Supplementary Materials

Study population selection

In untargeted metabolomic analyses, to screen the MetS-associated metabolites, 120 MetS patients and 120 controls matched by age and sex were randomly selected from our previous cross-sectional survey on MetS in Hangzhou, Zhejiang, China, which was a questionnaire-based epidemiological interview started in 2010 and consisted of 862 MetS patients and 880 healthy controls. The detailed information of this population has been previously published[1]. To internally replicate the screened MetS-associated metabolites, 575 MetS patients and 582 healthy controls were randomly selected from the same cross-sectional survey other than subjects in the discovery dataset. External replication was performed using a targeted metabolomics approach in a sub-population of the Zhejiang Metabolic Syndrome Cohort, namely Xiazhi sub-cohort (N=1420), which was an ongoing community-based study started in 2009[2]. According to the same MetS criterion adopted in the untargeted metabolomics, 149 MetS patients and 253 controls were included in this sub-cohort and were selected as the external replication dataset.

Targeted metabolomics analyses

Sample pretreatment 600 ul dichloromethane was added to 150 ul thawed plasma sample, followed by 1ml methanol containing internal standards stock solution. After vortex for 30 seconds, the sample was centrifuged at 3000 rcf at 4◦C for 5 minutes. The lower layer (400 ul) was pipetted into a 2.0 mL tube and evaporated under nitrogen gas. The dried residuals then were re-dissolved using isopropanol solution and centrifuged at 3000 rcf at 4◦C for 5 minutes to perform the MS analysis. The upper layer (800ul) was pipetted into a 96-well plate and dried under nitrogen gas. The dried residuals were then reconstituted in acetonitrile-water (1:1) and centrifuged at 3000 rcf at 4◦C for 5 minutes to perform the MS analysis. To ensure data quality, the aliquots of quality control samples were obtained by pooling 20 ul re-dissolved and centrifuged samples. The QCs samples were injected at the beginning and end of the analyses and every fifteen injections across the test.

Chromatographic separation Agilent 1290 infinity liquid chromatography system (Agilent Technologies) was used to perform the analysis. Two columns including Waters, BEH C18 column (1.7 μm, 2.1 mm×100 mm) and Waters, BEH Amide column (1.7 μm, 2.1 mm×100 mm) were used. The flow rate was maintained at 0.3 mL/min. The sampler and column temperature were maintained at 4◦C and 35 ◦C, respectively. The injection volume was 4 μl. For the C18 column, the mobile phase consists of (A) 10 mM NH4HCOO with 0.1% formic acid in methanol-water (3:2, v/v) and (B) 10 mM NH4HCOO with 0.1% formic acid in acetonitrile/isopropanol (1:9, v/v). The gradient duration program was as follows: 3 min hold at 20% B, a linear increase from 20% B to 40% B in 2 min, 40% B to 75% B in 4 min, 75% B to 99% B in 0.1 min, 3.9 min hold at 99% B, a linear decrease from 99% B to 20% B in 0.1 min and 2.9 min equilibration at 20% B. For the Amide column, the mobile phase was composed of (A) 25 mM NH4HCOO with 0.1% formic acid in water (3:2, v/v) and (B) 25 mM NH4HCOO with 0.1% formic acid in acetonitrile. The gradient duration program was as follows: 1min hold at 85% B, a linear decrease from 85% B to 70% B in 10 min, 70% B to 40% B in 0.1 min, 0.9 min hold at 40% B, a linear increase from 40% B to 85% B in 0.1 min, 2.9 min equilibration at 85% B. UPLC system control and data analyses were performed by Xcalibur software (Version 3.2).

Mass Spectrometer parameters Thermo Scientific TSQ Altis Triple Quadrupole Mass Spectrometer equipped with an electrospray ionization (ESI) source was used to perform the analyses under positive and negative ion modes. The conditions were as follows: the spray voltages were 3800 V and 3500 V in positive ion mode and negative ion mode, respectively. The sheath gas flow was 30 arbitrary units (Arb).

The auxiliary gas flow was 10 Arb. The sweep gas was 8 Arb. The collision gas was 1.5 mTorr. The ion transfer tube temperature was 350 °C. The vaporizer temperature was 300 °C. The spray voltage was 3.0 kV. All targets were monitored by transition precursor and product in dynamic multiple reaction mode (MRM). The optimized MRM transition, ionization mode, collision energy and RF lens voltage are presented at Table S2. Thermo Scientific TraceFinde software (version 4.1) was applied to obtain the data.

Method validation For the calibration curve, 150 ul serial dilution of standards solutions were spiked with 1ml methanol containing internal standards (IS) stock. After vortex for 30 seconds, 600 ul dichloromethane was added. Subsequent sample preparation was the same as abovementioned protocol. The calibration curves were drawn according to the peak area ratios of the serial diluted standards to IS on respective column. As to those metabolites without IS, their calibration curves were obtained according to their chromatographically neighboring or structurally similar IS. The linearity, limit of quantification (LOQ) and stability of the method were assessed (Table S3), which showed a good linearity and a low limit of quantification. The concentrations were quantified in ng/ml. The peak with signal-to-noise ratio <3 was manually checked.

Statistical analysis for the metabolomics data

In untargeted metabolomics analyses, the Mann-Whitney U test was used to test the difference between the MetS and control groups. Multiple comparisons were corrected using the false discovery rate (FDR). A multivariate analysis was performed using an orthogonal partial least-squared discriminant analysis (OPLS-DA). The variable importance in the projection (VIP) was calculated by OPLS-DA, which revealed the contribution of each variable to the discrimination between the MetS patients and controls. Variables with adjusted FDR P-value <0.05 & VIP>1 were selected as the differential metabolites of MetS. The differential metabolites that had consistent effect directions in the discovery and internal validation datasets were included into the external validation. External validation was conducted on scaled data using logistic regression analysis after adjustment for age and sex. Metabolites with raw P-values <0.05, and consistent association effect directions were considered as successfully replicated. A subgroup analysis by sex was performed. Sensitivity analyses were carried out by excluding the subjects with CVD or with a history of drug use in the recent two weeks, including antihypertensive, anti-hyperglycaemic, anti-hyperlipidaemic, and anti-inflammatory drugs, or with smoking, drinking, and type 2 diabetes.

Quality control procedure for the GWAS data

The initial quality control was performed by removing sex discrepancies, ethnic outliers, probable relatives, and those with a call rate <0.95 and excessive genome-wide heterozygosity. SNPs with minor allele frequency <0.01, Hardy-Weinberg equilibrium $P<1\times10^{-4}$, call-rate<0.95, and not in autosomal chromosomes were excluded. Imputation was performed using the University of Michigan imputation servers. Following imputation, SNPs with poor imputation quality (Rsq<0.3) were filtered. Consequently, 40,001,312 SNPs remained.

Statistical analysis for the GWAS data

GWAS analyses were performed with linear regression (for continuous variables) or logistic regression analysis (for dichotomous variables) under an additive genetic model in PLINK2. Prior to the analyses, inversed-normalized residuals adjusted for age, sex and the first two genetic principal components were calculated for each metabolite with the R package “GenABEL”. A significant GWAS threshold was set at $P < 5\times10^{-8}$. The suggested GWAS threshold was set at $P < 5\times10^{-5}$. A clump procedure in PLINK was run for the suggestive GWAS signals (1Mb, $R^2<0.5$). Clumped SNPs were subsequently selected into the

replication stage. SNPs with P <0.05 and consistent effect directions were successfully replicated.

Mendelian randomization (MR) analyses

One-sample MR analyses were used to evaluate the causal relationships between metabolites and MetS and its components. In this study, the SNPs that were independently and significantly associated with metabolites were used to construct an additive weighted genetic risk score (wGRS) as the instrumental variable (IV). The formula is as follows:

$$\text{wGRS}=\frac{\sum_1^i \beta \times N}{\sum_1^i \beta}$$

β, the coefficient of the association between SNP and metabolites; N, number of risk alleles; i, number of instrumental SNPs

To verify the consumption of MR, F statistics were calculated to evaluate the strength of the IV. The study design of the MR analyses was shown in Figure S2. First, a linear regression was performed to assess the associations between wGRS and the metabolites (βZX). Second, the associations of the wGRS with metabolic syndrome and its components were examined (βZY). Third, observational estimates of the relationships between metabolites and metabolic syndrome and its components were calculated (β XY). The causal estimates were assessed using the Wald-type estimator. All regression models were adjusted for age and sex. The statistical significance was set at P<0.05.

A two-sample MR analysis was conducted using summary statistics from Japan Biobank to replicate the causal associations between metabolites and metabolic markers (body mass index, systolic blood pressure, diastolic blood pressure, total triglycerides, and high-density lipoprotein cholesterol, https://gwas.mrcieu.ac.uk/).The inverse variance weighted method (IVW) was used as the main analysis. By calculating the Wald estimates (ratio of SNP on outcome to SNP on exposure), IVW provides a combined estimate of the causal estimate for each SNP[3]. The weighted median and MR-Egger methods were supplemented as sensitivity analyses. Through calculating the median of an empirical distribution of MR association estimates weighted by their precisions, this method provides a reliable estimate when at least 50% of the variants are invalid instrumental variables. MR-Egger regression also used an inverse-variance weighted estimator. But unlike IVW, it allows the intercept of the regression to be non-zero and provides a pleiotropy-corrected causal estimate. If the intercept is non-zero, it suggests the presence of horizontal pleiotropy[3].

References

1. Zhu Y, Zhang D, Zhou D, et al. Susceptibility loci for metabolic syndrome and metabolic components identified in Han Chinese: a multi-stage genome-wide association study. J Cell Mol Med 2017; 21(6): 1106-16.

2. Xu J, Zhang L, Wu Q, et al. Body roundness index is a superior indicator to associate with the cardio-metabolic risk: evidence from a cross-sectional study with 17,000 Eastern-China adults. BMC Cardiovasc Disord 2021; 21(1): 97.

3. Wu Q, Sun X, Chen Q, Zhang X, Zhu Y. Genetically predicted selenium is negatively associated with serum TC, LDL-C and positively associated with HbA1C levels. J Trace Elem Med Biol 2021; 67: 126785.

S Figure legends

Figure S1. Flow chart of the study design. UPLC-Q/TOF-MS, ultra-performance liquid chromatography-quadrupole/time of flight mass spectrometer; MetS, metabolic syndrome; SNP, single nucleotide polymorphism; MR, mendelian randomisation; mGWAS, genome-wide association study for metabolites.

Figure S2. Study design for the one-sample Mendelian Randomisation. GRS, gene risk score; SE, standard error; CI, confidence interval.

Figure S3. Distributions of each metabolic component in subjects with MetS in three datasets. Discovery dataset: N=240; Internal replication dataset: N=1157; External replication dataset: N=402. MetS, metabolic syndrome; BP, blood pressure; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; FPG, fasting plasma glucose.

Figure S4. Q-Q Plots for the five metabolite biomarkers of MetS in the discovery stage (N=1062). MetS, metabolic syndrome;

Figure S5. Manhattan Plots for the five metabolite biomarkers of MetS in the discovery stage (N=1062). MetS, metabolic syndrome; the red line indicates suggestive association ($P<5\times10^{-5}$)

Figure S6. Normalized LysoPC(15:0) levels in subjects with different SNP genotypes (N=1062). The error bar denotes the means±standard error.

Figure S7. GWAS reginal plots for the three SNPs associated with LysoPC(15:0) (N=1062).

Table S1. Regents and chemicals in targeted metabolomics analyses

	Chemicals	Manufactures
Internal standards	L-phenylalanine 13C9, N1515N	Cambridge Isotope Laboratories, Inc.
Internal standards	Isoleucine 13C9,15N	Cambridge Isotope Laboratories, Inc.
Internal standards	L-glutamyl-leucine 13C6,15N	Nanjing Peptide Biotech Co., Ltd
Internal standards	Propionyl carnitine d5	Shanghai Zhenzhun Biotech Co., Ltd
Internal standards	Docosapentaenoicacid-d5	Shanghai Zhenzhun Biotech Co., Ltd
Internal standards	LysoPC(14:0) d27	Avanti Polar Lipids
Internal standards	Tryptophan d3	Toronto Research Chemicals
Standards	L-phenylalanine	Cambridge Isotope Laboratories, Inc.
Standards	Isoleucine	Cambridge Isotope Laboratories, Inc.
Standards	Tryptophan	Toronto Research Chemicals
Standards	L-glutamyl-leucine	Nanjing Peptide Biotech Co., Ltd
Standards	Propionyl carnitine	Toronto Research Chemicals
Standards	5,8,11-Eicosatrienoic acid	Shanghai Zhenzhun Biotech Co., Ltd
Standards	Docosapentaenoic acid	Shanghai Zhenzhun Biotech Co., Ltd
Standards	LysoPC(14:0)	Shanghai Zhenzhun Biotech Co., Ltd
Standards	LysoPC(15:0)	Shanghai Zhenzhun Biotech Co., Ltd
Standards	LysoPE(16:0)	Shanghai Zhenzhun Biotech Co., Ltd
Standards	LPA(16:0)	Shanghai Zhenzhun Biotech Co., Ltd
Standards	LysoPC(16:1)	Sigma Anrich
Standards	Indole-3-acetic acid	Sigma Anrich
Standards	cis-p-Coumaric acid	Sigma Anrich
Standards	2-Phenylacetamide	Sigma Anrich
Reagents	Methanol	Fisher Chemical
Reagents	dichloromethane	Fisher Chemical
Reagents	acetonitrile	Sigma Anrich
Reagents	formic acid	Honeywell
Reagents	water	Fisher Chemical

Table S2. Optimized MS parameters in targeted metabolomic analyses

Compounds	Polarity	Precursor (m/z)	Product (m/z)	Collision Energy (V)	RF len voltage
L-Isoleucine	Positive	132.05	86.125	20	34
2-Phenylacetamide	Positive	136.1	91	20	52
L-phenylalanine	Positive	166.1	120.042	12.71	33
Indole-3-acetic acid	Positive	176.1	130.071	12.54	38
Tryptophan	Positive	205.1	188.125	9.47	34
cis-p-Coumaric acid	Negative	163.1	119.1	20	101
L-glutamyl-leucine	Positive	261.15	132.054	11.53	49
Propionyl carnitine	Positive	218.15	85.113	18.65	51
LysoPC(14:0)	Negative	512.299	227.201	20	74
LysoPC(15:0)	Positive	482.475	184.125	23.74	94
LysoPE(16:0)	Negative	452.325	255.292	23.45	94
LysoPC(16:1)	Negative	538.314	253.217	28	75
LPA(16:0)	Negative	409.2	153	15	80
5,8,11-Eicosatrienoic acid	Negative	305.248	261.148	16	80
Docosapentaenoic acid	Negative	329.2	329.2	5	78

MS, mass spectrometry; RF, radio frequency.

Table S3. The validation of the method in targeted metabolomic analyses

Compounds	RT (min)	Linear	R2	LOQ (ng/ml)	Repeatability	RSD (inter-day)	RSD(intra-day)														
							Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16
cis-p-Coumaric acid	6.9	y =4.67E-03x + 2.13E-01	0.9955	2.5	0.022	0.085	0.075	0.04	0.034	0.06	0.052	0.06	0.05	0.037	0.049	0.051	0.059	0.106	0.062	0.022	0.029	0.081
5,8,11-Eicosatrienoic acid	0.75	y =5.59E-07x + 9.17E-04	0.9967	100	0.05	0.196	0.251	0.22	0.093	0.14	0.183	0.14	0.1	0.056	0.141	0.106	0.162	0.072	0.122	0.094	0.069	0.3
L-phenylalanine	2.5	y =1.10E-07x + 1.14E-03	0.998	100	0.061	0.017	0.027	0.01	0.017	0.01	0.016	0.02	0.01	0.02	0.017	0.009	0.011	0.012	0.017	0.013	0.014	0.015
Tryptophan	2.7	y =1.32E-04x - 6.52E-04	0.9999	2.5	0.035	0.016	0.017	0.01	0.009	0.01	0.01	0.01	0.02	0.012	0.01	0.014	0.009	0.008	0.009	0.013	0.01	0.011
L-Isoleucine	3	y =6.81E-05x + 2.57E-03	0.9982	5	0.115	0.234	0.043	0.03	0.043	0.04	0.034	0.05	0.04	0.036	0.254	0.282	0.196	0.047	0.029	0.184	0.017	0.281
Indole-3-acetic acid	3.3	y =5.08E-05x - 4.00E-03	0.9983	2.5	0.039	0.265	0.237	0.13	0.072	0.04	0.057	0.08	0.14	0.13	0.106	0.157	0.125	0.157	0.11	0.138	0.179	0.212
L-glutamyl-leucine	3.5	y =7.71E-05x - 4.06E-03	0.9995	2.5	0.009	0.073	0.015	0.02	0.013	0.01	0.016	0.01	0.01	0.024	0.026	0.04	0.074	0.023	0.024	0.035	0.058	0.156
2-Phenylacetamide	4	y =1.71E-05x + 1.65E-03	0.9983	2.5	0.079	0.236	0.243	0.08	0.037	0.03	0.061	0.07	0.01	0.22	0.092	0.047	0.039	0.057	0.051	0.067	0.09	0.227
Docosapentaenoic acid	6.38	y =1.60E-03x + 2.50	0.9981	250	0.084	0.152	0.126	0.19	0.156	0.16	0.16	0.22	0.22	0.126	0.126	0.193	0.075	0.104	0.11	0.158	0.079	0.077
LysoPC (14:0)	1.9	y =9.18E-05x - 5.20E-03	0.9974	5	0.105	0.219	0.011	0.01	0.007	0.02	0.007	0.01	0.01	0.058	0.22	0.048	0.048	0.046	0.053	0.053	0.054	0.065
LysoPC (15:0)	2.43	y =7.85E-05x - 4.06E-03	0.9981	2.5	0.116	0.058	0.01	0.02	0.023	0.06	0.011	0.02	0.06	0.032	0.092	0.028	0.014	0.082	0.019	0.014	0.086	0.052
LysoPC (16:1)	1.85	y =4.17E-05x + 1.41E-02	0.9901	10	0.091	0.284	0.068	0.05	0.092	0.09	0.108	0.14	0.05	0.114	0.135	0.029	0.065	0.057	0.04	0.046	0.08	0.078

LysoPE (16:0)	3.36	y =4.56E-09x - 7.98E-07	0.9988	250	0.121	0.226	0.028	0.03	0.041	0.25	0.061	0.03	0.27	0.118	0.246	0.119	0.069	0.226	0.042	0.072	0.273	0.278
Propionyl carnitine	0.75	y =6.42E-05x - 6.21E-04	0.9997	2.5	0.028	0.032	0.028	0.02	0.01	0.02	0.013	0.02	0.01	0.014	0.018	0.027	0.011	0.021	0.03	0.082	0.034	0.03
LPA (16:0)	3.1	y =1.97E-07x + 8.16E-06	0.9995	50	0.087	0.171	0.116	0.07	0.089	0.24	0.073	0.04	0.22	0.147	0.074	0.115	0.069	0.159	0.143	0.033	0.215	0.183

RT, retention time; LOQ, limit of quantification; RSD, relative standard deviation.

Table S4. 36 metabolites that associated with MetS in the discovery stage (N=240)

Compounds	RT (min)	Mass-to charge ratio	HMDB	FC	VIP	P	Ion mode	Category
2-Phenylacetamide*	0.879	136.0752	HMDB10715	0.827	2.47	5.34E-13	+	Organic compounds
5,8,11-Eicosatrienoic acid*	10.382	305.249	HMDB10378	0.667	2.886	2.18E-16	-	Fatty acids
Linolenic acid*	8.874	279.2313	HMDB03073	0.632	1.559	7.80E-13	+	Fatty acids
cis-p-Coumaric acid*	0.877	165.0547	HMDB30677	0.799	2.481	7.08E-14	+	Organic compounds
Docosapentaenoic acid*	10.359	329.2485	HMDB06528	0.647	2.159	4.37E-14	-	Fatty acids
Indole-3-acetic acid	4.9	174.0557	HMDB38628	0.662	1.718	1.87E-11	-	Organic compounds
L-glutamyl-leucine*	2.712	261.1439	HMDB11171	0.727	1.375	8.22E-08	+	Organic compounds
L-Isoleucine*	1.029	132.1019	HMDB00172	0.846	2.374	5.34E-13	+	Amino acids
LPA (16:0)	10.179	409.2356	HMDB07849	0.776	2.323	9.86E-11	-	Glycerophospholipids
L-Phenylalanine*	1.397	166.0863	HMDB00159	0.863	2.182	8.08E-10	+	Amino acids
L-Tryptophan*	2.206	205.0969	HMDB00929	0.839	1.922	3.32E-07	+	Amino acids
L-Valine*	0.669	118.0866	HMDB00883	1.113	1.178	0.0263	+	Amino acids
LysoPC(14:0) *	7.361	468.3082	HMDB10379	0.609	2.456	1.26E-11	+	Glycerophospholipids
LysoPC(15:0) *	8.445	482.3237	HMDB10381	0.69	2.637	2.62E-12	+	Glycerophospholipids
LysoPC(16:1)	7.576	494.3239	HMDB10383	0.844	1.049	0.0015	+	Glycerophospholipids
LysoPC(18:3)	7.926	518.3224	HMDB10387	0.913	1.293	0.00021	+	Glycerophospholipids
LysoPE(16:0) *	7.898	454.2922	HMDB11473	0.708	2.294	1.32E-09	+	Glycerophospholipids
LysoPE(22:6)	7.79	526.2927	HMDB11496	0.768	2.02	3.28E-08	+	Glycerophospholipids
PE (18:2/P-18:0)	11.3	728.5645	HMDB09115	1.83	2.637	2.32E-15	+	Glycerophospholipids
15(S)-HETE*	9.602	319.2282	HMDB03876	0.815	1.499	0.0004	-	Fatty Acyls
3-Hydroxybutyric acid*	0.692	103.0388	HMDB00008	0.785	1.198	0.00029	-	Organic compounds
3-hydroxyhexade-canoic acid	9.246	271.2276	HMDB61658	0.819	1.053	3.95E-05	-	Fatty acids
5-HEPE	9.321	317.2119	HMDB05081	0.715	1.355	1.70E-08	-	Fatty Acyls
Alpha-dimorphecolic acid	9.339	295.2278	HMDB04670	0.679	1.588	1.94E-06	-	Fatty Acyls
Betaine*	0.735	116.0713	HMDB00043	0.79	2.399	1.43E-13	-	Amino acids
CPA (16:0)	9.898	391.2265	HMDB07003	0.787	1.275	6.48E-07	-	Glycerophospholipids

L-Alanine	0.668	88.0403	HMDB00161	0.848	1.828	8.08E-08	-	Amino acids
L-Histidine*	0.693	154.0615	HMDB00177	0.876	1.631	7.87E-05	-	Amino acids
L-Leucine*	1.128	130.0872	HMDB00687	0.769	2.43	5.34E-13	-	Amino acids
L-Proline*	0.693	114.0554	HMDB00162	0.809	1.723	4.36E-06	-	Amino acids
L-Tyrosine*	0.852	180.0661	HMDB00158	0.795	2.127	3.48E-10	-	Amino acids
LysoPC(20:3)	7.957	546.3541	HMDB10393	0.815	1.514	3.26E-06	+	Glycerophospholipids
LysoPE(20:0) *	10.698	508.3405	HMDB11511	0.852	1.733	2.79E-06	-	Glycerophospholipids
Trans-Cinnamic acid*	1.844	147.0447	HMDB00930	0.831	2.194	8.08E-10	-	Organic compounds
Propionyl carnitine	1.031	218.1382	HMDB00824	0.766	1.746	1.85E-06	+	Fatty Acyls
Tsuzuic acid	9.606	225.1861	HMDB05051	0.804	1.114	2.84E-05	-	Fatty Acyls

RT, retention time; FC, fold change (control/MetS). FC<1 signifies that the metabolite is upregulated in MetS; VIP, variable importance in the projection, which is calculated by orthogonal partial least-squared discriminant analysis and reveals the contribution of each variable for the discrimination between the MetS patients and controls. P values are corrected by the false discovery rate. The primary metabolite identification is based on its RT and mass to charge ratio. * means that metabolites were confirmed with available reference compounds.

Table S5. Subgroup analyses by sex for associations between the 15 metabolites and MetS in the external validation (N=402)

Compounds	Men		Women	
	OR (95%CI)	P	OR (95%CI)	P
Docosapentaenoic acid	1.65(1.15,2.36)	0.007	1.72(1.19,2.47)	0.004
LysoPC (14:0)	1.72(1.18,2.51)	0.005	1.92(1.37,2.69)	<0.001
LysoPC (15:0)	1.28(0.90,1.82)	0.164	1.53(1.14,2.07)	0.005
LysoPC (16:1)	1.02(0.76,1.38)	0.885	1.17(0.86,1.58)	0.316
LysoPE (16:0)	1.13(0.82,1.55)	0.451	1.31(0.93,1.83)	0.122
Propionyl carnitine	1.22(0.88,1.68)	0.233	2.15(1.49,3.11)	<0.001
LPA (16:0)	1.14(0.72,1.80)	0.585	0.89(0.70,1.13)	0.33
Cis-p-Coumaric-acid	0.89(0.66,1.21)	0.459	1.12(0.81,1.56)	0.496
5,8,11-Eicosatrienoic acid	1.13(0.85,1.51)	0.385	0.88(0.60,1.29)	0.517
L-phenylalanine	1.00(0.73,1.37)	0.985	1.34(0.95,1.87)	0.091
Tryptophan	0.94(0.68,1.30)	0.721	1.57(1.13,2.18)	0.007
L-Isoleucine	1.48(1.06,2.06)	0.023	1.08(0.78,1.48)	0.65
Indole-3-acetic-acid	0.81(0.58,1.12)	0.201	1.43(1.03,1.99)	0.034
L-glutamyl-leucine	1.31(0.89,1.91)	0.167	0.97(0.74,1.27)	0.828
2-Phenylacetamide	1.28(0.91,1.79)	0.157	1.29(0.92,1.81)	0.14

The OR was adjusted for age and sex. OR, odds ratio; CI, confidence interval.

Table S6. Sensitivity analyses for associations between the 15 metabolites and MetS

Compounds	Sensitivity Analysis [a]		Sensitivity Analysis [b]		Sensitivity Analysis [c]	
	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
Docosapentaenoic acid	1.59(1.24,2.05)	<0.001	1.53(1.17,2.00)	0.002	1.78(1.21,2.62)	0.004
LysoPC (14:0)	1.93(1.50,2.49)	<0.001	2.02(1.52,2.68)	<0.001	2.38(1.59,3.56)	<0.001
LysoPC (15:0)	1.45(1.15,1.82)	0.002	1.49(1.13,1.97)	0.005	1.57(1.11,2.23)	0.011
LysoPC (16:1)	1.02(0.83,1.26)	0.849	1.10(0.85,1.42)	0.484	0.95(0.69,1.32)	0.769
LysoPE (16:0)	1.24(0.98,1.55)	0.071	1.16(0.89,1.53)	0.273	1.01(0.68,1.49)	0.973
Propionyl carnitine	1.73(1.35,2.22)	<0.001	1.66(1.27,2.16)	<0.001	2.50(1.65,3.79)	<0.001
LPA (16:0)	0.97(0.79,1.19)	0.757	0.86(0.59,1.26)	0.441	0.76(0.47,1.21)	0.248
Cis-p-Coumaric-acid	1.00(0.80,1.25)	0.992	1.04(0.80,1.35)	0.765	1.01(0.72,1.42)	0.962
5,8,11-Eicosatrienoic acid	1.05(0.86,1.29)	0.618	1.04(0.83,1.29)	0.757	0.83(0.53,1.29)	0.403
L-phenylalanine	1.13(0.9,1.41)	0.295	1.14(0.84,1.53)	0.406	1.22(0.85,1.75)	0.277
Tryptophan	1.20(0.96,1.50)	0.115	1.37(1.04,1.80)	0.025	1.63(1.15,2.32)	0.006
L-Isoleucine	1.24(0.99,1.54)	0.057	1.25(0.96,1.61)	0.092	1.17(0.85,1.61)	0.342
Indole-3-acetic-acid	1.06(0.85,1.33)	0.614	1.11(0.85,1.45)	0.45	1.46(1.05,2.04)	0.026
L-glutamyl-leucine	1.04(0.84,1.29)	0.689	1.14(0.85,1.53)	0.389	1.25(0.87,1.80)	0.234
2-Phenylacetamide	1.33(1.05,1.68)	0.02	1.54(1.17,2.02)	0.002	1.63(1.15,2.31)	0.006

The OR was adjusted for age and sex. a: excluding the subjects with cardiovascular diseases in the group of MetS (N=394); b: excluding the subjects with a history of drug use in the recent two weeks, including antihypertensives, anti-hyperglycaemia, anti-hyperlipidaemic, and anti-inflammatory drugs (N=333); c: excluding the subjects with smoking, drinking and the subjects with type 2 diabetes in the group of MetS (N=230). OR, odds ratio; CI, confidence interval.

Table S7. Associations between quartiles of MRS and MetS and its components (N=402)

MRS	MetS	Overweight/Obesity	High BP	Dyslipidaemia	High FPG
	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Q1: <-0.75	Reference	Reference	Reference	Reference	Reference
Q2: -0.75~-0.02	3.04(1.3,7.11)	3.25(1.28,8.22)	3.81(1.52,9.59)	3.01(1.11,8.18)	2.04(0.81,5.13)
Q3: -0.02~0.73	7.44(3.26,16.99)	8.37(3.45,20.35)	7.08(2.88,17.4)	6.93(2.67,18.02)	4.25(1.78,10.14)
Q4: 0.73~4.84	11.88(5.19,27.18)	9.48(3.9,23.06)	10.2(4.18,24.89)	13.98(5.44,35.9)	7.74 (3.3,18.16)

The OR was adjusted for age and sex. MRS, metabolite risk score, MetS, metabolic syndrome, BP, blood pressure, FPG, fasting plasma glucose; OR, odds ratio; CI, confidence interval.

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Table S8. Characteristics of subjects in the GWAS analyses

	Discovery stage (N=1062)	Replication stage (N=227)	P
MetS, N(%)	557 (52.4)	112 (49.3)	0.42
Men, N(%)	530 (49.9)	139 (61.2)	<0.01
Age(Year)†	57.42 (0.32)	62.37 (0.84)	<0.01
BMI(kg/m^2)†	24.46 (0.11)	23.86 (0.21)	0.01
SBP(mmHg)†	140.6 (0.71)	141.48 (1.68)	0.63
DBP(mmHg)†	83.56 (0.40)	82.8 (0.90)	0.44
TG((mmol/L)*	1.66 (1.31)	1.61 (1.15)	0.34
Uric Acid(umol/L)*	5.75 (0.01)	5.76 (0.02)	0.47
HDL-C(mmol/L)†	1.5 (0.01)	1.51 (0.02)	0.8
Insulin(mmol/L)*	3.9 (3.4)	3.6 (3.2)	0.12
Glucose(mmol/L)*	5.14 (1.12)	5.16 (1.1)	0.25
HOMA-IR*	0.92 (0.96)	0.86 (0.98)	0.33

Data was presented as means (standard deviation) or median (interquartile range) or numbers (percentages). * denotes that data was presented as median (interquartile range). † denotes that data was presented as mean (standard deviation). BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; HDL-C, high density lipoprotein cholesterol; MetS, metabolic syndrome; HOMA-IR, homeostasis model assessment of insulin resistance.

Table S9. Genetic inflation factors for the five metabolite biomarkers of MetS (N=1062)

Compounds	Lambda
LysoPC (14:0)	1.005
LysoPC (15:0)	1.006
Docosapentaenoic acid	0.997
L-Phenylalanine	1.001
Propionyl carnitine	1.004

Table S10. Suggestive GWAS associations for the five metabolite biomarkers of MetS (N=1062)

Metabolites	SNP	CHR	POS	Gene	REF	ALT	BETA	SE	P
LysoPC(15:0)	rs1800588	15	58723675	LIPC	C	T	0.30	0.045	3.63E-11
LysoPC(15:0)	rs11635491	15	58719741	LIPC	G	A	0.27	0.044	2.92E-09
LysoPC(15:0)	rs7067822	10	110453691	-	A	G	0.21	0.045	5.46E-06
LysoPC(15:0)	rs724137	13	26284368	ATP8A2	T	C	0.20	0.043	5.70E-06
LysoPC(15:0)	rs1815952	11	120655623	GRIK4	G	A	-0.22	0.049	6.88E-06
LysoPC(15:0)	rs73590561	19	36198178	-	G	A	0.33	0.075	9.01E-06
LysoPC(15:0)	rs2589654	5	10478798	-	G	T	-0.27	0.062	1.03E-05
LysoPC(15:0)	rs7670211	4	185533332	-	G	A	0.22	0.050	1.17E-05
LysoPC(15:0)	rs1952458	6	51496168	PKHD1	T	C	-0.19	0.043	1.28E-05
LysoPC(15:0)	rs4708767	6	169024099	SMOC2	G	A	-0.22	0.051	1.36E-05
LysoPC(15:0)	rs11814873	10	8832403	-	C	T	-0.38	0.087	1.39E-05
LysoPC(15:0)	rs7733748	5	9559366	-	G	C	-0.41	0.095	2.02E-05
LysoPC(15:0)	rs4767016	12	113274679	RPH3A	A	G	-0.19	0.043	2.08E-05
LysoPC(15:0)	rs6923552	6	151862558	CCDC170	T	C	-0.20	0.048	2.34E-05
LysoPC(15:0)	rs852614	5	11006477	CTNND2	T	C	-0.21	0.050	2.77E-05
LysoPC(15:0)	rs4603925	3	154381756	-	A	G	-0.20	0.047	3.21E-05
LysoPC(15:0)	rs17074437	5	171633449	EFCAB9	A	G	0.19	0.046	3.37E-05
LysoPC(15:0)	rs6841347	4	55030785	PDGFRA	G	T	0.29	0.070	3.97E-05
LysoPC(15:0)	rs9405361	6	7953426	BLOC1S5-TXNDC5	C	T	0.29	0.070	4.16E-05
LysoPC(15:0)	rs2261677	13	54679864	-	C	T	0.23	0.056	4.29E-05
LysoPC(15:0)	rs56337010	2	39751575	LOC728730	T	C	0.27	0.065	4.36E-05
LysoPC(15:0)	rs2395699	6	38319951		G	A	-0.24	0.058	4.64E-05
LysoPC(15:0)	rs2281164	1	14130628	PRDM2	A	G	-0.21	0.052	4.78E-05
LysoPC(15:0)	rs12128085	1	157785144	FCRL1	A	G	-0.25	0.061	4.85E-05
LysoPC(15:0)	rs626814	11	58448566	-	C	G	-0.18	0.043	4.89E-05
Docosapentaenoic acid	rs17167621	5	133900974	PHF15	G	A	0.21	0.043	1.50E-06
Docosapentaenoic acid	rs58170751	3	123960388	KALRN	G	A	-0.21	0.044	2.97E-06
Docosapentaenoic acid	rs12457035	18	46157207	CTIF	T	C	0.43	0.091	3.26E-06
Docosapentaenoic acid	rs6450035	5	68656135	TAF9	A	C	-0.26	0.057	4.75E-06
Docosapentaenoic acid	rs35836251	1	3829244	LOC100133612	G	A	-0.34	0.075	5.04E-06
Docosapentaenoic acid	rs10077374	5	145285923	-	G	A	0.34	0.076	7.36E-06
Docosapentaenoic acid	rs10914883	1	34681365	C1orf94	C	G	-0.27	0.061	8.29E-06
Docosapentaenoic acid	rs961316	2	31520023	-	A	G	0.29	0.066	1.42E-05
Docosapentaenoic acid	rs2411069	17	75022811	-	A	G	0.20	0.046	1.76E-05
Docosapentaenoic acid	rs10848622	12	2274051	CACNA1C	G	A	0.19	0.044	2.07E-05
Docosapentaenoic acid	rs7774871	6	37565411	-	T	G	0.24	0.056	2.62E-05
Docosapentaenoic acid	rs7331224	13	25568364	-	A	G	0.40	0.096	2.70E-05
Docosapentaenoic acid	rs1831324	3	67644071	SUCLG2	T	C	0.18	0.044	2.78E-05
Docosapentaenoic acid	rs4716285	6	18558416	AK098665	G	A	-0.24	0.056	3.08E-05
Docosapentaenoic acid	rs2159068	22	17653955	-	C	G	-0.35	0.083	3.15E-05
Docosapentaenoic acid	rs6045738	20	18974853	-	G	A	-0.20	0.048	3.16E-05
Docosapentaenoic acid	rs2684303	3	132003117	CPNE4	T	C	0.19	0.045	3.18E-05
Docosapentaenoic acid	rs3935652	1	202699678	KDM5B	T	C	-0.22	0.052	3.21E-05
Docosapentaenoic acid	rs4821004	22	32366359	-	C	T	-0.24	0.058	3.34E-05
Docosapentaenoic acid	rs16842643	4	8606080	CPZ	A	G	-0.27	0.064	3.44E-05
Docosapentaenoic acid	rs231170	8	116403541	-	T	C	-0.34	0.082	3.48E-05

Docosapentaenoic acid	rs644503	2	31489826	EHD3	G	C	0.29	0.070	3.49E-05
Docosapentaenoic acid	rs1524432	7	156176573	-	A	G	0.20	0.048	3.59E-05
Docosapentaenoic acid	rs56233657	14	29910912	MIR548AI	C	A	0.22	0.054	3.62E-05
Docosapentaenoic acid	rs9790042	3	149900177	-	A	T	0.19	0.047	3.75E-05
Docosapentaenoic acid	rs2875295	13	39843614	-	A	C	-0.26	0.063	3.78E-05
Docosapentaenoic acid	rs8089159	18	49002076	LOC100287225	T	C	-0.37	0.091	4.18E-05
Docosapentaenoic acid	rs225470	12	126394467	-	A	G	-0.21	0.050	4.23E-05
Docosapentaenoic acid	rs11868624	17	7275379	-	C	T	0.21	0.052	4.96E-05
L-Phenylalanine	rs6588028	1	63872871	ALG6	A	G	-0.22	0.046	3.05E-06
L-Phenylalanine	rs9898042	17	17238058	NT5M	G	T	-0.32	0.069	4.59E-06
L-Phenylalanine	rs10737482	1	20173858	-	T	C	-0.31	0.068	6.10E-06
L-Phenylalanine	rs6790068	3	189607626	TP63	A	G	-0.20	0.044	8.61E-06
L-Phenylalanine	rs10773323	12	127229327	LINC00944	T	A	-0.34	0.075	8.99E-06
L-Phenylalanine	rs4554846	10	125923609	-	C	G	0.19	0.045	1.55E-05
L-Phenylalanine	rs2250361	4	179391633	-	A	G	-0.21	0.048	1.69E-05
L-Phenylalanine	rs6800260	3	21519145	ZNF385D	A	G	0.18	0.042	2.28E-05
L-Phenylalanine	rs10737483	1	20174139	-	G	T	-0.19	0.044	2.32E-05
L-Phenylalanine	rs7124972	11	81002799	-	C	T	-0.28	0.067	2.48E-05
L-Phenylalanine	rs13180979	5	114826454	-	G	A	0.19	0.044	2.53E-05
L-Phenylalanine	rs11224859	11	101434460	TRPC6	T	C	-0.46	0.110	2.66E-05
L-Phenylalanine	rs1809808	11	61444984	DAGLA	T	C	0.24	0.057	2.87E-05
L-Phenylalanine	rs2972822	5	75559550	SV2C	G	C	0.26	0.061	2.88E-05
L-Phenylalanine	rs61831491	10	4428895	AK095699	C	T	0.25	0.059	3.13E-05
L-Phenylalanine	rs116494824	7	13437103	-	T	C	0.37	0.088	3.39E-05
L-Phenylalanine	rs7030762	9	102166506	-	T	G	-0.21	0.050	3.46E-05
L-Phenylalanine	rs117135667	20	12429471	-	C	T	0.27	0.064	3.46E-05
L-Phenylalanine	rs12420414	11	69679342	-	G	A	-0.21	0.050	3.82E-05
L-Phenylalanine	rs1216511	11	100354209	-	T	C	-0.20	0.048	4.10E-05
L-Phenylalanine	rs1502282	11	100503707	-	G	C	-0.18	0.044	4.51E-05
L-Phenylalanine	rs9559244	13	87128596	-	C	T	-0.19	0.046	4.66E-05
L-Phenylalanine	rs2634739	3	67609711	SUCLG2	C	T	0.18	0.044	4.82E-05
L-Phenylalanine	rs2023238	6	84282761	SNAP91	A	G	-0.18	0.044	4.92E-05
LysoPC(14:0)	rs6827159	4	32912873	-	T	C	-0.24	0.048	9.27E-07
LysoPC(14:0)	rs9431106	1	218953878	-	G	A	0.30	0.063	1.97E-06
LysoPC(14:0)	rs6535261	4	82519643	-	A	G	0.22	0.046	2.03E-06
LysoPC(14:0)	rs7518437	1	187285254	-	T	C	-0.21	0.045	4.07E-06
LysoPC(14:0)	rs884392	11	122616553	UBASH3B	G	A	0.32	0.070	6.54E-06
LysoPC(14:0)	rs2356927	1	232533667	SIPA1L2	T	C	0.22	0.049	9.44E-06
LysoPC(14:0)	rs28571941	16	8509325	-	G	A	0.24	0.054	9.50E-06
LysoPC(14:0)	rs11814873	10	8832403	-	C	T	-0.38	0.087	1.08E-05
LysoPC(14:0)	rs2170772	12	94948566	-	G	A	0.23	0.054	1.60E-05
LysoPC(14:0)	rs1946539	2	43357022	-	A	C	-0.20	0.046	1.92E-05
LysoPC(14:0)	rs765722	11	95413118	-	T	A	-0.31	0.072	1.95E-05
LysoPC(14:0)	rs509023	15	55419915	-	A	G	0.55	0.129	2.55E-05
LysoPC(14:0)	rs1174864	7	53127559	-	G	A	-0.24	0.056	2.62E-05
LysoPC(14:0)	rs55699809	17	69329434	-	C	A	0.33	0.079	2.73E-05
LysoPC(14:0)	rs2084766	16	8506623	-	C	G	0.19	0.046	3.19E-05
LysoPC(14:0)	rs140967063	3	18369026	-	A	G	0.19	0.045	3.30E-05
LysoPC(14:0)	rs17039727	2	60532247	-	G	A	-0.20	0.048	3.52E-05

LysoPC(14:0)	rs6725161	2	57064177	-	T	A	0.22	0.052	3.65E-05
LysoPC(14:0)	rs3909878	16	14114137	BC039386	A	G	-0.20	0.048	4.62E-05
LysoPC(14:0)	rs4266432	5	35733096	SPEF2	A	T	0.29	0.071	4.77E-05
LysoPC(14:0)	rs4651374	1	187363621	-	G	A	-0.18	0.044	4.83E-05
Propionyl carnitine	rs726913	15	61495779	RORA	G	A	0.23	0.045	3.15E-07
Propionyl carnitine	rs72500277	22	29490783	KREMEN1	T	C	-0.34	0.069	1.36E-06
Propionyl carnitine	rs73233712	4	41521805	LIMCH1	C	T	0.35	0.075	3.13E-06
Propionyl carnitine	rs35310703	2	206029001	PARD3B	G	T	-0.40	0.088	8.15E-06
Propionyl carnitine	rs7737383	5	155748355	SGCD	G	A	0.28	0.063	8.33E-06
Propionyl carnitine	rs4819564	22	17712611	-	G	A	0.25	0.057	1.05E-05
Propionyl carnitine	rs2336661	3	52900424	TMEM110-MUSTN1	C	G	0.54	0.123	1.11E-05
Propionyl carnitine	rs502645	3	145687497	-	G	A	0.19	0.044	1.28E-05
Propionyl carnitine	rs10412849	19	3024624	TLE2	G	A	-0.20	0.046	1.51E-05
Propionyl carnitine	rs75523200	9	71422488	PIP5K1B	T	C	-0.21	0.049	1.76E-05
Propionyl carnitine	rs2116796	5	166269115	-	C	A	-0.19	0.044	1.79E-05
Propionyl carnitine	rs2722836	9	120818807	-	G	T	-0.33	0.078	1.96E-05
Propionyl carnitine	rs2301446	22	29542915	KREMEN1	G	A	-0.32	0.074	2.32E-05
Propionyl carnitine	rs6019456	20	47467379	-	A	C	0.37	0.088	2.37E-05
Propionyl carnitine	rs73681799	7	16285485	ISPD	A	C	0.22	0.053	2.46E-05
Propionyl carnitine	rs1559407	16	79229377	WWOX	T	C	-0.26	0.062	2.53E-05
Propionyl carnitine	rs11086862	20	41754601	PTPRT	T	C	0.20	0.048	2.61E-05
Propionyl carnitine	rs2033977	11	25878875	-	A	G	-0.26	0.061	2.90E-05
Propionyl carnitine	rs955908	1	187287948	-	C	T	-0.19	0.045	3.07E-05
Propionyl carnitine	rs76716735	1	14286149	-	A	G	-0.31	0.073	3.12E-05
Propionyl carnitine	rs17478850	10	8523830	-	G	T	-0.21	0.049	3.12E-05
Propionyl carnitine	rs4235722	5	155749584	SGCD	C	G	0.22	0.053	3.52E-05
Propionyl carnitine	rs3109036	4	165047368	MARCH1	G	A	-0.34	0.081	3.58E-05
Propionyl carnitine	rs9514131	13	104090848	-	G	T	-0.29	0.071	3.74E-05
Propionyl carnitine	rs441869	2	39178493	ARHGEF33	G	C	0.26	0.063	4.03E-05
Propionyl carnitine	rs4745466	9	71604123	PIP5K1B	A	C	-0.19	0.045	4.13E-05
Propionyl carnitine	rs4244897	15	92146615	-	A	G	-0.32	0.077	4.21E-05
Propionyl carnitine	rs3897731	13	35302209	-	C	T	-0.20	0.050	4.49E-05
Propionyl carnitine	rs12649326	4	137071676	-	T	C	-0.20	0.049	4.52E-05
Propionyl carnitine	rs7573966	2	37138046	STRN	C	A	0.19	0.046	4.60E-05
Propionyl carnitine	rs847100	20	45244632	SLC13A3	C	T	0.20	0.050	4.66E-05
Propionyl carnitine	rs12684083	9	79148591	-	G	A	-0.19	0.046	4.69E-05
Propionyl carnitine	rs694731	11	94338912	PIWIL4	G	A	0.17	0.043	4.79E-05

SNP, single nucleotide polymorphism; CHR, chromosome; POS, position; REF. reference allele; ALT, alternative allele; MAF: minor allele frequency.

Table S11. Associations of the suggestively associated SNPs with the five metabolite biomarkers of MetS in the replication stage (N=227)

Metabolites	SNP	CHR	POS	REF	ALT	BETA	SE	P	Direction
Docosapentaenoic acid	rs225470	12	126394467	A	G	0.30	0.10	0.005	-
LysoPC(15:0)	rs11635491	15	58719741	G	A	0.24	0.10	0.015	+
Docosapentaenoic acid	rs1831324	3	67644071	T	C	-0.22	0.09	0.017	-
Propionyl carnitine	rs35310703	2	206029001	G	T	0.46	0.21	0.030	-
LysoPC(15:0)	rs7067822	10	110453691	A	G	0.22	0.10	0.031	+
LysoPC(15:0)	rs1952458	6	51496168	T	C	-0.19	0.09	0.044	+
L-Phenylalanine	rs61831491	10	4428895	C	T	-0.25	0.13	0.048	-
L-Phenylalanine	rs13180979	5	114826454	G	A	-0.17	0.09	0.056	-
L-Phenylalanine	rs10737483	1	20174139	G	T	-0.19	0.10	0.063	+
LysoPC(15:0)	rs626814	11	58448566	C	G	-0.17	0.09	0.065	+
Propionyl carnitine	rs7573966	2	37138046	C	A	0.18	0.10	0.076	+
LysoPC(15:0)	rs1800588	15	58723675	C	T	0.18	0.10	0.077	+
Docosapentaenoic acid	rs4821004	22	32366359	C	T	-0.23	0.13	0.078	+
L-Phenylalanine	rs2972822	5	75559550	G	C	0.21	0.13	0.105	+
LysoPC(15:0)	rs9405361	6	7953426	C	T	-0.24	0.15	0.113	-
Propionyl carnitine	rs694731	11	94338912	G	A	0.15	0.09	0.120	+
Propionyl carnitine	rs4244897	15	92146615	A	G	0.24	0.16	0.131	-
Docosapentaenoic acid	rs2159068	22	17653955	C	G	0.25	0.17	0.140	-
Docosapentaenoic acid	rs56233657	14	29910912	C	A	0.17	0.12	0.150	+
Propionyl carnitine	rs76716735	1	14286149	A	G	-0.23	0.16	0.152	+
L-Phenylalanine	rs4554846	10	125923609	C	G	0.13	0.09	0.154	+
Propionyl carnitine	rs10412849	19	3024624	G	A	0.14	0.10	0.166	-
L-Phenylalanine	rs10737482	1	20173858	T	C	-0.23	0.17	0.182	+
LysoPC(15:0)	rs12128085	1	157785144	A	G	0.19	0.14	0.191	-
LysoPC(15:0)	rs7733748	5	9559366	G	C	-0.28	0.22	0.193	+
L-Phenylalanine	rs6790068	3	189607626	A	G	0.13	0.10	0.199	-
LysoPC(15:0)	rs4603925	3	154381756	A	G	-0.13	0.10	0.200	+
Propionyl carnitine	rs12684083	9	79148591	G	A	-0.12	0.10	0.207	+
LysoPC(15:0)	rs4767016	12	113274679	A	G	0.12	0.10	0.222	-
Docosapentaenoic acid	rs1524432	7	156176573	A	G	-0.13	0.11	0.233	-
L-Phenylalanine	rs116494824	7	13437103	T	C	0.24	0.20	0.241	+
LysoPC(15:0)	rs1815952	11	120655623	G	A	-0.12	0.11	0.243	+
LysoPC(14:0)	rs884392	11	122616553	G	A	0.17	0.15	0.252	+
Propionyl carnitine	rs2116796	5	166269115	C	A	0.11	0.10	0.252	-
L-Phenylalanine	rs1809808	11	61444984	T	C	-0.14	0.12	0.259	-
Propionyl carnitine	rs955908	1	187287948	C	T	0.11	0.10	0.262	-
L-Phenylalanine	rs11224859	11	101434460	T	C	0.29	0.26	0.266	-
LysoPC(14:0)	rs6725161	2	57064177	T	A	-0.13	0.12	0.268	-
Propionyl carnitine	rs4819564	22	17712611	G	A	0.12	0.12	0.292	+
Propionyl carnitine	rs2033977	11	25878875	A	G	-0.13	0.12	0.296	+
Docosapentaenoic acid	rs2875295	13	39843614	A	C	-0.15	0.14	0.298	+
Docosapentaenoic acid	rs4716285	6	18558416	G	A	-0.14	0.14	0.305	+
LysoPC(14:0)	rs140967063	3	18369026	A	G	0.10	0.10	0.309	+
Docosapentaenoic acid	rs2411069	17	75022811	A	G	-0.11	0.11	0.310	-
Propionyl carnitine	rs502645	3	145687497	G	A	-0.10	0.10	0.314	-
LysoPC(15:0)	rs73590561	19	36198178	G	A	0.19	0.19	0.321	+
Docosapentaenoic acid	rs10077374	5	145285923	G	A	0.17	0.17	0.326	+

LysoPC(14:0)	rs2170772	12	94948566	G	A	0.12	0.12	0.333	+
Docosapentaenoic acid	rs9790042	3	149900177	A	T	-0.11	0.11	0.336	-
LysoPC(15:0)	rs4708767	6	169024099	G	A	0.11	0.11	0.338	-
LysoPC(15:0)	rs852614	5	11006477	T	C	-0.10	0.11	0.340	+
LysoPC(15:0)	rs56337010	2	39751575	T	C	0.13	0.14	0.342	+
Docosapentaenoic acid	rs7331224	13	25568364	A	G	-0.22	0.23	0.343	-
LysoPC(14:0)	rs55699809	17	69329434	C	A	0.19	0.20	0.344	+
LysoPC(15:0)	rs6841347	4	55030785	G	T	0.15	0.16	0.347	+
Docosapentaenoic acid	rs6045738	20	18974853	G	A	0.09	0.10	0.364	-
Docosapentaenoic acid	rs6450035	5	68656135	A	C	-0.11	0.12	0.367	+
Propionyl carnitine	rs11086862	20	41754601	T	C	0.09	0.10	0.381	+
Propionyl carnitine	rs3109036	4	165047368	G	A	-0.15	0.18	0.400	+
Docosapentaenoic acid	rs644503	2	31489826	G	C	0.13	0.15	0.408	+
L-Phenylalanine	rs6800260	3	21519145	A	G	-0.07	0.09	0.413	-
Docosapentaenoic acid	rs3935652	1	202699678	T	C	0.09	0.11	0.428	-
LysoPC(14:0)	rs11814873	10	8832403	C	T	0.13	0.17	0.435	-
Propionyl carnitine	rs72500277	22	29490783	T	C	0.14	0.18	0.436	-
Propionyl carnitine	rs726913	15	61495779	G	A	0.07	0.10	0.446	+
L-Phenylalanine	rs10773323	12	127229327	T	A	0.12	0.16	0.448	-
Propionyl carnitine	rs73681799	7	16285485	A	C	0.09	0.12	0.451	+
LysoPC(14:0)	rs765722	11	95413118	T	A	-0.10	0.14	0.477	+
Propionyl carnitine	rs441869	2	39178493	G	C	-0.08	0.12	0.486	-
LysoPC(14:0)	rs28571941	16	8509325	G	A	0.09	0.13	0.501	+
L-Phenylalanine	rs9898042	17	17238058	G	T	0.09	0.14	0.543	-
Docosapentaenoic acid	rs961316	2	31520023	A	G	-0.09	0.15	0.557	-
Docosapentaenoic acid	rs2684303	3	132003117	T	C	-0.06	0.10	0.562	-
L-Phenylalanine	rs12420414	11	69679342	G	A	0.06	0.10	0.565	-
Docosapentaenoic acid	rs35836251	1	3829244	G	A	-0.10	0.17	0.569	+
L-Phenylalanine	rs2634739	3	67609711	C	T	0.05	0.10	0.573	+
Propionyl carnitine	rs2336661	3	52900424	C	G	-0.14	0.25	0.574	-
Docosapentaenoic acid	rs12457035	18	46157207	T	C	-0.11	0.19	0.580	-
LysoPC(15:0)	rs724137	13	26284368	T	C	0.05	0.09	0.595	+
Propionyl carnitine	rs7737383	5	155748355	G	A	-0.08	0.15	0.595	-
Docosapentaenoic acid	rs17167621	5	133900974	G	A	-0.05	0.09	0.600	-
Propionyl carnitine	rs6019456	20	47467379	A	C	0.10	0.19	0.600	+
LysoPC(14:0)	rs7518437	1	187285254	T	C	-0.05	0.10	0.608	+
Docosapentaenoic acid	rs10914883	1	34681365	C	G	-0.07	0.14	0.610	+
Docosapentaenoic acid	rs231170	8	116403541	T	C	-0.08	0.16	0.610	+
Propionyl carnitine	rs4745466	9	71604123	A	C	-0.05	0.10	0.629	+
Propionyl carnitine	rs847100	20	45244632	C	T	-0.05	0.11	0.636	-
L-Phenylalanine	rs7124972	11	81002799	C	T	-0.06	0.14	0.666	+
LysoPC(15:0)	rs2395699	6	38319951	G	A	0.05	0.12	0.683	-
LysoPC(14:0)	rs2356927	1	232533667	T	C	-0.04	0.11	0.684	-
Docosapentaenoic acid	rs7774871	6	37565411	T	G	-0.05	0.12	0.702	-
LysoPC(14:0)	rs1174864	7	53127559	G	A	0.05	0.12	0.703	-
Docosapentaenoic acid	rs8089159	18	49002076	T	C	-0.08	0.22	0.718	+
LysoPC(15:0)	rs6923552	6	151862558	T	C	0.04	0.10	0.718	-
Propionyl carnitine	rs75523200	9	71422488	T	C	-0.04	0.10	0.726	+
LysoPC(14:0)	rs17039727	2	60532247	G	A	-0.03	0.10	0.741	+
LysoPC(14:0)	rs3909878	16	14114137	A	G	-0.03	0.10	0.749	+

LysoPC(14:0)	rs6827159	4	32912873	T	C	-0.03	0.10	0.766	+
Propionyl carnitine	rs12649326	4	137071676	T	C	-0.03	0.11	0.768	+
Propionyl carnitine	rs4235722	5	155749584	C	G	-0.04	0.12	0.771	-
L-Phenylalanine	rs2023238	6	84282761	A	G	0.03	0.10	0.778	-
LysoPC(15:0)	rs7670211	4	185533332	G	A	-0.03	0.11	0.778	-
Propionyl carnitine	rs2301446	22	29542915	G	A	0.06	0.20	0.786	-
Propionyl carnitine	rs17478850	10	8523830	G	T	0.03	0.11	0.789	-
Propionyl carnitine	rs73233712	4	41521805	C	T	-0.04	0.16	0.791	-
L-Phenylalanine	rs7030762	9	102166506	T	G	-0.03	0.11	0.814	+
L-Phenylalanine	rs1502282	11	100503707	G	C	-0.02	0.09	0.822	+
LysoPC(14:0)	rs9431106	1	218953878	G	A	-0.03	0.14	0.827	-
Propionyl carnitine	rs9514131	13	104090848	G	T	-0.03	0.16	0.837	+
Docosapentaenoic acid	rs16842643	4	8606080	A	G	-0.03	0.15	0.858	+
Docosapentaenoic acid	rs10848622	12	2274051	G	A	-0.02	0.10	0.867	-
LysoPC(15:0)	rs2589654	5	10478798	G	T	0.02	0.14	0.874	-
Docosapentaenoic acid	rs58170751	3	123960388	G	A	-0.01	0.10	0.878	+
LysoPC(15:0)	rs2281164	1	14130628	A	G	-0.02	0.11	0.893	+
LysoPC(15:0)	rs17074437	5	171633449	A	G	-0.01	0.10	0.899	-
Propionyl carnitine	rs2722836	9	120818807	G	T	0.02	0.17	0.907	-
L-Phenylalanine	rs1216511	11	100354209	T	C	-0.01	0.10	0.912	+
L-Phenylalanine	rs9559244	13	87128596	C	T	-0.01	0.10	0.912	+
Propionyl carnitine	rs1559407	16	79229377	T	C	-0.01	0.13	0.912	+
LysoPC(14:0)	rs6535261	4	82519643	A	G	-0.01	0.10	0.916	-
L-Phenylalanine	rs117135667	20	12429471	C	T	-0.01	0.13	0.918	-
LysoPC(14:0)	rs1946539	2	43357022	A	C	0.01	0.10	0.925	-
LysoPC(14:0)	rs4651374	1	187363621	G	A	0.01	0.10	0.928	-
Docosapentaenoic acid	rs11868624	17	7275379	C	T	0.01	0.12	0.948	+
LysoPC(15:0)	rs2261677	13	54679864	C	T	0.01	0.12	0.950	+
LysoPC(14:0)	rs4266432	5	35733096	A	T	0.01	0.15	0.961	+
L-Phenylalanine	rs6588028	1	63872871	A	G	0.00	0.10	0.966	+
Propionyl carnitine	rs3897731	13	35302209	C	T	0.00	0.11	0.973	+
L-Phenylalanine	rs2250361	4	179391633	A	G	0.00	0.10	0.986	+
LysoPC(14:0)	rs2084766	16	8506623	C	G	0.00	0.10	0.997	+
LysoPC(15:0)	rs11814873	10	8832403	C	T	0.00	0.17	0.998	-

SNP, single nucleotide polymorphism; CHR, chromosome; POS, position; REF. reference allele; ALT, alternative allele; MAF, minor allele frequency. A direction of "+" denotes that the association effect direction is consistent between the discovery and validation stage. Rows marked in yellow show successfully replicated associations.

Table S12. Associations of the three LysoPC(15:0)-associated SNPs with MetS and its components

Traits	SNP	CHR	POS	REF	ALT	BETA	SE	P
BMI	rs11635491	15	58719741	G	A	0.184	0.163	2.58E-01
BMI	rs1952458	6	51496168	T	C	-0.548	0.156	4.52E-04
BMI	rs7067822	10	110453691	A	G	0.269	0.163	9.91E-02
DBP	rs11635491	15	58719741	G	A	0.616	0.570	2.80E-01
DBP	rs1952458	6	51496168	T	C	-0.699	0.550	2.04E-01
DBP	rs7067822	10	110453691	A	G	0.662	0.572	2.47E-01
SBP	rs11635491	15	58719741	G	A	0.858	0.991	3.86E-01
SBP	rs1952458	6	51496168	T	C	-1.417	0.954	1.38E-01
SBP	rs7067822	10	110453691	A	G	1.727	0.992	8.21E-02
FPG	rs11635491	15	58719741	G	A	-0.001	0.009	9.26E-01
FPG	rs1952458	6	51496168	T	C	-0.006	0.008	4.84E-01
FPG	rs7067822	10	110453691	A	G	-0.005	0.009	6.00E-01
HOMA-IR	rs11635491	15	58719741	G	A	0.060	0.031	5.81E-02
HOMA-IR	rs1952458	6	51496168	T	C	-0.057	0.030	6.15E-02
HOMA-IR	rs7067822	10	110453691	A	G	0.043	0.032	1.71E-01
Insulin	rs11635491	15	58719741	G	A	0.060	0.028	2.93E-02
Insulin	rs1952458	6	51496168	T	C	-0.051	0.027	5.67E-02
Insulin	rs7067822	10	110453691	A	G	0.047	0.028	8.76E-02
TG	rs11635491	15	58719741	G	A	0.012	0.011	2.88E-01
TG	rs1952458	6	51496168	T	C	-0.034	0.011	1.61E-03
TG	rs7067822	10	110453691	A	G	0.021	0.011	6.49E-02
HDL-C	rs11635491	15	58719741	G	A	0.023	0.017	1.80E-01
HDL-C	rs1952458	6	51496168	T	C	0.017	0.017	3.09E-01
HDL-C	rs7067822	10	110453691	A	G	-0.023	0.017	1.80E-01
Uric acid	rs11635491	15	58719741	G	A	3.742	3.539	2.91E-01
Uric acid	rs1952458	6	51496168	T	C	-8.614	3.412	1.17E-02
Uric acid	rs7067822	10	110453691	A	G	4.635	3.535	1.90E-01
MetS	rs11635491	15	58719741	G	A	1.058	0.093	5.43E-01
MetS	rs1952458	6	51496168	T	C	0.830	0.090	3.81E-02
MetS	rs7067822	10	110453691	A	G	1.111	0.093	2.60E-01

SNP, single nucleotide polymorphism; CHR, chromosome; POS, position; REF. reference allele; ALT, alternative allele; SE, standard error; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; MetS, metabolic syndrome; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance.

Table S13. One-sample MR analyses between LysoPC(15:0) and MetS and metabolic abnormalities (as dichotomized variables) (N=1062).

	Observational association			Causal association	
	OR (95%CI)	P	Power	OR (95%CI)	P
MetS	2.71 (2.31,3.19)	1.68E-33	0.79	1.60 (0.96,2.66)	0.070
Overweight/Obesity	1.96 (1.71,2.26)	6.30E-21	0.44	1.84 (1.10,3.08)	0.020
High BP	2.41 (2.07,2.82)	3.56E-29	0.71	1.44 (0.87,2.38)	0.155
Dyslipidaemia	2.83 (2.40,3.33)	1.67E-35	0.85	1.78 (1.07,2.98)	0.028
High UA	1.53 (1.31,1.78)	6.02E-08	0.21	2.59 (1.36,4.93)	0.004
High Insulin	1.93 (1.65,2.25)	2.77E-16	0.45	2.31 (1.27,4.18)	0.006
High FBP	1.65 (1.41,1.94)	4.27E-10	0.26	1.15 (0.63,2.09)	0.647
High HOMA-IR	2.08 (1.77,2.45)	4.20E-19	0.58	2.28 (1.26,4.13)	0.007

Data was presented as OR (95%CI). The OR was adjusted for age and sex. MetS, metabolic syndrome; BP, blood pressure; UA, uric acid; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; MR, mendelian randomization; OR, odds ratio; CI, confidence interval. The cutoff value for high UA, high HOMA-IR, and high insulin is based on their respective 75th percentile.

Table S14. One-sample MR analysis between LysoPC(15:0) and MetS components (as continuous variables) (N=1062).

	Observational association			Causal association	
	β(95%CI)	P	Power	β(95%CI)	P
BMI	1.09(0.88,1.30)	6.16E-24	0.61	1.42(0.48,2.35)	0.003
SBP	6.69(5.43,7.95)	3.06E-24	0.29	5.72(0.19,11.25)	0.043
DBP	3.75(3.02,4.48)	5.63E-23	0.37	2.84(-0.32,6.00)	0.078
TG	0.76(0.67,0.85)	1.04E-55	1.00	0.54(0.11,0.97)	0.013
HDL-C	0.01(-0.01,0.03)	3.65E-01	0.06	-0.02(-0.11,0.08)	1.277
UA	0.05(0.04,0.07)	1.08E-13	0.24	0.06(0.06,0.07)	0.045
Insulin	0.89(0.7,1.08)	1.50E-19	0.72	1.52(0.64,2.39)	0.001
Glucose	0.28(0.2,0.36)	4.23E-12	0.05	0.01(-0.32,0.34)	0.943
HOMA-IR	0.23(0.19,0.27)	3.82E-28	0.24	0.23(0.06,0.41)	0.010

Data was showed as β(95%CI). The OR was adjusted for age and sex. The values of uric acid (UA) and HOMA-IR were natural logarithm transformed. MR, mendelian randomization; MetS, metabolic syndrome; BMI, body mass index, SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; HDL-C, high density lipoprotein cholesterol; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; OR, odds ratio; CI, confidence interval.

Table S15. The two-sample MR analysis between LysoPC(15:0) and metabolic markers..

	β(95%CI)	P	P for interception of the MR Egger	Power
BMI				
IVW	0.011(-0.01,0.031)	0.306	-	0.06
WM	0.015(-0.019,0.05)	0.389	-	-
MR-Egger	0.704(-0.136,1.544)	0.101	0.106	-
SBP				
IVW	0.012(-0.01,0.034)	0.276	-	0.05
WM	0.013(-0.016,0.042)	0.373	-	-
MR-Egger	0.031(-0.521,0.583)	0.913	0.948	-
DBP				
IVW	0.009(-0.013,0.031)	0.433	-	0.05
WM	0.009(-0.019,0.037)	0.53	-	-
MR-Egger	0.014(-0.446,0.475)	0.951	0.981	-
HDL-C				
IVW	0.147(0.116,0.177)	0.001	-	1.00
WM	0.015(-0.034,0.064)	0.555	-	-
MR-Egger	-2.075(-9.256,5.106)	0.571	0.54	-
TG				
IVW	0.07(0.05, 0.10)	<0.001	-	1.00
WM	0.04(-0.01,0.09)	0.15	-	-
MR-Egger	-1.65(-4.64,1.34)	0.28	0.26	-

MR, mendelian randomization; TG, triglyceride; IVW, inverse variance weighted; WM, weighted Median; CI, confidence interval.

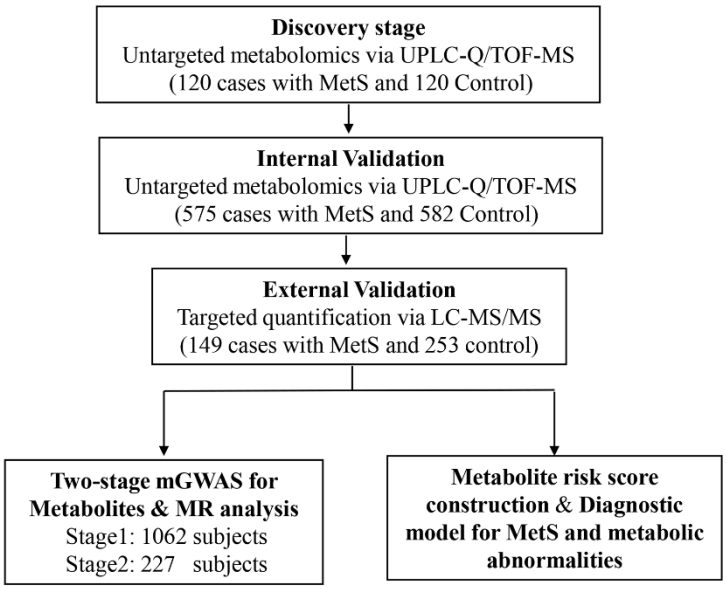
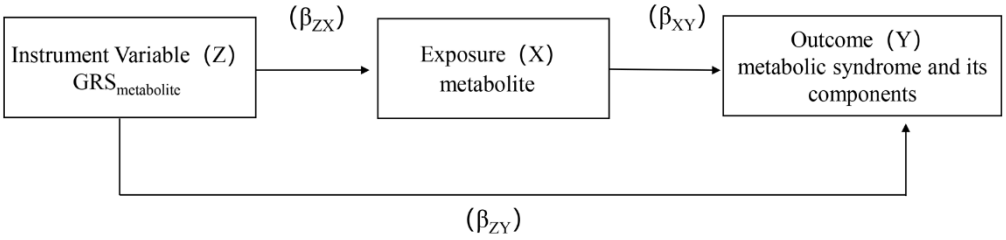


Figure S1. Flow chart of the study design



$$\beta_{IV} = \frac{\beta_{ZY}}{\beta_{ZX}}$$

$$95\%CI_{IV} = \beta_{IV} \pm 1.96 \times SE_{IV}$$

$$SE_{IV} = ABS\ (\beta_{IV}) \sqrt{(Se_{GRS\_exposure} / \beta_{GRS\_exposure})^2 + (Se_{GRS\_outcome} / \beta_{GRS\_outcome})^2}$$

Figure S2. Study design for the one-sample Mendelian Randomisation

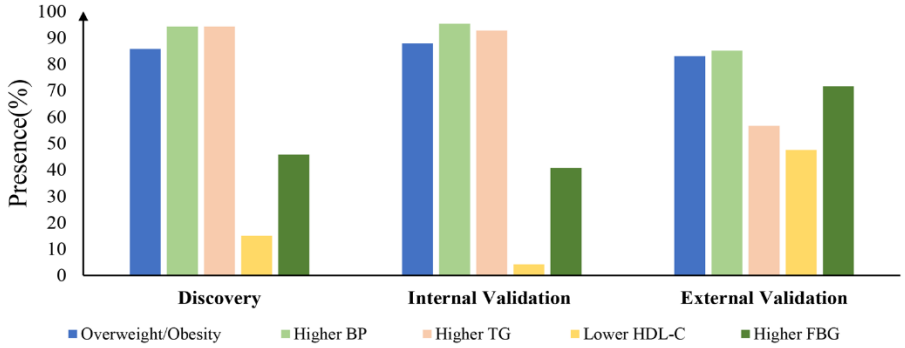


Figure S3. Distributions of each metabolic component in subjects with MetS in three datasets.

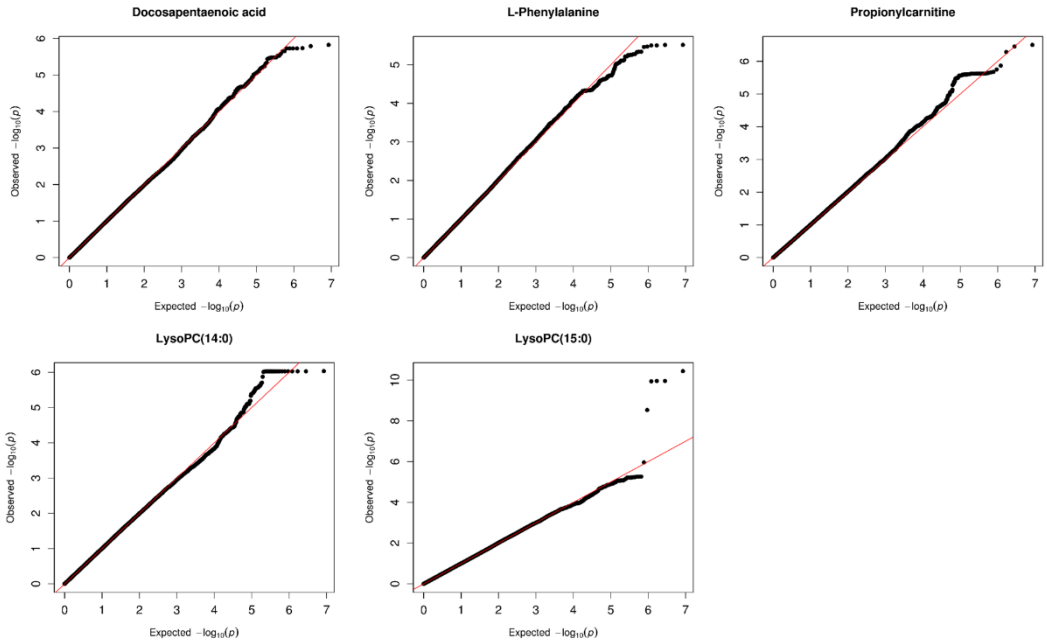


Figure S4. Q-Q Plots for the five metabolite biomarkers of MetS in the discovery stage (N=1062).

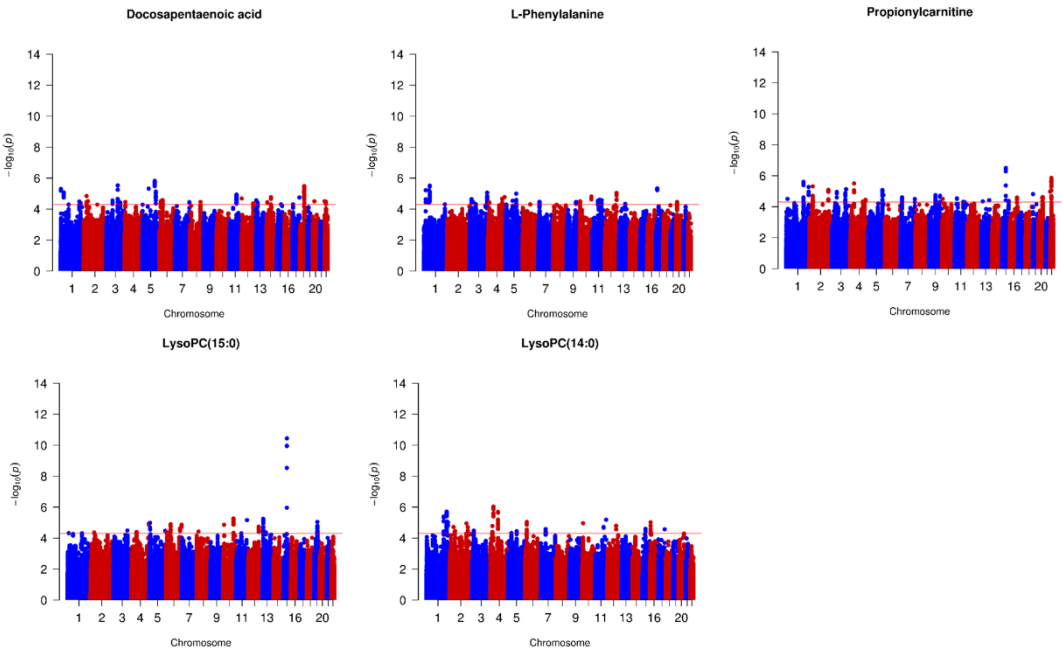


Figure S5. Manhattan Plots for the five metabolite biomarkers of MetS in the discovery stage (N=1062).

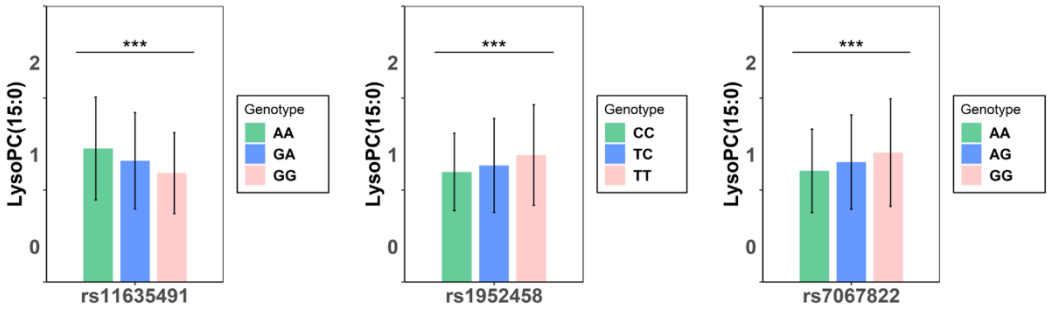


Figure S6. Normalized LysoPC(15:0) levels in subjects with different SNP genotypes (N=1062).

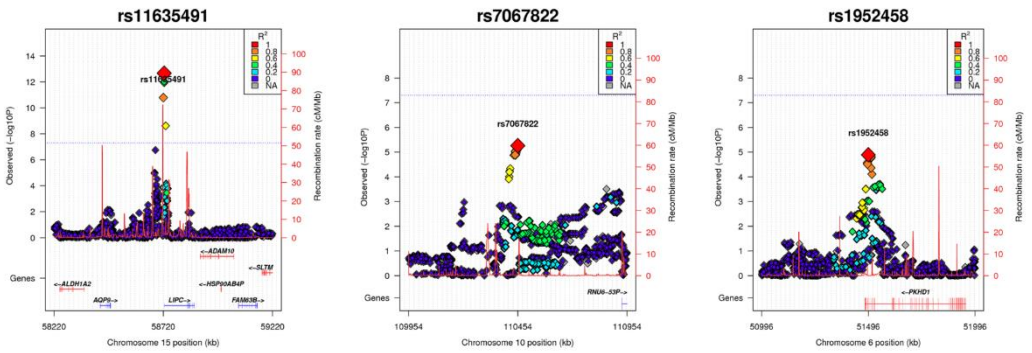


Figure S7. GWAS reginal plots for the three SNPs associated with LysoPC(15:0) (N=1062).