and MetS is anticipated, but whether this association persists independent of obesity is not known. Among the biomarkers associated with

increased risk of MetS, the relationship of apoB with incident MetS has been the most well described, although the driving mechanisms are still being elucidated.<sup>35–37</sup> In 10 340 Chinese participants with MetS, serum apoB was associated with an increased risk of prevalent MetS, particularly among individuals with a healthy weight.<sup>37</sup> This observation suggests that apoB may exert its effects on MetS risk via both obesity-dependent and obesity-independent pathways. apoB is intimately linked to lipid metabolism, and we found that many biomarkers were shared between metabolic and lipid traits, but not obesity or fat traits, suggesting that lipid pathways may contribute to the development of metabolic disease independent of obesity. Less is known about the relationship of KLKB1, C2, and FBN with MetS, but these findings point to the involvement of coagulation, complement activation, and fibrosis pathways in the pathogenesis of MetS.

Our study has several limitations. First, the selection of biomarkers was based on previously established associations with CVD. Given the significant overlap between metabolic disease and established CVD, our investigation was enriched for protein biomarkers with significant associations with cardiometabolic traits. A more unbiased selection strategy may have yielded additional novel targets for future discovery. Second, our study population included predominantly White participants, limiting the generalizability to other diverse populations. Metabolic disease is more prevalent among non-White populations, especially Black women, and protein targets may dramatically differ in other populations.<sup>38</sup> Finally, our study is an observational investigation, and conclusions about causation cannot be drawn.

We demonstrate significant associations of CVD-related protein biomarkers with obesity, cardiometabolic clinical traits, and CT measures of regional adiposity. Protein biomarkers clustered along 3 main axes: adipose, metabolic, and lipid traits. Although obesity shared similar proteomic profiles with fat, metabolic, and lipid traits, several biomarkers were unique to metabolic traits only. Further exploration of these novel protein targets and associated pathways may provide insight into the mechanisms responsible for the progression from obesity to cardiometabolic disease.

## ARTICLE INFORMATION

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### Supplementary Material

Table S1–S6

Figure S1

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# **Supplemental Material**

**Table S1. Biomarker assay performance characteristics**

Abbreviation	Name	Samples			Distribution (pg/ml)			Precision§		Accuracy¥	Linearity**	Detection£	
		Selection criteria*	n available	% missing	Median	25 %ile	75th %ile	Inter-CV, % QC1/QC2	Intra-CV, % QC1/QC2	Spike recovery %	% Of Origin	LLOQ (pg/mL)	ULOQ (pg/ml)
A1M	Alpha-1-microglobulin	2,3	7277	1	11100000	8800000	14200000	7.9/7.3	3.9/3.9	100.5	101.4	3640	71400000
ADAM15	Disintegrin and metalloproteinase domain-containing protein 15	2	7290	1	333	181	654	3.3/3.0	8.3/3.9	100	100.5	39	14100
Adipsin	Adipsin	2	7285	1	863000	724000	1050000	16.3/19.0	5.1/4.3	101.3	102.8	18600	7450000
ADM	Adrenomedullin	1	7312	1	297	252	352	10.9/6.3	5.0/6.3	109.1	95.4	11	827
AGP1	Alpha-1 acid glycoprotein	1,2	7334	0	670000000	555000000	805000000	4.6/5.7	8.1/8.3	101.1	99.7	29400000	2270000000
ANGPTL3	Angiopietin-like 3	1	7318	0	23000	16800	30300	4.0/4.8	17.6/12.0	89.6	113.5	1380	97700
APOA1	Apolipoprotein A-1	1	7328	0	596000000	488000000	724000000	7.1/7.3	28.9/11.8	101.8	96.9	22500000	1590000000
APOB	Apolipoprotein B	1	7265	1	684000000	569000000	823000000	13.4/13.4	3.0/6.6	98	103.1	56100000	3630000000
B2M	Beta-2-microglobulin	2	7262	1	1450000	1240000	1710000	17.7/14.0	3.7/4.2	98.4	98.1	154000	12000000
BCHE	Butyrylcholine esterase	2,3	7316	1	5990000	4990000	7140000	14.9/8.9	8.6/8.4	93.7	97.5	949	23300000
BIKUNIN	AMBP-bikunin (BIKUNIN)	2,3	7308	1	178000000	156000000	207000000	6.3/9.8	2.9/7.1	112.6	100.1	1918	499000000
NTproBNP	N-terminal prohormone of brain natriuretic peptide	1,2	7265	1	128	67.5	260	4.4/7.2	13.3/10.3	98.3	99.2	9.71	30100
C2	Complement C2	4	7269	1	443000000	400000000	491000000	16.1/11.9	3.2/3.9	99.8	101	6760000	1090000000
CD14	Monocyte differentiation antigen CD14	1,2	7267	1	15400000	13500000	17800000	15.4/14.5	3.5/3.6	100	100.2	2140000	63000000
CD163	Cluster of differentiation 163	2,3	7330	0	103000	72400	142000	3.4/4.3	8.5/4.8	100.2	103.3	5540	1180000
CD40L	Soluble CD40 ligand	1	6348	14	36.8	25.4	55.7	3.1/4.9	14.8/14.1	90.6	96.6	19.4	2010
CD5L	CD5 antigen-like	1	7339	0	208000	162000	266000	12.3/5.7	3.0/2.4	99.8	106.3	2	908000
CDH13	Cadherin 13	1	7271	1	52100	25400	127000	2.7/4.7	9.3/5.2	100	106.4	4680	3420000
Ceruloplasmin	Ceruloplasmin	2	7340	0	1270000000	1080000000	1535000000	5.0/3.5	9.4/5.4	100.4	99	60500000	4120000000
CLEC3B	Tetranectin	2	7334	0	4540000	4040000	5040000	5.4/2.8	8.5/5.8	100.2	101.4	630000	10500000
clusterin	Clusterin	1	7327	0	51100000	43800000	63600000	16.5/12.6	11.2/9.1	117.8	116.5	1.5	26700
CNTN1	Contactin 1	1	7328	0	46300	39700	54300	6.1/5.3	7.8/7.6	100.7	98.6	4500	131000
COL18A1	Collagen, type XVIII, alpha 1	1	7297	1	134000	112000	158000	3.0/5.9	17.1/12.9	88.6	119.1	2670	607000
CRP	C-Reactive Protein	1	7284	1	848000	353000	2170000	14.5/9.9	5.1/8.2	104.6	97.6	20	3740
CXCL16	Chemokine (C-X-C motif) ligand 16	1,2	7321	0	1090	933	1280	2.8/3.5	13.5/11.1	96.3	93.8	73.8	4070
Cystatin C	Cystatin-C	1	7317	1	537000	478000	612000	9.8/5.1	3.2/3.1	89.3	89	2480	2680000

DPP4	Dipeptidyl dipeptidase	3	7328	0	54000	41400	69300	2.5/2.3	7.8/3.4	124.2	263.4	4420	577000
EFEMP1	EGF containing fibulin-like extracellular matrix protein 1	2	7328	0	48500000	40100000	59800000	9.7/9.1	4.8/3.8	99.7	97.8	4790	349000000
FBN	Fibrinogen	2	7311	1	449000000	377000000	537000000	9.7/7.0	3.8/2.9	100.1	104.2	2740	3470000000
FGF23	Fibroblast growth factor 23	1	6976	5	46.2	34.15	67.3	5.5/5.7	13.4/14.0	91.6	101.4	18.7	11800
GAPDH	Glyceraldehyde 3-phosphate dehydrogenase	1	7283	0	71300	50500	96900	19.0/14.2	3.7/3.8	100.1	92.2	774	521000
GDF15	Growth differentiation factor 15	1,2	7348	0	466	353	661	11.9/6.8	5.4/5.0	91.5	97	40	20600
GMP140	Granule membrane protein 140	1,2	7332	0	15800	12900	19200	14.8/12.1	4.9/4.4	89.6	79	116	60500
GP5	Glycoprotein V (platelet)	1	7324	0	875	737	1050	15.1/7.6	3.9/3.5	104.9	100.4	65.4	94600
GRN	Granulin	1,2	7333	0	20000	17200	23300	6.4/4.4	4.2/1.2	99.1	102.4	2820	367000
Hemopexin	Hemopexin	2	7327	0	775000000	681000000	883000000	4.7/3.4	7.7/5.6	99.7	101.1	76100000	1600000000
IGF1	Insulin-like growth factor 1	1	7276	1	6350	4540	8550	6.8/3.7	9.1/5.5	88.9	105.2	285	422000
IGFBP1	Insulin-like growth factor-binding protein 1	1,2	7002	5	7140	3440	14300	6.9/5.4	2.5/2.5	99.8	101.5	979	267000
IGFBP2	Insulin-like growth factor binding protein 2	2	7306	1	9730000	6180000	14700000	8.7/10.2	2.8/6.0	99.8	98.8	5970	51100000
IGFBP3	Insulin-like growth factor-binding protein 3	1	7333	0	224000	190000	271000	15.2/18.0	3.9/4.4	101.1	113	272	618000
KLKB1	Plasma kallikrein	2	7343	0	6460000	5470000	7630000	16.2/24.5	10.2/3.2	98.8	110.6	24	13900000
LDLR	LDL receptor	2,3,4	7295	1	137000	68400	295000	3.4/3.9	8.9/4.7	100.1	109.3	7260	5230000
Leptin	Leptin	1,2	6824	7	3610	1580	8880	9.6/3.2	15.8/7.0	97.9	132	397	161000
Leptin-R	Leptin receptor	1	5673	23	2010	1040	3100	5.5/6.0	10.7/9.1	92.9	117.5	911	293000
LPA	Lipoprotein(a)	1,2	7081	4	57200000	19900000	187000000	15.5/14.0	9.8/8.2	100	104.4	320	6390000
MCAM	Melanoma cell adhesion molecule	2	7291	1	145000	125000	171000	11.1/5.1	4.5/3.8	95.8	99.6	29	486000
MCPI	Monocyte chemotactic molecule 1	1	7316	1	166	135	202	3.3/6.1	11.1/13.7	94.8	100.9	5.67	5030
MMP8	Matrix metalloproteinase 8	3,4	6343	14	309	155	517	8.3/5.6	16.9/13.9	100.3	106.8	68	53700
MMP9	Matrix metalloproteinase 9	1,2	7339	0	46000	36100	63300	8.1/10.0	4.7/3.9	81	74	243	974000
MPO	Myeloperoxidase	1,2	7348	0	9550	7430	12100	13.2/9.6	3.8/4.4	88.3	138	102	781100
Myoglobin	Myoglobin	1	7333	0	12800	9970	16900	6.6/6.2	6.6/8.0	88.7	107.1	1710	285000
NCAM	Neural cell adhesion molecule	2	7326	0	279000	233000	333000	7.2/4.3	2.4/1.6	100.1	100.2	13800	764000
Notch1	Notch 1	3	7323	0	149	118	186	6.2/5.5	2.3/2.3	100	102	34	1480
NRCAM	Neuronal cell adhesion molecule	2	6991	5	6410	2900	13800	3.4/2.5	9.0/4.4	97.9	95.9	943	566000
Osteocalcin	Osteocalcin	1	7165	3	2750	1770	4090	5.1/6.3	8.8/10.7	90.7	120.1	492	28800



PAI1	Plasminogen activator inhibitor 1	1	7331	0	16500	11400	23900	3.6/4.2	10.8/12.3	103.4	87.5	2420	205000
PMP2	Peripheral myelin protein 2	2	7299	1	521	322	864	3.1/4.7	5.8/6.6	98.2	120.5	81	59400
PON1	Serum paraoxonase/arylesterase 1	2	7336	0	30100	21200	42500	7.4/7.6	4.2/3.9	99.9	100.6	1190	149000
PPBP	Pro-platelet basic protein	3	7306	1	1180000	616000	2340000	6.0/6.4	3.0/3.8	97.9	97.7	222	16100000
REG1A	Lithostathine-1-alpha	1	7326	0	85400	67000	113000	7.7/8.8	6.9/11.3	86.8	97.4	22600	980000
Resistin	Resistin	1	7299	1	6480	5270	7970	5.0/4.6	11.2/11.0	101.3	91.5	236	31100
SAA1	Serum amyloid A1	2	7169	2	237000	128000	449500	21.9/23.4	13.6/8.5	97.5	100.3	19900	4960000
SDF1	Stromal cell-derived factor 1	2	7310	1	344	268	453	15.6/8.4	4.8/7.0	101	102.5	59	17500
SERPINA10	Protein Z-dependent protease inhibitor	2	7327	0	111000	95600	127000	7.0/6.0	3.4/4.7	100	112.1	28500	12000000
sGP130	Interleukin-6 receptor beta	1	7345	0	58700	52100	66100	9.1/3.9	3.0/3.0	101.1	94	417	229000
sICAM1	Intercellular adhesion molecule 1	1	7321	1	18700	16000	22300	11.2/9.3	4.5/4.5	85.1	102.5	2020	128000
sRAGE	Receptor for advanced glycation endproducts	1	7297	1	3440	2750	4240	5.6/4.0	14.5/15.0	91.9	97.2	103	12600
TIMP1	Tissue inhibitor of metalloproteinases 1	1	7335	0	31400	27700	35900	13.2/8.5	4.3/5.4	86.1	93.1	273	93600
TSC22D3	TSC22D3 domain family member 3	3	7088	4	1589	1266	1920	9.3/15.9	9.0/12.2	100.4	102.1	974	198900
UCMGP	Uncarboxylated MGP	1,2	7310	0	45500	33300	61700	17.8/17.8	11.5/10.1	100.2	118.8	9110	339000
VEGF	Vascular endothelial growth factor	1,2	6028	18	21.9	12.7	37	4.3/6.0	14.7/14.0	92.8	102.7	9.18	1880

**Table S2. Baseline demographic and clinical characteristics of incident metabolic syndrome sample**

	<b>Total</b>
	N=4662
Age, years	46 (13)
Women, n (%)	2738 (59%)
Body mass index, kg/m <sup>2</sup>	25.6 (4.5)
Obesity, n (%)	633 (14%)
Waist circumference, cm	90.3 (12.8)
Fasting glucose, mg/dL	92.7 (12.2)
Systolic Blood pressure, mmHg	116 (14)
Diastolic blood pressure, mmHg	73 (9)
Hypertension treatment, n (%)	337 (7%)
Triglycerides	89.5 (81.3-97.8)
Total cholesterol, mg/dL	192 (35)
HDL cholesterol, mg/dL	59 (16)
Diabetes mellitus, n (%)	45 (1%)
HOMA-IR, mg·IU/dL·mL	4.02 (2.78-5.97)
Current smoker, n (%)	672 (14%)

Values are means (standard deviations) or medians (inter-quartile ranges) unless otherwise noted.

Abbreviations: HDL = high-density lipoprotein, HOMA-IR = homeostatic model assessment of insulin resistance

**Table S3. Associations of single biomarkers with obesity**

<b>Biomarker</b>	<b>OR</b>	<b>Lower CI</b>	<b>Upper CI</b>	<b>p-value</b>	<b>FDR- p-value</b>
<b>A1M</b>	0.93	0.88	0.99	0.03	0.05
<b>ADAM15</b>	1.03	0.97	1.09	0.30	0.3
<b>Adipsin</b>	1.63	1.52	1.75	2.71E-43	2.31E-42
<b>ADM</b>	1.82	1.69	1.96	5.42E-55	5.76E-54
<b>AGP1</b>	1.52	1.42	1.62	4.18E-37	3.23E-36
<b>ANGPTL3</b>	1.77	1.65	1.90	2.30E-56	2.79E-55
<b>ApoA1</b>	0.95	0.88	1.03	0.19	0.27
<b>ApoB</b>	1.01	0.93	1.11	0.76	0.82
<b>B2M</b>	1.16	1.08	1.24	2.16E-05	4.97E-05
<b>BCHE</b>	1.23	1.15	1.31	1.80E-10	6.39E-10
<b>BIKUNIN</b>	0.84	0.79	0.89	1.71E-08	4.55E-08
<b>BNP</b>	0.82	0.77	0.88	1.61E-08	4.42E-08
<b>C2</b>	1.28	1.20	1.36	1.43E-14	6.09E-14
<b>CD14</b>	0.93	0.88	0.99	0.03	0.05
<b>CD163</b>	1.19	1.12	1.26	1.60E-08	4.42E-08
<b>CD40L</b>	1.08	1.01	1.14	0.02	0.03
<b>CD56</b>	0.69	0.65	0.74	1.05E-27	5.94E-27
<b>CD5L</b>	1.09	1.02	1.15	0.007	0.01
<b>CDH13</b>	1.04	0.98	1.10	0.17	0.25
<b>Ceruloplasmin</b>	1.17	1.10	1.26	3.75E-06	9.10E-06
<b>Clusterin</b>	1.01	0.95	1.07	0.75	0.81
<b>CNTN1</b>	0.69	0.65	0.74	9.43E-30	5.73E-29
<b>COL18A1</b>	1.00	0.94	1.07	0.92	0.95
<b>CRP</b>	2.21	2.05	2.37	7.10E-104	2E-102
<b>CXCL16</b>	1.25	1.18	1.33	4.03E-13	1.56E-12
<b>Cystatin_C</b>	1.24	1.16	1.33	1.50E-09	4.55E-09
<b>DPP4</b>	0.99	0.93	1.05	0.70	0.79
<b>EFEMP1</b>	1.45	1.35	1.56	8.18E-24	4.09E-23
<b>FBN</b>	1.49	1.39	1.59	7.48E-33	4.89E-32
<b>FGF23</b>	1.03	0.98	1.10	0.26	0.35
<b>GAPDH</b>	0.96	0.90	1.01	0.13	0.19
<b>GDF15</b>	1.07	0.99	1.17	0.10	0.15
<b>GMP140</b>	1.11	1.04	1.18	0.001	0.002
<b>GP5</b>	0.94	0.88	0.99	0.03	0.05
<b>GRN</b>	1.04	0.98	1.10	0.20	0.28
<b>Hemopexin</b>	1.41	1.32	1.51	3.65E-25	1.94E-24
<b>IGF1</b>	0.75	0.70	0.80	1.79E-17	8.02E-17
<b>IGFBP3</b>	0.97	0.91	1.03	0.32	0.42
<b>IGFBP1</b>	0.37	0.34	0.40	3.30E-134	1.40E-132
<b>IGFBP2</b>	0.48	0.45	0.52	2.54E-81	4.33E-80
<b>KLKB1</b>	1.18	1.11	1.26	3.73E-07	9.60E-07

<b>LDLR</b>	1.06	1.00	1.13	0.05	0.08
<b>Leptin</b>	6.99	6.22	7.85	1.10E-237	9.50E-236
<b>Leptin R</b>	0.89	0.84	0.94	0.0001	0.0003
<b>LPA</b>	1.03	0.97	1.09	0.37	0.46
<b>MCAM</b>	0.95	0.89	1.01	0.09	0.14
<b>MCP1</b>	1.17	1.10	1.24	1.02E-06	2.56E-06
<b>MMP9</b>	1.20	1.13	1.28	4.15E-09	1.22E-08
<b>MMP8</b>	1.15	1.08	1.22	7.45E-06	1.76E-05
<b>MPO</b>	1.25	1.18	1.33	3.68E-13	1.49E-12
<b>Myoglobin</b>	1.13	1.06	1.21	0.0004	0.0009
<b>Notch1</b>	1.00	0.95	1.06	0.93	0.95
<b>NRCAM</b>	1.05	0.99	1.11	0.12	0.18
<b>OSTEO</b>	0.73	0.69	0.78	6.84E-23	3.23E-22
<b>PAI1</b>	2.06	1.91	2.21	2.58E-83	5.49E-82
<b>PMP2</b>	1.01	0.96	1.07	0.67	0.77
<b>PON1</b>	1.00	0.94	1.07	0.95	0.96
<b>PPBP</b>	1.06	1.00	1.12	0.06	0.10
<b>PZI</b>	1.06	1.00	1.12	0.06	0.10
<b>REG1A</b>	0.82	0.77	0.88	1.10E-09	3.46E-09
<b>Resistin</b>	1.22	1.15	1.30	8.22E-11	3.04E-10
<b>SAA1</b>	1.81	1.70	1.94	2.67E-68	3.78E-67
<b>SDF1</b>	0.90	0.85	0.95	0.0003	0.0007
<b>sGP130</b>	1.02	0.96	1.08	0.62	0.72
<b>sICAM1</b>	1.22	1.15	1.30	2.39E-10	8.11E-10
<b>SRAGE</b>	0.68	0.64	0.73	9.40E-34	6.66E-33
<b>Tetranectin</b>	1.03	0.97	1.09	0.31	0.40
<b>TIMP1</b>	1.25	1.16	1.34	6.71E-10	2.19E-09
<b>TSC22D3</b>	1.02	0.96	1.08	0.49	0.59
<b>UCMGP</b>	1.69	1.57	1.81	1.51E-46	1.43E-45
<b>VEGF</b>	1.09	1.03	1.16	0.003	0.006

OR: odds ratio per 1-SD increase in rank normalized biomarker

MV model adjusts for age, sex, smoking status, HDL, total cholesterol, hypertension treatment, log triglycerides, SBP, and diabetes.

Statistically significant = FDR  $p < 0.05$



**Table S4. Associations of single biomarkers with cardiometabolic traits**

Biomarker	BMI				WC				FG				HDL				TG			
	$\beta$	SE	raw_p	fdr_p	$\beta$	SE	raw_p	fdr_p	$\beta$	SE	raw_p	fdr_p	$\beta$	SE	raw_p	fdr_p	$\beta$	SE	raw_p	fdr_p
A1M	-0.034	0.011	0.003	0.006	-0.011	0.011	0.30	0.43	0.007	0.012	0.56	0.74	0.019	0.009	0.05	0.08	0.062	0.009	4.6E-11	1.5E-10
ADAM15	0.002	0.011	0.86	0.90	-0.003	0.010	0.77	0.86	-0.004	0.011	0.75	0.85	0.009	0.009	0.30	0.39	0.021	0.009	0.02	0.03
Adipsin	0.232	0.012	1.3E-87	1.20E-86	0.207	0.011	3.0E-80	2.6E-79	-0.084	0.013	2.8E-11	4E-10	-0.051	0.010	4.7E-07	1.7E-06	0.003	0.010	0.743	0.80
ADM	0.266	0.012	1.0E-101	1.2E-100	0.245	0.011	1.7E-98	2.4E-97	-0.026	0.014	0.06	0.12	0.069	0.011	1.4E-10	6.4E-10	0.106	0.011	6E-23	6.4E-22
AGP1	0.199	0.011	2.8E-72	2.41E-71	0.197	0.010	5.0E-81	4.7E-80	-0.018	0.012	0.13	0.24	-0.097	0.009	3.2E-25	3.4E-24	0.015	0.010	0.11	0.15
ANGPTL3	0.249	0.012	1.2E-97	1.30E-96	0.227	0.011	8.3E-93	8.8E-92	-0.012	0.013	0.37	0.57	-0.095	0.010	7.9E-21	5.6E-20	0.144	0.010	3.6E-46	6E-45
ApoA1	-0.022	0.014	0.10	0.16	-0.024	0.013	0.06	0.10	-0.007	0.014	0.60	0.77	0.427	0.008	0	0	0.186	0.011	1.5E-63	6.3E-62
ApoB	0.005	0.017	0.79	0.86	-0.002	0.015	0.91	0.92	0.026	0.017	0.13	0.24	-0.419	0.011	9E-269	4E-267	0.061	0.014	8.3E-06	2E-05
B2M	0.065	0.012	1.4E-07	3.05E-07	0.066	0.011	8.8E-09	2.1E-08	-0.022	0.013	0.09	0.17	-0.105	0.010	2.2E-25	2.7E-24	0.033	0.010	0.001	0.002
BCHE	0.106	0.011	6.1E-21	2.24E-20	0.107	0.011	4.4E-24	1.7E-23	0.039	0.012	0.001	0.003	-0.048	0.009	2.3E-07	8.9E-07	0.064	0.009	1.1E-11	4.3E-11
BIKUNIN	-0.066	0.011	6.2E-10	1.55E-09	-0.055	0.010	4.6E-08	1.0E-07	-0.020	0.011	0.07	0.14	-0.016	0.009	0.08	0.12	0.030	0.009	0.001	0.002
BNP	-0.103	0.013	3.9E-16	1.19E-15	-0.087	0.012	1.1E-13	3.3E-13	-0.046	0.013	0.0005	0.002	0.053	0.010	3.6E-07	1.3E-06	-0.045	0.011	1.6E-05	3.6E-05
C2	0.127	0.011	5.8E-30	2.49E-29	0.112	0.010	7.7E-27	3.3E-26	0.134	0.012	9.2E-31	7.8E-29	-0.013	0.009	0.17	0.26	0.080	0.009	7.8E-18	4.7E-17
CD14	-0.033	0.011	0.003	0.005	-0.014	0.010	0.18	0.28	0.087	0.011	1.8E-14	7.7E-13	-0.014	0.009	0.12	0.19	-0.030	0.009	0.001	0.002
CD163	0.075	0.011	4.3E-12	1.15E-11	0.065	0.010	9.1E-11	2.4E-10	0.030	0.011	0.007	0.02	-0.034	0.009	0.0001	0.0004	0.014	0.009	0.11	0.15
CD40L	0.047	0.011	1.6E-05	3.31E-05	0.061	0.010	1.6E-09	3.9E-09	0.008	0.011	0.48	0.65	0.013	0.009	0.14	0.22	0.061	0.009	1.3E-11	4.9E-11
CD56	-0.176	0.012	4.9E-51	2.95E-50	-0.157	0.011	1.0E-46	5.7E-46	-0.035	0.012	0.01	0.01	-0.031	0.010	0.002	0.004	-0.009	0.010	0.34	0.39
CD5L	0.049	0.011	9.3E-06	1.94E-05	0.047	0.010	5.2E-06	1.1E-05	0.047	0.011	4.1E-05	0.0002	-0.105	0.009	1.6E-31	2.8E-30	-0.001	0.009	0.94	0.95
CDH13	0.006	0.011	0.55	0.67	0.002	0.010	0.83	0.89	-0.009	0.011	0.43	0.61	0.005	0.009	0.56	0.68	0.030	0.009	0.001	0.001
Ceruloplasmin	0.067	0.012	2.3E-08	5.33E-08	0.056	0.011	7.3E-07	1.6E-06	-0.024	0.012	0.06	0.12	0.084	0.010	2.1E-17	1.3E-16	0.077	0.010	1E-14	5.1E-14
Clusterin	0.019	0.011	0.07	0.11	0.002	0.010	0.81	0.88	-0.024	0.011	0.03	0.06	0.023	0.009	0.01	0.02	0.051	0.009	7.6E-09	2E-08
CNTN1	-0.165	0.011	1.0E-49	5.88E-49	-0.166	0.010	3.6E-57	2.6E-56	0.058	0.012	9.2E-07	6.5E-06	-0.036	0.009	0.0001	0.0003	-0.066	0.009	2.3E-12	9.6E-12
COL18A1	-0.002	0.011	0.89	0.91	-0.002	0.010	0.88	0.90	-0.033	0.012	0.004	0.01	-0.019	0.009	0.038	0.07	0.052	0.009	2E-08	5.2E-08
CRP	0.319	0.011	2.0E-186	5.5E-185	0.285	0.010	3E-169	1E-167	0.003	0.012	0.82	0.91	0.001	0.010	0.94	0.94	0.101	0.010	1.4E-24	1.9E-23
CXCL16	0.109	0.011	1.5E-23	5.65E-23	0.096	0.010	8.8E-21	3.3E-20	-0.006	0.011	0.62	0.77	0.037	0.009	5.5E-05	0.0002	0.056	0.009	8.6E-10	2.5E-09
Cystatin_C	0.093	0.012	8.4E-14	2.37E-13	0.094	0.012	4.9E-16	1.5E-15	-0.046	0.013	0.0003	0.001	-0.070	0.010	1.1E-11	6.2E-11	0.020	0.010	0.05	0.08
DPP4	0.002	0.011	0.83	0.89	0.002	0.010	0.87	0.90	0.029	0.011	0.009	0.02	0.035	0.009	8.6E-05	0.0002	0.006	0.009	0.51	0.57
EFEMP1	0.167	0.013	4.3E-40	2.01E-39	0.151	0.012	1.3E-37	6.2E-37	0.028	0.013	0.03	0.07	-0.029	0.011	0.01	0.01	-0.053	0.011	5E-07	1.2E-06
FBN	0.182	0.011	8.0E-58	5.22E-57	0.167	0.011	9.3E-56	6.1E-55	0.016	0.012	0.18	0.32	-0.097	0.009	2.2E-24	1.9E-23	-0.027	0.010	0.06	0.01
FGF23	0.026	0.011	0.02	0.03	0.037	0.010	0.0002	0.0004	0.003	0.011	0.82	0.91	-0.026	0.009	0.003	0.008	0.020	0.009	0.021	0.04
GAPDH	-0.010	0.011	0.37	0.48	-0.004	0.010	0.71	0.81	-0.009	0.011	0.41	0.60	0.017	0.009	0.05	0.09	0.068	0.009	1.3E-14	6E-14
GDF15	0.020	0.015	0.18	0.27	0.043	0.014	0.003	0.005	0.120	0.016	3E-14	8.6E-13	0.028	0.013	0.03	0.05	0.087	0.013	6E-12	2.4E-11
GMP140	0.054	0.011	1.1E-06	2.40E-06	0.062	0.010	2.3E-09	5.5E-09	0.053	0.012	5.3E-06	3E-05	-0.016	0.009	0.08	0.13	0.055	0.009	2.4E-09	6.9E-09
GP5	-0.021	0.011	0.05	0.08	-0.012	0.010	0.22	0.33	0.027	0.011	0.01	0.03	0.019	0.009	0.03	0.06	0.024	0.009	0.007	0.01
GRN	0.000	0.011	0.97	0.97	-0.004	0.010	0.67	0.78	0.052	0.011	2.9E-06	1.7E-05	-0.031	0.009	0.0004	0.001	0.001	0.009	0.93	0.95
Hemopexin	0.162	0.011	4.1E-45	2.04E-44	0.150	0.011	2.5E-44	1.4E-43	0.032	0.012	0.01	0.02	-0.023	0.010	0.02	0.03	0.084	0.010	4.6E-18	3.2E-17
IGF1	-0.134	0.012	5.9E-30	2.49E-29	-0.118	0.011	5.9E-27	2.6E-26	-0.041	0.012	0.001	0.003	-0.040	0.010	5.8E-05	0.0002	-0.079	0.010	7.1E-16	3.8E-15
IGFBP3	-0.023	0.011	0.04	0.06	-0.007	0.010	0.46	0.59	-0.025	0.011	0.03	0.06	-0.010	0.009	0.24	0.342	0.015	0.009	0.10	0.13
IGFBP1	-0.401	0.011	5.3E-266	2.3E-264	-0.377	0.010	1E-268	5.4E-267	0.075	0.014	2.8E-08	2.9E-07	0.163	0.010	9.6E-54	2E-52	0.044	0.011	6E-05	0.0001
IGFBP2	-0.292	0.012	1.1E-130	1.8E-129	-0.268	0.011	2E-125	2.8E-124	-0.055	0.013	3.1E-05	0.0001	-0.030	0.011	0.004	0.01	-0.233	0.010	1E-119	1E-117
KLKB1	0.088	0.011	1.4E-14	4.19E-14	0.095	0.011	5.6E-19	1.9E-18	0.035	0.012	0.003	0.01	0.086	0.009	7.3E-20	4.8E-19	0.147	0.009	4.6E-56	1.3E-54
LDLR	0.012	0.011	0.25	0.35	0.006	0.010	0.53	0.66	0.002	0.011	0.86	0.92	0.003	0.009	0.73	0.78	0.033	0.009	0.0002	0.0004
Leptin	0.613	0.010	0	0	0.576	0.010	0	0	-0.044	0.016	0.01	0.02	0.016	0.013	0.22	0.32	0.097	0.013	5.3E-14	2.4E-13
Leptin R	-0.051	0.011	2.4E-06	5.15E-06	-0.047	0.010	3.3E-06	6.9E-06	0.006	0.011	0.57	0.74	0.018	0.009	0.05	0.09	-0.012	0.009	0.17	0.20
Lpa	0.004	0.011	0.70	0.81	0.002	0.010	0.86	0.90	-0.034	0.011	0.002	0.007	-0.052	0.009	3.1E-09	1.3E-08	-0.076	0.009	5.9E-18	3.8E-17
MCAM	-0.001	0.011	0.90	0.91	0.001	0.011	0.95	0.95	0.050	0.012	1.8E-05	8.6E-05	0.063	0.009	1.6E-11	8.5E-11	-0.063	0.009	2E-11	7.3E-11
MCP1	0.074	0.011	4.7E-11	1.22E-10	0.077	0.011	3.7E-13	1.0E-12	0.017	0.012	0.16	0.29	-0.004	0.009	0.64	0.73	0.063	0.009	2.2E-11	7.4E-11
MMP9	0.091	0.011	1.0E-16	3.26E-16	0.088	0.010	1.0E-17	3.2E-17	-0.004	0.011	0.74	0.85	-0.047	0.009	2.1E-07	8.5E-07	-0.016	0.009	0.07	0.11
MMP8	0.061	0.011	4.3E-08	9.92E-08	0.069	0.010	3.0E-11	7.9E-11	0.002	0.012	0.89	0.93	-0.025	0.009	0.01	0.01	0.027	0.009	0.004	0.008
MP0	0.114	0.011	2.0E-26	8.02E-26	0.103	0.010	1.8E-24	7.1E-24	0.062	0.011	4.6E-08	4.4E-07	-0.093	0.009	7E-26	1E-24	-0.049	0.009	5.6E-08	1.4E-07
Myoglobin	0.074	0.012	2.2E-09	5.38E-09	0.050	0.012	1.5E-05	3.0E-05	-0.080	0.013	4.9E-10	5.9E-09	-0.066	0.010	1.4E-10	6.4E-10	-0.026	0.010	0.01	0.02
Notch1	0.003	0.011	0.78	0.86	-0.018	0.010	0.08	0.12	0.057	0.011	2.7E-07	2.3E-06	-0.058	0.009	3E-11	1.5E-10	0.024	0.009	0.007	0.01
NRCAM	0.007	0.011	0.48	0.60	0.004	0.010	0.71	0.81	-0.009	0.011	0.43	0.61	0.008	0.009	0.33	0.42	0.024	0.009	0.007	0.01
Osteo	-0.152	0.011	3.1E-45	1.65E-44	-0.136	0.010	7.9E-42	4.0E-41	-0.058	0.011	3.3E-07	2.5E-06	-0.084	0.009	7.5E-21	5.6E-20	-0.081	0.009	4.3E-19	3.7E-18

PAII	0.293	0.011	7.2E-137	1.5E-135	0.284	0.011	4E-148	9-147	0.092	0.013	1.2E-12	2E-11	-0.038	0.010	0.0002	0.001	0.146	0.010	3.1E-46	6E-45
PMP2	-0.005	0.011	0.63	0.74	-0.005	0.010	0.59	0.71	-0.008	0.011	0.46	0.64	-0.001	0.009	0.91	0.94	0.019	0.009	0.03	0.05
PON1	0.018	0.011	0.14	0.16	0.017	0.011	0.12	0.18	-0.002	0.012	0.86	0.92	0.149	0.009	2E-61	5.6E-60	0.082	0.009	1.4E-18	1E-17
PPBP	0.013	0.011	0.22	0.32	0.010	0.010	0.32	0.45	0.004	0.011	0.72	0.85	0.004	0.009	0.66	0.75	0.017	0.009	0.06	0.08
PZI	0.029	0.011	0.01	0.01	0.023	0.010	0.02	0.04	0.012	0.011	0.30	0.48	0.014	0.009	0.12	0.19	0.083	0.009	5E-21	4.7E-20
REG1A	-0.093	0.011	6.5E-17	2.22E-16	-0.057	0.010	4.2E-08	9.7E-08	0.042	0.012	0.0003	0.001	0.011	0.009	0.26	0.35	-0.032	0.009	0.001	0.001
Resistin	0.090	0.011	8.6E-17	2.82E-16	0.091	0.010	4.0E-19	1.4E-18	-0.010	0.011	0.38	0.57	-0.092	0.009	7.3E-25	6.8E-24	-0.001	0.009	0.95	0.95
SAA1	0.245	0.011	2.4E-110	3.4E-109	0.212	0.010	1.5E-94	1.9E-93	0.001	0.012	0.95	0.97	-0.005	0.010	0.64	0.73	0.039	0.010	5.8E-05	0.0001
SDF1	-0.034	0.011	0.001	0.003	-0.019	0.010	0.06	0.09	-0.026	0.011	0.02	0.05	-0.017	0.009	0.05	0.09	-0.059	0.009	2.4E-11	7.9E-11
sGP130	0.018	0.011	0.11	0.17	0.029	0.010	0.01	0.01	0.083	0.011	4.5E-13	9.7E-12	0.008	0.009	0.38	0.47	0.009	0.009	0.33	0.39
sICAM_1	0.094	0.011	4.7E-17	1.65E-16	0.092	0.010	1.0E-18	3.3E-18	0.051	0.012	1.5E-05	7.5E-05	-0.040	0.009	1.3E-05	4.2E-05	0.058	0.009	7E-10	2.1E-09
SRAGE	-0.174	0.011	1.6E-59	1.15E-58	-0.151	0.010	2.8E-51	1.7E-50	-0.036	0.011	0.001	0.006	-0.035	0.009	9.6E-05	0.0002	-0.015	0.009	0.11	0.15
Tetranectin	0.028	0.011	0.01	0.02	0.022	0.010	0.03	0.05	-0.052	0.011	2.4E-06	1.6E-05	-0.044	0.009	5.1E-07	1.7E-06	-0.088	0.009	3.1E-23	3.8E-22
TIMP1	0.092	0.013	1.9E-13	5.23E-13	0.086	0.012	2.2E-13	6.3E-13	0.058	0.013	1.2E-05	6.2E-05	-0.049	0.010	2.6E-06	8.4E-06	0.022	0.010	0.03	0.05
TSC22D3	0.010	0.011	0.35	0.47	0.008	0.010	0.43	0.56	-0.012	0.011	0.29	0.47	0.001	0.009	0.93	0.94	0.014	0.009	0.12	0.15
UCMGP	0.212	0.012	5.5E-69	4.22E-68	0.204	0.011	1.4E-73	1.1E-72	-0.045	0.013	0.0004	0.002	0.012	0.010	0.26	0.35	0.088	0.010	1E-17	5.8E-17
VEGF	0.023	0.011	0.03	0.06	0.024	0.010	0.01	0.03	-0.012	0.011	0.28	0.47	0.005	0.009	0.61	0.72	0.052	0.009	5.1E-09	1.4E-08
	<b>SBP</b>				<b>DBP</b>				<b>HOMA-IR (excluding DM)</b>				<b>SAT</b>				<b>VAT</b>			
<b>Biomarker</b>	<b>β</b>	<b>SE</b>	<b>raw_p</b>	<b>fdr_p</b>	<b>β</b>	<b>SE</b>	<b>raw_p</b>	<b>fdr_p</b>	<b>β</b>	<b>SE</b>	<b>raw_p</b>	<b>fdr_p</b>	<b>β</b>	<b>SE</b>	<b>raw_p</b>	<b>fdr_p</b>	<b>β</b>	<b>SE</b>	<b>raw_p</b>	<b>fdr_p</b>
AIM	0.014	0.011	0.21	0.49249	-0.020	0.012	0.09	0.20	-0.023	0.009	0.009	0.03	0.027	0.010	0.006	0.04	-0.040	0.011	0.0003	0.002
ADAM15	0.009	0.010	0.38	0.61199	-0.001	0.011	0.95	0.97	0.019	0.008	0.02	0.04	0.009	0.009	0.34	0.62	-0.002	0.010	0.87	0.93
Adipsin	0.010	0.012	0.40	0.63646	-0.041	0.013	0.001	0.005	-0.021	0.009	0.02	0.06	0.041	0.011	0.0001	0.002	-0.005	0.012	0.66	0.89
ADM	0.017	0.012	0.17	0.45867	-0.069	0.013	3.4E-07	4.9E-06	-0.012	0.010	0.22	0.32	0.036	0.011	0.002	0.01	0.023	0.013	0.06	0.17
AGPI	0.053	0.011	1.1E-06	2.3E-05	0.035	0.012	0.003	0.01	0.022	0.009	0.01	0.03	0.038	0.010	0.0001	0.002	0.069	0.011	5E-10	6.2E-09
ANGPTL3	0.018	0.012	0.12	0.34858	0.061	0.013	1.7E-06	1.4E-05	0.095	0.010	3.6E-23	5.1E-22	0.018	0.011	0.10	0.33	0.051	0.012	3.2E-05	0.0002
ApoA1	0.030	0.013	0.02	0.09039	0.013	0.014	0.34	0.57	-0.014	0.010	0.18	0.28	0.006	0.012	0.61	0.84	0.012	0.013	0.34	0.59
ApoB	0.038	0.016	0.02	0.0808	0.042	0.017	0.01	0.05	0.011	0.013	0.39	0.48	-0.009	0.015	0.53	0.76	0.037	0.016	0.02	0.07
B2M	0.003	0.012	0.77	0.8975	-0.045	0.013	0.0004	0.002	-0.004	0.009	0.69	0.73	0.020	0.011	0.05	0.21	-0.023	0.012	0.05	0.15
BCHE	0.024	0.011	0.03	0.10212	0.057	0.012	1.1E-06	1.2E-05	0.058	0.009	2E-11	2.4E-10	0.000	0.010	0.99	0.99	0.053	0.011	1.5E-06	1.1E-05
BIKUNIN	-0.012	0.010	0.24	0.50434	-0.004	0.011	0.73	0.87	-0.006	0.008	0.48	0.55	-0.001	0.009	0.90	0.97	0.002	0.010	0.85	0.92
BNP	0.047	0.012	8.3E-05	0.0011	-0.099	0.013	3.9E-14	1.7E-12	-0.101	0.010	2.4E-25	4.1E-24	0.017	0.011	0.13	0.42	-0.043	0.012	0.0003	0.002
C2	0.031	0.011	0.003	0.02117	0.027	0.012	0.02	0.07	0.024	0.009	0.01	0.02	0.029	0.010	0.003	0.02	0.005	0.011	0.68	0.89
CD14	0.014	0.010	0.19	0.46433	-0.002	0.011	0.84	0.90	0.004	0.008	0.67	0.72	0.016	0.009	0.08	0.28	-0.004	0.010	0.68	0.89
CD163	0.029	0.010	0.005	0.02658	0.017	0.011	0.13	0.28	0.044	0.008	7.4E-08	6.3E-07	0.003	0.009	0.76	0.89	0.009	0.010	0.37	0.62
CD40L	-0.009	0.010	0.41	0.64083	0.002	0.011	0.87	0.91	0.016	0.008	0.05	0.11	0.004	0.009	0.67	0.86	-0.005	0.010	0.64	0.89
CD56	0.039	0.011	0.001	0.00458	0.022	0.012	0.08	0.20	0.023	0.009	0.01	0.03	-0.026	0.010	0.01	0.06	-0.035	0.011	0.002	0.01
CD5L	-0.002	0.011	0.87	0.94774	-0.006	0.011	0.62	0.81	0.021	0.008	0.01	0.03	0.001	0.009	0.88	0.97	0.019	0.010	0.06	0.17
CDH13	0.011	0.010	0.26	0.51748	0.003	0.011	0.77	0.87	0.015	0.008	0.06	0.12	0.007	0.009	0.48	0.74	0.000	0.010	0.96	0.96
Ceruloplasmin	0.000	0.011	0.97	0.97017	-0.028	0.012	0.02	0.07	-0.033	0.009	0.0002	0.001	0.046	0.011	1.7E-05	0.0004	-0.003	0.012	0.81	0.92
Clusterin	0.010	0.010	0.35	0.58757	0.014	0.011	0.21	0.38	-0.012	0.008	0.15	0.25	0.003	0.009	0.75	0.89	0.001	0.010	0.95	0.96
CNTN1	-0.012	0.011	0.27	0.51748	-0.008	0.012	0.51	0.73	-0.008	0.009	0.34	0.44	-0.032	0.010	0.001	0.01	-0.076	0.011	2.2E-12	4.7E-11
COL18A1	0.011	0.011	0.29	0.52052	-0.033	0.011	0.004	0.02	-0.017	0.008	0.05	0.10	-0.007	0.010	0.50	0.74	-0.003	0.011	0.77	0.92
CRP	0.038	0.011	0.001	0.00544	-0.005	0.012	0.66	0.83	0.025	0.009	0.006	0.02	0.055	0.011	2.4E-07	1E-05	0.070	0.012	3.1E-09	3.3E-08
CXCL16	-0.005	0.011	0.66	0.83532	-0.016	0.011	0.17	0.31	0.015	0.008	0.08	0.14	0.007	0.010	0.47	0.74	0.009	0.011	0.40	0.65
Cystatin_C	-0.003	0.012	0.82	0.92645	-0.051	0.013	7E-05	0.0004	0.029	0.010	0.002	0.001	0.030	0.011	0.01	0.04	-0.016	0.012	0.18	0.36
DPP4	0.011	0.010	0.28	0.51748	0.010	0.011	0.37	0.60	0.015	0.008	0.06	0.11	-0.003	0.009	0.70	0.86	0.003	0.010	0.77	0.92
EFEMP1	0.044	0.012	0.0003	0.00325	-0.030	0.013	0.02	0.07	0.012	0.010	0.21	0.31	0.033	0.011	0.002	0.02	-0.037	0.012	0.002	0.01
FBN	-0.007	0.011	0.52	0.7278	-0.038	0.012	0.002	0.008	0.037	0.009	2.7E-05	0.0001	0.050	0.010	5E-07	1.4E-05	0.011	0.011	0.30	0.55
FGF23	-0.002	0.010	0.88	0.94774	0.016	0.011	0.16	0.31	0.008	0.008	0.33	0.43	0.007	0.009	0.41	0.70	0.002	0.010	0.85	0.92
GAPDH	0.001	0.010	0.93	0.95419	0.012	0.011	0.29	0.51	0.010	0.008	0.20	0.31	-0.005	0.009	0.57	0.79	-0.029	0.010	0.005	0.02
GDF15	-0.001	0.015	0.96	0.97017	-0.090	0.016	1.3E-08	2.7E-07	0.073	0.012	5.9E-10	6.3E-09	-0.006	0.014	0.66	0.86	0.020	0.016	0.20	0.38
GMP140	0.028	0.011	0.01	0.03795	0.025	0.012	0.03	0.08	0.042	0.008	5.7E-07	3.7E-06	0.008	0.009	0.37	0.68	0.005	0.011	0.62	0.89
GP5	0.002	0.010	0.81	0.92645	0.007	0.011	0.53	0.74	0.008	0.008	0.31	0.42	0.002	0.009	0.79	0.90	-0.014	0.010	0.17	0.36
GRN	0.017	0.010	0.10	0.31365	-0.010	0.011	0.38	0.60	-0.005	0.008	0.54	0.61	-0.007	0.009	0.47	0.74	-0.005	0.010	0.65	0.89
Hemopexin	0.044	0.011	9.1E-05	0.0011	0.021	0.012	0.08	0.20	0.027	0.009	0.002	0.01	0.036	0.010	0.0004	0.004	0.055	0.011	7.4E-07	5.7E-06
IGF1	-0.007	0.011	0.56	0.75045	-0.018	0.012	0.16	0.31	-0.003	0.009	0.71	0.73	-0.010	0.011	0.33	0.62	-0.031	0.012	0.008	0.03
IGFBP3	0.010	0.010	0.34	0.58757	0.008	0.011	0.46	0.67	-0.002	0.008	0.81	0.82	-0.001	0.010	0.93	0.98	-0.002	0.011	0.89	0.93
IGFBP1	-0.028	0.012	0.02	0.09624	-0.116	0.013	1.2E-17	9.9E-16	-0.244	0.010	1E-130	9E-129	-0.016	0.012	0.17	0.45	-0.130	0.013	7.6E-24	3.2E-22
IGFBP2	-0.040	0.012	0.001	0.00625	-0.083	0.013	3.1E-10	8.7E-09	-0.159	0.010	6.7E-60	2.9E-58	-0.012	0.0						

KLKB1	0.023	0.011	0.04	0.13158	0.042	0.012	0.0004	0.002	0.005	0.009	0.53	0.60	0.020	0.010	0.04	0.15	0.022	0.011	0.04	0.19
LDLR	0.012	0.010	0.23	0.50434	0.000	0.011	0.99	0.99	0.013	0.008	0.11	0.19	0.009	0.009	0.33	0.62	0.006	0.010	0.58	0.85
Leptin	0.002	0.015	0.91	0.95419	0.014	0.016	0.40	0.62	0.147	0.012	8.4E-36	1.8E-34	0.176	0.013	1.8E-40	1.5E-38	0.092	0.015	5.1E-10	6.2E-09
Leptin R	-0.001	0.010	0.92	0.95419	0.005	0.011	0.66	0.83	-0.041	0.008	6.4E-07	3.9E-06	-0.009	0.009	0.32	0.62	-0.020	0.010	0.06	0.16
Lpa	-0.003	0.010	0.76	0.8975	-0.003	0.011	0.81	0.89	-0.042	0.008	3.4E-07	2.6E-06	0.012	0.009	0.17	0.45	-0.003	0.010	0.78	0.92
MCAM	0.067	0.011	4.8E-10	2E-08	0.055	0.012	2E-06	1.5E-05	-0.024	0.009	0.006	0.02	0.004	0.010	0.71	0.86	-0.035	0.011	0.001	0.007
MCP1	-0.002	0.011	0.88	0.94774	-0.023	0.012	0.05	0.12	0.016	0.009	0.07	0.12	0.003	0.010	0.79	0.90	0.019	0.011	0.07	0.17
MMP9	0.007	0.011	0.49	0.69237	-0.003	0.011	0.77	0.87	0.030	0.008	0.0003	0.001	0.011	0.010	0.26	0.59	0.003	0.011	0.75	0.92
MMP8	0.015	0.011	0.16	0.45867	-0.005	0.012	0.68	0.84	0.031	0.008	0.0003	0.001	0.021	0.010	0.03	0.13	0.025	0.011	0.02	0.06
MPO	0.013	0.010	0.20	0.49105	-0.007	0.011	0.52	0.74	0.024	0.008	0.004	0.01	0.001	0.009	0.90	0.97	-0.016	0.011	0.13	0.30
Myoglobin	-0.013	0.012	0.26	0.51748	-0.021	0.013	0.11	0.23	-0.046	0.010	1.4E-06	8.2E-06	-0.038	0.011	0.001	0.01	-0.045	0.012	0.0002	0.001
Notch1	-0.004	0.010	0.67	0.83532	-0.032	0.011	0.004	0.02	0.018	0.008	0.02	0.06	-0.025	0.009	0.01	0.04	-0.028	0.010	0.005	0.02
NRCAM	0.004	0.010	0.67	0.83532	-0.004	0.011	0.69	0.84	0.016	0.008	0.05	0.11	0.009	0.009	0.30	0.62	-0.003	0.010	0.80	0.92
Osteo	0.003	0.010	0.75	0.8975	-0.054	0.011	1.6E-06	1.4E-05	-0.016	0.008	0.06	0.11	-0.007	0.010	0.47	0.74	-0.054	0.011	4.2E-07	3.5E-06
PAI1	0.063	0.012	1.2E-07	3.4E-06	0.064	0.013	8.6E-07	1E-05	0.134	0.009	3.2E-45	9E-44	0.029	0.011	0.007	0.04	0.109	0.012	7.8E-20	2.2E-18
PMP2	0.011	0.010	0.28	0.51748	0.005	0.011	0.65	0.83	0.019	0.008	0.02	0.05	0.011	0.009	0.22	0.51	0.001	0.010	0.94	0.96
PON1	-0.001	0.011	0.93	0.95419	0.018	0.012	0.12	0.26	-0.007	0.009	0.41	0.49	0.000	0.010	0.97	0.99	0.003	0.011	0.79	0.92
PPBP	0.010	0.010	0.31	0.54531	0.010	0.011	0.37	0.60	0.008	0.008	0.34	0.44	0.013	0.009	0.15	0.45	0.007	0.010	0.48	0.72
PZI	-0.018	0.010	0.07	0.23046	-0.015	0.011	0.17	0.31	0.016	0.008	0.05	0.11	0.007	0.009	0.45	0.74	0.018	0.010	0.08	0.18
REG1A	-0.032	0.011	0.003	0.0173	-0.059	0.012	3.5E-07	4.9E-06	-0.010	0.009	0.24	0.34	0.007	0.010	0.49	0.74	-0.016	0.011	0.14	0.30
Resistin	-0.009	0.010	0.37	0.61199	-0.021	0.011	0.06	0.15	0.010	0.008	0.21	0.31	0.017	0.009	0.07	0.25	-0.025	0.011	0.02	0.06
SAA1	0.002	0.011	0.85	0.94774	-0.033	0.012	0.005	0.02	0.042	0.009	2E-06	1E-05	0.025	0.010	0.01	0.06	0.025	0.011	0.03	0.08
SDF1	-0.003	0.010	0.74	0.8975	0.006	0.011	0.57	0.78	0.016	0.008	0.05	0.11	0.013	0.009	0.16	0.45	-0.023	0.010	0.02	0.07
sGP130	0.051	0.011	1.5E-06	2.5E-05	0.028	0.011	0.02	0.05	0.040	0.008	3.2E-06	1.6E-05	-0.004	0.010	0.65	0.86	-0.008	0.011	0.43	0.66
sICAM_1	0.020	0.011	0.06	0.20996	0.003	0.012	0.78	0.87	0.051	0.009	3E-09	2.8E-08	0.001	0.010	0.92	0.97	0.010	0.011	0.38	0.62
SRAGE	-0.036	0.010	0.001	0.00458	-0.028	0.011	0.01	0.05	-0.038	0.008	6.5E-06	3.1E-05	0.004	0.009	0.68	0.86	-0.069	0.010	3.1E-11	5.2E-10
Tetranectin	0.037	0.010	0.0002	0.00311	0.046	0.011	2.8E-05	0.0002	-0.006	0.008	0.45	0.53	-0.006	0.009	0.50	0.74	-0.023	0.010	0.02	0.07
TIMP1	0.019	0.012	0.11	0.33471	-0.028	0.013	0.03	0.09	0.049	0.010	5.5E-07	3.7E-06	-0.006	0.011	0.56	0.79	0.002	0.012	0.84	0.92
TSC22D3	-0.018	0.010	0.07	0.23046	-0.016	0.011	0.14	0.28	-0.002	0.008	0.82	0.82	-0.002	0.009	0.78	0.90	-0.009	0.010	0.38	0.63
UCMGP	0.086	0.012	3.1E-13	2.7E-11	0.052	0.013	5.6E-05	0.0004	0.038	0.010	8.5E-05	0.0004	0.011	0.011	0.31	0.62	0.062	0.012	2.1E-07	2E-06
VEGF	-0.011	0.010	0.28	0.51748	-0.009	0.011	0.41	0.63	0.006	0.008	0.45	0.53	0.000	0.009	0.98	0.99	-0.014	0.010	0.17	0.36

	Pericardial Fat				Liver Phantom Ratio				Intrathoracic Fat			
Biomarker	β	SE	raw_p	fdr_p	β	SE	raw_p	fdr_p	β	SE	raw_p	fdr_p
A1M	-0.005	0.015	0.73	0.82	-0.077	0.019	3.8E-05	0.0003	-0.014	0.013	0.29	0.56
ADAM15	-0.015	0.014	0.28	0.60	0.028	0.017	0.10	0.22	-0.017	0.012	0.17	0.44
Adipsin	0.015	0.017	0.36	0.64	-0.033	0.020	0.10	0.22	0.030	0.014	0.03	0.13
ADM	0.031	0.017	0.07	0.25	-0.013	0.021	0.53	0.64	0.036	0.015	0.02	0.08
AGP1	0.050	0.015	0.001	0.01	-0.025	0.019	0.18	0.32	0.059	0.013	7.9E-06	9.6E-05
ANGPTL3	0.013	0.017	0.45	0.69	0.065	0.021	0.002	0.008	0.021	0.015	0.14	0.39
ApoA1	0.000	0.018	0.98	0.99	0.000	0.022	0.99	0.99	0.008	0.015	0.58	0.71
ApoB	0.045	0.023	0.05	0.19	0.046	0.028	0.10	0.22	0.044	0.019	0.02	0.10
B2M	-0.010	0.016	0.52	0.72	-0.014	0.020	0.47	0.60	0.012	0.014	0.38	0.56
BCHE	0.009	0.015	0.57	0.74	0.062	0.019	0.001	0.004	0.025	0.013	0.05	0.16
BIKUNIN	0.019	0.014	0.20	0.48	-0.055	0.018	0.002	0.01	0.017	0.012	0.17	0.44
BNP	0.011	0.017	0.52	0.72	-0.120	0.021	5.5E-09	9.3E-08	0.001	0.014	0.95	0.99
C2	0.013	0.015	0.38	0.65	0.022	0.019	0.23	0.38	0.000	0.013	0.99	0.99
CD14	0.035	0.014	0.02	0.08	-0.042	0.018	0.02	0.05	0.006	0.012	0.64	0.77
CD163	-0.024	0.014	0.10	0.32	0.054	0.017	0.002	0.01	-0.026	0.012	0.03	0.12
CD40L	0.019	0.014	0.19	0.48	0.007	0.017	0.68	0.74	0.017	0.012	0.17	0.44
CD56	-0.093	0.016	6.7E-09	5.7E-07	-0.035	0.020	0.08	0.19	-0.042	0.014	0.002	0.01
CD5L	0.038	0.015	0.01	0.05	0.044	0.018	0.01	0.04	0.033	0.012	0.001	0.04
CDH13	-0.005	0.014	0.72	0.82	0.021	0.017	0.22	0.37	-0.003	0.012	0.83	0.90
Ceruloplasmin	-0.008	0.017	0.65	0.76	-0.019	0.020	0.34	0.5	0.018	0.014	0.19	0.47
Clusterin	-0.003	0.014	0.84	0.90	0.033	0.017	0.05	0.13	-0.009	0.012	0.44	0.61
CNTN1	-0.077	0.015	3.3E-07	9.5E-06	-0.043	0.019	0.02	0.06	-0.087	0.013	1.1E-11	9.7E-10
COL18A1	0.007	0.015	0.63	0.76	-0.008	0.018	0.68	0.74	0.005	0.013	0.69	0.79
CRP	0.030	0.016	0.07	0.23	0.124	0.020	3.2E-10	6.9E-09	0.058	0.014	3E-05	0.0003
CXCL16	-0.008	0.015	0.59	0.74	0.012	0.018	0.50	0.63	0.000	0.013	0.99	0.99
Cystatin_C	0.012	0.017	0.48	0.71	0.021	0.020	0.31	0.48	0.013	0.014	0.36	0.56

DPP4	-0.021	0.014	0.13	0.39	0.038	0.017	0.03	0.07	-0.020	0.012	0.09	0.27
EFEMP1	-0.010	0.017	0.57	0.74	-0.027	0.021	0.19	0.32	-0.010	0.014	0.49	0.62
FBN	0.018	0.016	0.26	0.57	0.031	0.019	0.10	0.22	0.027	0.013	0.04	0.14
FGF23	0.010	0.014	0.49	0.71	-0.011	0.017	0.52	0.63	0.010	0.012	0.40	0.57
GAPDH	-0.031	0.014	0.03	0.13	0.018	0.017	0.30	0.46	-0.014	0.012	0.26	0.56
GDF15	0.049	0.022	0.02	0.11	0.176	0.026	1.9E-11	5.4E-10	0.048	0.018	0.01	0.05
GMP140	-0.010	0.015	0.51	0.72	0.051	0.018	0.004	0.02	0.021	0.013	0.10	0.29
GP5	0.002	0.014	0.87	0.92	-0.006	0.017	0.74	0.78	0.010	0.012	0.42	0.59
GRN	0.014	0.014	0.31	0.61	0.041	0.017	0.02	0.05	0.011	0.012	0.38	0.56
Hemopexin	0.022	0.016	0.15	0.41	0.028	0.019	0.14	0.27	0.055	0.013	3.5E-05	0.0003
IGF1	-0.087	0.016	1.2E-07	5.2E-06	-0.072	0.020	0.0003	0.002	-0.031	0.014	0.03	0.12
IGFBP3	-0.015	0.015	0.31	0.61	0.016	0.018	0.39	0.53	0.009	0.013	0.50	0.63
IGFBP1	-0.070	0.018	0.0001	0.001	-0.105	0.022	1.8E-06	1.7E-05	-0.102	0.015	3.1E-11	1.3E-09
IGFBP2	-0.046	0.017	0.001	0.04946	-0.218	0.021	8.8E-26	7.5E-24	-0.075	0.015	3.4E-07	5.9E-06
KLKB1	0.018	0.015	0.23	0.55	0.052	0.018	0.004	0.02	0.012	0.013	0.37	0.56
LDLR	-0.013	0.014	0.36	0.64	0.024	0.017	0.17	0.31	-0.005	0.012	0.66	0.77
Leptin	0.080	0.021	0.0001	0.00	0.023	0.025	0.35	0.51	0.062	0.018	0.001	0.003
Leptin R	-0.020	0.014	0.16	0.41	-0.052	0.017	0.002	0.01	-0.015	0.012	0.23	0.53
Lpa	0.015	0.014	0.28	0.60	-0.060	0.017	0.001	0.003	0.012	0.012	0.34	0.56
MCAM	-0.035	0.015	0.02	0.10	-0.070	0.018	0.0002	0.001	-0.028	0.013	0.03	0.13
MCP1	0.014	0.015	0.34	0.63	0.021	0.018	0.25	0.40	0.013	0.013	0.30	0.56
MMP9	0.011	0.015	0.45	0.69	0.025	0.018	0.16	0.30	0.009	0.013	0.47	0.62
MMP8	0.050	0.015	0.001	0.01	0.029	0.018	0.11	0.24	0.039	0.013	0.002	0.01
MPO	0.004	0.015	0.77	0.83	0.017	0.018	0.34	0.50	0.001	0.012	0.96	0.99
Myoglobin	-0.061	0.017	0.0003	0.003	-0.025	0.021	0.23	0.38	-0.029	0.014	0.04	0.14
Notch1	-0.069	0.014	9.4E-07	2E-05	0.004	0.017	0.83	0.87	-0.041	0.012	0.001	0.004
NRCAM	-0.011	0.014	0.44	0.69	0.016	0.017	0.36	0.51	-0.012	0.012	0.30	0.56
Osteo	-0.041	0.015	0.01	0.04	-0.072	0.018	7.3E-05	0.001	-0.050	0.013	8.1E-05	0.001
PAI1	0.060	0.017	0.0003	0.003	0.163	0.020	7.4E-16	3.1E-14	0.078	0.014	4.7E-08	1E-06
PMP2	-0.007	0.014	0.62	0.76	0.023	0.017	0.18	0.32	-0.009	0.012	0.47	0.62
PON1	-0.015	0.015	0.33	0.63	0.000	0.018	0.99	0.99	-0.003	0.013	0.79	0.87
PPBP	-0.005	0.014	0.70	0.80	0.014	0.017	0.40	0.54	0.015	0.012	0.21	0.49
PZI	0.000	0.014	0.99	0.99	0.011	0.017	0.51	0.63	0.024	0.012	0.04	0.15
REG1A	0.011	0.015	0.49	0.71	-0.046	0.019	0.01	0.04	-0.015	0.013	0.27	0.56
Resistin	-0.001	0.015	0.94	0.96	-0.045	0.018	0.01	0.04	0.011	0.013	0.8	0.56
SAA1	0.012	0.016	0.45	0.69	0.094	0.019	6.5E-07	6.9E-06	0.034	0.013	0.01	0.05
SDF1	0.008	0.014	0.58	0.74	-0.025	0.017	0.13	0.27	0.000	0.012	0.98	0.99
sGP130	-0.032	0.015	0.03	0.14	0.049	0.018	0.01	0.02	-0.013	0.013	0.32	0.56
sICAM_1	0.005	0.015	0.75	0.82	0.097	0.018	1.2E-07	1.7E-06	0.012	0.013	0.34	0.56
SRAGE	-0.058	0.015	7.1E-05	0.001	-0.070	0.018	1E-04	0.001	-0.069	0.012	3.4E-08	9.5E-07
Tetranectin	-0.027	0.014	0.06	0.22	-0.037	0.017	0.04	0.09	-0.011	0.012	0.35	0.56
TIMP1	-0.002	0.017	0.88	0.92	0.103	0.020	4.1E-07	5E-06	0.014	0.014	0.33	0.56
TSC22D3	0.012	0.014	0.41	0.69	-0.014	0.017	0.43	0.56	0.003	0.012	0.80	0.87
UCMGP	0.075	0.017	7E-06	0.0001	0.043	0.020	0.04	0.10	0.070	0.014	7.3E-07	1E-05
VEGF	-0.030	0.014	0.04	0.16	0.002	0.018	0.91	0.93	-0.014	0.012	0.27	0.56

**Table S5. Associations of single biomarkers with cardiometabolic traits (restricted to patients with CT measures only)**

Biomarker	BMI				WC				FG				HDL			
	$\beta$	SE	raw_p	fdr_p	$\beta$	SE	raw_p	fdr_p	$\beta$	SE	raw_p	fdr_p	$\beta$	SE	raw_p	fdr_p
A1M	-0.048	0.017	0.006	0.01	-0.025	0.017	0.13	0.21	-0.017	0.018	0.36	0.53	0.020	0.014	0.15	0.27
ADAM15	0.028	0.016	0.08	0.13	0.024	0.015	0.12	0.19	0.012	0.017	0.48	0.65	0.008	0.013	0.53	0.71
Adipsin	0.242	0.018	2E-41	1E-40	0.220	0.017	1E-37	1E-36	-0.078	0.019	6E-05	0.001	-0.055	0.015	0.0003	0.001
ADM	-0.002	0.026	0.93	0.95	0.000	0.024	0.99	0.99	0.064	0.027	0.02	0.06	-0.453	0.017	4E-143	2E-141
AGP1	0.082	0.018	9E-06	2E-05	0.076	0.018	1E-05	4E-05	-0.012	0.019	0.52	0.68	-0.107	0.015	4E-13	5E-12
ANGPTL3	0.097	0.017	2E-08	5E-08	0.098	0.016	2E-09	8E-09	0.054	0.018	0.003	0.01	-0.056	0.014	5E-05	0.0002
ApoA1	-0.077	0.016	2E-06	6E-06	-0.068	0.015	1E-05	3E-05	-0.017	0.017	0.32	0.48	-0.023	0.013	0.08	0.16
ApoB	0.141	0.017	6E-17	3E-16	0.131	0.016	4E-16	2E-15	0.146	0.018	1E-16	1E-14	-0.003	0.014	0.83	0.91
B2M	-0.027	0.016	0.10	0.16	-0.012	0.016	0.43	0.52	0.081	0.017	2E-06	3E-05	-0.012	0.013	0.35	0.53
BCHE	0.083	0.016	2E-07	7E-07	0.069	0.015	8E-06	2E-05	0.029	0.017	0.08	0.18	-0.055	0.013	3E-05	0.0001
BIKUNIN	0.039	0.017	0.02	0.04	0.039	0.016	0.01	0.03	0.039	0.017	0.02	0.07	-0.086	0.013	8E-11	6E-10
BNP	0.023	0.016	0.16	0.24	0.022	0.015	0.15	0.23	-0.001	0.017	0.97	0.98	0.008	0.013	0.55	0.71
C2	0.123	0.019	6E-11	2E-10	0.106	0.018	4E-09	1E-08	-0.032	0.020	0.10	0.21	-0.077	0.015	5E-07	3E-06
CD14	0.027	0.016	0.09	0.15	0.020	0.015	0.19	0.27	0.035	0.016	0.04	0.09	0.031	0.013	0.02	0.04
CD163	0.162	0.019	4E-18	2E-17	0.146	0.018	3E-16	1E-15	0.001	0.020	0.96	0.98	-0.031	0.015	0.04	0.09
CD40L	0.163	0.017	3E-21	2E-20	0.156	0.016	2E-21	1E-20	0.059	0.018	0.001	0.01	-0.094	0.014	2E-11	2E-10
CD56	0.055	0.024	0.02	0.05	0.065	0.023	0.005	0.01	0.145	0.025	8E-09	2E-07	0.018	0.020	0.35	0.53
CD5L	0.064	0.017	0.0001	0.0002	0.072	0.016	5E-06	1E-05	0.075	0.017	1E-05	0.0001	-0.025	0.013	0.06	0.13
CDH13	-0.323	0.018	5E-71	1E-69	-0.303	0.017	2E-68	5E-67	-0.076	0.020	0.0002	0.001	-0.003	0.016	0.84	0.91
Ceruloplasmin	-0.037	0.017	0.03	0.05	-0.019	0.016	0.24	0.32	-0.037	0.018	0.04	0.09	-0.024	0.014	0.08	0.16
Clusterin	0.092	0.017	6E-08	2E-07	0.095	0.016	3E-09	1E-08	0.049	0.018	0.01	0.02	0.074	0.014	5E-08	4E-07
CNTN1	0.028	0.016	0.08	0.14	0.022	0.015	0.15	0.23	0.017	0.017	0.31	0.48	0.003	0.013	0.84	0.91
COL18A1	-0.018	0.017	0.31	0.38	-0.022	0.016	0.19	0.27	0.041	0.018	0.02	0.07	0.054	0.014	0.0001	0.0004
CRP	0.094	0.017	2E-08	5E-08	0.096	0.016	2E-09	7E-09	-0.006	0.018	0.73	0.82	-0.007	0.014	0.59	0.73
CXCL16	0.080	0.017	2E-06	4E-06	0.074	0.016	3E-06	9E-06	0.010	0.017	0.56	0.70	-0.042	0.013	0.002	0.01
Cystatin_C	0.102	0.016	6E-10	2E-09	0.092	0.016	6E-09	2E-08	0.089	0.017	2E-07	4E-06	-0.084	0.013	2E-10	2E-09
DPP4	0.021	0.016	0.19	0.27	0.019	0.015	0.22	0.30	0.005	0.017	0.77	0.86	0.008	0.013	0.56	0.72
EFEMP1	0.036	0.016	0.02	0.05	-0.003	0.015	0.84	0.91	0.040	0.016	0.02	0.06	-0.054	0.013	3E-05	0.0001
FBN	0.018	0.016	0.25	0.33	0.014	0.015	0.36	0.46	-0.007	0.017	0.67	0.78	-0.001	0.013	0.91	0.94
FGF23	0.007	0.016	0.66	0.72	0.013	0.015	0.38	0.47	0.030	0.016	0.06	0.14	-0.001	0.013	0.94	0.95
GAPDH	0.087	0.019	4E-06	1E-05	0.077	0.018	2E-05	4E-05	0.081	0.020	4E-05	0.0003	-0.056	0.015	0.0002	0.001
GDF15	0.024	0.016	0.14	0.21	0.026	0.015	0.09	0.16	0.003	0.017	0.88	0.91	-0.008	0.013	0.55	0.71
GMP140	0.198	0.018	5E-27	4E-26	0.189	0.017	4E-27	3E-26	-0.054	0.020	0.01	0.02	0.012	0.015	0.42	0.60
GP5	0.276	0.019	2E-48	2E-47	0.257	0.018	3E-46	4E-45	-0.009	0.021	0.67	0.78	0.052	0.016	0.001	0.003
GRN	0.183	0.017	1E-26	1E-25	0.189	0.016	3E-31	3E-30	-0.018	0.018	0.32	0.48	-0.102	0.014	3E-13	3E-12
Hemopexin	0.250	0.018	9E-42	9E-41	0.223	0.017	2E-36	2E-35	0.025	0.020	0.21	0.37	-0.113	0.015	2E-13	3E-12
IGF1	-0.025	0.020	0.22	0.30	-0.013	0.019	0.50	0.58	-0.014	0.021	0.52	0.68	0.411	0.012	9E-219	8E-217
IGFBP3	-0.086	0.019	5E-06	1E-05	-0.077	0.018	2E-05	5E-05	-0.093	0.020	2E-06	3E-05	0.062	0.015	5E-05	0.0002
IGFBP1	0.030	0.016	0.07	0.11	0.043	0.015	0.005	0.01	0.025	0.017	0.14	0.26	0.017	0.013	0.21	0.36
IGFBP2	-0.153	0.018	7E-18	4E-17	-0.160	0.017	5E-21	3E-20	-0.039	0.019	0.04	0.10	-0.020	0.015	0.16	0.29
KLKB1	0.109	0.019	6E-09	2E-08	0.095	0.018	8E-08	3E-07	-0.033	0.020	0.09	0.19	0.068	0.015	6E-06	3E-05
LDLR	0.012	0.016	0.44	0.50	0.000	0.015	0.99	0.99	-0.026	0.016	0.11	0.21	0.022	0.013	0.08	0.16
Leptin	-0.134	0.017	2E-15	8E-15	-0.150	0.016	8E-21	4E-20	0.040	0.018	0.02	0.07	-0.038	0.014	0.01	0.01
Leptin R	0.017	0.017	0.30	0.38	0.003	0.016	0.86	0.91	-0.012	0.018	0.48	0.65	-0.016	0.014	0.23	0.39
Lpa	0.353	0.016	3E-98	8E-97	0.325	0.016	3E-91	8E-90	0.003	0.019	0.88	0.91	-0.006	0.015	0.71	0.82

MCAM	0.086	0.017	2E-07	6E-07	0.081	0.016	3E-07	8E-07	0.020	0.017	0.25	0.41	0.024	0.013	0.07	0.15					
MCP1	0.020	0.016	0.20	0.28	0.036	0.015	0.02	0.03	-0.010	0.016	0.54	0.69	-0.018	0.013	0.16	0.29					
MMP9	-0.014	0.016	0.38	0.44	-0.006	0.015	0.71	0.79	0.009	0.017	0.58	0.73	0.010	0.013	0.43	0.61					
MMP8	-0.017	0.016	0.27	0.34	-0.009	0.015	0.55	0.62	0.036	0.016	0.03	0.07	0.007	0.013	0.57	0.72					
MPO	-0.002	0.016	0.88	0.91	-0.013	0.015	0.40	0.49	0.045	0.017	0.01	0.02	-0.034	0.013	0.01	0.02					
Myoglobin	0.167	0.017	2E-22	1E-21	0.163	0.016	2E-23	1E-22	0.034	0.018	0.06	0.14	-0.042	0.014	0.003	0.01					
Notch1	-0.150	0.018	3E-16	1E-15	-0.136	0.017	6E-15	3E-14	-0.042	0.019	0.03	0.08	-0.065	0.015	1E-05	7E-05					
NRCAM	-0.403	0.018	2E-107	7E-106	-0.386	0.017	1E-108	4E-107	0.041	0.021	0.05	0.12	0.179	0.016	8E-29	2E-27					
Osteo	0.620	0.016	7E-277	6E-275	0.591	0.015	2E-277	1E-275	-0.030	0.024	0.22	0.37	0.008	0.019	0.66	0.78					
PAI1	-0.045	0.016	0.006	0.01	-0.041	0.015	0.01	0.02	0.018	0.017	0.30	0.48	0.031	0.013	0.02	0.04					
PMP2	0.004	0.016	0.81	0.85	0.009	0.015	0.55	0.62	-0.051	0.017	0.002	0.01	-0.061	0.013	2E-06	1E-05					
PON1	0.074	0.017	1E-05	3E-05	0.077	0.016	2E-06	6E-06	0.028	0.018	0.11	0.21	0.004	0.014	0.79	0.90					
PPBP	0.090	0.019	2E-06	6E-06	0.053	0.018	0.004	0.01	-0.088	0.020	1E-05	0.0001	-0.081	0.015	1E-07	8E-07					
PZI	-0.173	0.016	1E-25	9E-25	-0.163	0.016	4E-25	3E-24	-0.061	0.018	0.001	0.003	-0.103	0.013	2E-14	4E-13					
REG1A	0.280	0.018	3E-55	6E-54	0.285	0.017	2E-63	4E-62	0.123	0.019	3E-10	1E-08	-0.043	0.015	0.01	0.01					
Resistin	0.023	0.017	0.18	0.26	0.027	0.016	0.09	0.16	0.005	0.018	0.79	0.87	0.146	0.013	3E-27	6E-26					
SAA1	0.037	0.016	0.02	0.04	0.032	0.015	0.04	0.07	0.002	0.017	0.88	0.91	0.011	0.013	0.38	0.56					
SDF1	-0.077	0.017	1E-05	2E-05	-0.049	0.017	0.003	0.01	0.062	0.018	0.001	0.003	0.013	0.014	0.36	0.53					
sGP130	0.100	0.016	2E-09	5E-09	0.096	0.016	9E-10	3E-09	-0.014	0.017	0.43	0.60	-0.088	0.013	3E-11	3E-10					
sICAM_1	0.036	0.017	0.03	0.06	0.035	0.016	0.03	0.05	0.105	0.017	1E-09	4E-08	0.013	0.014	0.34	0.53					
SRAGE	0.127	0.017	6E-14	2E-13	0.114	0.016	1E-12	6E-12	0.070	0.018	8E-05	0.001	-0.042	0.014	0.002	0.01					
Tetranectin	0.245	0.016	3E-48	3E-47	0.215	0.016	3E-41	4E-40	0.024	0.018	0.19	0.34	0.000	0.014	0.98	0.98					
TIMP1	-0.033	0.016	0.04	0.07	-0.020	0.015	0.18	0.27	-0.038	0.016	0.02	0.07	-0.001	0.013	0.91	0.94					
TSC22D3	-0.171	0.016	3E-26	2E-25	-0.147	0.015	2E-21	1E-20	-0.047	0.017	0.01	0.02	-0.053	0.013	8E-05	0.0003					
UCMGP	0.000	0.016	0.98	0.98	-0.003	0.015	0.87	0.91	-0.048	0.017	0.004	0.02	-0.054	0.013	3E-05	0.0001					
VEGF	0.032	0.016	0.05	0.08	0.030	0.015	0.06	0.10	-0.007	0.017	0.66	0.78	0.015	0.013	0.26	0.42					
			<b>TG</b>					<b>SBP</b>					<b>DBP</b>					<b>HOMA-IR (excluding DM)</b>			
<b>Biomarker</b>	<b>β</b>	<b>SE</b>	<b>raw_p</b>	<b>fdr_p</b>	<b>β</b>	<b>SE</b>	<b>raw_p</b>	<b>fdr_p</b>	<b>β</b>	<b>SE</b>	<b>raw_p</b>	<b>fdr_p</b>	<b>β</b>	<b>SE</b>	<b>raw_p</b>	<b>fdr_p</b>					
AIM	0.075	0.014	2E-07	1E-06	0.023	0.017	0.19	0.40	-0.035	0.018	0.05	0.22	-0.036	0.013	0.01	0.02					
ADAM15	0.018	0.013	0.18	0.26	0.017	0.016	0.27	0.49	-0.009	0.017	0.58	0.78	0.010	0.012	0.39	0.56					
Adipsin	0.023	0.016	0.14	0.22	-0.017	0.019	0.37	0.52	-0.029	0.019	0.13	0.34	-0.018	0.014	0.20	0.37					
ADM	0.049	0.021	0.02	0.04	0.022	0.025	0.38	0.52	0.058	0.026	0.03	0.16	0.044	0.019	0.02	0.06					
AGP1	0.035	0.015	0.02	0.04	-0.017	0.018	0.36	0.52	-0.030	0.019	0.12	0.33	0.001	0.014	0.96	0.97					
ANGPTL3	0.070	0.014	1E-06	5E-06	0.039	0.017	0.02	0.14	0.049	0.018	0.01	0.05	0.057	0.013	7E-06	8E-05					
ApoA1	0.022	0.014	0.10	0.17	-0.027	0.016	0.09	0.28	-0.028	0.017	0.09	0.30	-0.021	0.012	0.07	0.16					
ApoB	0.076	0.014	8E-08	6E-07	0.026	0.017	0.12	0.29	0.010	0.018	0.55	0.76	0.033	0.013	0.01	0.03					
B2M	-0.005	0.014	0.74	0.83	0.015	0.016	0.34	0.52	-0.009	0.017	0.59	0.78	0.002	0.012	0.87	0.92					
BCHE	0.015	0.013	0.26	0.36	0.018	0.016	0.25	0.47	0.005	0.017	0.76	0.87	0.033	0.012	0.01	0.02					
BIKUNIN	0.014	0.014	0.33	0.43	-0.010	0.016	0.55	0.64	0.008	0.017	0.66	0.79	0.030	0.012	0.01	0.05					
BNP	0.027	0.013	0.04	0.08	0.018	0.016	0.27	0.49	-0.013	0.016	0.43	0.68	0.008	0.012	0.51	0.67					
C2	0.020	0.016	0.21	0.29	-0.037	0.019	0.05	0.23	-0.035	0.020	0.07	0.26	0.008	0.014	0.55	0.71					
CD14	0.003	0.013	0.82	0.87	0.014	0.016	0.38	0.52	0.017	0.016	0.29	0.55	0.014	0.012	0.23	0.42					
CD163	-0.057	0.016	0.0003	0.001	0.033	0.019	0.08	0.28	-0.017	0.019	0.38	0.65	-0.007	0.014	0.61	0.73					
CD40L	-0.025	0.015	0.09	0.15	-0.011	0.017	0.53	0.64	-0.023	0.018	0.20	0.45	0.041	0.013	0.001	0.01					
CD56	0.083	0.020	4E-05	0.0001	-0.040	0.024	0.10	0.28	-0.110	0.025	1E-05	0.0003	0.066	0.018	0.0003	0.003					
CD5L	0.059	0.014	2E-05	7E-05	0.024	0.016	0.15	0.36	0.011	0.017	0.52	0.74	0.034	0.012	0.005	0.02					
CDH13	-0.226	0.015	2E-48	2E-46	-0.069	0.019	0.0003	0.01	-0.102	0.020	4E-07	3E-05	-0.168	0.014	1E-32	5E-31					
Ceruloplasmin	0.022	0.014	0.13	0.20	0.034	0.017	0.04	0.23	0.029	0.017	0.09	0.30	-0.002	0.012	0.89	0.93					
Clusterin	0.135	0.014	1E-22	2E-21	0.031	0.017	0.06	0.26	0.022	0.017	0.21	0.45	0.019	0.012	0.13	0.26					

CNTN1	0.021	0.013	0.11	0.19	0.026	0.016	0.11	0.28	-0.014	0.016	0.38	0.65	0.004	0.012	0.71	0.82
COL18A1	-0.065	0.014	5E-06	2E-05	0.068	0.017	5E-05	0.001	0.038	0.018	0.03	0.18	-0.044	0.013	0.0004	0.003
CRP	0.023	0.014	0.10	0.17	-0.003	0.017	0.87	0.89	-0.014	0.017	0.43	0.68	0.012	0.012	0.31	0.51
CXCL16	-0.007	0.014	0.61	0.72	0.011	0.017	0.52	0.63	-0.006	0.017	0.72	0.84	0.034	0.012	0.01	0.02
Cystatin_C	-0.042	0.014	0.003	0.01	0.038	0.016	0.02	0.14	0.009	0.017	0.58	0.78	0.026	0.012	0.03	0.09
DPP4	0.017	0.013	0.21	0.30	0.015	0.016	0.35	0.52	-0.011	0.017	0.52	0.74	0.011	0.012	0.37	0.56
EFEMP1	0.014	0.013	0.29	0.40	-0.016	0.016	0.30	0.52	-0.041	0.016	0.01	0.09	0.001	0.012	0.90	0.93
FBN	0.008	0.013	0.55	0.66	0.019	0.016	0.23	0.45	-0.001	0.017	0.97	0.98	0.010	0.012	0.38	0.56
FGF23	0.011	0.013	0.39	0.50	0.024	0.016	0.12	0.29	-0.007	0.016	0.65	0.79	-0.001	0.011	0.90	0.93
GAPDH	0.035	0.016	0.03	0.05	0.022	0.019	0.23	0.45	-0.030	0.020	0.12	0.33	0.031	0.014	0.03	0.08
GDF15	0.008	0.013	0.55	0.66	-0.029	0.016	0.06	0.26	-0.021	0.016	0.21	0.45	-0.006	0.012	0.63	0.74
GMP140	0.107	0.016	6E-12	8E-11	0.091	0.019	9E-07	8E-05	0.078	0.019	5E-05	0.001	0.033	0.014	0.02	0.06
GP5	0.096	0.016	5E-09	4E-08	-0.004	0.020	0.83	0.87	-0.038	0.020	0.06	0.24	-0.020	0.015	0.16	0.31
GRN	0.045	0.015	0.002	0.01	0.075	0.017	2E-05	0.001	0.037	0.018	0.04	0.18	0.032	0.013	0.01	0.05
Hemopexin	0.178	0.015	3E-30	1E-28	0.021	0.019	0.28	0.49	0.066	0.020	0.001	0.01	0.121	0.014	2E-17	4E-16
IGF1	0.173	0.016	2E-25	4E-24	0.047	0.020	0.02	0.13	0.024	0.021	0.26	0.51	-0.008	0.015	0.60	0.73
IGFBP3	-0.043	0.016	0.01	0.014	0.023	0.019	0.22	0.45	-0.075	0.019	0.0001	0.002	-0.108	0.014	7E-15	1E-13
IGFBP1	0.061	0.013	7E-06	2E-05	-0.004	0.016	0.79	0.85	0.008	0.017	0.64	0.79	0.013	0.012	0.27	0.46
IGFBP2	0.007	0.015	0.62	0.723	0.025	0.018	0.16	0.37	0.012	0.019	0.51	0.74	0.027	0.013	0.04	0.09
KLKB1	0.046	0.016	0.003	0.007	0.016	0.019	0.39	0.52	-0.032	0.019	0.09	0.30	-0.037	0.014	0.01	0.03
LDLR	0.062	0.013	3E-06	1E-05	0.014	0.016	0.37	0.52	0.020	0.016	0.21	0.45	-0.010	0.012	0.37	0.56
Leptin	-0.069	0.014	1E-06	5E-06	-0.012	0.017	0.49	0.60	0.008	0.018	0.64	0.79	-0.012	0.013	0.35	0.56
Leptin R	0.057	0.014	5E-05	0.0001	0.002	0.017	0.90	0.90	-0.022	0.017	0.20	0.45	-0.029	0.012	0.02	0.06
Lpa	0.104	0.015	1E-11	2E-10	0.049	0.018	0.01	0.06	0.018	0.019	0.33	0.60	0.023	0.014	0.08	0.18
MCAM	0.047	0.014	0.001	0.002	-0.010	0.016	0.55	0.64	-0.009	0.017	0.62	0.79	0.021	0.012	0.09	0.18
MCP1	0.017	0.013	0.20	0.29	0.025	0.016	0.10	0.28	0.051	0.016	0.001	0.02	0.004	0.011	0.73	0.84
MMP9	0.069	0.013	3E-07	2E-06	-0.016	0.016	0.32	0.52	0.015	0.017	0.36	0.63	0.022	0.012	0.06	0.13
MMP8	0.012	0.013	0.37	0.48	-0.002	0.016	0.87	0.89	0.026	0.016	0.11	0.32	0.016	0.011	0.16	0.31
MPO	-0.002	0.013	0.88	0.89	0.027	0.016	0.09	0.28	-0.011	0.016	0.50	0.74	-0.008	0.012	0.50	0.67
Myoglobin	0.075	0.014	2E-07	1E-06	0.049	0.017	0.01	0.04	0.023	0.018	0.20	0.45	0.029	0.013	0.03	0.07
Notch1	-0.094	0.015	1E-09	1E-08	-0.031	0.018	0.09	0.28	-0.036	0.019	0.06	0.24	-0.004	0.014	0.78	0.89
NRCAM	0.008	0.017	0.63	0.72	-0.033	0.020	0.10	0.28	-0.103	0.021	1E-06	4E-05	-0.257	0.014	7E-67	6E-65
Osteo	0.096	0.019	8E-07	4E-06	0.008	0.023	0.74	0.81	0.037	0.024	0.12	0.33	0.135	0.017	3E-15	5E-14
PAI1	-0.018	0.014	0.1767	0.26	0.021	0.016	0.19	0.40	0.031	0.017	0.06	0.24	-0.033	0.012	0.01	0.02
PMP2	-0.090	0.013	1E-11	1E-10	0.004	0.016	0.78	0.85	0.001	0.016	0.94	0.98	-0.033	0.012	0.01	0.02
PON1	0.071	0.014	5E-07	2E-06	-0.034	0.017	0.04	0.23	-0.039	0.017	0.02	0.16	0.035	0.012	0.01	0.02
PPBP	-0.048	0.016	0.003	0.01	-0.018	0.019	0.36	0.52	-0.003	0.020	0.90	0.98	-0.052	0.014	0.0002	0.002
PZI	-0.084	0.014	2E-09	2E-08	-0.007	0.017	0.66	0.75	-0.021	0.017	0.23	0.47	-0.024	0.012	0.05	0.12
REG1A	0.160	0.015	2E-25	4E-24	0.078	0.019	3E-05	0.001	0.063	0.019	0.001	0.01	0.135	0.014	8E-23	2E-21
Resistin	0.055	0.014	0.0001	0.0004	0.017	0.017	0.31	0.52	0.039	0.018	0.03	0.16	0.011	0.013	0.39	0.56
SAA1	0.070	0.013	2E-07	1E-06	-0.006	0.016	0.70	0.78	0.004	0.017	0.82	0.92	0.023	0.012	0.05	0.12
SDF1	-0.029	0.015	0.05	0.09	-0.031	0.017	0.07	0.28	-0.050	0.018	0.01	0.05	-0.029	0.013	0.02	0.06
sGP130	-0.003	0.014	0.81	0.87	-0.012	0.016	0.47	0.60	-0.004	0.017	0.83	0.93	-0.007	0.012	0.59	0.73
sICAM_1	0.019	0.014	0.17	0.25	0.052	0.017	0.002	0.03	0.017	0.017	0.32	0.60	0.029	0.012	0.02	0.06
SRAGE	0.066	0.014	3E-06	1E-05	0.031	0.017	0.06	0.26	0.008	0.018	0.66	0.79	0.043	0.012	0.001	0.004
Tetranectin	0.055	0.015	0.0002	0.0004	-0.012	0.017	0.48	0.60	-0.029	0.018	0.11	0.32	0.032	0.013	0.01	0.05
TIMP1	-0.047	0.013	0.0003	0.001	-0.016	0.016	0.32	0.52	0.013	0.016	0.41	0.68	0.020	0.011	0.09	0.18
TSC22D3	-0.032	0.014	0.02	0.0418	-0.042	0.016	0.01	0.07	-0.019	0.017	0.25	0.51	-0.043	0.012	0.0004	0.003
UCMGP	-0.069	0.013	3E-07	2E-06	0.047	0.016	0.004	0.04	0.039	0.017	0.02	0.14	0.000	0.012	0.97	0.97



VEGF	0.059	0.013	1E-05	4E-05	-0.020	0.016	0.22	0.45	-0.011	0.017	0.51	0.74	-0.012	0.012	0.32	0.52
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**Table S6. Associations of single biomarkers with incident metabolic syndrome**

<b>Biomarker</b>	<b>OR</b>	<b>Lower CI</b>	<b>Upper CI</b>	<b>p-value</b>	<b>FDR- p-value</b>
<b>A1M</b>	0.93	0.84	1.02	0.11	0.30
<b>ADAM15</b>	0.99	0.91	1.07	0.72	0.88
<b>Adipsin</b>	0.88	0.79	0.97	0.01	0.06
<b>ADM</b>	0.87	0.78	0.97	0.01	0.07
<b>AGP1</b>	1.12	1.02	1.23	0.02	0.10
<b>ANGPTL3</b>	1.09	0.99	1.21	0.09	0.24
<b>ApoA1</b>	1.14	1.02	1.28	0.02	0.11
<b>ApoB</b>	1.50	1.36	1.66	0.00	0.00
<b>B2M</b>	0.91	0.82	1.00	0.05	0.19
<b>BCHE</b>	1.13	1.03	1.24	0.01	0.07
<b>BIKUNIN</b>	1.06	0.97	1.15	0.19	0.39
<b>BNP</b>	0.86	0.77	0.95	0.00	0.04
<b>C2</b>	1.19	1.09	1.30	0.00	0.01
<b>CD14</b>	1.07	0.98	1.16	0.15	0.34
<b>CD163</b>	0.92	0.85	1.00	0.06	0.21
<b>CD40L</b>	1.01	0.93	1.10	0.78	0.88
<b>CD56</b>	0.94	0.85	1.03	0.17	0.37
<b>CD5L</b>	1.03	0.94	1.12	0.56	0.77
<b>CDH13</b>	1.01	0.93	1.10	0.82	0.89
<b>Ceruloplasmin</b>	1.10	0.99	1.21	0.07	0.21
<b>Clusterin</b>	1.12	1.02	1.22	0.01	0.07
<b>CNTN1</b>	0.96	0.88	1.05	0.38	0.60
<b>COL18A1</b>	0.99	0.90	1.08	0.75	0.88
<b>CRP</b>	1.14	1.04	1.26	0.01	0.05
<b>CXCL16</b>	1.04	0.95	1.13	0.40	0.61
<b>Cystatin_C</b>	0.91	0.82	1.01	0.07	0.21
<b>DPP4</b>	0.99	0.91	1.07	0.76	0.88
<b>EFEMP1</b>	0.89	0.80	0.98	0.02	0.10
<b>FBN</b>	1.18	1.07	1.29	0.00	0.01
<b>FGF23</b>	0.91	0.84	0.99	0.04	0.15
<b>GAPDH</b>	1.02	0.93	1.11	0.72	0.88
<b>GDF15</b>	1.02	0.90	1.15	0.79	0.88
<b>GMP140</b>	1.05	0.96	1.15	0.29	0.49
<b>GP5</b>	0.98	0.90	1.07	0.62	0.81
<b>GRN</b>	0.94	0.86	1.02	0.16	0.35
<b>Hemopexin</b>	1.10	1.00	1.21	0.05	0.19
<b>IGF1</b>	1.06	0.96	1.17	0.27	0.48
<b>IGFBP3</b>	1.06	0.97	1.15	0.21	0.41
<b>IGFBP1</b>	0.86	0.77	0.96	0.01	0.05
<b>IGFBP2</b>	0.83	0.75	0.92	0.00	0.01
<b>KLKB1</b>	1.36	1.24	1.49	0.00	0.00

<b>LDLR</b>	1.01	0.93	1.10	0.85	0.90
<b>Leptin</b>	1.03	0.91	1.17	0.64	0.83
<b>Leptin R</b>	0.96	0.88	1.05	0.40	0.61
<b>LPA</b>	1.07	0.98	1.17	0.13	0.31
<b>MCAM</b>	0.88	0.80	0.96	0.00	0.05
<b>MCP1</b>	0.99	0.91	1.08	0.81	0.89
<b>MMP9</b>	0.94	0.86	1.03	0.17	0.36
<b>MMP8</b>	0.88	0.81	0.96	0.01	0.05
<b>MPO</b>	0.95	0.87	1.04	0.29	0.49
<b>Myoglobin</b>	1.04	0.94	1.15	0.45	0.65
<b>Notch1</b>	0.90	0.83	0.98	0.02	0.10
<b>NRCAM</b>	0.99	0.92	1.08	0.90	0.92
<b>OSTEO</b>	0.94	0.86	1.03	0.19	0.39
<b>PAI1</b>	1.07	0.97	1.18	0.18	0.37
<b>PMP2</b>	0.99	0.91	1.08	0.83	0.89
<b>PON1</b>	0.92	0.84	1.01	0.07	0.22
<b>PPBP</b>	1.01	0.93	1.10	0.84	0.89
<b>PZI</b>	0.94	0.86	1.02	0.14	0.34
<b>REG1A</b>	0.95	0.87	1.04	0.28	0.48
<b>Resistin</b>	0.93	0.85	1.02	0.12	0.30
<b>SAA1</b>	1.05	0.95	1.15	0.34	0.55
<b>SDF1</b>	1.00	0.92	1.09	0.97	0.97
<b>sGP130</b>	0.98	0.90	1.08	0.73	0.88
<b>sICAM1</b>	1.08	0.99	1.17	0.10	0.28
<b>SRAGE</b>	0.89	0.82	0.98	0.01	0.08
<b>Tetranectin</b>	0.97	0.89	1.06	0.54	0.77
<b>TIMP1</b>	0.90	0.81	1.00	0.05	0.19
<b>TSC22D3</b>	0.94	0.86	1.02	0.13	0.31
<b>UCMGP</b>	0.97	0.88	1.07	0.57	0.77
<b>VEGF</b>	0.92	0.85	1.01	0.07	0.21

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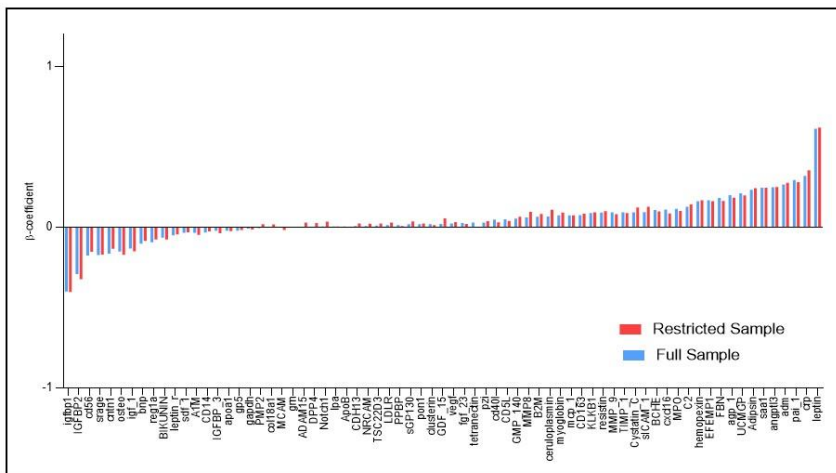
OR: odds ratio per 1-SD increase in rank normalized biomarker

MV model adjusts for age, sex, waist circumference, HDL, log triglycerides, SBP, hypertension treatment, fasting glucose, and statins.

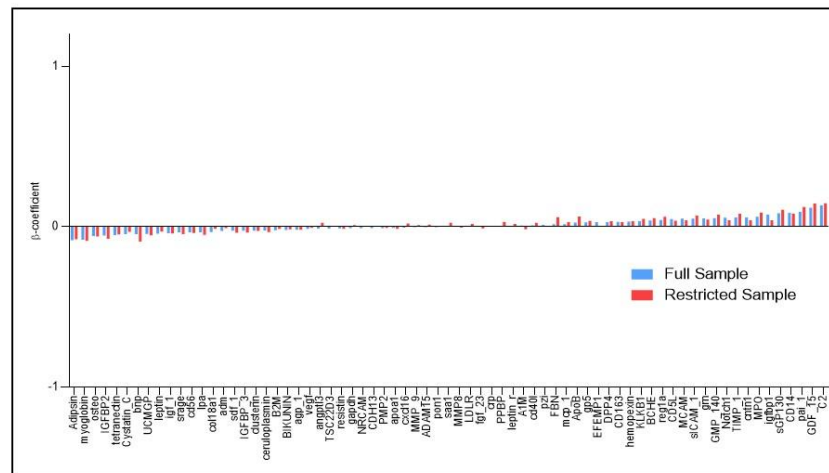
Statistically significant = FDR  $p < 0.05$

**Figure S1. Multivariable-adjusted associations of single biomarkers with cardiometabolic traits in the full sample vs restricted sample (restricted to patients with CT measures only).**

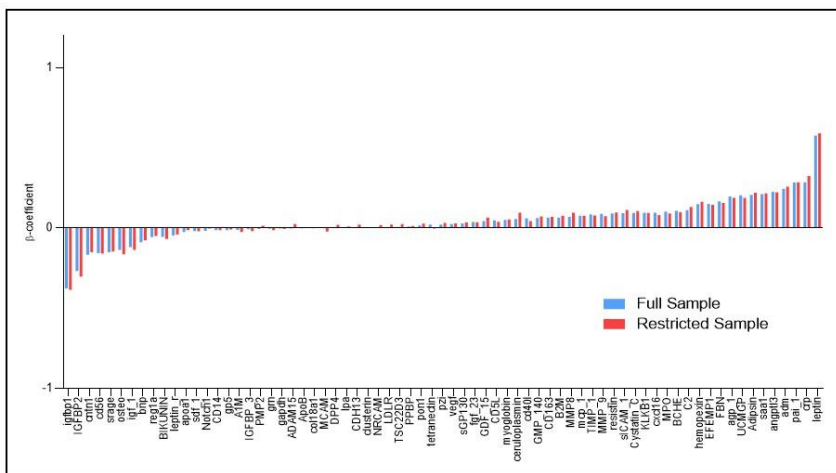
**A. BMI**



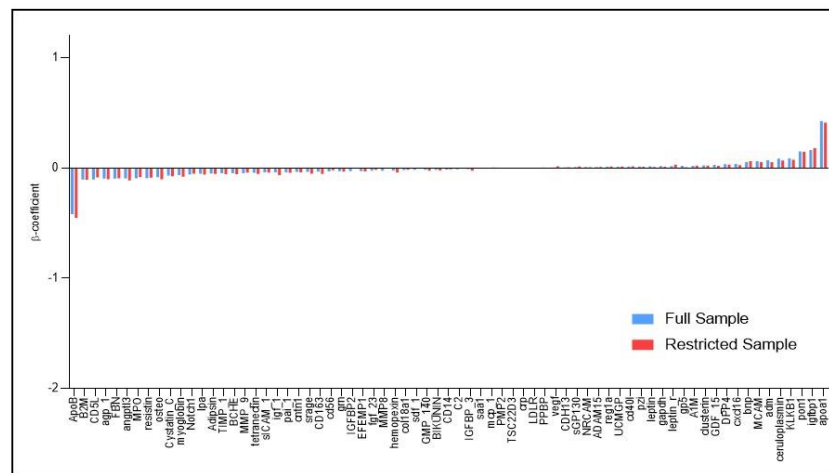
**B. Fasting glucose**



**C. WC**



**D. HDL**



Bars represent standardized  $\beta$  regression coefficients for individual biomarkers (X-SD change in trait per 1-SD change in biomarker): (A) BMI, (B) Fasting glucose, (C) WC, and (D) HDL cholesterol. Abbreviations: BMI = body mass index, HDL = high-density lipoprotein, WC = waist circumference.