

## **Supplemental material**

Ahmad et al., The Effect of General Adiposity and Central Body Fat Distribution on the Circulating Metabolome: A Multicohort Nontargeted Metabolomics Observational and Mendelian Randomization Study

**Supplementary Table 1** List of 97 BMI-associated genetic variants used for Mendelian randomization and their allele frequencies in TwinGene, PIVUS and ULSAM cohorts, respectively

Variant	Nearest Gene	Chr: Position	Effect/Other Allele	Published EAF	Published Beta	Published SE	TwinGene EAF	PIVUS EAF	ULSAM EAF
rs977747	<i>TAL1</i>	1:47,457,264	T/G	0.39	0.017	0.003	0.38	0.38	0.38
rs657452	<i>AGBL4</i>	1:49,362,434	A/G	0.39	0.023	0.003	0.38	0.38	0.40
rs11583200	<i>ELAVL4</i>	1:50,332,407	C/T	0.40	0.018	0.003	0.40	0.39	0.41
rs3101336	<i>NEGR1</i>	1:72,523,773	C/T	0.61	0.033	0.003	0.59	0.59	0.59
rs12566985	<i>FPGT-TNNI3K</i>	1:74,774,781	G/A	0.45	0.024	0.003	0.45	0.46	0.43
rs12401738	<i>FUBP1</i>	1:78,219,349	A/G	0.35	0.021	0.003	0.37	0.34	0.37
rs11165643	<i>PTBP2</i>	1:96,696,685	T/C	0.58	0.022	0.003	0.57	0.57	0.57
rs17024393	<i>GNAT2</i>	1:109,956,211	C/T	0.04	0.066	0.009	0.03	0.04	0.04
rs543874	<i>SEC16B</i>	1:176,156,103	G/A	0.19	0.048	0.004	0.22	0.23	0.21
rs2820292	<i>NAV1</i>	1:200,050,910	C/A	0.56	0.02	0.003	0.57	0.59	0.57
rs10182181	<i>ADCY3</i>	2:25,003,800	G/A	0.46	0.031	0.003	0.47	0.47	0.47
rs11126666	<i>KCNK3</i>	2:26,782,315	A/G	0.28	0.021	0.003	0.26	0.27	0.28
rs1016287	<i>LINC01122</i>	2:59,159,129	T/C	0.29	0.023	0.003	0.29	0.28	0.28
rs13021737	<i>TMEM18</i>	2:622348	G/A	0.83	0.06	0.004	0.83	0.83	0.84
rs11688816	<i>EHBPI</i>	2:62,906,552	G/A	0.52	0.017	0.003	0.55	0.54	0.51
rs2121279	<i>LRP1B</i>	2:142,759,755	T/C	0.15	0.025	0.004	0.15	0.14	0.15
rs1460676	<i>FIGN</i>	2:164,275,935	C/T	0.17	0.020	0.004	0.16	0.15	0.16
rs1528435	<i>UBE2E3</i>	2:181,259,207	T/C	0.63	0.018	0.003	0.64	0.65	0.63
rs17203016	<i>CREB1</i>	2:207,963,763	G/A	0.20	0.021	0.004	0.21	0.22	0.21
rs7599312	<i>ERBB4</i>	2:213,121,476	G/A	0.72	0.022	0.003	0.72	0.72	0.70
rs492400	<i>USP37</i>	2:219,057,996	C/T	0.42	0.016	0.003	0.42	0.41	0.43
rs2176040	<i>LOC646736</i>	2:226,801,046	A/G	0.37	0.014	0.003	0.37	0.36	0.40
rs6804842	<i>RARB</i>	3:25,081,441	G/A	0.57	0.019	0.003	0.59	0.59	0.58
rs2365389	<i>FHIT</i>	3:61,211,502	C/T	0.58	0.02	0.003	0.57	0.59	0.58
rs3849570	<i>GBE1</i>	3:81,874,802	A/C	0.36	0.019	0.003	0.37	0.38	0.35
rs13078960	<i>CADM2</i>	3:85,890,280	G/T	0.20	0.03	0.004	0.18	0.19	0.19

Variant	Nearest Gene	Chr: Position	Effect/Other Allele	Published EAF	Published Beta	Published SE	TwinGene EAF	PIVUS EAF	ULSAM EAF
rs16851483	<i>RASA2</i>	3:142,758,126	T/G	0.07	0.048	0.008	0.06	0.05	0.06
rs1516725	<i>ETV5</i>	3:187,306,698	C/T	0.87	0.045	0.005	0.89	0.89	0.88
rs10938397	<i>GNPDA2</i>	4:44,877,284	G/A	0.43	0.04	0.003	0.41	0.40	0.42
rs17001654	<i>SCARB2</i>	4:77,348,592	G/C	0.15	0.031	0.005	0.14	0.13	0.13
rs13107325	<i>SLC39A8</i>	4:103,407,732	T/C	0.07	0.048	0.007	0.04	0.04	0.04
rs11727676	<i>HHIP</i>	4:145,878,514	T/C	0.91	0.036	0.006	0.92	0.92	0.91
rs2112347	<i>POC5</i>	5:75,050,998	T/G	0.63	0.026	0.003	0.63	0.62	0.63
rs7715256	<i>GALNT10</i>	5:153,518,086	G/T	0.42	0.016	0.003	0.42	0.42	0.42
rs205262	<i>C6orf106</i>	6:34,671,142	G/A	0.27	0.022	0.004	0.27	0.26	0.26
rs2033529	<i>TDRG1</i>	6:40,456,631	G/A	0.29	0.019	0.003	0.29	0.29	0.30
rs2207139	<i>TFAP2B</i>	6:50,953,449	G/A	0.18	0.045	0.004	0.16	0.17	0.19
rs9400239	<i>FOXO3</i>	6:109,084,356	C/T	0.69	0.019	0.003	0.72	0.73	0.74
rs9374842	<i>LOC285762</i>	6:120,227,364	T/C	0.75	0.019	0.004	0.75	0.75	0.72
rs13201877	<i>IFNGR1</i>	6:137,717,234	G/A	0.14	0.023	0.005	0.15	0.15	0.17
rs13191362	<i>PARK2</i>	6:162,953,340	A/G	0.88	0.028	0.005	0.88	0.89	0.88
rs1167827	<i>HIP1</i>	7:75,001,105	G/A	0.55	0.02	0.003	0.57	0.54	0.58
rs2245368	<i>PMS2L11</i>	7:76,446,079	C/T	0.18	0.032	0.006	0.19	0.19	0.19
rs9641123	<i>CALCR</i>	7:93,035,668	C/G	0.43	0.019	0.004	0.40	0.40	0.41
rs6465468	<i>ASB4</i>	7:95,007,450	T/G	0.30	0.017	0.004	0.29	0.30	0.30
rs17405819	<i>HNF4G</i>	8:76,969,139	T/C	0.70	0.022	0.003	0.72	0.70	0.71
rs16907751	<i>ZBTB10</i>	8:81,538,012	C/T	0.91	0.035	0.007	0.90	0.90	0.89
rs2033732	<i>RALYL</i>	8:85,242,264	C/T	0.75	0.019	0.004	0.72	0.77	0.75
rs4740619	<i>C9orf93</i>	9:15,624,326	T/C	0.54	0.018	0.003	0.58	0.56	0.56
rs10968576	<i>LINGO2</i>	9:28,404,339	G/A	0.32	0.025	0.003	0.31	0.33	0.32
rs6477694	<i>EPB41L4B</i>	9:110,972,163	C/T	0.37	0.017	0.003	0.39	0.39	0.42
rs1928295	<i>TLR4</i>	9:119,418,304	T/C	0.55	0.019	0.003	0.53	0.53	0.52
rs10733682	<i>LMX1B</i>	9:128,500,735	A/G	0.48	0.017	0.003	0.48	0.50	0.51
rs7899106	<i>GRID1</i>	10:87,400,884	G/A	0.05	0.04	0.007	0.04	0.04	0.05
rs17094222	<i>HIF1AN</i>	10:102,385,430	C/T	0.21	0.025	0.004	0.19	0.20	0.21

Variant	Nearest Gene	Chr: Position	Effect/Other Allele	Published EAF	Published Beta	Published SE	TwinGene EAF	PIVUS EAF	ULSAM EAF
rs11191560	<i>NT5C2</i>	10:104,859,028	C/T	0.09	0.031	0.005	0.10	0.10	0.11
rs7903146	<i>TCF7L2</i>	10:114,748,339	C/T	0.71	0.023	0.003	0.75	0.76	0.72
rs11030104	<i>BDNF</i>	11:27,641,093	A/G	0.79	0.041	0.004	0.80	0.82	0.80
rs2176598	<i>HSD17B12</i>	11:43,820,854	T/C	0.25	0.02	0.004	0.25	0.24	0.23
rs3817334	<i>MTCH2</i>	11:47,607,569	T/C	0.41	0.026	0.003	0.41	0.40	0.40
rs4256980	<i>TRIM66</i>	11:8,630,515	G/C	0.65	0.021	0.003	0.65	0.64	0.66
rs12286929	<i>CADMI</i>	11:114,527,614	G/A	0.52	0.022	0.003	0.53	0.53	0.54
rs7138803	<i>BCDIN3D</i>	12:48,533,735	A/G	0.38	0.032	0.003	0.42	0.42	0.42
rs11057405	<i>CLIP1</i>	12:121,347,850	G/A	0.90	0.031	0.006	0.90	0.90	0.89
rs12016871	<i>MTIF3</i>	13:26,915,782	T/C	0.20	0.03	0.005	0.22	0.21	0.21
rs12429545	<i>OLFM4</i>	13:53,000,207	A/G	0.13	0.033	0.005	0.14	0.14	0.13
rs9540493	<i>MIR548X2</i>	13:65,103,705	A/G	0.46	0.017	0.004	0.46	0.43	0.45
rs1441264	<i>MIR548A2</i>	13:78,478,920	A/G	0.61	0.018	0.003	0.61	0.60	0.62
rs10132280	<i>STXBP6</i>	14:24,998,019	C/A	0.68	0.023	0.003	0.69	0.70	0.71
rs12885454	<i>PRKD1</i>	14:28,806,589	C/A	0.64	0.021	0.003	0.63	0.63	0.65
rs11847697	<i>PRKD1</i>	14:29,584,863	T/C	0.04	0.049	0.008	0.04	0.03	0.04
rs7141420	<i>NRXN3</i>	14:78,969,207	T/C	0.53	0.024	0.003	0.52	0.52	0.52
rs3736485	<i>DMXL2</i>	15:49,535,902	A/G	0.45	0.018	0.003	0.42	0.41	0.42
rs16951275	<i>MAP2K5</i>	15:65,864,222	T/C	0.78	0.031	0.004	0.70	0.78	0.79
rs7164727	<i>LOC100287559</i>	15:70,881,044	T/C	0.69	0.018	0.003	0.71	0.69	0.70
rs758747	<i>NLRC3</i>	16:3,567,359	T/C	0.24	0.022	0.004	0.24	0.24	0.22
rs12446632	<i>GPRC5B</i>	16:19,842,890	G/A	0.86	0.036	0.005	0.88	0.87	0.87
rs2650492	<i>SBK1</i>	16:28,240,912	A/G	0.30	0.021	0.004	0.28	0.32	0.33
rs3888190	<i>ATP2A1</i>	16:28,796,987	A/C	0.40	0.031	0.003	0.41	0.42	0.44
rs4787491	<i>INO80E</i>	16:29,922,838	G/A	0.51	0.016	0.003	0.51	0.48	0.51
rs9925964	<i>KAT8</i>	16:31,037,396	A/G	0.62	0.019	0.003	0.61	0.58	0.60
rs2080454	<i>CBLN1</i>	16:47,620,091	C/A	0.41	0.017	0.003	0.42	0.43	0.44
rs1558902	<i>FTO</i>	16:52,361,075	A/T	0.42	0.082	0.003	0.42	0.41	0.40
rs9914578	<i>SMG6</i>	17:1,951,886	G/C	0.21	0.02	0.004	0.22	0.23	0.22

Variant	Nearest Gene	Chr: Position	Effect/Other Allele	Published EAF	Published Beta	Published SE	TwinGene EAF	PIVUS EAF	ULSAM EAF
rs1000940	<i>RABEP1</i>	17:5,223,976	G/A	0.32	0.019	0.003	0.31	0.31	0.31
rs12940622	<i>RPTOR</i>	17:76,230,166	G/A	0.57	0.018	0.003	0.55	0.56	0.57
rs1808579	<i>C18orf8</i>	18:19,358,886	C/T	0.53	0.017	0.003	0.51	0.50	0.51
rs7239883	<i>LOC284260</i>	18:38,401,669	G/A	0.39	0.016	0.003	0.39	0.38	0.40
rs7243357	<i>GRP</i>	18:55,034,299	T/G	0.81	0.022	0.004	0.84	0.81	0.82
rs6567160	<i>MC4R</i>	18:55,980,115	C/T	0.24	0.048	0.004	0.25	0.24	0.25
rs17724992	<i>PGPEP1</i>	19:18,315,825	A/G	0.75	0.019	0.004	0.76	0.75	0.75
rs29941	<i>KCTD15</i>	19:39,001,372	G/A	0.67	0.018	0.003	0.67	0.66	0.68
rs2075650	<i>TOMM40</i>	19:50,087,459	A/G	0.85	0.026	0.005	0.85	0.84	0.83
rs2287019	<i>QPCTL</i>	19:50,894,012	C/T	0.80	0.036	0.004	0.78	0.79	0.78
rs3810291	<i>ZC3H4</i>	19:52,260,843	A/G	0.67	0.028	0.004	0.69	0.66	0.67
rs6091540	<i>ZFP64</i>	20:50,521,269	C/T	0.72	0.019	0.004	0.73	0.73	0.72
rs2836754	<i>ETS2</i>	21:39,213,610	C/T	0.61	0.016	0.003	0.64	0.64	0.64

In the TwinGene dataset, rs12016871 was merged into rs9581854 on January 27, 2015 (Build 36) <https://www.ncbi.nlm.nih.gov/snp/rs12016871>.

Chr: chromosome number; EAF: effect allele frequency; SE: standard error. Published Beta, Published SE and Published EAF were extracted from Locke *et al.* Nature 2015(1).

**Supplementary Table 2** List of 47 WHR-associated genetic variants used for Mendelian randomization and their allele frequencies in females from the TwinGene and PIVUS cohorts

Variant	Chr: Position	Nearest Gene	Effect Allele	Other Allele	Published EAF	Published Beta Females	P-values	TwinGene EAF	PIVUS EAF
rs905938	1:154991389	<i>DCST2</i>	T	C	0.75	0.034	$4.9 \times 10^{-10}$	0.72	0.74
rs10919388	1:170372503	<i>GORAB</i>	C	A	0.72	0.033	$4.8 \times 10^{-10}$	0.73	0.73
rs1569135	2:188115398	<i>CALCRL</i>	A	G	0.53	0.023	$6.9 \times 10^{-7}$	0.52	0.49
rs10804591	3:129334233	<i>PLXND1</i>	A	C	0.79	0.04	$6.1 \times 10^{-13}$	0.8	0.80
rs17451107	3:156797609	<i>LEKRI</i>	T	C	0.61	0.023	$1.0 \times 10^{-6}$	0.61	0.62
rs3805389	4:56482750	<i>NMU</i>	A	G	0.28	0.027	$4.6 \times 10^{-8}$	0.27	0.26
rs9991328	4:89713121	<i>FAM13A</i>	T	C	0.49	0.028	$3.4 \times 10^{-10}$	0.47	0.48
rs303084	4:124066948	<i>SPATA5-FGF2</i>	A	G	0.80	0.029	$3.4 \times 10^{-7}$	0.79	0.80
rs9687846	5:55861894	<i>MAP3K1</i>	A	G	0.19	0.041	$3.8 \times 10^{-12}$	0.14	0.13
rs7759742	6:32381736	<i>BTNL2</i>	A	T	0.51	0.024	$1.7 \times 10^{-7}$	0.49	0.48
rs1776897	6:34195011	<i>HMGA1</i>	G	T	0.08	0.052	$6.8 \times 10^{-9}$	0.08	0.08
rs7801581	7:27223771	<i>HOXA11</i>	T	C	0.24	0.025	$7.7 \times 10^{-6}$	0.24	0.25
rs7830933	8:23603324	<i>NKX2-6</i>	A	G	0.77	0.037	$1.2 \times 10^{-12}$	0.78	0.78
rs12679556	8:72514228	<i>MSC</i>	G	T	0.25	0.033	$2.1 \times 10^{-10}$	0.23	0.24
rs10991437	9:107735920	<i>ABCA1</i>	A	C	0.11	0.04	$2.8 \times 10^{-8}$	0.12	0.12
rs7917772	10:104487443	<i>SFXN2</i>	A	G	0.62	0.027	$5.5 \times 10^{-9}$	0.58	0.60
rs11231693	11:63862612	<i>MACROD1-VEGFB</i>	A	G	0.06	0.068	$2.7 \times 10^{-11}$	0.07	0.07
rs4765219	12:124440110	<i>CCDC92</i>	C	A	0.67	0.037	$1.0 \times 10^{-14}$	0.67	0.64
rs8042543	15:31708263	<i>KLF13</i>	C	T	0.79	0.023	$6.7 \times 10^{-5}$	0.79	0.78
rs8030605	15:56504598	<i>RFX7</i>	A	G	0.15	0.031	$1.0 \times 10^{-5}$	0.11	0.11
rs1440372	15:67033151	<i>SMAD6</i>	C	T	0.71	0.022	$1.1 \times 10^{-5}$	0.7	0.71

Variant	Chr: Position	Nearest Gene	Effect Allele	Other Allele	Published EAF	Published Beta Females	P-values	TwinGene EAF	PIVUS EAF
rs2925979	16:81534790	<i>CMIP</i>	T	C	0.31	0.032	$3.4 \times 10^{-11}$	0.31	0.32
rs4646404	17:17420199	<i>PEMT</i>	G	A	0.66	0.034	$5.3 \times 10^{-11}$	0.63	0.64
rs8066985	17:68453345	<i>KCNJ2</i>	A	G	0.51	0.026	$4.0 \times 10^{-9}$	0.55	0.56
rs12454712	18:60845884	<i>BCL2</i>	T	C	0.61	0.035	$1.1 \times 10^{-9}$	0.57	0.56
rs4081724	19:33824946	<i>CEBPA</i>	G	A	0.85	0.033	$9.2 \times 10^{-7}$	0.87	0.87
rs979012	20:6623374	<i>BMP2</i>	T	C	0.35	0.026	$1.0 \times 10^{-7}$	0.35	0.35
rs6090583	20:45558831	<i>EYA2</i>	A	G	0.48	0.029	$2.8 \times 10^{-10}$	0.46	0.45
rs2645294	1:119574587	<i>TBX15-WARS2</i>	T	C	0.58	0.035	$1.5 \times 10^{-14}$	0.6	0.64
rs714515	1:172352990	<i>DNM3-PIGC</i>	G	A	0.43	0.029	$1.8 \times 10^{-10}$	0.45	0.46
rs2820443	1:219753509	<i>LYPLAL1</i>	T	C	0.72	0.062	$5.7 \times 10^{-35}$	0.71	0.70
rs10195252	2:165513091	<i>GRB14-COBL1</i>	T	C	0.59	0.052	$4.7 \times 10^{-30}$	0.56	0.57
rs17819328	3:12489342	<i>PPARG</i>	G	T	0.43	0.035	$4.6 \times 10^{-14}$	0.44	0.45
rs2276824	3:52637486	<i>PBRM1</i>	C	G	0.43	0.028	$3.7 \times 10^{-9}$	0.44	0.44
rs2371767	3:64718258	<i>ADAMTS9</i>	G	C	0.72	0.056	$1.2 \times 10^{-26}$	0.74	0.74
rs1045241	5:118729286	<i>TNFAIP8-HSD17B4</i>	C	T	0.71	0.035	$6.6 \times 10^{-12}$	0.72	0.72
rs7705502	5:173320815	<i>CPEB4</i>	A	G	0.32	0.027	$1.9 \times 10^{-8}$	0.35	0.34
rs1294410	6:6738752	<i>LY86</i>	C	T	0.63	0.037	$1.6 \times 10^{-15}$	0.65	0.64
rs1358980	6:43764551	<i>VEGFA</i>	T	C	0.47	0.06	$3.7 \times 10^{-34}$	0.45	0.42
rs1936805	6:127452116	<i>RSPO3</i>	T	C	0.51	0.052	$3.7 \times 10^{-30}$	0.53	0.53
rs1534696	7:26397239	<i>SNX10</i>	C	A	0.44	0.027	$2.1 \times 10^{-8}$	0.4	0.40
rs10245353	7:25858614	<i>NFE2L3</i>	A	C	0.20	0.041	$7.9 \times 10^{-13}$	0.17	0.18
rs10842707	12:26471364	<i>ITPR2-SSPN</i>	T	C	0.23	0.041	$6.1 \times 10^{-15}$	0.25	0.25
rs1443512	12:54342684	<i>HOXC13</i>	A	C	0.24	0.04	$1.1 \times 10^{-14}$	0.23	0.24
rs2294239	22:29449477	<i>ZNRF3</i>	A	G	0.59	0.028	$6.9 \times 10^{-10}$	0.58	0.59

Chr: chromosome number; EAF: effect allele frequency. Published Beta and Published EAF estimates were extracted from Shungin et al. Nature 2015(2).

**Supplementary Table 3** List of 22 WHR-associated genetic variants used for Mendelian randomization and their allele frequencies in males from the TwinGene, PIVUS and ULSAM cohorts

Variant	Chr: Position	Nearest Gene	Effect Allele	Other Allele	Published EAF	Published Beta Males	P-values	TwinGene EAF	PIVUS EAF	ULSAM EAF
rs1385167	2:66200648	<i>MEISI</i>	G	A	0.14	0.036	$2.3 \times 10^{-7}$	0.14	0.16	0.15
rs1569135	2:188115398	<i>CALCRL</i>	A	G	0.53	0.019	$1.5 \times 10^{-4}$	0.52	0.49	0.52
rs17451107	3:156797609	<i>LEKR1</i>	T	C	0.62	0.03	$1.4 \times 10^{-8}$	0.61	0.62	0.63
rs6556301	5:176527577	<i>FGFR4</i>	T	G	0.36	0.029	$1.0 \times 10^{-6}$	0.36	0.35	0.36
rs7759742	6:32381736	<i>BTNL2</i>	A	T	0.5	0.023	$5.5 \times 10^{-6}$	0.49	0.48	0.49
rs7801581	7:27223771	<i>HOXA11</i>	T	C	0.24	0.029	$2.4 \times 10^{-6}$	0.24	0.25	0.26
rs8042543	15:31708263	<i>KLF13</i>	C	T	0.79	0.03	$1.0 \times 10^{-6}$	0.79	0.78	0.77
rs8030605	15:56504598	<i>RFX7</i>	A	G	0.15	0.031	$5.9 \times 10^{-5}$	0.11	0.11	0.12
rs1440372	15:67033151	<i>SMAD6</i>	C	T	0.70	0.027	$1.4 \times 10^{-6}$	0.7	0.71	0.71
rs12608504	19:18389135	<i>JUND</i>	A	G	0.35	0.028	$1.1 \times 10^{-7}$	0.33	0.32	0.35
rs4081724	19:33824946	<i>CEBPA</i>	G	A	0.86	0.039	$1.4 \times 10^{-7}$	0.87	0.87	0.87
rs979012	20:6623374	<i>BMP2</i>	T	C	0.34	0.028	$6.6 \times 10^{-8}$	0.35	0.35	0.34
rs224333	20:34023962	<i>GDF5</i>	G	A	0.63	0.036	$9.0 \times 10^{-12}$	0.64	0.61	0.61
rs2645294	1:119574587	<i>TBX15- WARS2</i>	T	C	0.58	0.027	$1.5 \times 10^{-7}$	0.6	0.64	0.61
rs714515	1:172352990	<i>DNM3- PIGC</i>	G	A	0.43	0.025	$8.5 \times 10^{-7}$	0.45	0.46	0.44
rs2276824	3:52637486	<i>PBRM1</i>	C	G	0.43	0.02	$1.4 \times 10^{-4}$	0.44	0.44	0.45
rs7705502	5:173320815	<i>CPEB4</i>	A	G	0.33	0.027	$2.3 \times 10^{-7}$	0.35	0.34	0.34
rs1294410	6:6738752	<i>LY86</i>	C	T	0.63	0.025	$1.4 \times 10^{-6}$	0.65	0.64	0.65
rs1936805	6:127452116	<i>RSPO3</i>	T	C	0.51	0.031	$3.1 \times 10^{-10}$	0.53	0.53	0.54
rs10245353	7:25858614	<i>NFE2L3</i>	A	C	0.20	0.027	$1.4 \times 10^{-5}$	0.17	0.18	0.18
rs10842707	12:26471364	<i>ITPR2- SSPN</i>	T	C	0.23	0.022	$1.4 \times 10^{-4}$	0.25	0.25	0.25
rs2294239	22:29449477	<i>ZNRF3</i>	A	G	0.59	0.024	$2.3 \times 10^{-6}$	0.58	0.59	0.61

Chr: chromosome number; EAF: effect allele frequency. Published Beta and Published EAF estimates were extracted from Shungin et al. Nature 2015(2).



**Supplementary Table 4.** BMI-associated metabolites in meta-analysis of the ULSAM (N=1,035) and PIVUS (N=970) cohorts.

<b>Metabolite</b>	<b>Beta (95% CI)</b>	<b>P-value</b>
2-Methylbutyroylcarnitine	0.04 (0.03, 0.05)	1.9E-15
L-Acetylcarnitine	0.02 (0.01, 0.03)	7.4E-05
L-Carnitine	0.02 (0.01, 0.03)	2.3E-03
Piperine	0.06 (0.05, 0.07)	3.0E-26
1, 7 Dimethyluric acid	0.02 (0.01, 0.04)	1.6E-03
Creatine	0.02 (0.01, 0.03)	5.6E-03
DL-2-Aminooctanoic acid	-0.03 (-0.05, -0.02)	7.09E-06
Hippuric acid	-0.02 (-0.03, -0.01)	5.8E-03
L-Leucine	0.04 (0.02, 0.05)	5.6E-08
L-Tyrosine	0.03 (0.01, 0.04)	7.0E-04
Ornithine	0.02 (0.01, 0.04)	6.0E-04
Chenodeoxycholic acid	0.03 (0.02, 0.05)	6.5E-10
Chenodeoxycholic acid glycine conjugate	0.01 (0.00, 0.03)	3.8E-02
Deoxycholic acid	0.04 (0.02, 0.05)	2.0E-10
Deoxycholic acid glycine conjugate	0.04 (0.03, 0.05)	9.1E-10
Glycocholic acid	0.01 (0.00, 0.03)	0.0096
Hyodeoxycholic acid	0.03 (0.02, 0.04)	1.7E-06
4E,15Z-Bilirubin IX <sup>a</sup>	-0.02 (-0.03, -0.01)	1.6E-03
Bilirubin	-0.02 (-0.03, -0.01)	1.2E-04
Biliverdin a	-0.02 (-0.03, -0.01)	5.4E-04
I-Urobilin	0.03 (0.01, 0.04)	5.1E-04
C <sub>12</sub> H <sub>14</sub> O <sub>5</sub>	-0.02 (-0.04, -0.01)	1.3E-05
Flavone	0.02 (0.01, 0.03)	1.6E-03
1-Linoleoyl-2-stearoyl-sn-glycerol	0.02 (0.00, 0.04)	0.012
Diacylglycerol(34:1)	0.03 (0.01, 0.06)	8.7E-03
Monoacylglycerol(14:0)	0.03 (0.02, 0.04)	1.5E-07
Monoacylglycerol(16:0)	0.03 (0.02, 0.04)	1.2E-07
Monoacylglycerol(16:1)	0.05 (0.04, 0.06)	1.8E-17
Monoacylglycerol(18:0)	0.01 (0.00, 0.03)	8.8E-03
Monoacylglycerol(18:1)	0.04 (0.03, 0.05)	2.8E-11
Monoacylglycerol(18:2)	0.05 (0.04, 0.06)	4.7E-17
Lysophosphatidylethanolamine(18:1)c	-0.04 (-0.05, -0.03)	1.0E-11
Lysophosphatidylethanolamine(18:1-P)	-0.04 (-0.06, -0.02)	1.1E-03
Lysophosphatidylethanolamine(18:2)	-0.05 (-0.06, -0.04)	6.4E-18
Lysophosphatidylethanolamine(20:4)	-0.02 (-0.03, -0.01)	7.4E-05
Phosphoethanolamine(38:2)	-0.04 (-0.06, -0.01)	6.6E-03
Lyso-PAF C-18	-0.05 (-0.08, -0.02)	0.0027
Lysophosphatidylcholine(0:0/18:2)	-0.05 (-0.08, -0.03)	1.0E-05
Lysophosphatidylcholine(17:0)	-0.07 (-0.08, -0.05)	6.0E-22
Lysophosphatidylcholine(18:1) <sup>a</sup>	-0.05 (-0.08, -0.03)	1.99E-05
Lysophosphatidylcholine(18:1) <sup>b</sup>	-0.05 (-0.07, -0.03)	3.7E-06
Lysophosphatidylcholine(18:2/0:0)	-0.05 (-0.08, -0.03)	3.4E-07
Lysophosphatidylcholine(18:3)	-0.04 (-0.06, -0.02)	8.1E-04

Metabolite	Beta (95% CI)	P-value
Lysophosphatidylcholine(20:0)	-0.07 (-0.08, -0.06)	5.7E-38
Lysophosphatidylcholine(20:1)	-0.05 (-0.08, -0.01)	5.3E-03
Lysophosphatidylcholine(20:2)	-0.03 (-0.05, -0.01)	9.81E-05
Lysophosphatidylcholine(20:3) <sup>a</sup>	0.02 (0.01, 0.03)	2.5E-04
Lysophosphatidylcholine(20:3) <sup>b</sup>	0.02 (0.01, 0.03)	1.3E-03
Lysophosphatidylcholine(22:5) <sup>a</sup>	-0.02 (-0.03, -0.01)	0.0059
Lysophosphatidylcholine(22:5) <sup>b</sup>	-0.02 (-0.03, -0.01)	5.0E-03
Lysophosphatidylcholine(P-16:0)	-0.05 (-0.07, -0.04)	3.2E-09
Phosphatidylcholine(16:2)	-0.04 (-0.06, -0.03)	4.9E-09
Phosphatidylcholine(18:1)	-0.04 (-0.06, -0.02)	5.8E-04
Phosphatidylcholine(32:0)	-0.02 (-0.03, -0.01)	7.9E-05
Phosphatidylcholine(32:1)	0.02 (0.01, 0.03)	3.0E-05
Phosphatidylcholine(36:2)	-0.02 (-0.03, -0.00)	9.4E-03
Phosphatidylcholine(36:5)	0.02 (0.01, 0.03)	3.6E-03
Phosphatidylcholine(38:3)	0.03 (0.01, 0.04)	2.8E-04
Phosphatidylcholine(38:4)	0.02 (0.00, 0.03)	4.3E-02
Phosphatidylcholine(38:6)	0.01 (0.00, 0.02)	4.7E-02
Phosphatidylcholine(40:5)	0.01 (0.00, 0.02)	3.5E-02
Phosphatidylcholine(42:7)	-0.02 (-0.04, -0.00)	2.1E-02
Caffeine	0.04 (0.03, 0.05)	1.2E-10
Paraxanthine; Theophylline	0.02 (0.01, 0.03)	1.9E-04
Uric acid	0.04 (0.02, 0.07)	6.0E-04
3-Indolepropionic acid	-0.02 (-0.03, -0.00)	1.4E-02
Indolelactic acid	0.01 (0.00, 0.03)	3.6E-02
Creatinine	0.01 (0.00, 0.02)	6.4E-03
Sum-Hexose	0.05 (0.04, 0.06)	1.6E-14
Propranolol	0.02 (0.01, 0.03)	1.4E-03
1-N-(tetradecanoyl)-1-b-lactosyl-sphing-4-enine	-0.03 (-0.05, -0.02)	8.2E-05
Dipeptide	0.02 (0.01, 0.04)	5.4E-03
Gamma-Glutamyl-leucine	0.04 (0.03, 0.05)	4.4E-13
Phosphoethanolamine(P-34:1)	-0.04 (-0.06, -0.02)	1.3E-04
Phosphoethanolamine(40:0)	-0.03 (-0.04, -0.01)	1.3E-04
Lactosyl ceramide(d18:1/16:0)	-0.04 (-0.06, -0.02)	3.9E-06
Sphingomyelin(32:1-OH)	-0.03 (-0.04, -0.02)	8.9E-08
Prostaglandin J2	-0.02 (-0.03, -0.01)	2.0E-03
L-proline-betaine	-0.02 (-0.03, -0.00)	4.8E-03
Dodecanedioic acid	-0.04 (-0.05, -0.02)	4.1E-10
Dodecanoic acid	-0.02 (-0.04, -0.01)	4.7E-04
Heptadecanoic acid	-0.02 (-0.03, -0.01)	7.1E-04
Palmitic acid	0.02 (0.00, 0.03)	5.0E-03
Sphingomyelin(28:1)	-0.03 (-0.05, -0.02)	1.3E-10
Sphingomyelin(34:1)	-0.03 (-0.05, -0.02)	3.6E-10
Sphingosine	0.04 (0.03, 0.05)	3.7E-08
Sphingomyelin(32:1)	-0.02 (-0.03, -0.01)	5.4E-04
Sphingomyelin(41:2)	-0.02 (-0.03, -0.01)	3.7E-04

<b>Metabolite</b>	<b>Beta (95% CI)</b>	<b>P-value</b>
Sphingomyelin(42:3)	-0.01 (-0.02, -0.00)	2.2E-02
Cholesterol	-0.01 (-0.02, -0.00)	2.4E-02
Corticosterone	0.02 (0.01, 0.04)	3.9E-03
Cortisol	-0.03 (-0.05, -0.02)	5.8E-10
Dehydroepiandrosterone sulfate (sodium salt)	-0.02 (-0.03, -0.01)	7.2E-05
10-Nitro-9E-octadecenoic acid	0.02 (0.00, 0.03)	6.1E-03
Alpha-Linolenic acid	0.02 (0.00, 0.03)	4.1E-03
Arachidonic acid	0.02 (0.01, 0.03)	3.8E-03
Arachidonic acid ethyl ester	0.03 (0.02, 0.04)	1.9E-08
Docosahexaenoic Acid	0.02 (0.01, 0.03)	1.4E-04
Docosapentaenoic acid	0.02 (0.01, 0.03)	1.8E-04
Eicosadienoic acid	-0.01 (-0.02, -0.00)	3.6E-02
Eicosatrienoic Acid	0.03 (0.02, 0.04)	1.1E-06
Eicosatrienoic Acid methyl ester	0.02 (0.00, 0.03)	2.7E-02
Linolenyl aldehyde	-0.03 (-0.05, -0.01)	9.5E-03
Palmitoleic acid	0.02 (0.00, 0.04)	3.6E-02
Vaccenic acid	-0.02 (-0.03, -0.00)	4.1E-02
Pantothenic acid	0.02 (0.00, 0.03)	8.8E-03
Vitamin D3 derivative I	0.03 (0.02, 0.04)	5.2E-09
Vitamin D3 derivative II	-0.01 (-0.03, -0.00)	5.0E-02
Alpha-Tocopherol	-0.02 (-0.03, -0.01)	1.1E-03

Analyses were adjusted for both age and sex in the PIVUS cohort but age only in the ULSAM.

**Supplementary Table 5.** 77 metabolites associated with BMI in meta-analysis of the ULSAM (N=1,135) and PIVUS (N=970), and replicated in TwinGene (N= 2,059).

Metabolite	ULSAM and PIVUS		TwinGene	
	Beta (95% CI)	P-value	Beta (95% CI)	P-value
<b>Acylcarnitines</b>				
L-Acetylcarnitine	0.02 (0.01, 0.03)	7.4E-05	0.01 (0.00, 0.02)	0.031
2-Methylbutyrylcarnitine	0.04 (0.03, 0.05)	1.9E-15	0.03 (0.02, 0.04)	2.7E-07
L-Carnitine	0.02 (0.01, 0.03)	0.0023	0.03 (0.02, 0.05)	6.0E-08
<b>Alkaloids and Derivatives</b>				
Piperine	0.06 (0.05, 0.07)	3.0E-26	0.04 (0.03, 0.05)	2.4E-08
1, 7 Dimethyluric acid	0.02 (0.01, 0.04)	0.0016	0.02 (0.00, 0.03)	0.014
<b>Amino Acids and Derivatives</b>				
L-Leucine	0.04 (0.02, 0.05)	5.6E-08	0.05 (0.04, 0.07)	3.1E-14
Ornithine	0.02 (0.01, 0.04)	6.0E-04	0.04 (0.02, 0.05)	1.6E-08
Creatine	0.02 (0.01, 0.03)	0.0056	0.02 (0.01, 0.03)	0.0059
DL-2-Aminooctanoic acid	-0.03 (-0.05, -0.02)	7.1E-06	-0.03 (-0.04, -0.01)	8.0E-05
L-Tyrosine	0.03 (0.01, 0.04)	7.0E-04	0.04 (0.02, 0.05)	9.0E-09
Hippuric acid	-0.02 (-0.03, -0.01)	0.0058	-0.02 (-0.03, -0.01)	0.0027
<b>Bile Acids</b>				
Deoxycholic acid glycine conjugate	0.04 (0.03, 0.05)	9.1E-10	0.03 (0.02, 0.05)	1.4E-08
Deoxycholic acid	0.04 (0.02, 0.05)	2.0E-10	0.04 (0.03, 0.06)	8.9E-14
Hyodeoxycholic acid	0.03 (0.02, 0.04)	1.7E-06	0.04 (0.03, 0.05)	2.6E-09
Chenodeoxycholic acid	0.03 (0.02, 0.05)	6.5E-10	0.05 (0.03, 0.06)	1.5E-13
Glycocholic acid	0.01 (0.00, 0.03)	0.0096	0.02 (0.01, 0.03)	0.0011
<b>Bilirubins</b>				
4E,15Z-Bilirubin IX <sup>a</sup>	-0.02 (-0.03, -0.01)	0.0016	-0.02 (-0.04, -0.01)	0.0043
I-Urobilin	0.03 (0.01, 0.04)	5.1E-04	0.03 (0.02, 0.04)	3.1E-06
Biliverdin a	-0.02 (-0.03, -0.01)	5.4E-04	-0.03 (-0.04, -0.01)	1.5E-04
Bilirubin	-0.02 (-0.03, -0.01)	1.2E-04	-0.02 (-0.04, -0.01)	0.0045

Metabolite	ULSAM and PIVUS		TwinGene	
	Beta (95% CI)	P-value	Beta (95% CI)	P-value
<b>Cinnamic Acid and Derivatives</b>				
C <sub>12</sub> H <sub>14</sub> O <sub>5</sub>	-0.02 (-0.04, -0.01)	1.3E-05	-0.03 (-0.04, -0.01)	0.00014
<b>Glycerolipids</b>				
1-Linoleoyl-2-stearoyl-sn-glycerol	0.02 (0.00, 0.04)	0.012	0.03 (0.02, 0.04)	4.5E-09
Monoacylglycerol(18:0)	0.01 (0.00, 0.03)	0.0088	0.06 (0.05, 0.07)	1.4E-21
Monoacylglycerol(16:0)	0.03 (0.02, 0.04)	1.2E-07	0.07 (0.06, 0.08)	2.1E-27
Monoacylglycerol(18:1)	0.04 (0.03, 0.05)	2.8E-11	0.06 (0.05, 0.07)	1.8E-19
Diacylglycerol(34:1)	0.03 (0.01, 0.06)	0.0087	0.05 (0.04, 0.06)	3.1E-15
Monoacylglycerol(14:0)	0.03 (0.02, 0.04)	1.5E-07	0.06 (0.05, 0.07)	1.8E-23
Monoacylglycerol(18:2)	0.05 (0.04, 0.06)	4.7E-17	0.05 (0.04, 0.06)	1.5E-15
Monoacylglycerol(16:1)	0.05 (0.04, 0.06)	1.8E-17	0.06 (0.05, 0.07)	3.1E-20
<b>Glycerophosphoethanolamines</b>				
Lysophosphatidylethanolamine(18:2)	-0.05 (-0.06, -0.04)	6.4E-18	-0.02 (-0.04, -0.01)	1.3E-04
Phosphoethanolamine(38:2)	-0.04 (-0.06, -0.01)	0.0066	-0.03 (-0.04, -0.02)	4.3E-07
Lysophosphatidylethanolamine(18:1-P)	-0.04 (-0.06, -0.02)	0.0011	-0.03 (-0.04, -0.01)	1.9E-05
<b>Imidazopyrimidines</b>				
Uric acid	0.04 (0.02, 0.07)	0.0006	0.06 (0.05, 0.08)	4.0E-17
<b>Indoles</b>				
3-Indolepropionic acid	-0.02 (-0.03, -0.00)	0.014	-0.03 (-0.05, -0.02)	5.0E-07
<b>Monosaccharides</b>				
Sum-Hexose	0.05 (0.04, 0.06)	1.6E-14	0.05 (0.04, 0.07)	1.1E-13
<b>Peptides</b>				
Gamma-Glutamyl-leucine	0.04 (0.03, 0.05)	4.4E-13	0.05 (0.04, 0.06)	1.4E-12
<b>Phosphoethanolamine</b>				
Phosphoethanolamine(P-34:1)	-0.04 (-0.06, -0.02)	1.3E-04	-0.03 (-0.04, -0.02)	1.8E-06
Phosphoethanolamine(40:0)	-0.03 (-0.04, -0.01)	1.3E-04	-0.02 (-0.04, -0.01)	0.0031
<b>Phosphosphingolipids</b>				
Sphingomyelin(32:1-OH)	-0.03 (-0.04, -0.02)	8.9E-08	-0.02 (-0.03, -0.01)	4.3E-04

Metabolite	ULSAM and PIVUS		TwinGene	
	Beta (95% CI)	P-value	Beta (95% CI)	P-value
<b>Prostaglandins</b>				
Prostaglandin J2	-0.02 (-0.03, -0.01)	0.002	-0.02 (-0.04, -0.01)	7.1E-04
<b>Pyrrolidines</b>				
L-Proline-betaine	-0.02 (-0.03, -0.00)	0.0048	-0.02 (-0.03, -0.00)	0.015
<b>Saturated Fatty Acids</b>				
Dodecanedioic acid	-0.04 (-0.05, -0.02)	4.1E-10	-0.02 (-0.04, -0.01)	4.3E-06
Palmitic acid	0.02 (0.00, 0.03)	0.005	0.03 (0.01, 0.04)	4.6E-05
<b>Spingolipids</b>				
Sphingosine	0.04 (0.03, 0.05)	3.7E-08	0.05 (0.04, 0.07)	1.5E-15
<b>Spingomyelins</b>				
Sphingomyelin(34:1)	-0.03 (-0.05, -0.02)	3.6E-10	-0.02 (-0.03, -0.01)	0.0027
Sphingomyelin(28:1)	-0.03 (-0.05, -0.02)	1.3E-10	-0.02 (-0.03, -0.01)	9.2E-04
<b>Steroid and Steroid Derivatives</b>				
Dehydroepiandrosterone sulfate (sodium salt)	-0.02 (-0.03, -0.01)	7.2E-05	-0.04 (-0.05, -0.02)	4.0E-09
Cortisol	-0.03 (-0.05, -0.02)	5.8E-10	-0.02 (-0.04, -0.01)	0.0079
Corticosterone	0.02 (0.01, 0.04)	0.0039	0.03 (0.02, 0.04)	8.3E-06
<b>Unsaturated Fatty Acids</b>				
Eicosatrienoic Acid	0.03 (0.02, 0.04)	1.1E-06	0.05 (0.04, 0.06)	7.6E-15
10-Nitro-9E-octadecenoic acid	0.02 (0.00, 0.03)	0.006	0.01 (0.00, 0.02)	0.035
Docosapentaenoic acid	0.02 (0.01, 0.03)	1.8E-04	0.03 (0.01, 0.04)	2.0E-04
Arachidonic acid ethyl ester	0.03 (0.02, 0.04)	1.9E-08	0.04 (0.03, 0.05)	1.3E-09
Arachidonic acid	0.02 (0.01, 0.03)	0.0038	0.02 (0.01, 0.04)	1.9E-04
Alpha-Linolenic acid	0.02 (0.00, 0.03)	0.004	0.03 (0.02, 0.04)	2.6E-06
Linolenyl aldehyde	-0.03 (-0.05, -0.01)	0.01	-0.03 (-0.04, -0.02)	5.7E-06
<b>Vitamin B</b>				
Pantothenic acid	0.02 (0.00, 0.03)	0.0088	0.02 (0.00, 0.03)	6.8E-03
<b>Vitamin D3 Derivatives</b>				
Vitamin D3 derivative I	0.03 (0.02, 0.04)	5.2E-09	0.04 (0.02, 0.05)	1.1E-07

Metabolite	ULSAM and PIVUS		TwinGene	
	Beta (95% CI)	P-value	Beta (95% CI)	P-value
<b>Glycerophospholipids</b>				
Lyso-PAF C-18	-0.05 (-0.08, -0.02)	0.0027	-0.04 (-0.05, -0.03)	8.0E-10
Lysophosphatidylcholine(20:1)	-0.05 (-0.08, -0.01)	0.0053	-0.04 (-0.05, -0.02)	3.0E-06
Lysophosphatidylcholine(20:2)	-0.03 (-0.05, -0.01)	9.8E-05	-0.02 (-0.03, -0.01)	7.5E-04
Lysophosphatidylcholine(22:5) <sup>a</sup>	-0.02 (-0.03, -0.01)	0.0059	-0.02 (-0.03, -0.01)	0.0022
Lysophosphatidylcholine(P-16:0)	-0.05 (-0.07, -0.04)	3.2E-09	-0.04 (-0.05, -0.03)	3.6E-11
Lysophosphatidylcholine(18:2/0:0)	-0.05 (-0.08, -0.03)	3.4E-07	-0.06 (-0.07, -0.05)	2.6E-17
Phosphatidylcholine(18:1)	-0.04 (-0.06, -0.02)	5.8E-04	-0.02 (-0.03, -0.00)	9.5E-03
Lysophosphatidylcholine(20:3) <sup>b</sup>	0.02 (0.01, 0.03)	0.0013	0.04 (0.03, 0.05)	1.2E-09
Lysophosphatidylcholine(18:1) <sup>b</sup>	-0.05 (-0.07, -0.03)	3.7E-06	-0.05 (-0.06, -0.03)	1.2E-11
Lysophosphatidylcholine(18:3)	-0.04 (-0.06, -0.02)	8.1E-04	-0.03 (-0.05, -0.02)	2.9E-08
Lysophosphatidylcholine(20:0)	-0.07 (-0.08, -0.06)	5.7E-38	-0.06 (-0.08, -0.05)	7.9E-17
Lysophosphatidylcholine(18:1) <sup>a</sup>	-0.05 (-0.08, -0.03)	2.0E-05	-0.04 (-0.06, -0.03)	1.2E-10
Lysophosphatidylcholine(17:0)	-0.07 (-0.08, -0.05)	6.0E-22	-0.03 (-0.04, -0.02)	2.5E-05
Lysophosphatidylcholine(20:3) <sup>a</sup>	0.02 (0.01, 0.03)	2.5E-04	0.04 (0.03, 0.05)	1.0E-09
Lysophosphatidylcholine(22:5) <sup>b</sup>	-0.02 (-0.03, -0.01)	0.005	-0.02 (-0.03, -0.01)	0.0012
Phosphatidylcholine(32:1)	0.02 (0.01, 0.03)	3.0E-05	0.02 (0.01, 0.03)	0.0056
Phosphatidylcholine(36:2)	-0.02 (-0.03, -0.00)	0.009	-0.01 (-0.02, -0.00)	0.038
Phosphatidylcholine(38:3)	0.03 (0.01, 0.04)	2.8E-04	0.03 (0.02, 0.04)	3.6E-06
Lysophosphatidylcholine(0:0/18:2)	-0.05 (-0.08, -0.03)	1.0E-05	-0.06 (-0.07, -0.05)	1.0E-16

Regression models were adjusted for age and sex. In the ULSAM cohort, the regression models were only adjusted for age as the cohort contain only male participants. [<sup>a</sup>] or [<sup>b</sup>] indicates that two distinct peaks of the same metabolite (isomers) were detected.

**Supplementary Table 6.** Meta-analysis of WHRadjBMI-metabolites estimates across the ULSAM (N=1,112) and PIVUS (N=483) cohorts among males.

Metabolite	Beta (95% CI)	P-value
L-Acetylcarnitine	1.52 (0.44, 2.60)	5.7E-03
L-Carnitine	1.34 (0.24, 2.44)	1.7E-02
Piperine	1.96 (0.91, 3.02)	2.6E-04
Creatine	3.06 (1.44, 4.67)	2.0E-04
L-Aspartyl-L-phenylalanine	2.03 (0.29, 3.78)	2.3E-02
Chenodeoxycholic acid glycine conjugate	1.62 (0.14, 3.10)	3.2E-02
Cholic acid	-1.39 (-2.73, -0.05)	4.2E-02
Deoxycholic acid glycine conjugate	1.59 (0.53, 2.64)	3.1E-03
Glycocholic acid	1.90 (0.42, 3.38)	1.2E-02
C <sub>12</sub> H <sub>14</sub> O <sub>5</sub>	-2.09 (-3.17, -1.01)	1.5E-04
Monoacylglycerol(16:1)	1.37 (0.28, 2.46)	1.3E-02
Lysophosphatidylcholine(0:0/16:1)	1.15 (0.07, 2.24)	3.8E-02
Lysophosphatidylcholine(17:0)	-1.98 (-3.73, -0.23)	2.7E-02
Lysophosphatidylcholine(18:1)a	-1.20 (-2.36, -0.04)	4.3E-02
Lysophosphatidylcholine(18:2/0:0)	-2.27 (-4.33, -0.21)	3.0E-02
Lysophosphatidylcholine(20:0)	-1.12 (-2.18, -0.07)	3.7E-02
Lysophosphatidylcholine(20:2)	-2.01 (-3.09, -0.93)	2.7E-04
Phosphatidylcholine(32:1)	1.53 (0.20, 2.87)	2.5E-02
Theobromine	2.84 (0.94, 4.73)	3.3E-03
Propranolol	1.23 (0.14, 2.31)	2.6E-02
Ceramide phosphoethanolamine(38:2)	-1.11 (-2.15, -0.07)	3.7E-02
Lactosyl ceramide(d18:1/16:0)	-1.53 (-2.85, -0.20)	2.4E-02
Sphingosine	1.94 (0.13, 3.76)	3.6E-02
Sphingomyelin(32:2)	-1.03 (-2.06, -0.00)	4.9E-02
Sphingomyelin(36:3)	-1.41 (-2.45, -0.36)	8.3E-03
Sphingomyelin(40:2)	-1.23 (-2.30, -0.15)	2.6E-02
3a,6b,7b-Trihydroxy-5b-cholanoic acid	-1.69 (-2.80, -0.58)	2.8E-03
Corticosterone	1.20 (0.15, 2.25)	2.6E-02
Dehydroepiandrosterone sulfate (sodium salt)	-1.92 (-3.00, -0.85)	4.3E-04
Palmitoleic acid	1.39 (0.32, 2.46)	1.1E-02
Pantothenic acid	2.17 (0.39, 3.95)	1.7E-02

Waist-to-hip ratio (WHR) analysis were adjusted for age and BMI.



**Supplementary Table 7. 11** WHRadjBMI-associated metabolites in females in the PIVUS (N=487) and TwinGene (N=879) cohorts, and 4 WHRadjBMI-associated metabolites in males in the PIVUS (N=483) and ULSAM (N=1,112) cohorts, and replicated in TwinGene (N=1,167).

Metabolite	WHRadjBMI			
	Beta (95% CI)	P-value	Beta (95% CI)	P-value
<b>Female</b>	<b>PIVUS</b>		<b>TwinGene</b>	
<b>Amino Acids and Derivatives</b>				
L-Proline	2.55 (0.89, 4.22)	0.003	1.20 (0.29, 2.11)	0.010
<b>Bile Acids</b>				
Hyodeoxycholic acid	3.69 (2.03, 5.34)	1.5E-05	0.72 (0.04, 1.39)	0.037
<b>Glycerolipids</b>				
Monoacylglycerol(20:5)	2.67 (0.95, 4.39)	0.0025	0.81 (0.04, 1.58)	0.038
Monoacylglycerol(18:2)	2.64 (0.84, 4.44)	0.004	1.53 (0.60, 2.46)	0.001
Monoacylglycerol(14:0)	3.18 (1.41, 4.94)	0.0005	1.64 (0.79, 2.50)	0.0002
Diacylglycerol(34:1)	3.57 (1.88, 5.26)	4.2E-05	0.91 (0.02, 1.81)	0.044
Monoacylglycerol(18:1)	3.84 (2.08, 5.59)	2.3E-05	1.75 (0.83, 2.68)	0.0003
Monoacylglycerol(16:1)	3.01 (1.24, 4.77)	0.0009	1.46 (0.52, 2.40)	0.002
Monoacylglycerol(16:0)	3.74 (1.96, 5.51)	4.4E-05	1.92 (1.01, 2.83)	4.0E-05
<b>Peptides</b>				
Gamma-Glutamyl-leucine	2.73 (1.25, 4.21)	0.0003	1.40 (0.67, 2.13)	0.0002
<b>Sphingomyelins</b>				
Sphingomyelin(32:2)	-2.46 (-3.78, -1.14)	0.0003	-0.71 (-1.30, -0.12)	0.019
<b>Male</b>	<b>PIVUS and ULSAM</b>		<b>TwinGene</b>	
<b>Amino Acids and Derivatives</b>				
Creatine	3.06 (1.44, 4.67)	0.0002	1.40 (0.60, 2.20)	0.0006
<b>Cinnamic Acid and Derivates</b>				
C <sub>12</sub> H <sub>14</sub> O <sub>5</sub>	-2.09 (-3.17, -1.01)	0.0001	-0.89 (-1.73, -0.06)	0.036
<b>Steroids and Steroid Derivatives</b>				
Dehydroepiandrosterone sulfate (sodium salt)	-1.92 (-3.00, -0.85)	0.0004	-1.22 (-2.03, -0.40)	0.004

Waist-to-hip ratio (WHR) analysis were adjusted for age and BMI.

**Supplementary Table 9.** Pearson correlation between BMI and metabolites with evidence of causal association in Mendelian randomization analysis in the Swedish cohorts.

	PIVUS (N=970)		ULSAM (N=1,138)		TwinGene (N=2,059)	
	r	P-value	r	P-value	r	P-value
Dodecanedioic acid	-0.13	<0.0001	-0.14	<0.0001	-0.12	<0.0001
Lysophosphatidylcholine(P-16:0)	-0.27	<0.0001	-0.15	<0.0001	-0.19	<0.0001
Arachidonic acid	0.08	0.011	0.05	0.11	0.11	<0.0001
*Creatine	0.08	0.013			0.07	0.001

\*Creatine was not available in the ULSAM cohort.

r represents Pearson correlation coefficient.

**Supplementary Table 10.** Metabolite class enrichment analysis for the BMI-associated metabolites, and WHRadjBMI among females and males, respectively.

	<b>BMI</b>	<b>WHRadjBMI females</b>	<b>WHRadjBMI males</b>
<b>Class</b>	<b>p<sub>adj</sub>*</b>	<b>p<sub>adj</sub>*</b>	<b>p<sub>adj</sub>*</b>
Acylcarnitines	0.06	0.75	0.68
Amino Acids and Derivatives	0.11	0.83	0.68
Glycerophosphoethanolamines	0.64	0.33	0.48
Glycerophospholipids	0.30	0.33	0.68
Unsaturated Fatty Acids	0.61	0.86	0.48

p<sub>adj</sub> represents the Benjamini-Hochberg-corrected P-value.

**Supplementary Table 11.** Mendelian randomization analysis using the combined sample (N=3,610) from the ULSAM, PIVUS and TwinGene cohort, employing weighted median method and MR-Egger method.

<b>Metabolite</b>	<b>Weighted Median Method</b>		<b>MR-Egger Method</b>	
	<b>Beta (95% CI)</b>	<b>P-value</b>	<b>Beta (95% CI)</b>	<b>P-value</b>
<b>BMI</b>				
Dodecanedioic acid	-0.36 (-0.72, 0.01)	0.05	0.04 (-0.56, 0.65)	0.89
Lysophosphatidylcholine(P-16:0)	-0.26 (-0.64, 0.11)	0.17	0.02 (-0.60, 0.64)	0.95
Arachidonic acid	-0.49 (-0.83, -0.15)	0.005	-0.29 (-0.86, 0.27)	0.31
Creatine	0.095 (-0.32, 0.51)	0.65	0.25 (-0.39, 0.89)	0.44
<b>WHRadjBMI (Females)</b>				
Sphingomyelin(32:2)	-0.31 (-0.87, 0.25)	0.29	-0.32 (-1.63, 0.98)	0.62

**Supplementary Table 12.** Mendelian randomization analysis using the weighted median method and MR-Egger method in the KORA/TwinsUK cohort (N=7,373), the CHARGE Consortium (N= 8,631), the DIRECT Consortium (N=3,029) and the FHS cohort (N=2,076).

Metabolite	Weighted Median Method		MR-Egger Method	
	Beta (95% CI)	P-value	Beta (95% CI)	P-value
<b>KORA/TwinsUK Cohort</b>				
Dodecanedioic acid	-0.01 (-0.06, 0.04)	0.64	-0.01 (-0.09, 0.07)	0.79
Arachidonic acid	-0.02 (-0.05, 0.01)	0.19	-0.04 (-0.09, 0.02)	0.16
Creatine	0.04 (-0.01, 0.10)	0.11	0.07 (-0.01, 0.15)	0.10
<b>CHARGE Consortium</b>				
Arachidonic acid	-0.58 (-0.98, -0.18)	0.004	-0.73 (-1.40, -0.05)	0.034
<b>DIRECT Consortium</b>				
Arachidonic acid	0.04 (-0.15, 0.23)	0.70	0.07 (-0.24, 0.39)	0.66
Creatine	0.08 (-0.12, 0.27)	0.43	-0.17 (-0.49, 0.16)	0.31
<b>FHS Cohort</b>				
Creatine	-0.05 (-0.51, 0.41)	0.84	0.34 (-0.42, 1.11)	0.38

**Supplementary Table 13.** Mean correlation coefficients across the randomized duplicate injections for the metabolites discovered through Mendelian randomization analysis in the ULSAM, PIVUS and TwinGene.

<b>BMI-associated Metabolites</b>			
	<b>PIVUS</b>	<b>TwinGene</b>	<b>ULSAM</b>
Dodecanedioic acid	0.65	n.d.	n.d.
Lysophosphatidylcholine(P-16:0)	0.61	0.74	0.69
Arachidonic acid	0.74	0.54	0.63
Creatine	0.74	0.54	0.63
<b>WHRadjBMI-associated Metabolites (Females)</b>			
Sphingomyelin(32:2)	0.86	0.63	0.65

n.d. denotes no duplicates are available.

## Supplemental Text 1

**Metabolite annotation:** In total 7,522 metabolomic features were detected from PIVUS, 10,162 from ULSAM, and 9,755 from the TwinGene cohorts were identified. Common metabolomic features between ULSAM, PIVUS, and TwinGene cohorts were identified through matching retention time, mass-to-charge ( $m/z$ ) ratio, and fragmentation patterns. For each metabolomic feature, retention time,  $m/z$ , and fragmentation pattern were compared to in-house standards, as well as with public database reference libraries, and were matched according to Metabolomics Standard Initiative guidelines(3). All metabolomic features with a retention time  $<35s$  were excluded from the current analysis. We combined strongly correlated features with shared retention times for the construction of representative fragmentation spectra for annotation according to the 4-level metabolites accuracy classification suggested by Metabolomics Standards Initiative(3). In this 4-level accuracy approach, level 1 indicates identification based upon matching by retention time, mass, and fragmentation patterns to in-house standards while level 4 represents unknown metabolites which are not matched in the public databases in relation to retention time, mass-to-charge ratio, and fragmentation patterns with named metabolites (level 2) or based upon chemical classes (level 3). Details about the annotations for the metabolites discovered through Mendelian randomization (MR) analysis for general as well as for central body fat distribution have been presented: dodecanedioic acid (Supplementary Fig. 3), lysophosphatidylcholine P-16:0 (Supplementary Fig. 4), arachidonic acid (Supplementary Fig. 5), creatine (Supplementary Fig. 6) and sphingomyelin (32:2) (Supplementary Fig. 7).

The metabolite data transformation procedure is described in detail elsewhere(4). In summary, the metabolites features were  $\log_2$  transformed to approximate normal transformation. Potential sample outliers were identified and removed through plotting the total sample intensity of each sample, as, the samples show extreme intensities might be due to degradation or technical

errors. ANOVA-type normalization was used for taking into accounts the factors of unwanted consideration. This normalization procedure outperforms the other commonly normalization approaches. Normalization procedure was performed through regression each metabolite intensity feature against several factors of unwanted variability. Residuals from the regression were used as intensity features. In each of the Swedish cohorts (TwinGene, ULSAM and PIVUS), the intensity features were identified through using following technical variables,

**TwinGene:** retention time correction, analysis date, storage time, unknown cluster effect;

**ULSAM:** retention time correction, analysis date, sample collection, plate effect;

**PIVUS:** retention time correction, analysis date, storage time, season effect.

The intensity features were averaged between technical duplicates to rule the potential effect of inherent instrumental variability and features with poor correlation (if p-values threshold was  $>0.05$ ) between duplicates were removed(4). Finally, intensities were SD-transformed before association analysis.

For quality control (QC), prior to each batch of two 96-well plates of samples, instrument maintenance (cone cleaning, mass calibration, and detector gain calibration) was performed, and an external QC standard mix was injected containing  $2\text{ }\mu\text{g mL}^{-1}$  each of caffeine, terfenadine, sulfadimethoxime, and reserpine. The QC standards were evaluated for retention time ( $\pm 0.05$  min), signal intensity ( $< 25\%$  relative standard deviation), and mass accuracy ( $< 3$  ppm). All samples were randomized prior to instrumental analysis. Since internal standards were not available at the time of analysis, randomized duplicate injections were performed to mitigate potential within-sample variation originating from the instrumental analysis. Spearman correlation between features across duplicate injections was assessed and a correlation between technical duplicates was considered significant with Bonferroni P value  $< 0.05$ . Average peak



areas of the duplicate injections were then used for the relative quantitation, features with poor correlation between the duplicate injections were excluded. The mean Spearman correlation between duplicate injections across samples was 0.43 in PIVUS, 0.38 in TwinGene, and 0.46 in ULSAM. The mean feature correlation for the top BMI-associated metabolic features are provided in Supplemental Information Supplementary Table 13 and ranged from 0.48-0.87. Moreover, all three studies were comparable in terms of mean coefficient of variation across features; 2.9 % in PIVUS, 3.7% in TwinGene, and 5.2 % in ULSAM as has been previously described in Ganna *et al* 2014(5) and Fall *et al* 2016(6).

## Supplemental Text 2

We applied a random effect meta-analysis as it assumes that all the studies in a meta-analysis are estimating different yet unrelated true underlying effects, each effect representing a random sample from a particular distribution of effect sizes. In a random effect meta-analysis approach, the study weights are more similar compared to the fixed effect meta-analysis approach (small studies that are part of meta-analysis gain influence while the larger sample size studies lose influence) and summary effect confidence intervals are usually larger(7).

In the below system of equations,  $T_i$  represents the observed effect,  $\theta_i$  represents the true effect and  $\varepsilon_i$  represents the deviation from the true effect due to sampling error.  $\theta$  represents the average effect across studies, and  $u_i$  the individual study deviation from the average effect. Both  $\varepsilon_i$  and  $u_i$  are assumed to follow a normal distribution.

$$T_i = \theta_i + \varepsilon_i$$

$$\theta_i = \theta + u_i$$

### Supplemental Text 3

Details and equations about the Mendelian randomization approaches that we used in the current analysis have previously been described in detail(8-10).

#### Inverse-Variance Weighted (IVW) Method

The causal effect of an exposure on the outcome, which is the ratio of the gene variants outcome association to the genetic variants exposure association, can be estimated using  $n$  number of variants conditional on the variants being uncorrelated. Then the ratio can be estimated using the below formula which is called inverse variance weighted (IVW) estimator.

$$\hat{\beta}_{IVW} = \frac{\sum_j \hat{\gamma}_j^2 \sigma_{Yj}^{-2} \hat{\beta}_j}{\sum_j \hat{\gamma}_j^2 \sigma_{Yj}^{-2}}$$

$\hat{\gamma}_j$  denotes the estimated coefficient for the  $j_{th}$  variant for the exposure-instrument regression.  $\hat{\beta}_j$  is the ratio between the coefficient for the exposure-instrument regression and the coefficient for the outcome-instrument regression for the  $j_{th}$  variant.  $\sigma_{Yj}$  is the standard error of the outcome-instrument association for the  $j_{th}$  variant. The IVW method is asymptotically equal to the two-stage least squares estimator which is commonly used for individual level data. If all the studied genetic variants satisfy the instrumental variable (IV) assumptions, then the IVW estimate is a consistent estimate of the causal effect, as it is a weighted mean of the individual ratio estimates.

#### Weighted Median Method (WMM)

The IVW method is an efficient approach to assess the causal estimate between an exposure to an outcome, however, it is biased when even one genetic variant is invalid e.g. due to pleiotropy. However, an estimator can provide consistent causal estimates even if 50% of the genetic variants are valid using the weighted median method (WMM).

A regular median estimate can be obtained through calculating the causal ratio estimates from each genetic variants  $\theta_{aj} = \beta_{Yj}/\beta_{Xj}$ , ordering them, and finding the median. This estimator is inefficient, and the weighted median estimator improves by instead calculating percentiles  $P_j$  according to the formula

$$P_j = 100(s_j + w_j/2)$$

Where  $w_j$  is a weight assigned to estimate  $j$  and  $s_j$  is the sum of all weights from the lowest estimate up to estimate  $j$ . Weights  $w_j$  are calculated according to the formula:

$$w'_j = \frac{\hat{\gamma}_j^2}{\sigma_{Yj}^2}$$

The WMM estimate will then be a weighted average of the largest estimate smaller than the 50<sup>th</sup> percentile and the smallest estimate larger than the 50<sup>th</sup> percentile. The weights are derived from the delta method for the variance of the ratio of two random variables, and represent the reciprocal of the variance of the ratio estimates.

### MR-Egger Method

MR-Egger is another method for Mendelian randomization that is less sensitive to bias from pleiotropy. MR-Egger performs a weighted linear regression of the genetic variants-outcome coefficients on the genetic variants-exposure ( $\hat{\gamma}_j$ ) coefficients:

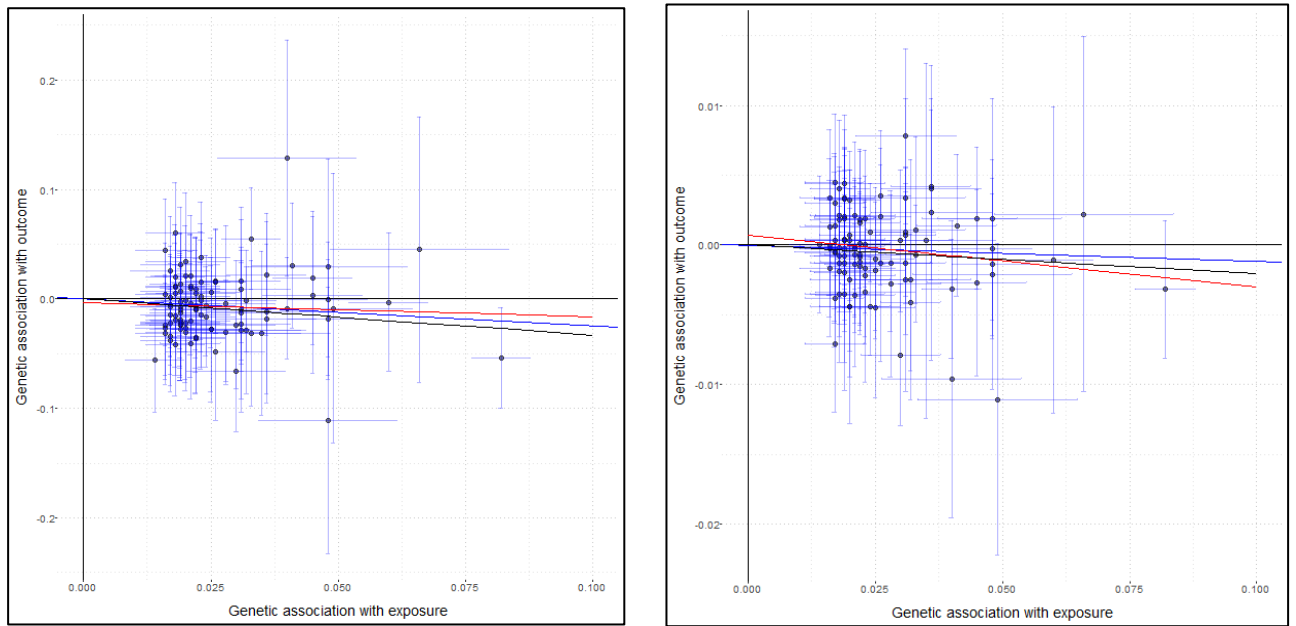
$$\hat{\Gamma}_j = \beta_{0E} + \beta_E \hat{\gamma}_j$$

The value of the intercept term “ $\beta_{0E}$ ” can be interpreted as the average pleiotropic effect across the genetic variants. Pleiotropic effect can be defined as the effect of the genetic variant on the outcome that is not mediated by the exposure.

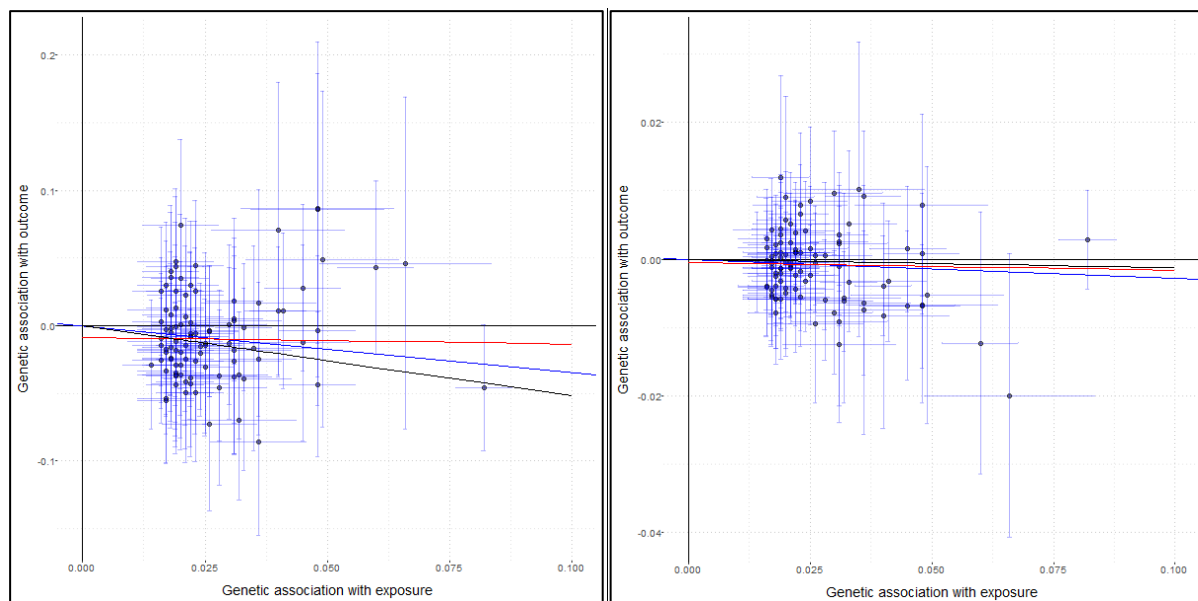
MR-Egger provides a causal estimate even when all the genetic variants are invalid but under a weaker assumption known as the InSIDE (instrument strength independent of direct effect) assumption. For example, if the association of the  $j$ th variant with the outcome  $\hat{\Gamma}_j$  is

$$\hat{\Gamma}_j = \beta\gamma_j + \alpha_j$$

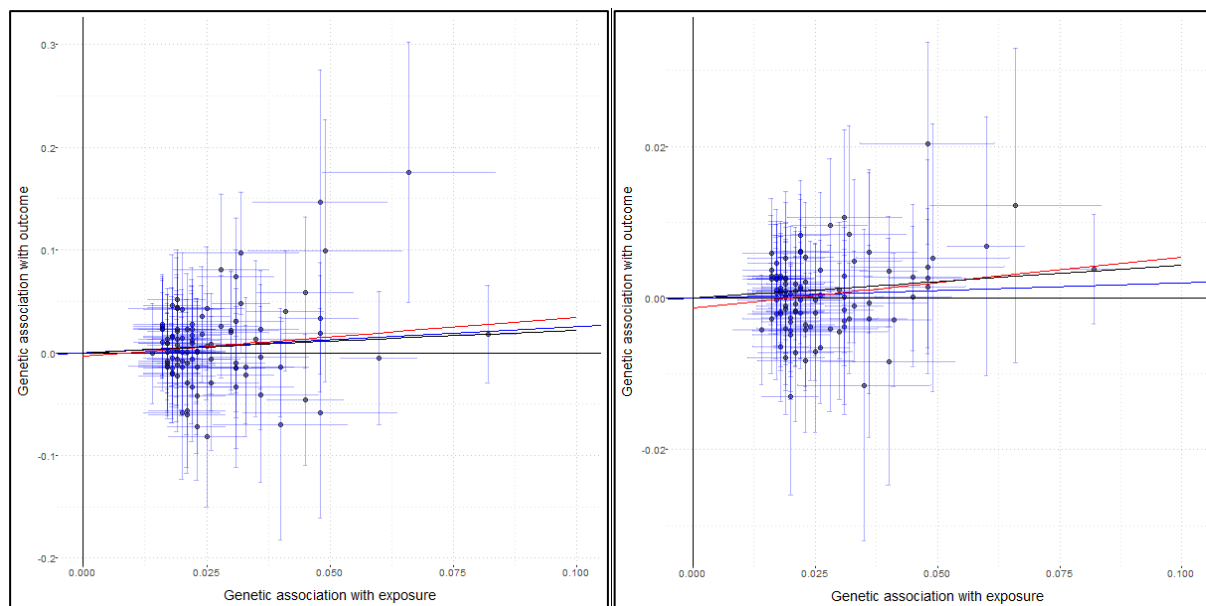
Where  $\alpha_j$  is the pleiotropic effect of the variant, then the InSIDE assumption postulates that the pleiotropic effects  $\alpha$  must be independent of the parameters  $\gamma$  denoting the strength of the instrument.



**Supplementary Fig. 1A** Scatter plots of genetic association between exposure (BMI) and outcome (arachidonic acid) across the combined sample of three Swedish cohorts (PIVUS, ULSAM and TwinGene) (left) and KORA/TwinsUK (right). Regression lines indicate instrumental variable estimates for Mendelian randomization analyses using the inverse variance weighted method (blue), weighted median method (black), and MR-Egger method (red).

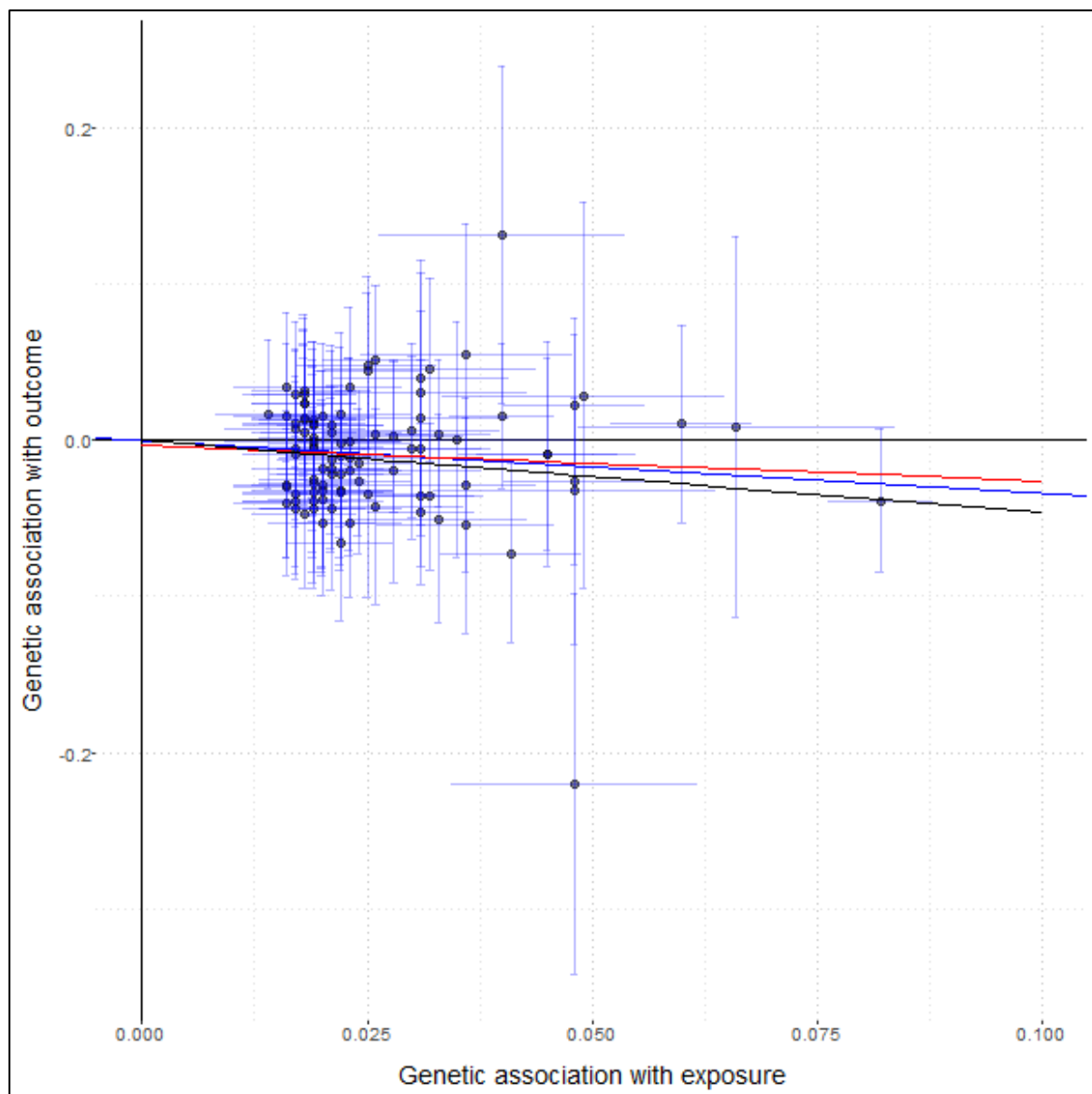


**Supplementary Fig. 1B** Scatter plots of genetic association between exposure (BMI) and outcome (dodecanedioic acid) across the combined sample of three Swedish cohorts (PIVUS, ULSAM and TwinGene) (left) and KORA/TwinsUK (right). Regression lines indicate instrumental variable estimates for Mendelian randomization analyses using the inverse variance weighted method (blue), weighted median method (black), and MR-Egger method (red).

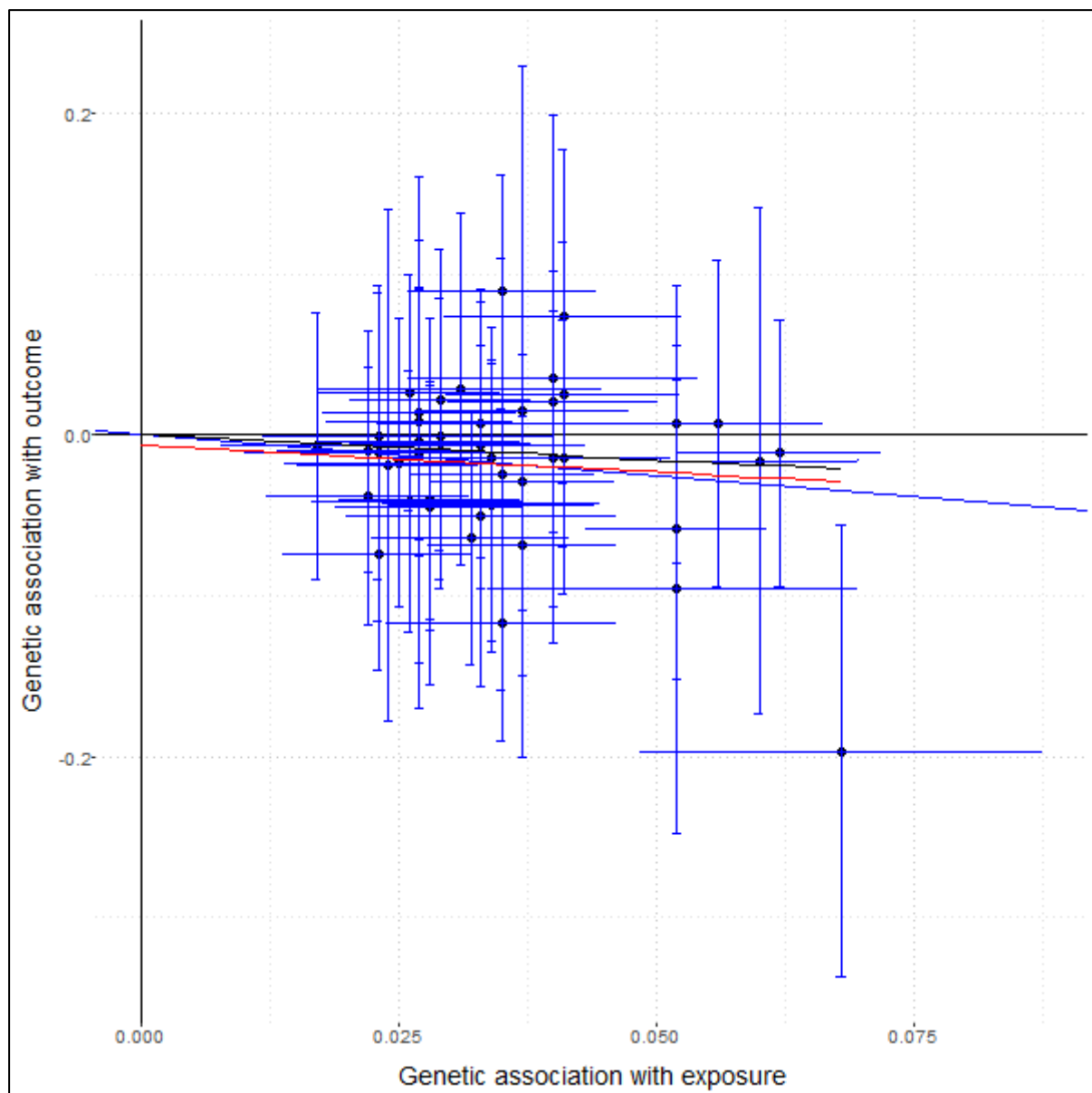


**Supplementary Fig. 1C** Scatter plots of genetic association between exposure (BMI) and outcome (creatinine) across the combined sample of three Swedish cohorts (PIVUS, ULSAM and TwinGene) (left) and KORA/TwinsUK (right). Regression lines indicate instrumental variable estimates for Mendelian randomization analyses using the inverse variance weighted method (blue), weighted median method (black), and MR-Egger method (red).

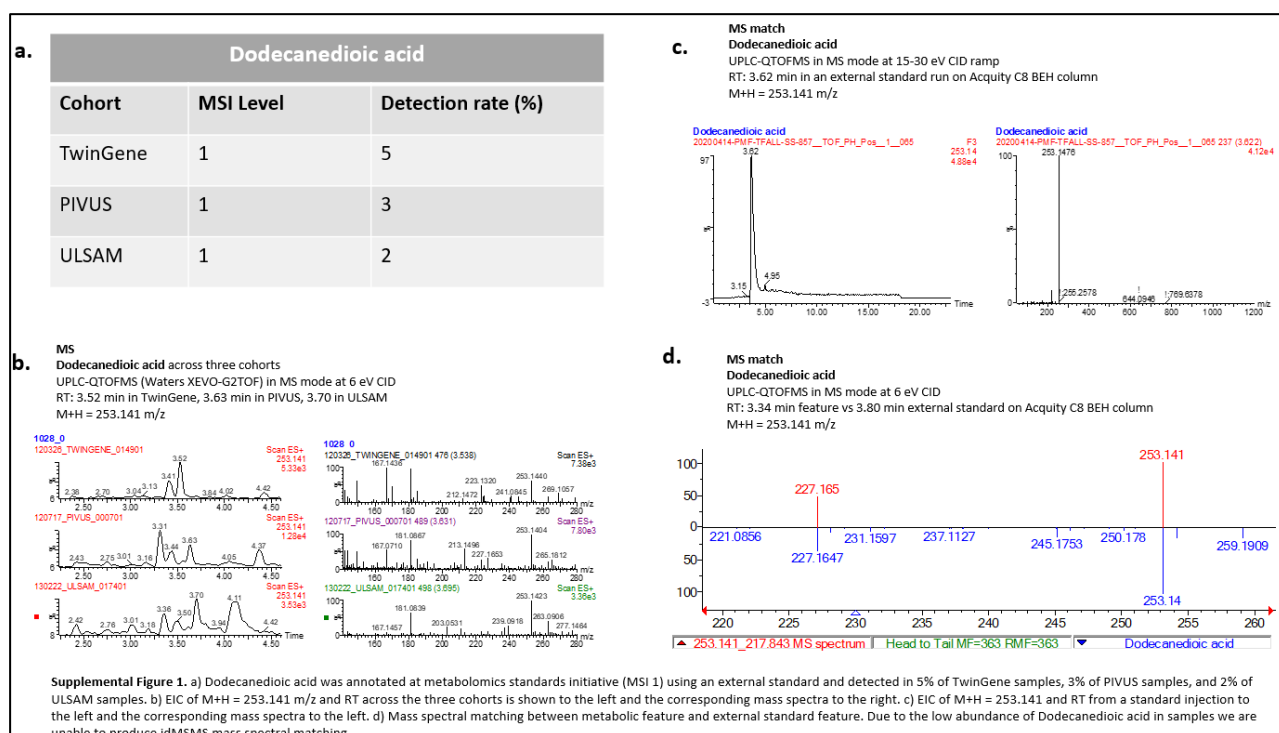




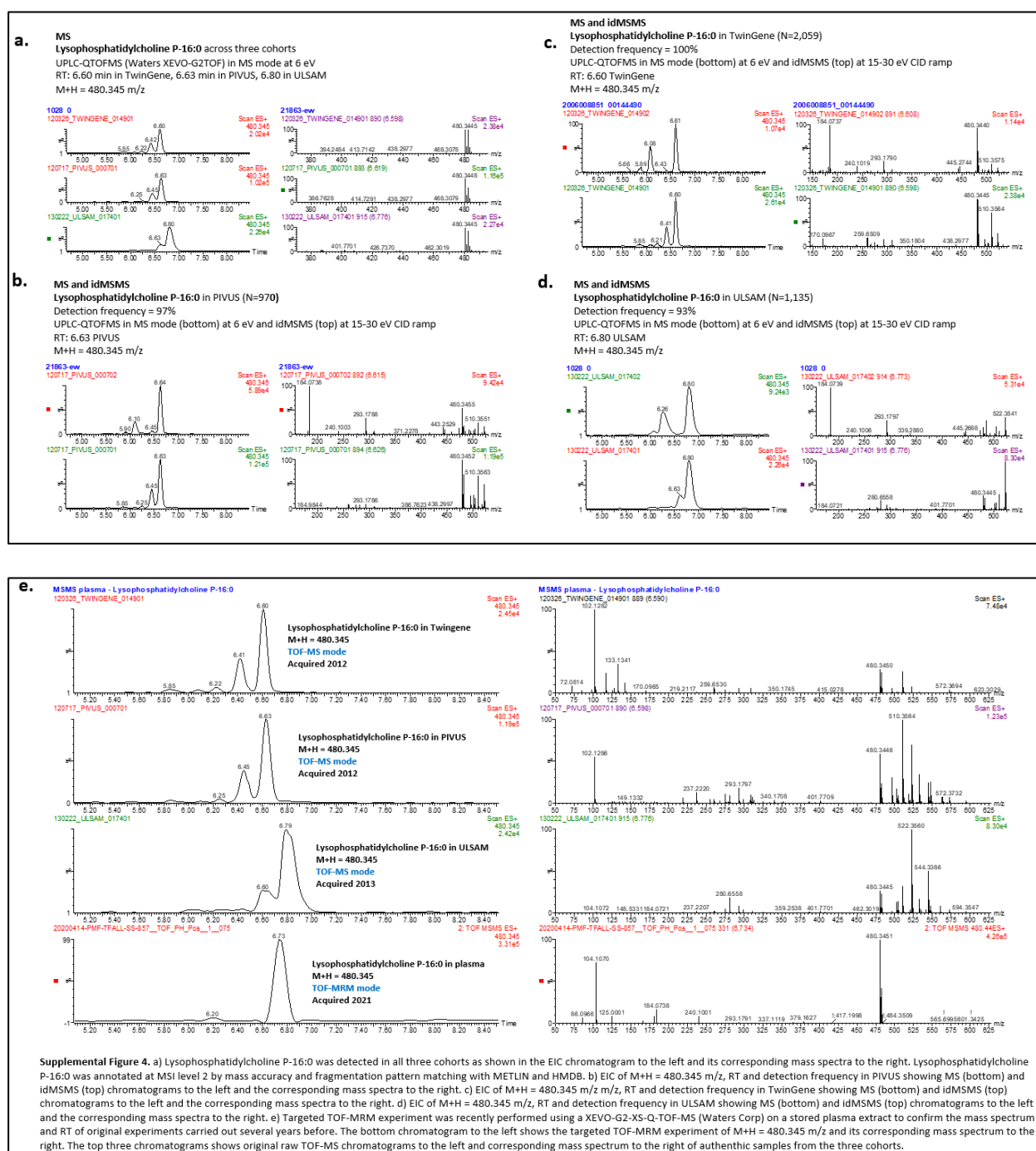
**Supplementary Fig. 1D** Scatter plots of genetic association between exposure (BMI) and outcome (Lysophosphatidylcholine(P-16:0)) across the combined sample of three Swedish cohorts (PIVUS, ULSAM and TwinGene). Regression lines indicate instrumental variable estimates for Mendelian randomization analyses using the inverse variance weighted method (blue), weighted median method (black), and MR-Egger method (red).



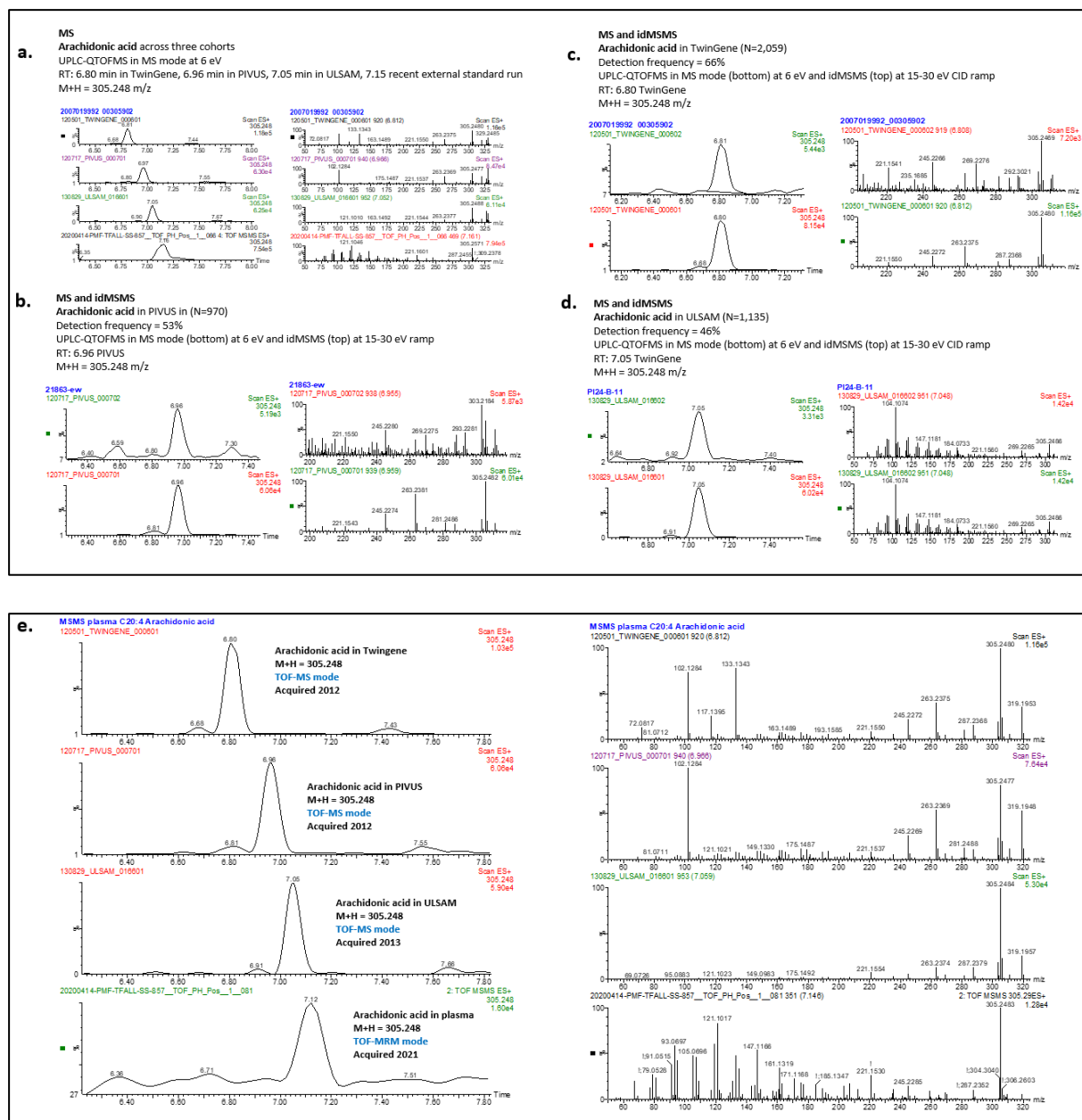
**Supplementary Fig. 2A** Scatter plots of genetic association with exposure (WHRadjBMI) and outcome (Sphingomyelin (32:2)) across the combined sample of three Swedish cohorts (PIVUS, ULSAM and TwinGene). Regression lines indicate instrumental variable estimates for Mendelian randomization analysis using the inverse variance weighted (blue), weighted median method (black), and MR-Egger method (red) Mendelian randomization analysis.



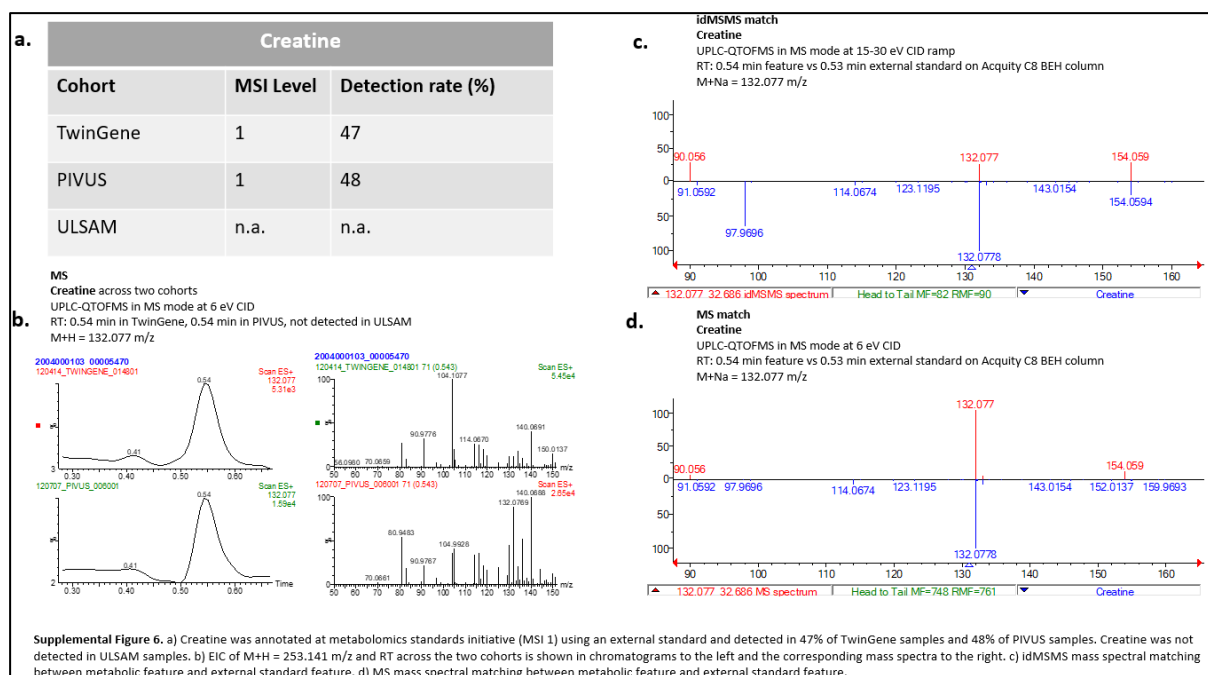
**Supplementary Fig. 3.** a) Dodecanedioic acid was annotated at metabolomics standards initiative (MSI 1) using an external standard and detected in 5% of TwinGene samples, 3% of PIVUS samples, and 2% of ULSAM samples. b) EIC of M+H = 253.141 m/z and RT across the three cohorts is shown to the left and the corresponding mass spectra to the right. c) EIC of M+H = 253.141 and RT from a standard injection to the left and the corresponding mass spectra to the right. d) Mass spectral matching between metabolic feature and external standard feature. Due to the low abundance of dodecanedioic acid in samples we are unable to produce idMSMS mass spectral matching.



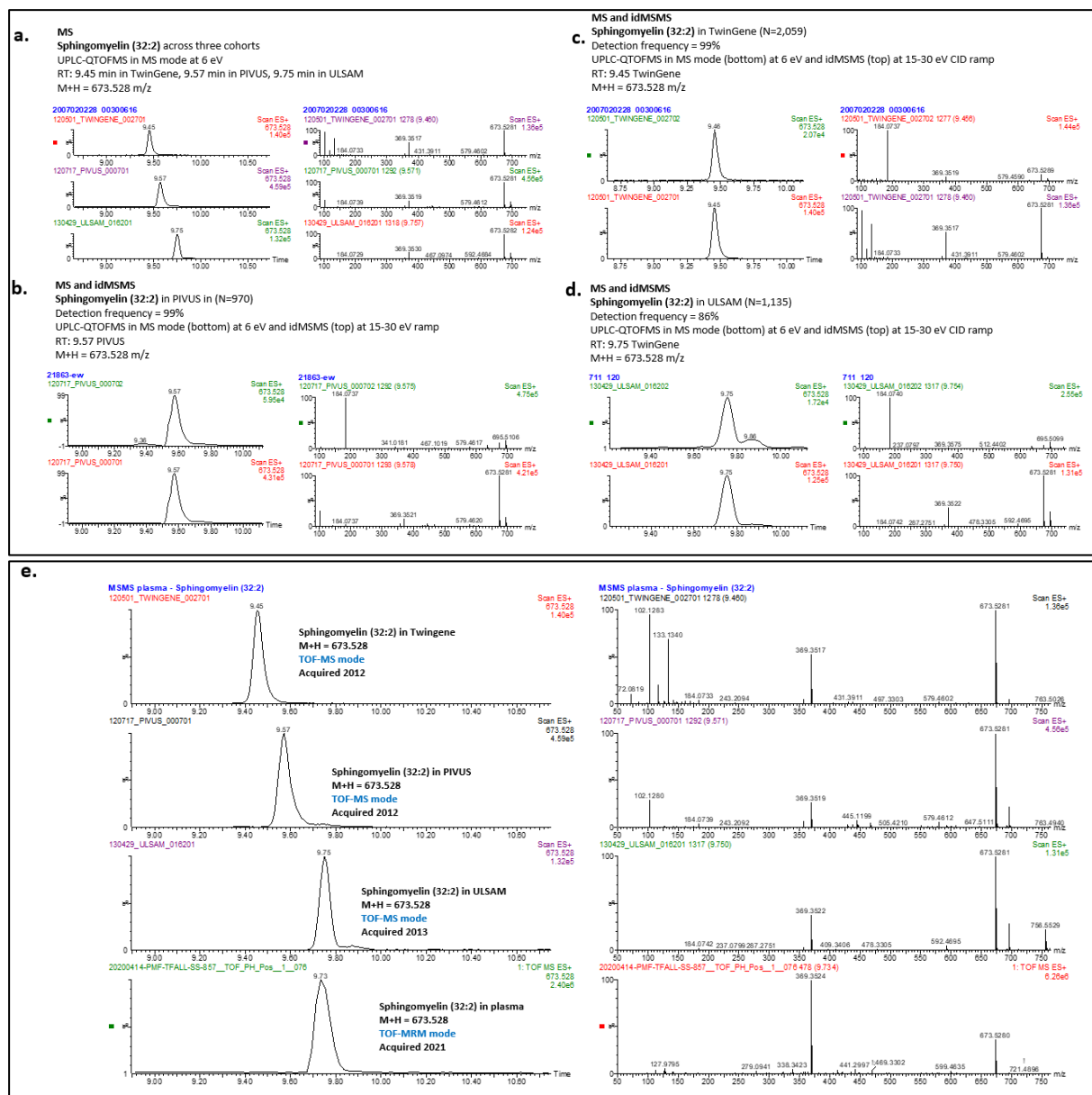
**Supplementary Fig. 4.** a) Lysophosphatidylcholine P-16:0 was detected in all three cohorts as shown in the EIC chromatogram to the left and its corresponding mass spectra to the right. Lysophosphatidylcholine P-16:0 was annotated at MSI level 2 by mass accuracy and fragmentation pattern matching with METLIN and HMDB. b) EIC of M+H = 480.345 m/z, RT and detection frequency in PIVUS showing MS (bottom) and idMSMS (top) chromatograms to the left and the corresponding mass spectra to the right. c) EIC of M+H = 480.345 m/z, RT and detection frequency in TwinGene showing MS (bottom) and idMSMS (top) chromatograms to the left and the corresponding mass spectra to the right. d) EIC of M+H = 480.345 m/z, RT and detection frequency in ULSAM showing MS (bottom) and idMSMS (top) chromatograms to the left and the corresponding mass spectra to the right. e) Targeted TOF-MRM experiment was recently performed using a XEVO-G2-XS-Q-TOF-MS (Waters Corp) on a stored plasma extract to confirm the mass spectrum and RT of original experiments carried out several years ago. The bottom chromatogram to the left shows the targeted TOF-MRM experiment of M+H = 480.345 m/z and its corresponding mass spectrum to the right. The top three chromatograms shows original raw TOF-MS chromatograms to the left and corresponding mass spectrum to the right of authentic samples from the three cohorts.



**Supplementary Fig. 5.** a) Arachidonic acid was detected in all three cohorts and external standard as shown in the EIC chromatogram to the left and its corresponding mass spectra to the right. Arachidonic acid was annotated at MSI level 1 by mass spectral and RT matching. b) EIC of M+H = 305.248 m/z, RT and detection frequency in PIVUS showing MS (bottom) and idMSMS (top) chromatograms to the left and the corresponding mass spectra to the right. c) EIC of M+H = 305.248 m/z, RT and detection frequency in TwinGene showing MS (bottom) and idMSMS (top) chromatograms to the left and the corresponding mass spectra to the right. d) EIC of M+H = 305.248 m/z, RT and detection frequency in ULSAM showing MS (bottom) and idMSMS (top) chromatograms to the left and the corresponding mass spectra to the right. e) Targeted TOF-MRM experiment was recently performed using a XEVO-G2-XS-Q-TOF-MS (Waters Corp) on a stored plasma extract to confirm the mass spectrum and RT of original experiments carried out several years before. The bottom chromatogram to the left shows the targeted TOF-MRM experiment of M+H = 305.248 m/z and its corresponding mass spectrum to the right. The top three chromatograms shows original raw TOF-MS chromatograms to the left and corresponding mass spectrum to the right of authentic samples from the three cohorts.



**Supplementary Fig. 6.** a) Creatine was annotated at metabolomics standards initiative (MSI 1) using an external standard and detected in 47% of TwinGene samples and 48% of PIVUS samples. Creatine was not detected in ULSAM samples. b) EIC of M+H = 253.141 m/z and RT across the two cohorts is shown in chromatograms to the left and the corresponding mass spectra to the right. c) idMSMS mass spectral matching between metabolic feature and external standard feature. d) MS mass spectral matching between metabolic feature and external standard feature.



**Supplementary Fig. 7.** a) Sphingomyelin (32:2) was detected in all three cohorts as shown in the EIC chromatogram to the left and its corresponding mass spectra to the right. Sphingomyelin (32:2) was annotated at MSI level 2 by mass accuracy and fragmentation pattern matching with METLIN and HMDB. b) EIC of M+H = 673.528 m/z, RT and detection frequency in PIVUS showing MS (bottom) and idMSMS (top) chromatograms to the left and the corresponding mass spectra to the right. c) EIC of M+H = 673.528 m/z, RT and detection frequency in TwinGene showing MS (bottom) and idMSMS (top) chromatograms to the left and the corresponding mass spectra to the right. d) EIC of M+H = 673.528 m/z, RT and detection frequency in ULSAM showing MS (bottom) and idMSMS (top) chromatograms to the left and the corresponding mass spectra to the right. e) Targeted TOF-MRM experiment was recently performed using a XEVO-G2-XS-Q-TOF-MS (Waters Corp) on a stored plasma extract to confirm the mass spectrum and RT of original experiments carried out several years before. The bottom chromatogram to the left shows the targeted TOF-MRM experiment of M+H = 673.528 m/z and its corresponding mass spectrum to the right. The top three chromatograms shows original raw TOF-MS chromatograms to the left and corresponding mass spectrum to the right of authentic samples from the three cohorts.

## REFERENCES

1. Locke AE, Kahali B, Berndt SI, et al.: Genetic studies of body mass index yield new insights for obesity biology. *Nature* 2015;518:197-206
2. Shungin D, Winkler TW, Croteau-Chonka DC, et al.: New genetic loci link adipose and insulin biology to body fat distribution. *Nature* 2015;518:187-196
3. Sumner LW, Amberg A, Barrett D, et al.: Proposed minimum reporting standards for chemical analysis Chemical Analysis Working Group (CAWG) Metabolomics Standards Initiative (MSI). *Metabolomics* 2007;3:211-221
4. Ganna A, Fall T, Salihovic S, et al.: Large-scale non-targeted metabolomic profiling in three human population-based studies. *Metabolomics* 2015;12:4
5. Ganna A, Salihovic S, Sundstrom J, et al.: Large-scale metabolomic profiling identifies novel biomarkers for incident coronary heart disease. *PLoS Genet* 2014;10:e1004801
6. Fall T, Salihovic S, Brandmaier S, et al.: Non-targeted metabolomics combined with genetic analyses identifies bile acid synthesis and phospholipid metabolism as being associated with incident type 2 diabetes. *Diabetologia* 2016;59:2114-2124
7. Borenstein M, Hedges LV, Higgins JP, et al.: A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res Synth Methods* 2010;1:97-111
8. Burgess S, Bowden J, Fall T, et al.: Sensitivity Analyses for Robust Causal Inference from Mendelian Randomization Analyses with Multiple Genetic Variants. *Epidemiology* 2017;28:30-42
9. Bowden J, Holmes MV: Meta-analysis and Mendelian randomization: A review. *Res Synth Methods* 2019;10:486-496
10. Bowden J, Davey Smith G, Haycock PC, et al.: Consistent Estimation in Mendelian Randomization with Some Invalid Instruments Using a Weighted Median Estimator. *Genet Epidemiol* 2016;40:304-314