Supplemental Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods 1. Study Populations

The Jackson Heart Study

The JHS is a single-site, prospective, population-based cohort study of CVD and its risk factors in AA individuals between 21 and 84 years old, residing in the three counties surrounding Jackson, MS.[1] Participants were recruited and examined according to standardized protocols at baseline (2000–2004) and in follow-up visits. Clinic visits included physical examination, anthropometry, surveys of medical history and of cardiovascular risk factors, and collection of blood and urine for analysis. Ongoing surveillance methods include annual follow-up telephone interviews and medical records review for adjudication of selected events.[1] The JHS was approved by the institutional review boards of Jackson State University, Tougaloo College, and the University of Mississippi Medical Center in Jackson, Mississippi. Written informed consent was obtained from all study participants. Details of the study design have been published.[2,3] The current metabolomics analyses were also approved by the institutional review board at Beth Israel Deaconess Medical Center.

Among the 2,751 JHS participants who underwent plasma metabolomic profiling, 875 were excluded due to prevalent CHD, missing covariates, or < 8 hours of fasting by the participant, leaving 1,876 for incident CHD analyses in our fully adjusted model. 1,311 subjects did not have CAC scores, leaving 1,439 for CAC analyses. The clinical characteristics of these groups resembled those of the overall JHS cohort. (eTable 1).

Women's Health Initiative

The replication cohort was from the Women's Health Initiative (WHI), a long-term National Heart, Lung, and Blood Institute (NHLBI)-sponsored, national health study that focused on heart disease, breast and colorectal cancer, and osteoporosis in postmenopausal women recruited from 40 sites in 23 states. The WHI included an observational study (WHI-OS), and clinical trials of hormone therapy (WHI-HT) and dietary intervention. The full WHI-OS consisted of 93,676 postmenopausal women ineligible or unwilling to participate in the related hormone trials, enrolled between 1994 and 1998 in the United States. The WHI-HT randomly assigned 16,608 postmenopausal women to estrogen plus progesterone or placebo, whereas the other 10,739 women with prior hysterectomy were randomly assigned to estrogen or placebo. For our study we used samples from participants in the WHI-OS and the placebo arms of the WHI-HT, that were part of a prior study of the metabolomics of CHD.[4] All participants provided written informed consent. Details of the study design have been published.[5] For the purposes of these analyses, WHI participants were categorized as follows; "Black" indicates self-reported Black or African American, "White" indicates self-reported non-Hispanic White, and "others" includes self-reported American Indian or Alaskan Native, Asian or Pacific Islander, Hispanic/Latino, and others. The current analysis included 1,219 White women, 217 Black women, and 152 women with other self-reported race categories (Table 1b).

eMethods 2. Assessment of Incident Coronary Heart Disease and Covariates

iCHD was defined as definite fatal CHD, definite or probable myocardial infarction (MI), silent MI between examinations as determined by electrocardiogram (ECG), or coronary revascularization. Prevalent CHD status was assessed by questionnaire for history of MI, history of coronary revascularization, or evidence of MI on ECG at Visit 1. For the current study, adjudication of incident events had been completed through December 31, 2016. Covariates used in the analyses were measured at the baseline examination at JHS. the WHI analyses, CHD was defined as incident fatal or nonfatal CHD; silent MI and coronary revascularization were not included.

Exclusions in JHS are summarized in eFigure 1. 159 participants were excluded for prevalent CHD. 207 participants were excluded for fasting < 8 hours. Missing covariates were as follows: 420 excluded for missing statin medication status, 19 for smoking status, 6 for HDL measurement, 5 for total cholesterol measurement, 4 for systolic blood pressure (SBP), and 3 for body mass index (BMI). A total of 470 participants were excluded from the fully adjusted analysis due to missing covariates.

Body mass index (BMI) was calculated as body weight indexed to height (kg/ m^2). Glomerular filtration rate (eGFR) was estimated by the chronic kidney disease epidemiologic collaboration (CKD-EPI) equation. Diabetes mellitus (DM) status was determined by fasting glucose of >126, hemoglobin A1C >6.5% or use of anti-diabetic medication. Hypertension was defined as systolic blood pressure of >140, diastolic blood pressure >90 or use of anti-hypertensive medication. Systolic blood pressure (SBP) was calculated by averaging two resting measurements. High-density lipoprotein (HDL-C), total cholesterol (TC), and creatinine were assayed directly using standard techniques .[6]

Statin use was determined by interview with validation by a pharmacist, or medical record review. Current smoking status was obtained by questionnaire. Serum C-reactive protein (CRP) levels (mg/L) were collected at all 3 examinations, measured using immunoturbidimetric CRP-Latex assay from Kamiya Biomedical Company following the manufacturer's protocol. The measurements were conducted in duplicate; any duplicates whose results fell outside 3 SDs from each other were rerun. The interassay coefficients of variation on control samples were 4.5% and 4.4% at CRP concentrations of 0.45 mg/L and 1.56 mg/L, respectively. The reliability coefficient for these replicates was 0.95 for the CRP assay.[7] Plasma N-terminal prohormone brain natriuretic peptide (NT-proBNP) concentrations were measured in the Jackson Heart Study using a chemiluminescent immunoassay performed on the Siemens Advia Centaur. Quality control samples were assayed within each batch of JHS samples. The coefficient of variation (CV) of the assay was measured at three concentrations: Level 1 (mean = 48.47 pg/mL, CV = 4.2%), Level 2 (mean = 472.94 pg/mL, CV = 3.1%) and Level 3 (mean = 1810.03 pg/mL, CV = 3.4%). The minimal detectable concentration of NT-proBNP with this assay was 2.0 pg/mL (35).[8] Education was measured as years of schooling completed and included 4 categories: less than high school (<12 years), high school graduate or GED equivalent, some college, and college graduate and above. Participants were assigned to 1 of 4 income categories, according to the US census poverty levels based on household income and family size: poor, representing income less than poverty level; lower‐middle, representing income 1 to 1.5 times the poverty level; upper‐middle, representing income >1.5 but <3.5 times the poverty level; and affluent, representing income ≥3.5 times the poverty level.[9]

eMethods 3. Assessment of Coronary Artery Calcium Score

The procedure for gated cardiac CT scans of the coronary arteries was based on standard protocols developed by the NHLBI, MESA and CARDIA studies using a multi-detector CT (GE Healthcare Lightspeed 16 Pro, Wakeshau, Wisconsin), during Exam 2.[10] Participants were scanned in the supine position with a three sample calcium calibration QCT Phantom (Image Analysis, Columbia, KY) posterior to the spine. To ensure complete coverage of the heart, a minimum of 10.5 cm of image data in the head to foot direction was acquired with each scan. This coverage resulted in approximately 4460 slices, depending upon the length of the heart. The heart scan was reconstructed centered on the heart using a display field of view of 35 cm. Technical settings include: prospective ECG gating at 75% of the R-R interval, 8 x 2.5 mm collimation (8i axial) mode with 20 mm table increment (contiguous scans), 120 KVp, 2.5 mm slice thickness, 35 cm display field of view, gantry speed was 0.50 seconds and a segmented reconstruction resulting in an effective temporal resolution of 0.26 seconds. Scan coverage was 2 cm below the carina extending to the apex of the heart. Tube current was 400 mA and was increased, as needed, by 25% for participants weighing ≥220 lbs (100 Kg) to compensate for body size and maintain a more constant signal-to-noise ratio (photon flux) across participants.[11] Scans were read centrally at the Wake Forest University School of Medicine. Images were viewed and scored using a TeraRecon Aquarius Workstation (TeraRecon, Inc., San Mateo, CA).

In our study, a total of 1,439 participants who had metabolomic analysis also had CAC scores. To analyze CAC in a continuous fashion and account for CAC scores that were 0, we analyzed the metabolite associations with log(CAC+1). Of note, metabolomic

profiling used plasma samples from JHS Visit 1, whereas CAC scores were measured approximately four years later at Visit 2. To address differences in this interval between participants we included the time between Visits 1 and 2 as a covariate in the CAC analyses. Individuals with prevalent CHD were excluded from CAC analyses.

eMethods 4. Plasma Sample Selection and Metabolomic Profiling

To measure water-soluble metabolites in the positive ionization mode, hydrophilic interaction liquid chromatography (HILIC, Waters; Mildford, MA) was performed using a Shimadzu Nexera X2 U-HPLC (Shimadzu Corp.; Marlborough, MA) coupled to a Q Exactive mass spectrometer (Thermo Fisher Scientific; Waltham, MA). Raw data were processed using TraceFinder 3.1 software (Thermo Fisher Scientific; Waltham, MA) and Progenesis QI (Nonlinear Dynamics; Newcastle upon Tyne, UK).

To measure organic acids and other intermediary metabolites in negative ionization or amide mode, chromatography was performed on an Agilent 1290 infinity LC system equipped with a Waters XBridge Amide column, coupled to an Agilent 6490 triple quadrupole mass spectrometer. Metabolite transitions were assayed using a dynamic multiple reaction monitoring system. LC-MS data were analyzed with Agilent Masshunter QQQ Quantitative analysis software.

LC-MS peaks were manually reviewed in a blinded manner to assess peak quality. As part of our QC protocol, isotopically labeled standards were interspersed throughout the run every 10 injections in order to monitor and correct for temporal drift in mass spectrometry performance. The nearest neighbor flanking pair of pooled plasma was used to normalize experimental samples in a metabolite-by-metabolite manner by dividing the experimental sample's peak area by the average of the two nearest neighbor flanking pairs. Additionally, a separate pooled plasma injection was included every 20 injections in order to gauge the effectiveness of the normalization and to determine the coefficient of variation of each metabolite over the run. Un-normalized and normalized metabolite data were plotted (injection number on the x axis, relative abundance on the y axis) for both

experimental samples and pooled samples, allowing for visualization of instrument drift over time and subsequent correction using normalization techniques. These data were then subjected to review during a full laboratory meeting to discuss data quality. Metabolites that were not measured well, defined as having a biological to analytical CV ratio of less than 1 were removed from analysis. Metabolites that were determined to have poor peak quality during blinded peak review were also removed from subsequent processing. Finally, metabolites that failed QC as determined by group review were removed from subsequent processing. The median CV of the final metabolites analyzed was 4.2%, indicating that these metabolites were well-measured overall. For metabolites with > 10% missingness, these values were imputed to minimum detection value of metabolite, subsequently log-transformed, and then scaled (mean 0 and SD 1) within batch. We have used this process previously.[12-14]

The samples profiled in JHS included nested case-control studies for CHD (n=400) and chronic kidney disease (CKD) (n=400), plus 1,546 randomly selected samples. We adjusted for batch to account for the different runs of metabolite analyses.

From the WHI-OS, we analyzed 472 participants who developed CHD after the baseline examination and 472 non-CHD control participants matched for 5-year age interval, self-identified race/ethnicity, hysterectomy status, and 2-year enrollment window. From the WHI-HT study, we analyzed 321 iCHD cases and 323 frequency-matched controls from the 2 placebo arms matched for 5-year age interval, self-identified race/ethnicity, hysterectomy status, and 2-year enrollment window. The methods for the metabolite profiling in the WHI have previously been published.[4]

eMethods 5. Statistics

Patient characteristics are presented as frequencies and percentages for categorical data, and means and standard deviations for continuous variables. Continuous variables were compared with the paired Student t test or the Wilcoxon rank-sum test as appropriate. Two-tailed P values <0.05 were considered significant. Metabolite levels were standardized to those in pooled plasma samples that were included in all assay plates, and natural log-transformed to approximate a normal distribution. Non-normally distributed clinical measures were log-transformed. Cox regression was performed to determine the relationship between metabolite levels (independent variable) and iCHD (dependent variable) and linear regression was used to determine the relationship between metabolite levels and log (CAC score +1) (dependent variable). Metabolite levels were standardized to multiples of 1 SD. Two sets of covariates were used in iCHD and CAC analyses. The first set included age, sex, and batch. The second included age, sex and batch in addition to traditional CHD risk factors: body mass index (BMI), estimated glomerular filtration rate (eGFR), diabetes status, hypertension status, systolic blood pressure (SBP), total and high-density lipoprotein (HDL) cholesterol, statin use and smoking status. Metabolites were tested one at a time while adjusting for demographic and clinical risk factors. Time between Visits 1 and 2 was an additional covariate in the CAC analysis. Batch effect was addressed by treating batches as a categorical covariate. Correction for multiple hypothesis testing was performed using the Benjamini-Hochberg False Discovery Rate (FDR) method; a significance threshold of q-value < 0.1 was established. In the cross-cohort analysis performed for replication of our findings in the WHI, we used a significance cutoff of p-value < 0.05 with consistent direction of effect.

To assess the significance of differences in beta estimates between JHS and WHI, a Z-score was created for each metabolite comparison by dividing the difference in beta estimates in the two studies by the square root of the sum of the variances. As the beta estimates were normally distributed in each cohort, the p-value for this difference was calculated using the probnorm function in SAS 9.4 (SAS Institute, Cary, NC). Given the exploratory nature of this analysis, we focused on differences having a significance level of $p<0.1$. All statistical analyses were performed using R version 3.3.1 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria)

eMethods 6. Prediction Models

Receiver Operating Characteristic Curves

To investigate whether the identified metabolites improved iCHD risk prediction, we constructed receiver operating characteristic (ROC) curves and calculated C-statistics for three models in JHS: 1) covariates alone; 2) covariates plus CRP and NT-proBNP; and 3) model 2 plus the 46 iCHD-associated metabolites from our fully adjusted model. We constructed ROC curves in the WHI cohort as well, using the 32 metabolites available for replication. We also constructed three models in WHI: 1) covariates alone; 2) covariates plus CRP (NT-proBNP was not available in the WHI); and 3) model 2 plus the 32 iCHD-associated metabolites from our fully adjusted model in JHS that were available for replication. We used Harrell's C-index method for survival data. We went on to correct for optimism in JHS given the over-fitting due to testing in derivation cohort. We used the "validation" function from the "rms" package.[15]

Metabolite Risk Score

To further investigate whether metabolites of interest improved CHD risk prediction, we constructed a metabolite risk score (MRS). Cox model regularized by Ridge (L2) penalties was conducted to predict survival free of iCHD. The Ridge models were optimized by 5-fold cross validation. A summary score was calculated by summing the multiplication products of the log and standardized (mean 0, SD 1) metabolite (n=46) serum concentrations and the coefficient for the corresponding metabolite from the Ridge regression, which was defined as the "metabolite risk score" (MRS) for iCHD. The analyses were conducted in R 4.0.2. The glmnet package (4.1-1) in R was used for the

Ridge regression. We than applied the MRS for the 32 metabolites available for replication in WHI.

eTable 1. Clinical Characteristics of the Entire Jackson Heart Study and the Population of Profiled Samples

Clinical Trait	Full Cohort (N=5306)	Samples Profiled (N=2750)
Age, mean (SD)	55.4 (12.8)	56.4 (12.7)
BMI, mean (SD)	31.8 (7.2)	31.7 (7.1)
eGFR, mean (SD)	85.7 (18.5)	84.8 (19)
TC, mean (SD)	199 (40.1)	200 (41)
HDL, mean (SD)	51.8 (14.6)	51.8 (14.7)
SBP, mean (SD)	127 (18.4)	127 (18.2)
Male, n (%)	1934 (36.5)	1046 (38)
Current Smoker, n (%)	693 (13.1)	335 (12.2)
HTN, n (%)	3252 (61.3)	1746 (63.5)
Diabetes, n (%)	1152 (21.7)	659 (24)

BMI: body mass index; eGFR: estimated glomerular filtration rate; TC: total cholesterol, HDL: high density lipid lipoprotein; SBP: systolic blood pressure; HTN: hypertension

eTable 2. Participants Without Prevalent Coronary Heart Disease in the Jackson Heart Study Cohort

Among participants without prevalent CHD, comparing the clinical characteristics of those who underwent metabolomics profiling versus those who did not.

	With Metabolomic Data	Without Metabolomic Data
N (%) Total: 4,901	2,560	2,341
Age, mean	56	54
Sex, n (% male)	960 (38)	791 (34)
Body Mass Index, mean	32 (7)	32 (7)
eGFR, mean	85 (18)	87 (17)
Diabetes, n (%)	580 (23)	410 (18)
Hypertension, n (%)	1,584 (62)	1,324 (57)
Systolic Blood Pressure (mmHg), mean	127	126
Total Cholesterol (mg/dL), mean	200	199
HDL, mean	52	52
Current Smoker, n (%)	304 (12)	312 (13)
Statin Use, n (%)	261 (12)	211 (11)

eTable 3. Participants With Computed Tomographic Scans at Visit 2 in the Jackson Heart Study Cohort

Among participants with CHT scans at Visit 2, comparing the clinical characteristics of those who underwent metabolomics profiling versus those who did not.

	With Metabolomic Data	Without Metabolomic Data
N (%) Total:	1,439	1,271
Age, mean	56	54
Sex, n (% male)	506 (35)	432 (34)
Body Mass Index, mean	31 (6)	31 (7)
eGFR, mean	86 (17)	87 (16)
Diabetes, n (%)	275 (19)	201 (16)
Hypertension, n (%)	875 (61)	722 (57)
Systolic Blood Pressure (mmHg), mean	126 (17)	125 (17)
Total Cholesterol (mg/dL), mean	201 (41)	201 (39)
HDL, mean	52 (14)	52 (15)
Current Smoker, n (%)	145 (10)	128 (10)
Statin Use, n (%)	137 (11)	124 (12)

eTable 4. Baseline Participant Characteristics by Self-Identified Race in the Women's Health Initiative Cohort

	All	White	Black	Others*
N (sample size)	1588	1219	217	152
CHD Case/control, N	793/795	608/611	109/108	76/76
Age, years	67 (6.95)	67.6 (6.5)	64.6 (7.82)	65.5 (8.13)
Body Mass Index, kg/m²	28.4 (6.12)	28.1 (6.06)	30.7 (6.2)	27.7 (5.88)
Diabetes, cases, n (%)	198 (12.47%)	133 (10.91%)	46 (21.2%)	19 (12.5%)
Hypertension, cases, n (%)	880 (55.42%)	649 (53.24%)	155 (71.43%)	76 (50%)
SBP, mmHg	133.1 (18.84)	132.6 (18.39)	137.1 (20.07)	131.1 (19.92)
Total cholesterol, mg/dL	233.1 (44.93)	235.4 (44.18)	224.1 (46.26)	227.8 (47.22)
HDL-cholesterol, mg/dL	52.1 (15.41)	51.9 (15.41)	54.4 (15.22)	50.7 (15.48)
Statin use, n (%)	177 (11.15%)	146 (11.98%)	18 (8.29%)	13 (8.55%)
Smoking status				
Never smoker, n (%)	763 (48.05%)	595 (48.81%)	92 (42.4%)	76 (50%)
Former smoker, n (%)	642 (40.43%)	494 (40.53%)	89 (41.01%)	59 (38.82%)
Current smoker, n (%)	165 (10.39%)	116 (9.52%)	32 (14.75%)	17 (11.18%)

* Others indicates self-reported American Indian or Alaskan Native, Asian or Pacific Islander, Hispanic/Latino, and others.

eTable 5. Comparison of Metabolites Across Published Studies

Results from eight prior studies of metabolomics associations with incident coronary heart disease. Green highlighted values indicate findings with consistent direction of effect both in our cohort and paper referenced. Red highlighted values are findings in other publications that were either non-significant in our study or significant with opposite direction of effect. Bold metabolites indicate statistically significant findings in our analysis of the JHS cohort.

Jackson Heart Study			Wang et al.		Paynter et al.		Stegemann et al.		Cavus et al.		Shah et al.		Wurtz et al.		Magnusson et al.			Murthy et al.
Metabolite	HR	q-value	β	q-value	HR	p-value	HR	p-value	HR	p-value	Direction	p-value	HR	p-value	HR	p-value	β	Direction of Effect
Homoarginine	**0.7**	**0.001**																(-)
Niacinamide	**0.75**	**0.001**																(-)
36.2 PE	**1.40**	**0.002**					1.32	0.001										
2-Hydroxyglutarate	**1.36**	**0.003**			1.45	1.00E-05												
DMGV	**1.47**	**0.006**																(+)
Biliverdin	**0.76**	**0.010**																(-)
Histidine	**0.78**	**0.020**							1.08	0.02								
34.2 PE	**1.29**	**0.025**					1.28	0.006										
Methionine	**0.79**	**0.067**							1.1	0.005								
Glychochenodeoxycholate	**1.22**	**0.067**	0.08	0.064	1.68	9.00E-10												
Leucine	**0.79**	**0.075**									(+)	0.004	1.13	0.002				(+)
Uridine	**0.82**	**0.079**	-0.1	0.036														
Fumarate	**1.21**	**0.094**			1.22	2.10E-02												
Xanthine	0.82	0.106	-0.07	0.095														(+)
Glycocholate	1.21	0.106																(-)
Methionine Sulfoxide	0.83	0.139	-0.07	0.089														
38.4 PE	1.20	0.141					1.32	0.003										
Hypoxanthine	0.85	0.183																(+)
20.4 LPC	0.85	0.188							1.07	0.03								
2-hydoxybutyrate	0.84	0.189	-0.02	0.59	1.73	2.30E-10												
Glutamate	0.86	0.239			1.64	5.50E-09												(+)
Isoleucine	0.84	0.241											1.17	4.00E-05	1.25	p>0.05	0.225	(+)
18.1 SM	1.20	0.284							1.04	0.03								
C34:1 DAG	0.87	0.292			1.4	5.90E-05												
Hippurate	1.14	0.354																(-)
36.4 PE	1.14	0.355					1.3	0.006										
Valine	0.88	0.449											1.11	0.01				(+)
Phenylalanine	0.88	0.451											1.4	1.00E-17	1.25	p>0.05	0.22	(+)
38.6 PC Plasmalogen	1.13	0.472							1.11	4.61E-05								
Asparagine	0.89	0.478	0.1	0.024	0.75	4.20E-04												(-)
Acetoacetate	1.10	0.514											0.88	0.0003				

Tyrosine	0.90	0.514											1.17	4.00E-05	1.19	p>0.05	0.17	(+)
Tryptophan	0.89	0.536																(-)
Hydroxyproline	1.09	0.545																(+)
Taurine	1.09	0.580																(-)
Inosine	0.91	0.607																(+)
Glycine	1.07	0.741	-0.09	0.064														(-)
Dimethylglycine	1.05	0.754	0.12	0.009														
Glutamine	1.07	0.799			0.61	1.40E-08			1.1	0.04	(+)	<0.0001	0.86	2.00E-05				(-)
Citruline	1.07	0.801									(-)	0.003						(-)
Uracil	0.95	0.837			0.8	6.50E-03												
Alanine	1.05	0.840											1.19	2.00E-06				
Ornithine	1.04	0.920																(+)
Linoleic Acid	1.28	0.920	-0.12	0.023									1.08	0.03				
Urate	1.04	0.920																(+)
N-acetlyalanine	0.97	0.938	0.14	0.006														
C8 carnintine	1.03	0.938									(-)	0.04						
C2 Carnitine	1.03	0.940									(-)	0.01						
C14-2 Carnitine	1.03	0.940									(-)	0.02						
36.5 PC Plasmalogen	1.03	0.940							1.08	0.002								
3-hydroxybuytrate	0.97	0.958											0.85	1.00E-05				
Cortisol	0.98	0.963	-0.08	0.064														
Xanthosine	1.02	0.973			0.8	7.50E-03												(-)
Adipic Acid	1.02	0.989	-0.08	0.071														
18.2 LPC	1.02	0.989							1.08	0.02								
34.3 PC Plasmalogen	1.01	0.996							1.08	7.27E-04								
Betaine	0.98	0.996																(-)
Choline	0.98	0.998																(+)

eTable 6. Metabolites Associated With Incident Coronary Heart Disease in the Jackson Heart Study Cohort: Adjusted for Age, Sex, and Batch

Metabolite	HR	95% CI	p-value	FDR q-value
4-Acetamidobutanoate	1.40	1.24 - 1.57	2.11E-08	3.19E-06
36:2 PE	1.56	1.33 - 1.82	1.67E-08	3.19E-06
2-Hydroxyglutaric Acid	1.42	1.24 - 1.62	2.15E-07	1.62E-05
Linoleoyl Ethanolamide	1.41	1.23 - 1.60	1.85E-07	1.62E-58
34:2 PE	1.47	1.25 - 1.71	8.75E-07	5.29E-05
1-Methylnicotinamide	0.70	0.60 - 0.82	3.52E-06	0.0002
1,5 Anhydroglucitol	0.75	0.66 - 0.85	6.19E-06	0.0002
Trimethylbenzene	0.71	0.61 - 0.82	5.45E-06	0.0002
Biliverdin	0.71	0.61 - 0.83	8.04E-06	0.0002
DMGV	1.46	1.23 - 1.73	9.82E-06	0.0002
Homoarginine	0.71	0.61 - 0.83	9.26E-06	0.0002
Pseudouridine	1.36	1.18 - 1.56	9.47E-06	0.0002
N-Acetyltryptophan	1.36	1.17 - 1.57	3.23E-05	0.0008
Malic Acid	1.37	1.18 - 1.59	3.49E-05	0.0008
N-Acetylaspartic Acid	1.36	1.17 - 1.57	4.36E-05	0.0009
Niacinamide	0.75	0.65 - 0.86	5.18E-05	0.0010
Myristoleate	0.75	0.65 - 0.87	7.67E-05	0.001
Acetylglutamic Acid	1.26	1.12 - 1.42	8.50E-05	0.001
N-Acetylputrescine	1.33	1.15 - 1.54	9.02E-05	0.001
38:4 PE	1.35	1.16 - 1.57	9.86E-05	0.001
1-Methyladenosine	1.35	1.15 - 1.56	0.0001	0.002
D-Gluconic Acid	1.34	1.15 - 1.56	0.0001	0.002
Arginine	0.76	0.66 - 0.87	0.0001	0.002
Cystine	1.46	1.19 - 1.77	0.0002	0.002
Histidine	0.76	0.66 - 0.88	0.0002	0.003
36:4 PE	1.32	1.13 - 1.53	0.0003	0.004
NMMA	0.78	0.68 - 0.90	0.0005	0.006
Uridine	0.78	0.67 -0.90	0.0007	0.007
18:0 LPE-B	0.78	0.67 - 0.90	0.0007	0.007
Aconitic Acid	1.49	1.18 - 1.88	0.0008	0.008
1-Methylguanine	1.27	1.11 - 1.46	0.0008	0.008
N4-Acetylcytidine	1.27	1.10 - 1.47	0.001	0.010
2-Deoxyuridine	1.29	1.11 - 1.50	0.001	0.01
16:1 LPC Plasmalogen	0.79	0.68 - 0.91	0.001	0.01
Indole-3-Lactic Acid	1.29	1.11 - 1.51	0.001	0.01
N2,N2-Dimethylguanosine	1.27	1.09 - 1.46	0.001	0.01
N-Acetylleucine	1.23	1.08 - 1.40	0.001	0.01
Oxaloacetic Acid	1.24	1.08 - 1.43	0.002	0.02
C4-Carnitine	1.27	1.09 - 1.48	0.002	0.02

Lysine	0.81	0.71 - 0.93	0.003	0.02
18:1 LPC Plasmalogen	0.80	0.69 - 0.93	0.003	0.02
Imidazole Propionate	1.25	1.07 - 1.45	0.003	0.02
4-Hydroxy-3-Methylacetophenone	0.81	0.70 - 0.93	0.004	0.03
Methionine	0.80	0.68 - 0.93	0.005	0.03
Homogentisic Acid	1.25	1.06 - 1.47	0.006	0.04
Aspartic Acid	1.27	1.07 - 1.51	0.006	0.04
Oleoyl Serine	0.79	0.66 - 0.94	0.006	0.04
Glycochenodeoxycholic Acid	1.22	1.05 - 1.40	0.007	0.04
16:1 LPC	0.81	0.7 - 0.94	0.007	0.04
20:1 LPC	0.83	0.72 - 0.96	0.009	0.05
C4-OH Carnitine	1.21	1.04 - 1.39	0.01	0.06
N6-Acetyllysine	1.22	1.04 - 1.43	0.01	0.06
Hippurate	1.21	1.04 - 1.41	0.01	0.06
N-Carbamoyl-Beta-Alanine	1.19	1.03 - 1.37	0.01	0.07
Threonine	0.83	0.71 - 0.96	0.01	0.07
Glycocholate	1.20	1.03 - 1.39	0.01	0.07
Methylhistidine	1.21	1.03 - 1.41	0.02	0.08
24:0 LPC	0.84	0.73 - 0.97	0.02	0.08
36:3 PE Plasmalogen	1.20	1.03 - 1.40	0.02	0.09
18:2 LPE	1.19	1.02 - 1.38	0.02	0.09
Xanthine	0.83	0.70 - 0.97	0.02	0.09

eTable 7. Metabolites Associated With Incident Coronary Heart Disease: Fully-Adjusted Model With Sensitivity Analysis for Myocardial Infarction

Bold indicates metabolites that remained significant (FDR q < 0.1) in MI-only analysis

	JHS - Model 2				JHS - MI Only			
Metabolite	**HR**	**95% CI**	**p-value**	**FDR q-value**	**HR**	**SE**	**p-value**	**FDR q-value**
1-Methylnicotinamide	**0.69**	**0.59 - 0.81**	**3.62E-06**	**0.001**	**0.67**	**0.09**	**0.00002**	**0.001**
Linoleoyl Ethanolamide	**1.38**	**1.19 - 1.60**	**0.00001**	**0.001**	**1.49**	**0.09**	**3.15E-06**	**0.0005**
N-Acetylaspartic Acid	**1.44**	**1.22 - 1.69**	**9.72E-06**	**0.001**	**1.51**	**0.10**	**0.00002**	**0.001**
4-Acetamidobutanoate	**1.46**	**1.22 - 1.73**	**0.00002**	**0.001**	**1.54**	**0.10**	**0.00001**	**0.001**
Homoarginine	**0.71**	**0.60 - 0.83**	**0.00002**	**0.001**	**0.63**	**0.10**	**1.99E-06**	**0.0005**
Niacinamide	**0.75**	**0.65 - 0.85**	**0.00001**	**0.001**	**0.67**	**0.10**	**0.0001**	**0.003**
Trimethylbenzene	**0.73**	**0.62 - 0.85**	**0.00004**	**0.002**	**0.69**	**0.09**	**0.00009**	**0.002**
36:2 PE	**1.41**	**1.18 - 1.66**	**0.00006**	**0.002**	**1.37**	**0.11**	**0.003**	**0.04**
2-Hydroxyglutaric Acid	**1.36**	**1.16 - 1.58**	**0.00008**	**0.003**	**1.44**	**0.09**	**0.00007**	**0.002**
NMMA	**0.75**	**0.64 - 0.86**	**0.00010**	**0.003**	**0.69**	**0.09**	**0.00006**	**0.002**
Oxaloacetic Acid	**1.36**	**1.16 - 1.59**	**0.0001**	**0.003**	**1.43**	**0.09**	**0.00006**	**0.002**
Pseudouridine	**1.48**	**1.20 - 1.82**	**0.0002**	**0.005**	**1.65**	**0.12**	**0.00004**	**0.002**
DMGV	**1.47**	**1.19 - 1.81**	**0.0003**	**0.006**	**1.65**	**0.13**	**0.00009**	**0.002**
16:0 SM	1.46	1.17 - 1.81	0.0006	0.01	1.32	0.13	0.03	0.15
Biliverdin	**0.76**	**0.65 - 0.89**	**0.0007**	**0.01**	**0.78**	**0.10**	**0.01**	**0.08**
Lysine	**0.78**	**0.67 - 0.90**	**0.0008**	**0.01**	**0.75**	**0.09**	**0.0009**	**0.02**
Myristoleate	**0.77**	**0.66 - 0.90**	**0.0008**	**0.01**	**0.76**	**0.09**	**0.004**	**0.04**
18:0 LPE B	**0.77**	**0.65 - 0.90**	**0.0009**	**0.02**	**0.71**	**0.10**	**0.0004**	**0.008**
4-Hydroxy-3-Methylacetophenone	0.79	0.67 - 0.91	0.001	0.02	0.81	0.09	0.02	0.13
Indole-3-Lactic Acid	**1.31**	**1.11 - 1.55**	**0.001**	**0.02**	**1.34**	**0.10**	**0.004**	**0.04**
Histidine	**0.78**	**0.66 - 0.91**	**0.001**	**0.02**	**0.76**	**0.10**	**0.006**	**0.05**
Cystine	**1.39**	**1.13 - 1.71**	**0.002**	**0.02**	**1.38**	**0.13**	**0.01**	**0.08**
N2,N2 - Dimethylguanosine	**1.32**	**1.10 - 1.57**	**0.002**	**0.02**	**1.44**	**0.10**	**0.0002**	**0.006**
34:2 PE	1.30	1.10 - 1.52	0.002	0.02	1.22	0.10	0.05	0.23
1-Methyladenosine	**1.33**	**1.10 - 1.59**	**0.002**	**0.03**	**1.45**	**0.11**	**0.0008**	**0.02**
36:3 PE Plasmalogen	**1.31**	**1.10 - 1.56**	**0.002**	**0.03**	**1.39**	**0.11**	**0.002**	**0.03**
Arginine	0.80	0.68 - 0.93	0.004	0.04	0.82	0.10	0.04	0.19
1,5 Anhydroglucitol	**0.79**	**0.67 - 0.93**	**0.005**	**0.04**	**0.75**	**0.10**	**0.004**	**0.04**
Homogentisic Acid	**1.29**	**1.08 - 1.53**	**0.004**	**0.04**	**1.31**	**0.11**	**0.01**	**0.09**
2-Deoxyuridine	**1.31**	**1.08 - 1.59**	**0.005**	**0.04**	**1.44**	**0.11**	**0.001**	**0.02**
16:1 LPC	**0.79**	**0.67 - 0.93**	**0.005**	**0.04**	**0.75**	**0.10**	**0.004**	**0.04**
16:1 LPC Plasmalogen	**0.80**	**0.68 - 0.93**	**0.005**	**0.04**	**0.76**	**0.10**	**0.005**	**0.05**
N-Acetyltryptophan	**1.26**	**1.07 - 1.47**	**0.005**	**0.04**	**1.31**	**0.10**	**0.004**	**0.04**
Malic Acid	**1.26**	**1.06 - 1.48**	**0.006**	**0.06**	**1.38**	**0.10**	**0.001**	**0.03**

Methionine	**0.79**	**0.66 - 0.94**	**0.008**	**0.07**	**0.77**	**0.11**	**0.01**	**0.09**
Glycochenodeoxycholic Acid	**1.23**	**1.05 - 1.42**	**0.008**	**0.07**	**1.26**	**0.09**	**0.01**	**0.09**
Leucine	0.79	0.65 - 0.94	0.009	0.07	0.82	0.11	0.08	0.30
36:2 PC	**1.26**	**1.05 - 1.51**	**0.009**	**0.08**	**1.41**	**0.11**	**0.002**	**0.03**
Uridine	**0.82**	**0.70 - 0.95**	**0.01**	**0.08**	**0.79**	**0.09**	**0.01**	**0.08**
N4-Acetylcytidine	**1.25**	**1.05 - 1.49**	**0.01**	**0.08**	**1.34**	**0.10**	**0.004**	**0.04**
D-Gluconic Acid	**1.30**	**1.06 - 1.58**	**0.01**	**0.08**	**1.43**	**0.12**	**0.002**	**0.03**
20:1 LPC	0.82	0.70 - 0.96	0.01	0.08	0.85	0.10	0.10	0.33
18:3 LPC	**0.82**	**0.69 - 0.96**	**0.01**	**0.08**	**0.79**	**0.10**	**0.02**	**0.09**
Aconitic Acid	**1.38**	**1.07 - 1.79**	**0.01**	**0.08**	**1.45**	**0.15**	**0.01**	**0.09**
Fumaric Acid	**1.21**	**1.03 - 1.41**	**0.01**	**0.09**	**1.31**	**0.10**	**0.005**	**0.05**
18:0 SM	1.25	1.04 - 1.50	0.02	0.09	1.14	0.11	0.23	0.58

Covariates: age, sex, batch, total cholesterol, high-density lipoprotein, hypertension, systolic blood pressure, body mass index, diabetes status, estimated glomerular filtration rate, smoking status, and statin medication use.

eTable 8. Metabolites Associated With Incident Coronary Heart Disease: Fully-Adjusted Model With Additional Adjustment for Triglyceride Levels and Waist Circumference

Bold indicates metabolites that remained significant (FDR q < 0.1) with additional adjustments

	Model 2				Model 2 + Adj TG and WC		
Metabolite	HR	95% CI	p-value	FDR q-value	HR	p-value	FDR q-value
1-Methylnicotinamide	**0.69**	**0.59 - 0.81**	**3.62E-06**	**0.001**	**0.70**	**4.18E-06**	**0.0006**
Linoleoyl Ethanolamide	**1.38**	**1.19 - 1.60**	**0.00001**	**0.001**	**1.38**	**1.19E-05**	**0.0009**
N-Acetylaspartic Acid	**1.44**	**1.22 - 1.69**	**9.72E-06**	**0.001**	**1.44**	**1.01E-05**	**0.0009**
4-Acetamidobutanoate	**1.46**	**1.22 - 1.73**	**0.00002**	**0.001**	**1.43**	**5.32E-05**	**0.002**
Homoarginine	**0.71**	**0.60 - 0.83**	**0.00002**	**0.001**	**0.71**	**2.88E-05**	**0.002**
Niacinamide	**0.75**	**0.65 - 0.85**	**0.00001**	**0.001**	**0.77**	**3.47E-05**	**0.002**
Trimethylbenzene	**0.73**	**0.62 - 0.85**	**0.00004**	**0.002**	**0.74**	**0.0001**	**0.003**
36:2 PE	**1.41**	**1.18 - 1.66**	**0.00006**	**0.002**	**1.70**	**7.66E-07**	**0.0002**
2-Hydroxyglutaric Acid	**1.36**	**1.16 - 1.58**	**0.00008**	**0.003**	**1.35**	**0.0001**	**0.003**
NMMA	**0.75**	**0.64 - 0.86**	**0.00010**	**0.003**	**0.74**	**9.15E-05**	**0.003**
Oxaloacetic Acid	**1.36**	**1.16 - 1.59**	**0.0001**	**0.003**	**1.32**	**0.0006**	**0.015**
Pseudouridine	**1.48**	**1.20 - 1.82**	**0.0002**	**0.005**	**1.43**	**0.001**	**0.018**
DMGV	**1.47**	**1.19 - 1.81**	**0.0003**	**0.006**	**1.43**	**0.0007**	**0.016**
16:0 SM	**1.46**	**1.17 - 1.81**	**0.0006**	**0.01**	**1.63**	**5.66E-05**	**0.002**
Biliverdin	**0.76**	**0.65 - 0.89**	**0.0007**	**0.01**	**0.77**	**0.001**	**0.018**
Lysine	**0.78**	**0.67 - 0.90**	**0.0008**	**0.01**	**0.79**	**0.001**	**0.019**
Myristoleate	**0.77**	**0.66 - 0.90**	**0.0008**	**0.01**	**0.78**	**0.001**	**0.019**
18:0 LPE B	**0.77**	**0.65 - 0.90**	**0.0009**	**0.02**	**0.78**	**0.002**	**0.023**
4-Hydroxy-3-Methylacetophenone	**0.79**	**0.67 - 0.91**	**0.001**	**0.02**	**0.78**	**0.001**	**0.019**
Indole-3-Lactic Acid	**1.31**	**1.11 - 1.55**	**0.001**	**0.02**	**1.35**	**0.0009**	**0.018**
Histidine	**0.78**	**0.66 - 0.91**	**0.001**	**0.02**	**0.77**	**0.001**	**0.021**
Cystine	**1.39**	**1.13 - 1.71**	**0.002**	**0.02**	**1.38**	**0.002**	**0.026**
N2,N2 - Dimethylguanosine	**1.32**	**1.10 - 1.57**	**0.002**	**0.02**	**1.29**	**0.004**	**0.045**
34:2 PE	**1.30**	**1.10 - 1.52**	**0.002**	**0.02**	**1.45**	**0.0002**	**0.004**
1-Methyladenosine	**1.33**	**1.10 - 1.59**	**0.002**	**0.03**	**1.29**	**0.006**	**0.051**
36:3 PE Plasmalogen	**1.31**	**1.10 - 1.56**	**0.002**	**0.03**	**1.34**	**0.002**	**0.026**
Arginine	**0.80**	**0.68 - 0.93**	**0.004**	**0.04**	**0.79**	**0.004**	**0.042**
1,5 Anhydroglucitol	**0.79**	**0.67 - 0.93**	**0.005**	**0.05**	**0.80**	**0.006**	**0.051**
Homogentisic Acid	**1.29**	**1.08 - 1.53**	**0.004**	**0.05**	**1.27**	**0.008**	**0.061**
2-Deoxyuridine	**1.31**	**1.08 - 1.59**	**0.005**	**0.05**	**1.28**	**0.010**	**0.074**
16:1 LPC	**0.79**	**0.67 - 0.93**	**0.005**	**0.05**	**0.79**	**0.004**	**0.045**
16:1 LPC Plasmalogen	**0.80**	**0.68 - 0.93**	**0.005**	**0.05**	**0.80**	**0.005**	**0.051**
N-Acetyltryptophan	**1.26**	**1.07 - 1.47**	**0.005**	**0.05**	**1.28**	**0.004**	**0.045**
Malic Acid	**1.26**	**1.06 - 1.48**	**0.006**	**0.06**	**1.24**	**0.011**	**0.080**
Methionine	**0.79**	**0.66 - 0.94**	**0.008**	**0.07**	**0.79**	**0.008**	**0.063**
Glycochenodeoxycholic Acid	**1.23**	**1.05 - 1.42**	**0.008**	**0.07**	**1.25**	**0.004**	**0.045**

Leucine	**0.79**	**0.65 - 0.94**	**0.009**	**0.07**	**0.78**	**0.007**	**0.056**
36:2 PC	**1.26**	**1.05 - 1.51**	**0.009**	**0.08**	**1.28**	**0.008**	**0.061**
Uridine	**0.82**	**0.70 - 0.95**	**0.01**	**0.08**	**0.81**	**0.006**	**0.051**
N4-Acetylcytidine	1.25	1.05 - 1.49	0.01	0.08	1.23	0.022	0.133
D-Gluconic Acid	1.30	1.06 - 1.58	0.01	0.08	1.27	0.028	0.147
20:1 LPC	0.82	0.70 - 0.96	0.01	0.08	0.83	0.018	0.113
18:3 LPC	0.82	0.69 - 0.96	0.01	0.08	0.82	0.015	0.102
Aconitic Acid	**1.38**	**1.07 - 1.79**	**0.01**	**0.08**	**1.40**	**0.011**	**0.076**
Fumaric Acid	**1.21**	**1.03 - 1.41**	**0.01**	**0.09**	**1.23**	**0.008**	**0.061**
18:0 SM	1.25	1.04 - 1.50	0.02	0.10	1.25	0.018	0.113

Covariates in Model 2: age, sex, batch, total cholesterol, high-density lipoprotein, hypertension, systolic blood pressure, body mass index, diabetes status, estimated glomerular filtration rate, smoking status, and statin medication use.

eTable 9. Metabolites Associated With Coronary Artery Calcium in the Jackson Heart Study Cohort: Adjusted for Age, Sex, and Batch

Metabolites associations with log (CAC+1)

Metabolite	β	95% CI	p-value	FDR q-value
34:1 DAG	0.28	0.16 - 0.40	3.40E-06	0.0002
34:2 PE	0.29	0.17 - 0.41	2.60E-06	0.0002
36:4 PE	0.30	0.17 - 0.42	1.60E-06	0.0002
38:4 PE	0.29	0.16 - 0.41	3.90E-06	0.0002
34:3 DAG or TAG Fragment	0.27	0.15 - 0.39	6.30E-06	0.0003
36:2 PE	0.28	0.15 - 0.40	9.10E-06	0.0004
Urate	0.26	0.13 - 0.39	5.70E-05	0.002
Glutamine	-0.24	-0.36 - -0.12	8.70E-05	0.003
2-Hydroxyglutaric Acid	0.24	0.11 - 0.36	0.0002	0.004
20:4 LPE	0.23	0.10 - 0.35	0.0002	0.004
N-Acetylputrescine	0.24	0.11 - 0.36	0.0002	0.004
36:3 DAG or TAG Fragment	0.23	0.11 - 0.36	0.0002	0.004
40:6 PE	0.23	0.10 - 0.35	0.0003	0.006
Xanthosine	0.22	0.10 - 0.34	0.0003	0.007
Malic Acid	0.23	0.10 - 0.35	0.0004	0.007
Glycine	-0.21	-0.33 - -0.10	0.0004	0.007
30:0 PC	0.21	0.09 - 0.33	0.0004	0.007
46:2 TAG	0.21	0.09 - 0.33	0.0004	0.007
18:1 LPE	0.21	0.08 - 0.33	0.0007	0.01
34:4 PC	0.21	0.08 - 0.33	0.0009	0.01
46:3 TAG	0.20	0.08 - 0.32	0.0009	0.01
18:0 LPE - B	-0.19	-0.30 - -0.08	0.001	0.02
Glutamate	0.19	0.07 - 0.31	0.001	0.02
20:0 LPE	-0.18	-0.30 - -0.07	0.002	0.02
34:3 PC Plasmalogen	-0.19	-0.31 - -0.07	0.002	0.02
1,5 Anhydroglucitol	-0.22	-0.35 - -0.08	0.002	0.02
38:6 PE	0.19	0.06 - 0.31	0.002	0.02
Cotinine	0.20	0.06 - 0.33	0.003	0.03
2-Hydroxybutyric Acid	0.19	0.06 - 0.31	0.003	0.03
1-Methylnicotinamide	-0.18	-0.29 - -0.06	0.003	0.03
24:1 Ceramide (d18:1/24:1(15Z))	0.18	0.06 - 0.30	0.003	0.03
Cortisol	0.18	0.06 - 0.30	0.003	0.03
Alanine	0.17	0.05 - 0.29	0.005	0.04
16:0 Ceramide (d18:1/24:1(15Z))	0.17	0.05 - 0.29	0.005	0.04
C4-Carnitine	0.18	0.05 - 0.31	0.005	0.04
Histidine	-0.18	-0.3 - -0.05	0.005	0.04
N-Acetylleucine	0.16	0.04 - 0.28	0.006	0.05
N-Acetyltryptophan	0.18	0.05 - 0.31	0.006	0.05

Aconitic Acid	0.16	0.04 - 0.28	0.007	0.05
α-Ketoglutaric Acid	0.17	0.04 - 0.30	0.006	0.05
16:0 LPE	0.16	0.04 - 0.28	0.007	0.05
Citrulline	-0.18	-0.31 - -0.05	0.006	0.05
Proline	0.17	0.04 - 0.29	0.007	0.05
36:4 DAG or TAG Fragment	0.17	0.04 - 0.29	0.007	0.05
DMGV	0.18	0.04 - 0.31	0.008	0.05
2-Aminooctanoate	-0.16	-0.27 - -0.04	0.009	0.06
18:3 LPE	0.16	0.03 - 0.28	0.009	0.06
Uridine	-0.18	-0.31 - -0.04	0.01	0.06
Allantoin	0.17	0.04 - 0.30	0.01	0.06
D-Gluconic Acid	0.19	0.04 - 0.34	0.01	0.07
C3-Carnitine	0.16	0.03 - 0.29	0.01	0.07
Pipecolic Acid	0.15	0.03 - 0.27	0.01	0.07
2-Ketoisovaleric Acid	0.16	0.03 - 0.29	0.01	0.07
Arachindonoyl-Phenylalanine	0.18	0.03 - 0.32	0.01	0.07
22:6 LPE	0.16	0.03 - 0.28	0.01	0.08
Glycocholate	0.15	0.02 - 0.27	0.01	0.08
N-Acetylhistidine	-0.16	-0.29 - -0.03	0.02	0.08
Carnitine	0.15	0.02 - 0.28	0.02	0.08
Linoleic Acid	-0.19	-0.34 - -0.03	0.02	0.09
18:0 LPE-A	0.14	0.02 - 0.26	0.02	0.09
Imidazole Propionate	0.15	0.02 - 0.27	0.02	0.09
N-Methylproline	-0.15	-0.26 - -0.03	0.02	0.09
Niacinamide	-0.14	-0.26 - -0.02	0.02	0.09
32:2 PC	0.14	0.02 - 0.27	0.02	0.09
4-Acetamidobutanoate	0.19	0.02 - 0.36	0.02	0.09

eTable 10. Metabolites Associated With Coronary Artery Calcium in a Fully-Adjusted Model of the Jackson Heart Study Cohort With Additional Adjustment for Statin Medication Receipt

	Model 2				Model 2 Plus Statin Adjustment			
Metabolite	**β**	**95% CI**	**p-value**	**FDR q-value**	**β**	**95% CI**	**p-value**	**FDR q-value**
Xanthosine	0.24	0.12 - 0.37	0.0002	0.045	0.21	0.07 - 0.34	0.002	0.11
N-Acetylputrescine	0.23	0.1 - 0.35	0.0003	0.045	0.20	0.06 -0.33	0.003	0.11
18:0 LPE-B	-0.19	-0.30 - -0.08	0.001	0.07	-0.19	- 0.32 - -0.07	0.001	0.11
34:2 PE	0.20	0.08 - 0.33	0.001	0.07	0.25	0.12 - 0.39	0.0002	0.06
36:4 PE	0.21	0.08 - 0.33	0.0010	0.07	0.23	0.09 - 0.37	0.0009	0.09
2-Hydroxyglutaric Acid	0.18	0.06 - 0.30	0.003	0.09	0.19	0.05 - 0.32	0.005	0.12
18:1 LPE	0.19	0.06 - 0.31	0.003	0.09	0.20	0.06 - 0.33	0.003	0.11
20:0 LPE	-0.18	-0.30 - -0.07	0.002	0.09	-0.18	-0.31 - -0.06	0.003	0.11
20:4 LPE	0.19	0.07 - 0.31	0.002	0.09	0.19	0.05 - 0.32	0.005	0.12

log(CAC+1) was used as the outcome. Covariates used for adjustment in Model 2 include age, sex, batch, total cholesterol, high-density lipoprotein, hypertension, systolic blood pressure, body mass index, diabetes status, estimated glomerular filtration rate, smoking status, and time between Visit 1 and Visit 2. Statin medication use was the additional adjustment in the second set of results in the right panel.

eTable 11. Adjustment for Socioeconomic Status Factors

Bold indicates metabolites that remained significant (FDR q < 0.1) with additional adjustments

	JHS - Fully Adjusted Model				JHS - Fully Adjusted Model + SES Factors			
Metabolite	**HR**	**95% CI**	**p-value**	**FDR q-value**	**HR**	**95% CI**	**p-value**	**FDR q-value**
1-Methylnicotinamide	**0.69**	**0.59 - 0.81**	**3.62E-06**	**0.001**	**0.73**	**0.61 - 0.86**	**0.0001**	**0.005**
Linoleoyl Ethanolamide	**1.38**	**1.19 - 1.60**	**0.00001**	**0.001**	**1.44**	**1.23 - 1.68**	**3.86E-06**	**0.001**
N-Acetylaspartic Acid	**1.44**	**1.22 - 1.69**	**9.72E-06**	**0.001**	**1.43**	**1.19 - 1.71**	**0.0001**	**0.005**
4-Acetamidobutanoate	**1.46**	**1.22 - 1.73**	**0.00002**	**0.001**	**1.43**	**1.19 - 1.72**	**0.0001**	**0.005**
Homoarginine	**0.71**	**0.60 - 0.83**	**0.00002**	**0.001**	**0.72**	**0.61 - 0.86**	**0.0002**	**0.006**
Niacinamide	**0.75**	**0.65 - 0.85**	**0.00001**	**0.001**	**0.78**	**0.68 - 0.90**	**0.0005**	**0.01**
Trimethylbenzene	**0.73**	**0.62 - 0.85**	**0.00004**	**0.002**	**0.77**	**0.65 - 0.91**	**0.002**	**0.03**
36:2 PE	**1.41**	**1.18 - 1.66**	**0.00006**	**0.002**	**1.43**	**1.19 - 1.71**	**0.0001**	**0.005**
2-Hydroxyglutaric Acid	**1.36**	**1.16 - 1.58**	**0.00008**	**0.003**	**1.35**	**1.15 - 1.59**	**0.0002**	**0.006**
NMMA	**0.75**	**0.64 - 0.86**	**0.00010**	**0.003**	**0.73**	**0.62 - 0.85**	**0.0001**	**0.005**
Oxaloacetic Acid	**1.36**	**1.16 - 1.59**	**0.0001**	**0.003**	**1.33**	**1.10 - 1.60**	**0.002**	**0.03**
Pseudouridine	**1.48**	**1.20 - 1.82**	**0.0002**	**0.005**	**1.39**	**1.11 - 1.74**	**0.004**	**0.04**
DMGV	**1.47**	**1.19 - 1.81**	**0.0003**	**0.006**	**1.38**	**1.11 - 1.72**	**0.004**	**0.04**
16:0 SM	**1.46**	**1.17 - 1.81**	**0.0006**	**0.01**	**1.55**	**1.22 - 1.95**	**0.0002**	**0.006**
Biliverdin	**0.76**	**0.65 - 0.89**	**0.0007**	**0.01**	**0.76**	**0.63 - 0.89**	**0.001**	**0.02**
Lysine	**0.78**	**0.67 - 0.90**	**0.0008**	**0.01**	**0.78**	**0.67 - 0.91**	**0.001**	**0.03**
Myristoleate	0.77	0.66 - 0.90	0.0008	0.01	0.81	0.68 - 0.96	0.01	0.10
18:0 LPE B	**0.77**	**0.65 - 0.90**	**0.0009**	**0.02**	**0.74**	**0.62 - 0.88**	**0.0005**	**0.01**
4-Hydroxy-3-Methylacetophenone	0.79	0.67 - 0.91	0.001	0.02	0.83	0.70 - 0.98	0.02	0.14
Indole-3-Lactic Acid	**1.31**	**1.11 - 1.55**	**0.001**	**0.02**	**1.33**	**1.11 - 1.58**	**0.002**	**0.03**
Histidine	**0.78**	**0.66 - 0.91**	**0.001**	**0.02**	**0.74**	**0.63 - 0.88**	**0.0005**	**0.01**
Cystine	**1.39**	**1.13 - 1.71**	**0.002**	**0.02**	**1.37**	**1.09 - 1.70**	**0.005**	**0.05**
N2,N2 - Dimethylguanosine	1.32	1.10 - 1.57	0.002	0.02	1.26	1.04 - 1.51	0.02	0.11
34:2 PE	**1.30**	**1.10 - 1.52**	**0.002**	**0.02**	**1.28**	**1.07 - 1.53**	**0.005**	**0.05**
1-Methyladenosine	**1.33**	**1.10 - 1.59**	**0.002**	**0.03**	**1.32**	**1.09 - 1.60**	**0.004**	**0.04**
36:3 PE Plasmalogen	**1.31**	**1.10 - 1.56**	**0.002**	**0.03**	**1.34**	**1.11 - 1.61**	**0.002**	**0.03**
Arginine	**0.80**	**0.68 - 0.93**	**0.004**	**0.04**	**0.77**	**0.65 - 0.91**	**0.002**	**0.03**
1,5 Anhydroglucitol	**0.79**	**0.67 - 0.93**	**0.005**	**0.05**	**0.72**	**0.60 - 0.85**	**9.75E-05**	**0.005**
Homogentisic Acid	**1.29**	**1.08 - 1.53**	**0.004**	**0.05**	**1.31**	**1.07 - 1.58**	**0.006**	**0.06**
2-Deoxyuridine	1.31	1.08 - 1.59	0.005	0.05	1.24	1.01 - 1.53	0.04	0.18
16:1 LPC	**0.79**	**0.67 - 0.93**	**0.005**	**0.05**	**0.76**	**0.63 - 0.91**	**0.003**	**0.04**
16:1 LPC Plasmalogen	**0.80**	**0.68 - 0.93**	**0.005**	**0.05**	**0.77**	**0.65 - 0.91**	**0.003**	**0.03**
N-Acetyltryptophan	1.26	1.07 - 1.47	0.005	0.05	1.22	1.03 - 1.45	0.02	0.13
Malic Acid	**1.26**	**1.06 - 1.48**	**0.006**	**0.06**	**1.26**	**1.06 - 1.50**	**0.008**	**0.06**
Methionine	**0.79**	**0.66 - 0.94**	**0.008**	**0.07**	**0.75**	**0.62 - 0.90**	**0.003**	**0.03**
Glycochenodeoxycholic Acid	1.23	1.05 - 1.42	0.008	0.07	1.17	0.99 - 1.37	0.05	0.22
Leucine	**0.79**	**0.65 - 0.94**	**0.009**	**0.07**	**0.76**	**0.63 - 0.92**	**0.005**	**0.05**

36:2 PC	1.26	1.05 - 1.51	0.009	0.08	1.27	1.04 - 1.53	0.02	0.11
Uridine	0.82	0.70 - 0.95	0.01	0.08	0.82	0.69 - 0.97	0.02	0.13
N4-Acetylcytidine	1.25	1.05 - 1.49	0.01	0.08	1.19	0.98 - 1.44	0.07	0.25
D-Gluconic Acid	1.30	1.06 - 1.58	0.01	0.08	1.24	1.01 - 1.53	0.04	0.21
20:1 LPC	0.82	0.70 - 0.96	0.01	0.08	0.84	0.71 - 0.99	0.03	0.16
18:3 LPC	**0.82**	**0.69 - 0.96**	**0.01**	**0.08**	**0.78**	**0.65 - 0.92**	**0.003**	**0.04**
Aconitic Acid	**1.38**	**1.07 - 1.79**	**0.01**	**0.08**	**1.44**	**1.09 - 1.88**	**0.009**	**0.07**
Fumaric Acid	1.21	1.03 - 1.41	0.01	0.09	1.18	1.01 - 1.38	0.03	0.16
18:0 SM	1.25	1.04 - 1.50	0.02	0.10	1.26	1.04 - 1.52	0.02	0.12

Covariates adjusted for in JHS include age, sex, batch, total cholesterol, high-density lipoprotein, hypertension, systolic blood pressure, body mass index, diabetes status, estimated glomerular filtration rate, smoking status, and statin medication use. Socioeconomic factors adjust for included education level, income level, and health insurance status.

eTable 12. Participant Characteristics of the Women's Health Initiative Cohort

	Cases	Controls	p-value
N Total:	793	795	
Age, mean	67.1	66.8	0.45
Body Mass Index, mean	29	27.9	< 0.001
Diabetes, n (%)	143 (18)	55 (6.9)	< 0.001
Hypertension, n (%)	506 (63.8)	374 (47)	< 0.001
Systolic Blood Pressure (mmHg), mean	136	130.2	< 0.001
Total Cholesterol (mg/dL), mean	233.1	233.1	0.99
HDL, mean	49.4	54.9	< 0.001
Current Smoker, n (%)	104 (13.1)	61 (7.7)	< 0.001
Statin Use, n (%)	103 (13)	74 (9.3)	0.02
Race/ethnicity, n (%)			
White	608 (76.7)	611 (76.9)	
Black	109 (13.7)	108 (13.6)	
Others*	76 (9.6)	76 (9.6)	

HDL: High-density Lipoprotein Cholesterol

* Others indicates self-reported American Indian or Alaskan Native, Asian or Pacific Islander, Hispanic/Latino, and others.

eTable 13. Replication of Metabolite Findings in the Age-, Sex-, and Batch-Adjusted Analysis

Metabolites listed below were associated with iCHD in JHS in the age, sex and batch adjusted model and available for replication in WHI. Metabolites with at least nominally significant p-values and concordant direction of effect in WHI are in bold.

	JHS - Model 1				WHI - Model 1		
Metabolite	**HR**	**95% CI**	**p-value**	**FDR q-value**	**HR**	**95% CI**	**p-value**
4-Acetamidobutanoate	**1.40**	**1.24 - 1.57**	**2.11E-08**	**3.19E-06**	**1.18**	**1.05 - 1.32**	**0.005**
36:2 PE	**1.56**	**1.33 - 1.82**	**1.67E-08**	**3.19E-06**	**1.17**	**1.05 - 1.30**	**0.004**
Linoleoyl Ethanolamide	**1.41**	**1.23 - 1.60**	**1.85E-07**	**1.62E-58**	**2.15**	**1.19 - 3.90**	**0.01**
34:2 PE	**1.47**	**1.25 - 1.71**	**8.75E-07**	**5.29E-05**	**1.19**	**1.07 - 1.32**	**0.001**
1.-Methylnicotinamide	**0.70**	**0.60 - 0.82**	**3.52E-06**	**0.0002**	**0.86**	**0.78 - 0.96**	**0.005**
Trimethylbenzene	0.71	0.61 - 0.82	5.45E-06	0.0002	1.18	1.05 - 1.32	0.004
Biliverdin	**0.71**	**0.61 - 0.83**	**8.04E-06**	**0.0002**	**0.84**	**0.74 - 0.95**	**0.004**
Homoarginine	**0.71**	**0.61 - 0.83**	**9.26E-06**	**0.0002**	**0.84**	**0.75 - 0.93**	**0.001**
Pseudouridine	**1.36**	**1.18 - 1.56**	**9.47E-06**	**0.0002**	**1.23**	**1.10 - 1.38**	**0.0003**
Malic Acid	**1.37**	**1.18 - 1.59**	**3.49E-05**	**0.0008**	**1.17**	**1.04 - 1.32**	**0.007**
N-Acetylaspartic Acid	1.36	1.17 - 1.57	4.36E-05	0.0009	0.87	0.77 - 0.98	0.03
Niacinamide	0.75	0.65 - 0.86	5.18E-05	0.0010	0.98	0.88 - 1.08	0.63
Myristoleate	0.75	0.65 - 0.87	7.67E-05	0.001	1.01	0.90 - 1.12	0.90
N-Acetylputrescine	1.33	1.15 - 1.54	9.02E-05	0.001	0.83	0.74 - 0.93	0.002
38:4 PE	1.35	1.16 - 1.57	9.86E-05	0.001	1.03	0.93 - 1.14	0.60
1-Methyladenosine	1.35	1.15 - 1.56	0.0001	0.002	0.99	0.89 - 1.09	0.82
Arginine	**0.76**	**0.66 - 0.87**	**0.0001**	**0.002**	**0.90**	**0.81 - 1.00**	**0.06**
Histidine	**0.76**	**0.66 - 0.88**	**0.0002**	**0.003**	**0.77**	**0.69 - 0.87**	**8.48E-06**
36:4 PE	1.32	1.13 - 1.53	0.0003	0.004	1.07	0.96 - 1.18	0.21
NMMA	**0.78**	**0.68 - 0.90**	**0.0005**	**0.006**	**0.87**	**0.78 - 0.97**	**0.01**
Uridine	**0.78**	**0.67 -0.90**	**0.0007**	**0.007**	**0.77**	**0.69 - 0.86**	**1.42E-06**
Aconitic Acid	**1.49**	**1.18 - 1.88**	**0.0008**	**0.008**	**1.21**	**1.07 - 1.36**	**0.002**
1-Methylguanine	**1.27**	**1.11 - 1.46**	**0.0008**	**0.008**	**0.76**	**0.66 - 0.86**	**3.92E-05**
N4-Acetylcytidine	**1.27**	**1.10 - 1.47**	**0.001**	**0.010**	**1.28**	**1.14 - 1.43**	**1.79E-05**
16:1 LPC Plasmalogen	0.79	0.68 - 0.91	0.001	0.01	1.00	0.90 - 1.11	1.00
N2,N2-Dimethylguanosine	**1.27**	**1.09 - 1.46**	**0.001**	**0.01**	**1.29**	**1.12 - 1.48**	**0.0004**
C4-Carnitine	1.27	1.09 - 1.48	0.002	0.02	0.99	0.90 - 1.10	0.89
Lysine	**0.81**	**0.71 - 0.93**	**0.003**	**0.02**	**0.85**	**0.76 - 0.94**	**0.002**
18:1 LPC Plasmalogen	**0.80**	**0.69 - 0.93**	**0.003**	**0.02**	**1.17**	**1.05 - 1.30**	**0.003**
Methionine	**0.80**	**0.68 - 0.93**	**0.005**	**0.03**	**0.83**	**0.75 - 0.92**	**0.0003**
Glycochenodeoxycholic Acid	1.22	1.05 - 1.40	0.007	0.04	1.09	0.99 - 1.21	0.09
16:1 LPC	0.81	0.7 - 0.94	0.007	0.04	1.01	0.91 - 1.13	0.86
20:1 LPC	0.83	0.72 - 0.96	0.009	0.05	1.03	0.93 - 1.15	0.55
C4-OH-Carnitine	**1.21**	**1.04 - 1.39**	**0.01**	**0.06**	**1.17**	**1.06 - 1.30**	**0.002**
N6-Acetyllysine	**1.22**	**1.04 - 1.43**	**0.01**	**0.06**	**1.17**	**1.05 - 1.31**	**0.004**
Hippurate	1.21	1.04 - 1.41	0.01	0.06	1.00	0.90 - 1.11	0.98

N-Carbamoyl-Beta-Alanine	1.19	1.03 - 1.37	0.01	0.07	1.16	1.00 - 1.35	0.05
Threonine	**0.83**	**0.71 - 0.96**	**0.01**	**0.07**	**0.86**	**0.77 - 0.95**	**0.005**
Methylhistidine	1.21	1.03 - 1.41	0.02	0.08	0.98	0.89 - 1.09	0.73
24:0 LPC	0.84	0.73 - 0.97	0.02	0.08	0.91	0.81 - 1.01	0.08
36:3 PE Plasmalogen	**1.20**	**1.03 - 1.40**	**0.02**	**0.09**	**1.21**	**1.09 - 1.35**	**0.0004**
18:2 LPE	1.19	1.02 - 1.38	0.02	0.09	1.05	0.95 - 1.18	0.34
Xanthine	0.83	0.70 - 0.97	0.02	0.09	0.97	0.87 - 1.08	0.58

Bold indicates metabolites that replicated with a significance level $p < 0.05$.

eTable 14. Metabolite Risk Score

MRS constructed in JHS with 46 metabolites associated with iCHD. Validation in WHI with 32 out of the 46 metabolites available for replication in WHI.

	JHS			WHI		
MRS scores	**HR**	**95% CI**	**p-value**	**HR**	**95%_CI**	**p-value**
MRS	4.5	3.3 – 6.2	6.5E-21	1.67	1.23 - 2.28	0.001
MRS Top 10th vs. Bottom 90th	3.6	2.4 – 5.3	2.7E-10	2.22	1.28 - 3.86	0.004

MRS score indicates increase in risk of iCHD for each standard deviation increase in MRS.

Metabolite Risk Scores for Incident CHD by Self-Identified Race in WHI

MRS constructed in JHS with 46 metabolites associated with iCHD. Validation in WHI by self-identified race using 32 out of the 46 metabolites available for replication in WHI

	WHI		
MRS scores	**HR**	**95% CI**	**p-value**
AA Only	1.58	1.12 – 2.23	0.009
NHW Only	1.29	0.49 – 3.39	0.6

MRS score indicates increase in risk of iCHD for each standard deviation increase in MRS.

eTable 15. β Comparisons Between Self-Identified Race in the Women's Health Initiative Cohort

	WHI African Americans			WHI Non-Hispanic White			
Metabolite	**β AA**	**SE**	**p-value**	**β NHW**	**SE**	**p-value**	**Δβ p WHI AA vs. NHW**
Hippurate	-0.52	0.231	0.02	0.05	0.065	0.44	0.02
Methionine	-0.58	0.227	0.01	-0.08	0.064	0.24	0.03
3-Hydroxyhippurate	-0.37	0.223	0.09	0.11	0.069	0.10	0.04
Choline	0.38	0.218	0.08	-0.06	0.067	0.36	0.05
Leucine	-0.50	0.218	0.02	-0.10	0.069	0.14	0.08
16:0 SM	0.76	0.352	0.03	0.13	0.086	0.14	0.08

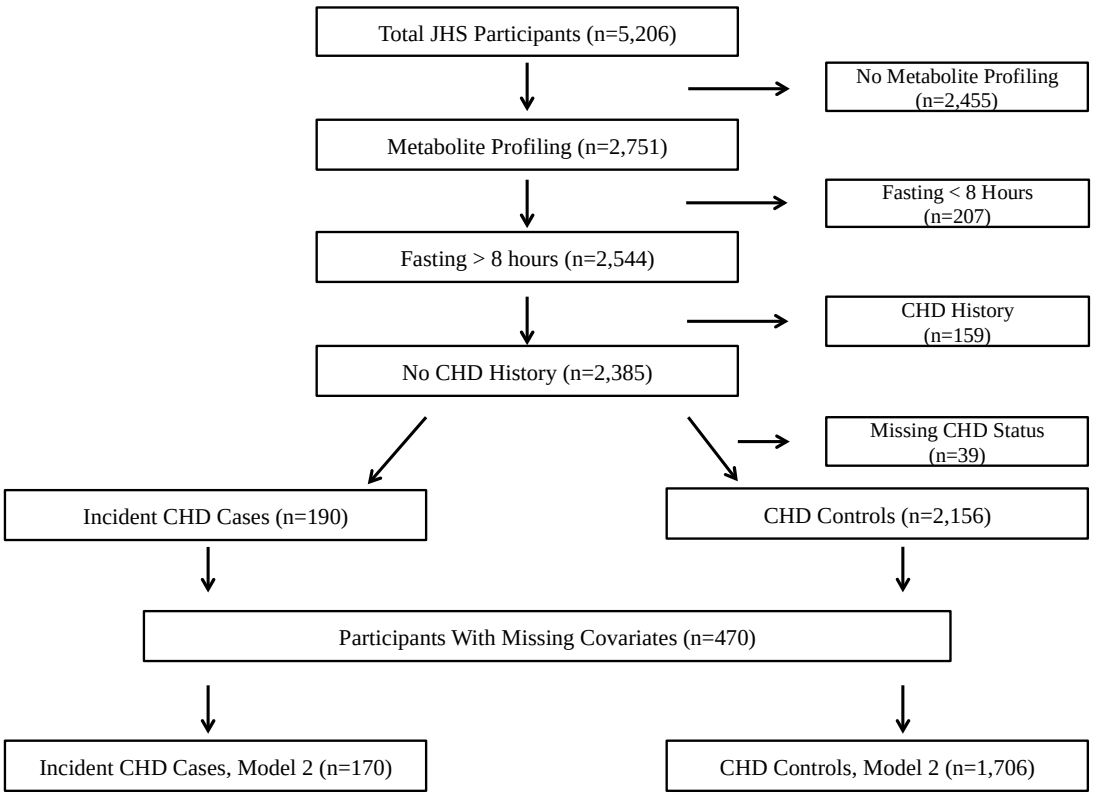
β indicates the association between each metabolite and risk of iCHD by race group. Δβ p indicates statistical significance of difference between the reported β's by race group.

eTable 16. β Comparisons Between Self-Identified Race Among African American Individuals in the Jackson Heart Study Cohort vs Non-Hispanic White Individuals in the Women's Health Initiative Cohort

Metabolite	JHS β	JHS p-value	JHS FDR q-value	WHI NHW β	WHI NHW p-value	p-value for Δβ JHS vs NHW
1-Methylnicotinamide	-0.37	3.60E-06	0.001	-0.19	0.005	0.08
Linoleoyl Ethanolamide	0.32	1.00E-05	0.001	0.37	0.11	0.86
N-Acetylaspartic Acid*	0.37	9.70E-06	0.001	0.03	0.74	0.002
4-Acetamidobutanoate	0.38	1.00E-05	0.001	0.18	0.01	0.09
Homoarginine	-0.35	2.0E_05	0.001	-0.15	0.03	0.07
Niacinamide*	-0.29	1.00E-05	0.001	-0.07	0.27	0.01
Trimethylbenzene	**-0.32**	**4.00E-05**	**0.002**	**0.19**	**0.01**	**1.90E-06**
36:2 PE*	0.34	6.00E-05	0.002	-0.07	0.35	0.0002
NMMA	-0.29	9.00E-05	0.003	-0.14	0.05	0.13
Pseudouridine*	0.39	0.0002	0.005	0.14	0.05	0.04
16:0 SM	0.38	0.0006	0.01	0.13	0.14	0.07
Biliverdin*	-0.27	0.0007	0.01	-0.04	0.61	0.04
Lysine	-0.25	0.0008	0.01	-0.15	0.02	0.32
Myristoleate*	-0.26	0.0008	0.01	0.07	0.32	0.001
Histidine	-0.25	0.001	0.02	-0.16	0.02	0.40
N2,N2 - Dimethylguanosine	0.28	0.002	0.02	0.09	0.20	0.10
34:2 PE*	0.26	0.002	0.02	-0.05	0.46	0.004
1-Methyladenosine*	0.28	0.002	0.03	-0.07	0.26	0.001
36:3 PE Plasmalogen	0.27	0.002	0.03	0.19	0.009	0.46
Arginine*	-0.23	0.004	0.04	0.05	0.51	0.008
16:1 LPC*	-0.23	0.005	0.05	0.01	0.86	0.02
16:1 LPC Plasmalogen*	-0.23	0.005	0.05	0.08	0.21	0.003
Malic Acid	0.23	0.006	0.06	0.13	0.07	0.37
Methionine	-0.23	0.008	0.07	-0.08	0.24	0.15
Glycochenodeoxycholic Acid	0.20	0.008	0.07	0.01	0.89	0.05
Leucine	-0.24	0.009	0.07	-0.10	0.14	0.24
36:2 PC	0.23	0.009	0.08	0.03	0.67	0.08
Uridine	-0.20	0.01	0.08	-0.19	0.004	0.98
N4-Acetylcytidine	0.23	0.01	0.08	0.18	0.009	0.68
20:1 LPC*	-0.20	0.01	0.08	0.06	0.35	0.01
Aconitic Acid	0.33	0.01	0.08	0.09	0.21	0.12
18:0 SM	0.22	0.02	0.09	0.09	0.25	0.27

β indicates the association between each metabolite and risk of iCHD by race group. Δβ p indicates statistical significance of difference between the reported β's by race group. Asterisk represents metabolites who had a significant p-value (<0.05) for a difference in β's by race group.

eFigure 1. Exclusions From the Jackson Heart Study Analysis



eFigure 2. Metabolite Classes Associated With Incident Coronary Heart Disease

Indoles and derivatives
Indole 3 Lactic Acid

Organooxygen compounds
4-Hydroxy-3-methylacetophenone

Pyrimidine nucleosides
Deoxyuridine

Fatty Acyls
Myristoleate (Omega-5 Fatty Acid)

Carboxylic acids and derivatives
Homoarginine, Lysine, Histidine, Cystine, Arginine, N-acetyltryptophan, NMMA, 4-Acetamidobutanoate

Purine nucleosides
N2,N2 Dimethylguanosine, 1- Methyladenosine

Keto acids and derivatives
Oxaloacetic Acid, DMGV

Tetrapyrroles and derivatives
Biliverdin

Nucleoside Analogues
Pesudouridine

Benzene & Derivatives
Trimethylbenzene, Homogentisic Acid

Pyridines and derivatives
1-Methylnicotinamide, Niacinamide

Organonitrogen compounds
16:0 SM

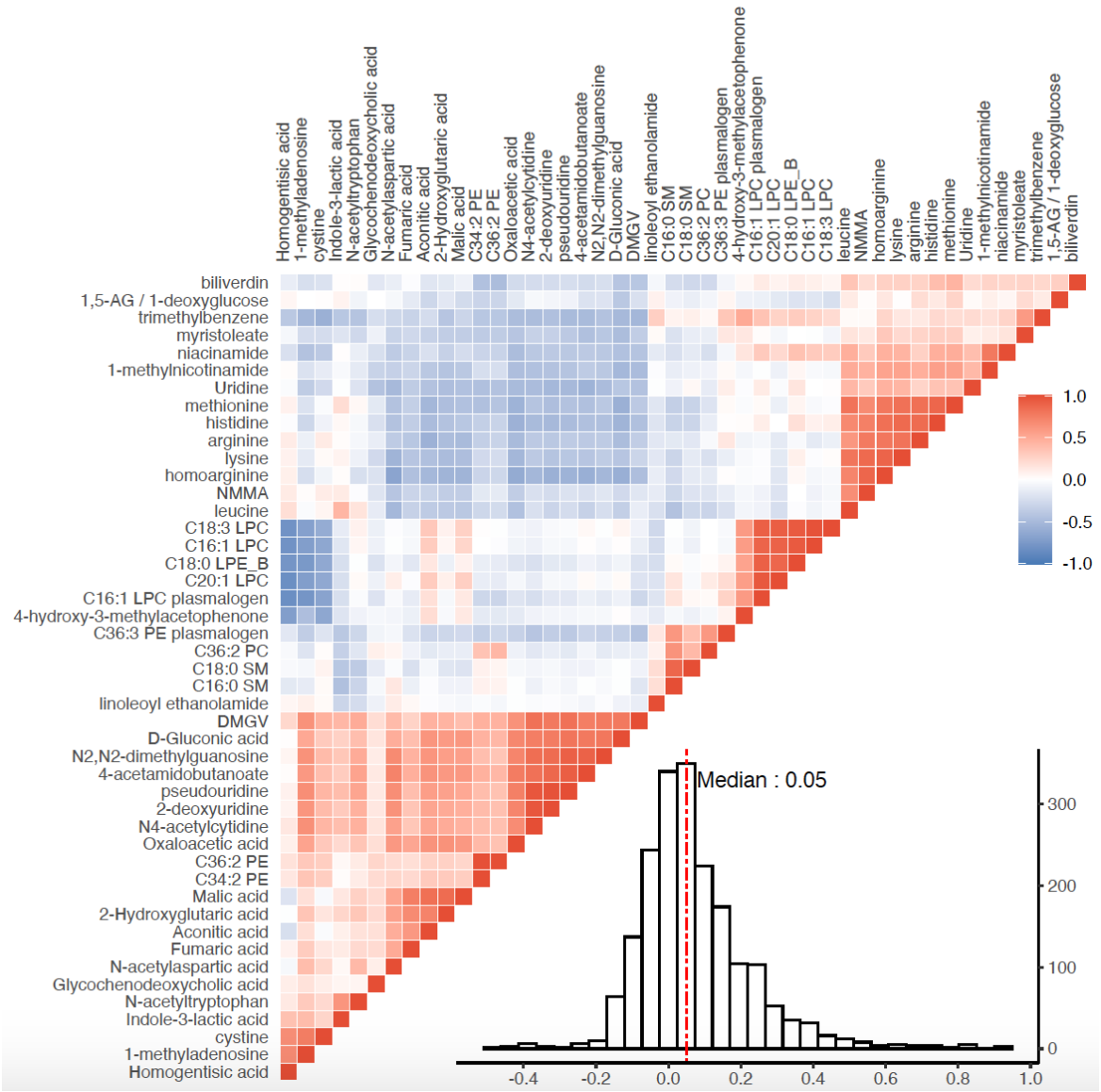
Glycerophospholipids
36:2 PE, 34:2 PE, 36:3 PE Plasmalogen, 18:0 LPE B, 16:1 LPC, 16:1 LPC Plasmalogen

Hydroxy acids and derivatives
2-Hydroxyglutaric Acid

Acetylated Amides
Acetylaspartic Acid, Linoleoyl ethanolamide

eFigure 3. Metabolite Correlations

Correlation matrix with darker tone of color representing stronger correlation between represented metabolites.

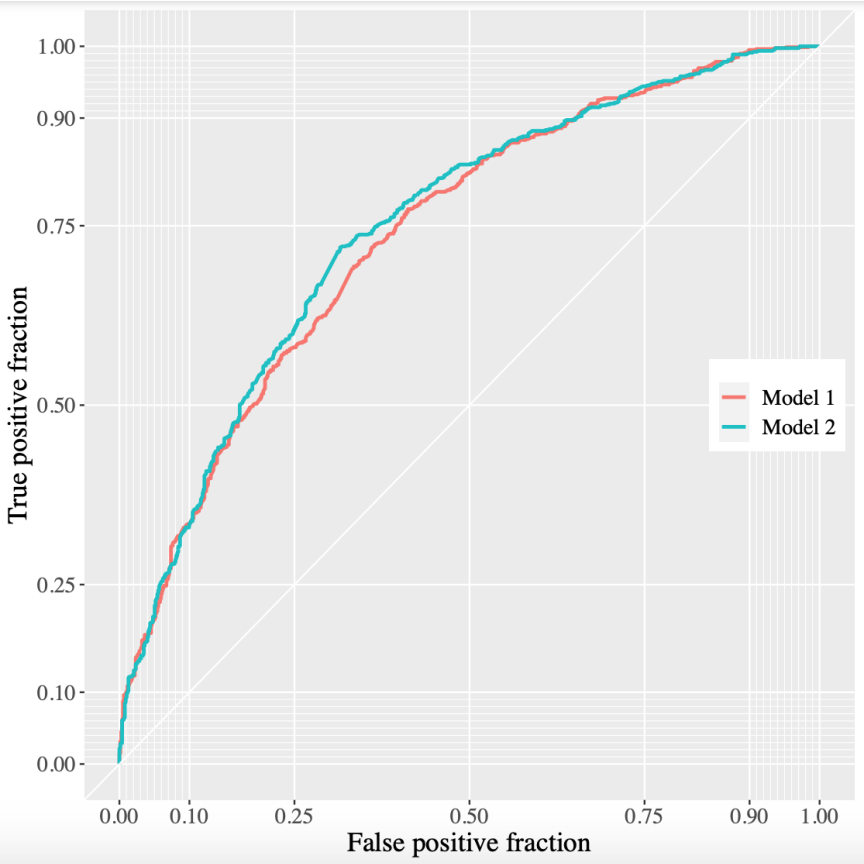


x-axis: r^2

y-axis: Number of metabolites pairs

eFigure 4. Receiver Operating Characteristic Curves for Metabolite Risk Score in the Women's Health Initiative Cohort

Receiver Operating Characteristic (ROC) curves of four prediction models. ROC curves representing the predictive value of traditional clinical risk factors + C-reactive protein (Model 1) and the added value of the MRS to Model 1 (Model 2).



WHI – ALL: C-statistic
Model 1: Clinical Risk Factors + C-Reactive Protein in WHI
Model 2: Model 2 + MRS

Model 1: 0.684; 95% Confidence Interval: (0.637-0.731)
Model 2: 0.706; 95% Confidence Interval: (0.660-0.752)

Δ C-Statistic:
Model 2 to Model 1 = 0.022

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