

Supplementary Materials

Multivariate genome-wide analyses of insulin resistance phenotypes unravel novel loci and therapeutic targets for cardiometabolic health and longevity

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Supplementary Methods. Multivariate genome-wide analysis of IR phenotypes

To integrate the four IR measures, we performed a meta-analysis of summary statistics from four largest GWASs on HOMA-IR, ISI, Fins, and TG:HDL-C, involving approximately 644,158 participants of European ancestry. This analysis utilized three complementary tools including N-weighted genome-wide association meta-analysis (NGWAMA)¹, multi-trait analysis of genome-wide association study (MTAG)², and cross-phenotype association analysis (CPASSOC)³⁻⁴, designed to analyze genetically correlated traits to improve the power for genetic discovery while addressing sample overlap.

NGWAMA is based on quantifying the dependence between summary statistics using the pair-wise cross-trait LD-score intercepts (CTI)¹. The CTI is similar to the covariance between the test statistics of the traits between two univariate GWASs. Using the estimated covariances between effect sizes, the univariate GWASs are meta-analyzed by calculating the multivariate test statistic per SNP. We first generated a matrix of CTIs using the intercepts of LDSC genetic correlations between the four input IR phenotypes. We then performed NGWAMA by feeding the CTI matrix and a vector of SNP heritability of each trait using the N-weighted-GWAMA function (version 1.2.6)¹. In MTAG (<https://github.com/JonJala/mtag>), the SNP effect estimated for each trait can be improved when different traits that are correlated are included in the analysis². This approach can increase the likelihood of detecting loci in any of the traits assessed. The MTAG could be implemented when the assume of equal SNP heritability for each trait and perfect genetic covariance between traits is valid. Furthermore, we conducted a cross-trait meta-analysis using CPASSOC (https://github.com/futurologist/UKB_phenotypes_and_scripts/) following the CPASSOC manual⁵. This method accommodates differences in the degree of heritability for the four IR phenotypes and does not assume equal SNP heritability or perfect genetic covariance between traits, allowing for a more flexible model of genetic relationships across traits. CPASSOC estimates the cross-trait statistic heterogeneity (S_{Het}) and p-value through a sample size weighted meta-analysis of GWAS summary data^{3,4}.

We reversed the effect directions in the ISI GWAS summary statistics to align genetic effect directions for IR. Of note, these three tools can only output SNPs common across all input GWAS summary statistics¹⁻⁴. Consequently, due to the limited genome coverage of the HOMA-IR GWAS dataset, which contains 2,455,189 variants, there is a significant reduction in the number of SNPs after the multivariate GWAMA. To address this issue, we applied a strategy for handling GWAS datasets with significant disparities in SNP counts to minimize unnecessary variant reduction⁶. We included SNPs in the final multivariate GWAS selected in two steps: first, by taking the intersection of SNPs across all four IR GWAS datasets; and second, by taking the intersection of SNPs across the three IR GWAS datasets excluding the HOMA-IR dataset, which has limited genome coverage and the smallest number of SNPs.

Finally, the significant SNPs were identified as those achieving genome-wide significance ($P < 5 \times 10^{-8}$) across NGWAMA, CPASSOC, and MTAG. Subsequently,

genomic loci for mvIR were identified using FUMA v1.6.3 (<https://fuma.ctglab.nl/>) with the default parameters (250-kb-window linkage disequilibrium >0.1)⁷. Here, we briefly explain the procedure. FUMA first finds independent significant SNPs with a genome-wide significance ($P < 5 \times 10^{-8}$) such that they are independent from each other at $r^2 < 0.6$. Then, independent lead SNPs are identified from the independent significant SNPs such that they are independent from each other at $r^2 < 0.1$. FUMA then forms genomic loci by grouping independent significant SNPs if they are less apart than 250 kb. As a result, a genomic risk locus can contain multiple independent significant SNPs and multiple lead SNPs. To define the border of each locus, SNPs that have $r^2 \geq 0.6$ are identified for each of the independent significant SNPs from the reference data, including those not available in the input GWAS summary statistics. We used the 1000 Genomes Project as the reference data, which is readily available in FUMA. Novel loci were defined as lead SNPs located more than 1000-kb away from any of the genomic loci identified in the four GWASs (i.e., HOMA-IR, ISI, Fins, and TG:HDL-C) comprising the mvIR.

References

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Supplementary Notes 1. Genetic instrument information of mvIR_NGWAMA

SNP	Allele 1	Allele 2	Beta	SE	P	CHR	POS
rs10044259	T	C	0.014486	0.001866	8.29782E-15	5	78471854
rs10091267	A	T	0.010768	0.001811	2.77279E-09	8	64810701
rs10425186	T	C	0.014364	0.002629	4.6433E-08	19	56077305
rs1044531	T	C	-0.02098	0.00256	2.44829E-16	9	117098650
rs1052169	A	C	0.011795	0.002145	3.84522E-08	17	43189049
rs10741726	T	G	-0.00983	0.001777	3.14829E-08	11	2861578
rs10773000	T	G	-0.01812	0.001861	2.17215E-22	12	123736084
rs10835211	A	G	0.013662	0.002037	2.00647E-11	11	27701365
rs10840457	A	G	-0.01457	0.001924	3.63961E-14	11	10675738
rs10887774	A	G	0.013479	0.001988	1.18859E-11	10	89766043
rs11021232	T	C	-0.01181	0.002161	4.58053E-08	11	95320808
rs11664369	T	C	0.015075	0.001995	4.11799E-14	18	57739072
rs11727676	T	C	-0.01414	0.002554	3.10986E-08	4	145659064
rs11751891	A	C	0.031135	0.005524	1.73782E-08	6	16101755
rs11786900	C	G	0.016848	0.003061	3.70852E-08	8	9239958
rs1178979	T	C	0.063996	0.002091	1E-200	7	72856430
rs12369443	A	G	0.019485	0.002055	2.44549E-21	12	20582651
rs12454712	T	C	0.016671	0.001854	2.42299E-19	18	60845884
rs12530679	A	G	0.00972	0.001779	4.64882E-08	7	106632113
rs12691219	A	G	0.014419	0.00192	5.86895E-14	3	15881120
rs12856169	A	G	-0.0124	0.002012	7.03048E-10	13	31017268
rs13107325	T	C	0.036549	0.003347	9.18153E-28	4	103188709
rs13389219	T	C	-0.0413	0.001799	1.3613E-116	2	165528876
rs1340819	A	C	0.011047	0.001846	2.14896E-09	13	29145323
rs1423561	A	G	0.010399	0.001837	1.52013E-08	5	52723007
rs1425486	T	C	-0.0178	0.001883	3.28734E-21	4	157683685
rs1461396	C	G	-0.01984	0.002803	1.48773E-12	11	26281664
rs1471251	A	T	-0.02669	0.001818	9.33952E-49	4	87976359
rs1472267	A	G	-0.01152	0.001857	5.39412E-10	6	166185025
rs1520456	A	T	-0.01164	0.001814	1.40847E-10	2	50691898
rs1538742	A	C	0.024306	0.001787	3.95792E-42	1	219668252
rs16861373	A	G	-0.01612	0.002743	4.15901E-09	3	129309455
rs16934748	T	C	-0.01286	0.002287	1.90718E-08	10	33970319
rs17326656	T	G	0.016609	0.002142	8.9189E-15	2	48962291
rs17508368	T	C	0.025329	0.003593	1.79721E-12	2	227651446
rs1784559	A	T	0.011332	0.001811	3.92471E-10	11	118901614
rs1906252	A	C	-0.01034	0.001809	1.09527E-08	6	98550289
rs1931788	A	G	0.010829	0.001942	2.46911E-08	6	19972602
rs1938566	T	C	-0.01299	0.002214	4.38719E-09	1	98478981
rs1991928	A	G	0.013238	0.001995	3.24368E-11	8	103873091
rs1997833	T	C	-0.01217	0.00191	1.85925E-10	20	39690342
rs2051821	T	C	0.016021	0.002087	1.62779E-14	17	46143515

rs2053594	T	C	-0.01414	0.001873	4.41545E-14	15	64151344
rs2070971	T	G	0.016989	0.002529	1.83771E-11	7	44197583
rs2071197	A	G	0.017981	0.002881	4.35949E-10	20	43030435
rs2159935	A	G	-0.01343	0.001804	9.69047E-14	4	55521017
rs2161796	T	C	0.010667	0.001853	8.65991E-09	18	40750455
rs2227198	A	G	0.015885	0.001786	5.79336E-19	1	172360164
rs2240533	T	C	0.01562	0.001917	3.73208E-16	14	71541026
rs2248071	T	C	-0.01103	0.001867	3.4807E-09	9	33857803
rs2249105	A	G	0.019731	0.00182	2.25342E-27	2	65287896
rs2254737	T	C	0.016338	0.001838	6.07352E-19	7	17811797
rs2276864	T	C	-0.01648	0.001909	6.00582E-18	3	49894030
rs2287109	T	G	0.011907	0.001933	7.21086E-10	2	171574217
rs2302263	T	C	0.040816	0.003077	3.76462E-40	11	64021821
rs2343595	C	G	0.01017	0.001816	2.14576E-08	8	106591207
rs2737225	T	G	-0.01758	0.001816	3.65828E-22	8	116639462
rs275184	T	G	0.018067	0.00224	7.34178E-16	15	39444679
rs281	A	T	-0.02394	0.001914	6.66196E-36	8	19815023
rs2820295	A	G	0.01088	0.001917	1.38065E-08	1	201800868
rs2925979	T	C	0.031357	0.001936	5.07973E-59	16	81534790
rs2971575	A	G	0.009972	0.001783	2.24826E-08	12	102780879
rs2971669	T	C	0.013817	0.002137	1.0031E-10	7	44231778
rs310796	T	G	-0.01074	0.001873	9.65498E-09	12	77453226
rs38172	T	C	-0.01297	0.001991	7.26304E-11	7	15893576
rs3820897	T	C	-0.02202	0.002333	3.78881E-21	2	3642361
rs3822072	A	G	0.01723	0.001769	2.04286E-22	4	89741269
rs3848125	A	G	-0.01492	0.001802	1.20909E-16	15	61957236
rs3903399	T	C	-0.01544	0.0021	1.94832E-13	1	205041542
rs429150	T	C	-0.01632	0.001793	8.95755E-20	6	32075563
rs4418728	T	G	-0.0221	0.001789	4.56049E-35	10	94839724
rs4617527	T	G	0.016589	0.002586	1.40715E-10	10	77257791
rs4661637	C	G	-0.01234	0.001806	8.44746E-12	1	15829457
rs4714001	A	G	0.012038	0.001864	1.04667E-10	6	36638175
rs4719841	A	G	-0.0198	0.001797	3.02819E-28	7	25997536
rs4722593	A	G	-0.01153	0.001859	5.58547E-10	7	26370190
rs4738141	A	G	-0.01691	0.001961	6.52809E-18	8	72469742
rs4783718	T	C	0.011902	0.001801	3.85659E-11	16	69547741
rs4857091	A	G	0.011634	0.001848	3.08484E-10	3	94056338
rs4865796	A	G	0.017374	0.001878	2.25002E-20	5	53272664
rs4902630	A	G	0.011887	0.001824	7.18033E-11	14	69142390
rs4930352	T	G	-0.01392	0.001805	1.23094E-14	11	66066993
rs495033	T	C	-0.0232	0.002678	4.56728E-18	11	116352622
rs4976033	A	G	-0.01953	0.001794	1.27837E-27	5	67714246
rs4976553	A	G	0.01281	0.002117	1.43552E-09	5	167867953
rs498475	A	G	-0.01266	0.001825	4.03599E-12	7	28256240

rs5112	C	G	-0.04222	0.001842	3.3324E-116	19	45430280
rs524468	A	G	-0.01109	0.001957	1.44444E-08	12	371786
rs546240	T	C	-0.01035	0.001838	1.80822E-08	11	30533622
rs6066141	T	C	0.01881	0.00195	5.13624E-22	20	45597546
rs646123	A	G	0.019646	0.002005	1.12018E-22	17	40720632
rs6486121	T	C	0.014902	0.001828	3.56844E-16	11	13355770
rs6507716	A	G	0.011796	0.001804	6.1609E-11	18	21115060
rs6517522	T	C	0.010654	0.001811	4.02511E-09	21	40553845
rs6561937	A	T	-0.01162	0.00203	1.03495E-08	13	58257667
rs6569648	T	C	0.015172	0.002007	4.00754E-14	6	130349119
rs6572807	A	G	-0.01387	0.001986	2.86884E-12	14	52480621
rs6705285	T	G	-0.01037	0.001848	2.01782E-08	2	66709468
rs6769442	A	G	-0.01256	0.002094	2.01019E-09	3	171565463
rs6805563	A	G	0.010618	0.001831	6.60598E-09	3	69879323
rs6968865	A	T	-0.01619	0.001862	3.5692E-18	7	17287269
rs7093348	T	C	0.012839	0.001775	4.70176E-13	10	122981248
rs7133378	A	G	-0.03312	0.001882	2.76222E-69	12	124409502
rs7199293	A	G	0.010189	0.001805	1.66905E-08	16	81614892
rs7215055	A	G	-0.02606	0.002772	5.3787E-21	17	17458353
rs747472	T	C	-0.01286	0.001883	8.52431E-12	5	173353514
rs7592050	A	G	0.01411	0.00233	1.39583E-09	2	136459227
rs767432	T	C	0.012956	0.001919	1.47705E-11	9	119258187
rs7781417	A	C	-0.01321	0.002228	3.04524E-09	7	46526434
rs7816345	T	C	0.017306	0.002395	4.98447E-13	8	36846109
rs7818350	T	G	-0.0123	0.002043	1.73157E-09	8	71270004
rs7847285	T	C	0.010021	0.001831	4.43709E-08	9	13723175
rs7923609	A	G	0.024769	0.001773	2.39701E-44	10	65133822
rs799227	C	G	0.010609	0.001787	2.89E-09	6	133487440
rs8021491	T	C	0.011286	0.001889	2.31282E-09	14	90034799
rs8124053	A	C	0.010196	0.001809	1.73537E-08	20	1395793
rs9584870	T	C	0.010901	0.001856	4.25858E-09	13	99245866
rs9647379	C	G	0.012003	0.001842	7.22425E-11	3	171785168
rs9870954	A	G	-0.01131	0.001837	7.48574E-10	3	81978850
rs9989419	A	G	0.061731	0.001811	1E-200	16	56985139
rs583104	T	G	0.017934	0.002172	1.50501E-16	1	109821307
rs11578059	C	G	-0.01382	0.00184	5.75053E-14	1	110499847
rs146802096	T	C	-0.02928	0.003479	3.89841E-17	1	149777979
rs7518156	A	C	-0.01143	0.001922	2.71016E-09	1	150945794
rs12135346	A	G	-0.01565	0.00203	1.26543E-14	1	154254317
rs58877113	A	G	-0.01274	0.001924	3.61748E-11	1	178504590
rs646201	T	G	0.014371	0.002395	1.96716E-09	1	183244839
rs2821231	T	C	0.015064	0.001914	3.58602E-15	1	203518382
rs1256570	T	C	-0.01236	0.002196	1.82247E-08	1	219266883
rs35730037	C	G	0.01234	0.002022	1.04296E-09	1	220988745

rs903918	A	T	-0.01495	0.002666	2.06114E-08	1	2226333
rs10916239	T	C	0.01393	0.001916	3.62173E-13	1	228088833
rs11122450	T	G	0.051423	0.001859	1.8788E-168	1	230301811
rs1043897	T	G	-0.01314	0.001846	1.09031E-12	1	230416399
rs114165349	C	G	0.083272	0.005855	6.54195E-46	1	27021913
rs12138928	T	C	0.011487	0.002088	3.76223E-08	1	29554506
rs7413250	A	T	-0.01554	0.002681	6.80656E-09	1	39350453
rs3768321	T	G	0.034596	0.002353	6.3309E-49	1	40035928
rs3131696	A	T	-0.01112	0.001971	1.66992E-08	1	40441964
rs2784135	A	G	-0.01518	0.001869	4.64226E-16	1	50852249
rs79731440	T	G	-0.02007	0.003651	3.87463E-08	1	61705904
rs9436222	C	G	0.038401	0.001934	1.03195E-87	1	62903363
rs2613497	A	T	-0.01448	0.002339	6.05287E-10	1	72753825
rs10922907	A	T	0.010203	0.001863	4.35389E-08	1	91193049
rs57533288	A	G	0.012647	0.002138	3.28267E-09	1	9334993
rs35628716	T	G	-0.02071	0.002409	8.07125E-18	1	93839608
rs4627572	T	C	0.012998	0.001859	2.72655E-12	2	111873378
rs11688682	C	G	-0.01884	0.002098	2.68988E-19	2	121347612
rs60802178	A	G	-0.01877	0.002502	6.26806E-14	2	135268836
rs11901391	T	C	0.013139	0.002385	3.62901E-08	2	160914549
rs4128205	A	C	-0.01344	0.001839	2.76179E-13	2	165467068
rs13420749	T	C	-0.01295	0.002352	3.67428E-08	2	186029481
rs10208512	A	G	-0.02692	0.004517	2.53329E-09	2	205373721
rs4665710	A	C	-0.06479	0.002238	2.5188E-184	2	21221035
rs151200853	T	C	0.042082	0.004591	4.86336E-20	2	219291481
rs61733623	A	G	-0.05739	0.007263	2.7392E-15	2	220101974
rs2138161	T	C	-0.04794	0.001896	4.8413E-141	2	227095159
rs34097052	A	G	0.011661	0.002073	1.8661E-08	2	230122664
rs59104589	T	C	-0.01119	0.001953	9.95088E-09	2	242237902
rs13394970	T	G	-0.0133	0.001877	1.39855E-12	2	26929282
rs62114548	C	G	0.010749	0.001933	2.70047E-08	2	274672
rs4665972	T	C	0.053586	0.001851	3.3199E-184	2	27598097
rs13407288	T	G	0.018485	0.002984	5.82678E-10	2	28611855
rs2110942	T	C	0.011257	0.001871	1.78664E-09	2	37097009
rs10172544	A	C	-0.01179	0.00189	4.41147E-10	2	85788270
rs78846589	A	T	-0.05074	0.005207	1.93927E-22	3	12346108
rs71304101	A	G	-0.03899	0.002776	8.49023E-45	3	12396913
rs895893	T	C	0.028695	0.002168	5.32729E-40	3	135955604
rs62271373	A	T	0.052176	0.003961	1.26335E-39	3	150066540
rs7631606	T	G	0.013366	0.002125	3.20032E-10	3	187628006
rs35740053	A	C	-0.01304	0.002315	1.76537E-08	3	194135256
rs75413736	C	G	0.018522	0.00302	8.61931E-10	3	24286322
rs7645905	T	G	0.011256	0.001861	1.45537E-09	3	4758244
rs34261027	A	G	-0.03078	0.002344	2.20791E-39	3	52490391

rs9851195	A	C	0.011714	0.002108	2.74148E-08	3	66903172
rs830663	T	C	0.013337	0.001893	1.84802E-12	3	71643451
rs13066793	A	G	0.023539	0.003349	2.08779E-12	3	87037543
rs148827772	A	G	-0.04418	0.006588	1.99746E-11	4	110766064
rs114236092	A	C	-0.04156	0.007202	7.91218E-09	4	124263310
rs112675878	A	G	0.026112	0.002782	6.22116E-21	4	18027696
rs12513287	T	C	0.027383	0.002516	1.35103E-27	4	26065924
rs113697915	A	C	-0.01044	0.001871	2.36622E-08	4	26322759
rs13108218	A	G	0.019928	0.001927	4.66799E-25	4	3443931
rs34722008	A	G	0.012645	0.001959	1.09255E-10	4	38659594
rs59684169	A	G	-0.01117	0.001861	1.9235E-09	4	39693947
rs11722924	C	G	0.013467	0.001864	5.04289E-13	4	77396854
rs4705767	T	G	0.011578	0.001902	1.14641E-09	5	112395949
rs7720409	A	G	-0.0227	0.002094	2.16721E-27	5	118728256
rs253942	T	C	0.028339	0.00379	7.63884E-14	5	131320462
rs72801474	A	G	-0.02703	0.003282	1.79324E-16	5	132444128
rs13160735	A	G	0.01149	0.001992	7.98718E-09	5	144485978
rs7379358	A	T	0.013193	0.001884	2.52436E-12	5	156403593
rs2914221	T	C	-0.02577	0.002243	1.54268E-30	5	157989980
rs389737	T	C	0.012182	0.002062	3.48423E-09	5	40828478
rs28650790	T	C	0.048559	0.002342	1.57475E-95	5	55861464
rs192249	C	G	0.013911	0.001918	4.13988E-13	5	56197514
rs37538	C	G	-0.01098	0.001875	4.73084E-09	5	57610069
rs55951719	A	G	0.01354	0.002384	1.34373E-08	5	81569672
rs72771232	T	C	0.020285	0.003485	5.86895E-09	5	82857040
rs11153046	A	G	-0.01436	0.002005	7.92192E-13	6	107441753
rs11752394	C	G	-0.01764	0.002185	6.8216E-16	6	109189664
rs2210601	T	C	-0.01034	0.00188	3.74438E-08	6	127218090
rs72959041	A	G	0.052986	0.004253	1.25127E-35	6	127454893
rs635769	T	C	0.031366	0.001917	3.65511E-60	6	139831981
rs607335	A	C	-0.01241	0.001882	4.34029E-11	6	153465230
rs117733303	A	G	0.059365	0.007088	5.51738E-17	6	160922870
rs11751347	T	C	0.040535	0.003141	4.15974E-38	6	161092438
rs2569880	A	C	0.011483	0.001875	9.10807E-10	6	1618966
rs4709746	T	C	-0.02787	0.00276	5.79714E-24	6	164133001
rs62398908	T	C	0.015928	0.002244	1.26993E-12	6	20502195
rs2074493	A	C	-0.03456	0.002222	1.51588E-54	6	31239776
rs114370702	A	C	-0.07109	0.005335	1.66676E-40	6	32518909
rs147627829	A	G	0.050018	0.004833	4.25091E-25	6	34335088
rs11967262	C	G	-0.04321	0.00182	1.3126E-124	6	43760327
rs1317840	A	C	-0.01382	0.001859	1.08204E-13	6	43806921
rs73744635	T	C	0.029076	0.004158	2.69992E-12	6	55437238
rs1080064	A	G	-0.03792	0.006827	2.79452E-08	6	72598878
rs72920452	A	C	0.021199	0.003777	1.98591E-08	6	86061009

rs71538127	C	G	-0.02215	0.002897	2.05853E-14	7	1010801
rs112362553	T	G	0.011662	0.001851	2.97929E-10	7	116566729
rs10260148	T	C	0.031116	0.002031	5.28101E-53	7	130430969
rs35241484	T	G	-0.02002	0.002178	3.8912E-20	7	150216171
rs39104	A	G	0.010796	0.001894	1.20631E-08	7	29315357
rs852388	C	G	0.014399	0.002325	5.91951E-10	7	5574239
rs4717804	A	C	0.032409	0.003531	4.38623E-20	7	73111504
rs10954750	C	G	0.015468	0.002243	5.39556E-12	7	75664921
rs6985890	T	C	0.02412	0.002087	6.58739E-31	8	10685951
rs6999569	A	G	0.068131	0.001818	1E-200	8	126475770
rs12546096	A	G	-0.02862	0.002131	3.95452E-41	8	126628841
rs7832515	A	G	0.018244	0.00239	2.29837E-14	8	144306379
rs35246381	T	C	-0.02435	0.002166	2.59384E-29	8	18272535
rs77032723	T	C	-0.09527	0.00274	1E-200	8	19763992
rs6989064	T	C	-0.05321	0.00183	5.6094E-186	8	19941448
rs12549825	C	G	0.01179	0.001924	8.98608E-10	8	30956654
rs2407278	A	G	0.034087	0.005283	1.10489E-10	8	37399290
rs1580180	T	C	0.013641	0.001959	3.31387E-12	8	59387337
rs35957544	T	G	-0.01045	0.001874	2.44885E-08	8	73440371
rs7012814	A	G	-0.031	0.001822	6.511E-65	8	9173358
rs1567353	C	G	-0.01857	0.001998	1.48194E-20	9	1033773
rs10756218	T	C	0.011347	0.001899	2.28841E-09	9	11274206
rs62543565	A	C	-0.01468	0.001904	1.29645E-14	9	16901067
rs696825	T	C	-0.01539	0.002112	3.23302E-13	9	86583076
rs10752651	T	C	0.013819	0.001864	1.21362E-13	9	92201811
rs12686780	T	C	0.019902	0.00242	1.97677E-16	9	95382297
rs2803611	A	G	-0.02404	0.00203	2.3587E-32	10	113922728
rs2419605	A	G	-0.02554	0.002621	1.95724E-22	10	113978097
rs1133400	A	G	-0.01454	0.00228	1.7944E-10	10	134459388
rs10906428	A	G	0.012793	0.002239	1.11062E-08	10	13670441
rs113344423	A	G	0.037174	0.003604	6.10302E-25	10	95316037
rs10883026	T	C	-0.01302	0.001862	2.63854E-12	10	99793865
rs513533	A	G	-0.09106	0.002939	1E-200	11	116519358
rs61905078	A	C	-0.16703	0.003506	1E-200	11	116596309
rs150423652	T	G	0.259822	0.011558	6.5814E-112	11	116603816
rs34144542	A	G	0.032314	0.003603	2.99083E-19	11	116774447
rs55967045	T	G	-0.03142	0.004875	1.14818E-10	11	116808857
rs4980395	T	C	0.014423	0.002442	3.47886E-09	11	1876594
rs74528759	A	G	0.026636	0.004853	4.05617E-08	11	24727178
rs11038647	A	C	-0.01938	0.002873	1.52556E-11	11	45794136
rs59663860	C	G	-0.03156	0.001977	2.44307E-57	11	47276350
rs174566	A	G	-0.04619	0.001897	6.06E-131	11	61592362
rs10750766	A	C	0.020492	0.002065	3.21417E-23	11	65473798
rs6606645	T	C	0.011972	0.001859	1.20996E-10	11	69301859

rs140201358	C	G	-0.05395	0.008451	1.72175E-10	11	823586
rs12371573	T	C	0.013755	0.002125	9.64841E-11	12	107319150
rs7137828	T	C	-0.01811	0.001817	2.16746E-23	12	111932800
rs11057450	A	G	-0.02152	0.001909	1.81445E-29	12	124585336
rs837500	T	C	-0.0106	0.001923	3.54414E-08	12	125077567
rs11057853	T	C	-0.01183	0.00185	1.58057E-10	12	125329313
rs11045171	A	G	0.028711	0.002327	5.47442E-35	12	20470199
rs11494834	C	G	0.011989	0.001891	2.27706E-10	12	34276084
rs117233107	A	G	-0.06673	0.007634	2.30875E-18	12	4328521
rs35763453	T	C	-0.0226	0.003981	1.37892E-08	12	46215895
rs4759319	T	G	-0.01348	0.001903	1.37259E-12	12	54424731
rs2229357	A	G	-0.02514	0.002157	2.2694E-31	12	57843711
rs145775785	T	C	-0.04808	0.007252	3.35084E-11	12	65902265
rs2947793	A	G	0.017831	0.003233	3.47635E-08	12	66199734
rs7308584	A	G	0.017866	0.002413	1.31618E-13	12	6706744
rs1391073	T	C	0.011046	0.001937	1.17652E-08	12	84059739
rs7140110	T	C	-0.02036	0.002071	8.19669E-23	13	114544024
rs76757240	T	C	-0.02547	0.002786	5.99439E-20	13	114606156
rs9319211	A	C	-0.01499	0.002541	3.63734E-09	13	25832230
rs2812208	C	G	-0.04637	0.006024	1.38364E-14	13	50707087
rs12870915	T	C	0.013504	0.002228	1.35718E-09	13	71803515
rs4885108	T	C	-0.01361	0.001853	2.01377E-13	13	74146049
rs61993685	T	C	0.023892	0.003604	3.3648E-11	14	100765823
rs2498787	T	C	-0.01996	0.003309	1.62356E-09	14	105256581
rs79873985	A	G	0.045098	0.00797	1.52589E-08	14	24560159
rs117311385	A	G	0.033582	0.00593	1.48604E-08	14	52363937
rs12897637	T	C	-0.01717	0.002573	2.51526E-11	14	64239351
rs3825667	A	T	-0.01296	0.002363	4.11127E-08	14	89804373
rs7170463	A	G	0.01774	0.00199	4.95399E-19	15	41888918
rs139974673	T	C	-0.12594	0.005932	4.8917E-100	15	44027885
rs2729780	C	G	0.022701	0.002253	6.99755E-24	15	63404639
rs58790817	A	G	0.015344	0.002204	3.32818E-12	15	66868983
rs11072479	T	C	0.011452	0.002023	1.51679E-08	15	74649262
rs35482321	T	C	0.013214	0.002019	5.92398E-11	16	1255832
rs12928099	A	C	-0.02777	0.002057	1.58408E-41	16	15150505
rs194808	A	C	-0.01459	0.002383	9.08082E-10	16	23805492
rs12921996	T	C	0.0153	0.001859	1.86105E-16	16	30011618
rs75152587	T	G	0.048909	0.008633	1.46708E-08	16	56579961
rs4784709	A	T	0.031703	0.004835	5.5099E-11	16	56711375
rs11860701	T	G	-0.04172	0.003095	2.11389E-41	16	56876845
rs77517043	A	G	-0.02377	0.003164	5.78662E-14	16	68301410
rs34682685	A	G	0.029182	0.003035	6.85447E-22	16	72096227
rs56078619	A	G	0.012986	0.00236	3.72396E-08	16	85249184
rs4843752	A	G	0.014058	0.001865	4.75809E-14	16	88003242

rs12600110	T	C	0.01133	0.001917	3.41667E-09	16	962154
rs16953523	A	G	0.017154	0.002567	2.3314E-11	17	453534
rs7024300	T	C	-0.04216	0.005675	1.10076E-13	9	107589567
rs62568199	T	G	-0.02193	0.003247	1.44535E-11	9	107672526
rs79149713	A	C	-0.01214	0.002192	3.02387E-08	9	119087240
rs2004354	A	G	-0.01262	0.002012	3.48132E-10	9	123487903
rs2417125	A	G	-0.0124	0.00208	2.50606E-09	9	131562232
rs532436	A	G	-0.01651	0.002328	1.33142E-12	9	136149830
rs8065497	A	G	0.011767	0.001879	3.79549E-10	17	17782649
rs71372293	A	G	0.01567	0.002716	7.95172E-09	17	18715701
rs72836561	T	C	0.135982	0.005386	1.2234E-140	17	41926126
rs28528789	T	C	-0.0128	0.001881	1.02414E-11	17	46986616
rs76731691	T	G	-0.02093	0.003795	3.49647E-08	17	63960269
rs8079754	A	G	-0.0247	0.002261	8.93506E-28	17	65887896
rs34931250	T	C	0.027414	0.003884	1.68876E-12	17	66879927
rs1642764	T	C	-0.01458	0.001862	4.70129E-15	17	7557834
rs12451715	A	C	0.018249	0.001911	1.28497E-21	17	76397334
rs6501250	T	C	0.010992	0.001868	3.99616E-09	17	76808726
rs35321365	T	C	-0.01504	0.001862	6.46138E-16	18	19905141
rs11664106	A	T	0.01565	0.001959	1.37277E-15	18	2846812
rs6506032	A	G	-0.02606	0.003479	6.80879E-14	18	287534
rs77960347	A	G	0.056557	0.008278	8.38392E-12	18	47109955
rs1970696	T	C	0.023875	0.002356	3.90183E-24	18	47169989
rs12463315	A	G	-0.01325	0.001888	2.24487E-12	19	18397788
rs150057262	C	G	0.086324	0.008712	3.82706E-23	19	19320825
rs58542926	T	C	-0.06004	0.00347	4.52799E-67	19	19379549
rs62102718	A	T	-0.0252	0.00203	2.22771E-35	19	33891013
rs7257735	T	G	0.019149	0.003233	3.15302E-09	19	34039678
rs1672991	A	G	-0.02818	0.003752	5.81949E-14	19	35556659
rs79182576	A	G	0.028035	0.004589	1.00124E-09	19	4077426
rs483082	T	G	0.065033	0.002179	8.5328E-196	19	45416178
rs2238689	T	C	-0.01452	0.001857	5.35775E-15	19	46178661
rs35650232	T	G	0.014798	0.00229	1.0243E-10	19	49259973
rs56883673	T	C	0.019306	0.002212	2.60206E-18	19	54793280
rs11670474	A	G	-0.01116	0.001866	2.19383E-09	19	57488280
rs4804101	T	G	0.018866	0.001872	7.0007E-24	19	7220745
rs11878235	A	G	-0.01487	0.001899	5.00864E-15	19	7976698
rs111500536	A	G	-0.0452	0.004048	6.07543E-29	19	8425558
rs116843064	A	G	-0.17423	0.006755	1.0369E-146	19	8429323
rs149142833	T	C	0.01494	0.002498	2.21631E-09	20	32188142
rs6088461	T	G	0.013121	0.001876	2.70017E-12	20	32905161
rs6073958	T	C	-0.05534	0.002254	3.8956E-133	20	44551855
rs6018652	A	G	-0.01571	0.002348	2.18996E-11	20	46340974
rs6123685	A	G	-0.01752	0.002099	7.09208E-17	20	55836040

rs144033177	A	C	-0.05854	0.007497	5.79928E-15	20	571467
rs76602912	T	C	-0.03832	0.005986	1.5405E-10	20	57459868
rs6122049	T	C	0.013495	0.00224	1.68822E-09	20	62692789
rs7280197	T	C	-0.01153	0.001927	2.17891E-09	21	16415732
rs2823303	T	C	0.013851	0.002272	1.07719E-09	21	16862737
rs4820323	C	G	-0.02397	0.001887	5.5328E-37	22	38599767
rs2071887	A	T	0.018032	0.001947	1.97924E-20	22	38879010

The genetic instruments for mvIR_NGWAMA were at a genome-wide significant level ($P < 5.00 \times 10^{-8}$) and independent of each other (linkage disequilibrium $r^2 < 0.001$ within 10,000 kb).

Abbreviations: NGWAMA, N-weighted genome-wide association meta-analysis; SNP, single nucleotide polymorphism.

Supplementary Notes 2. Genetic instrument information of mvIR_MTAG

SNP	Allele 1	Allele 2	Beta	SE	P	CHR	POS
rs10205233	T	C	0.036597	0.005492	2.67406E-11	2	227614005
rs1044531	T	C	-0.01723	0.002399	6.90148E-13	9	117098650
rs10761762	T	C	0.024476	0.002145	3.75833E-30	10	65184717
rs10773000	T	G	-0.01717	0.002243	1.98958E-14	12	123736084
rs10779835	T	C	0.045057	0.002196	1.61711E-93	1	230299949
rs10796821	A	G	-0.01228	0.0022	2.42044E-08	11	69305417
rs10840457	A	G	-0.01588	0.002362	1.76501E-11	11	10675738
rs10887774	A	G	0.014998	0.002417	5.49969E-10	10	89766043
rs1106766	T	C	-0.02204	0.00255	5.51761E-18	12	57809456
rs11150580	T	C	0.013788	0.002196	3.43585E-10	16	30014564
rs11929253	A	G	0.019398	0.002826	6.74453E-12	3	150074251
rs12062275	T	C	-0.03475	0.002474	7.89205E-45	1	62991905
rs12369443	A	G	0.01859	0.002216	4.9187E-17	12	20582651
rs12454712	T	C	0.018398	0.002231	1.61874E-16	18	60845884
rs1260326	T	C	0.04046	0.002192	4.5069E-76	2	27730940
rs12896370	T	C	-0.0171	0.002369	5.32581E-13	14	71521340
rs12934497	A	G	-0.01273	0.002204	7.62713E-09	16	87995200
rs13107325	T	C	0.030791	0.004008	1.56879E-14	4	103188709
rs13136833	T	C	-0.01772	0.00238	9.87641E-14	4	18030282
rs13234407	A	G	-0.02741	0.002157	5.52813E-37	7	130438214
rs13273592	T	C	-0.02466	0.002238	3.07714E-28	8	126645810
rs13389219	T	C	-0.04326	0.002179	1.0083E-87	2	165528876
rs13429408	A	C	-0.01359	0.002211	7.9439E-10	2	219142860
rs1425486	T	C	-0.0199	0.002284	3.02709E-18	4	157683685
rs1538742	A	C	0.026783	0.002161	2.79687E-35	1	219668252
rs154255	T	C	0.013938	0.002145	8.19851E-11	5	55819966
rs1639123	T	C	-0.01323	0.002332	1.4148E-08	12	6714668
rs1650505	A	G	0.025276	0.002645	1.20375E-21	5	158029734
rs17036126	T	C	0.028618	0.003298	4.01182E-18	3	12287863
rs17091574	T	C	-0.01666	0.00244	8.71971E-12	8	19727569
rs17326656	T	G	0.015694	0.002641	2.79844E-09	2	48962291
rs174574	A	C	0.039992	0.002228	4.60125E-72	11	61600342
rs180327	T	C	-0.06267	0.002158	1.8725E-185	11	116623659
rs1991928	A	G	0.012493	0.002275	3.96595E-08	8	103873091
rs1997833	T	C	-0.01226	0.00221	2.85845E-08	20	39690342
rs2051821	T	C	0.014136	0.002289	6.6192E-10	17	46143515
rs2053594	T	C	-0.01385	0.002184	2.30446E-10	15	64151344
rs2074489	T	C	0.033274	0.002685	2.80803E-35	6	31240128
rs2121107	T	C	-0.01529	0.002343	6.85861E-11	5	78468004
rs2159607	T	G	0.024042	0.002264	2.4239E-26	3	52501451
rs2159935	A	G	-0.01246	0.002204	1.57648E-08	4	55521017
rs2249105	A	G	0.019847	0.002167	5.27638E-20	2	65287896
rs2254737	T	C	0.015653	0.002259	4.2676E-12	7	17811797
rs2276864	T	C	-0.01789	0.002264	2.80325E-15	3	49894030

rs2302263	T	C	0.038802	0.003542	6.22334E-28	11	64021821
rs2303566	A	G	-0.01657	0.002232	1.12109E-13	2	219557738
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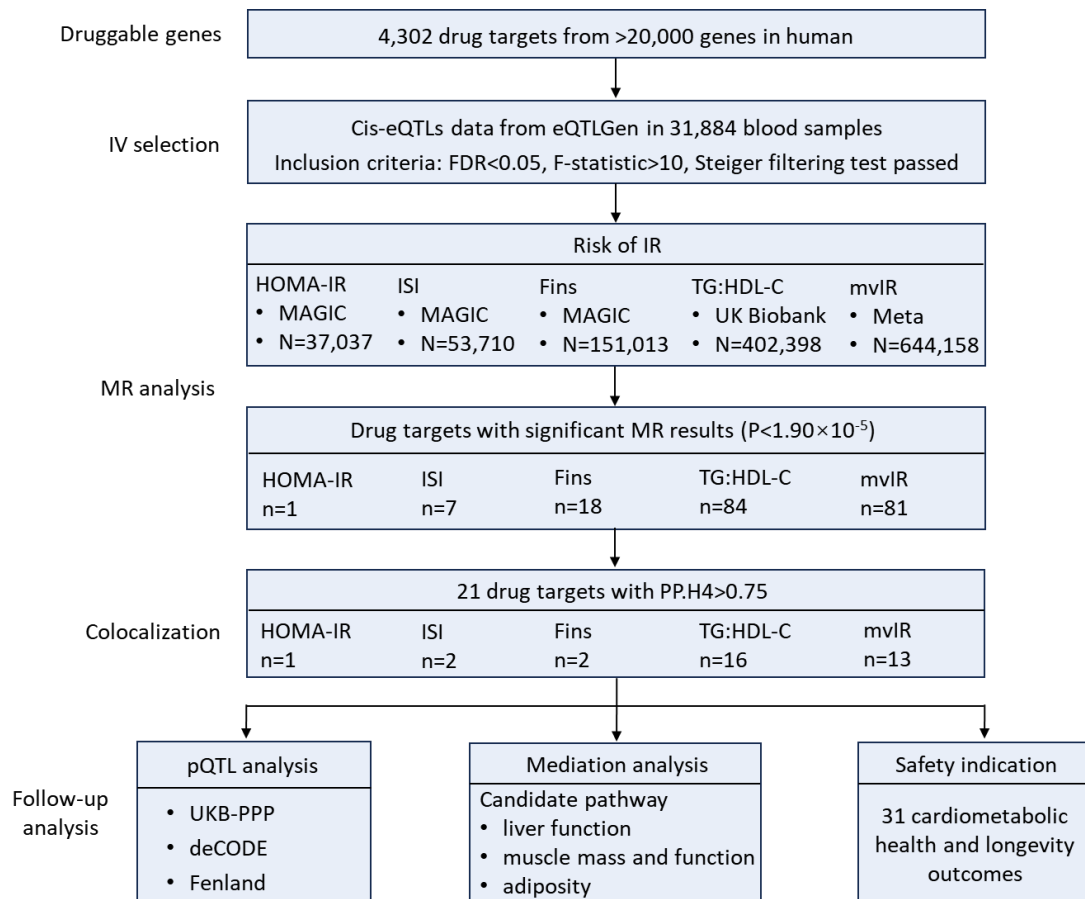
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rs2066572	T	C	0.016365	0.002597	2.92855E-10	13	50648487
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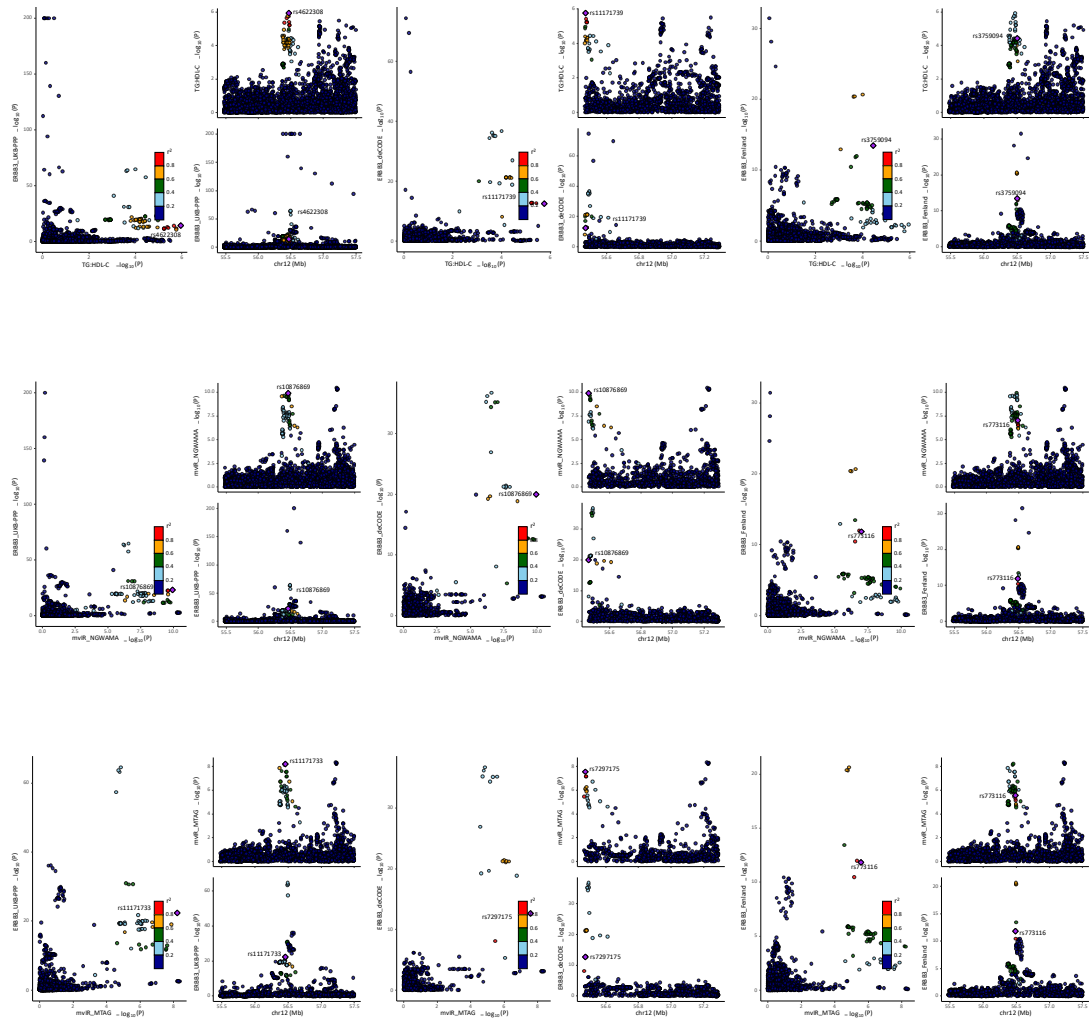
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rs144033177	A	C	-0.05682	0.008846	1.33424E-10	20	571467
rs4820325	A	G	0.023738	0.002277	1.89222E-25	22	38599978
rs138430	T	C	-0.017	0.002306	1.6575E-13	22	38874396

The genetic instruments for mvIR_MTAG were at a genome-wide significant level ($P < 5.00 \times 10^{-8}$) and independent of each other (linkage disequilibrium $r^2 < 0.001$ within 10,000 kb).

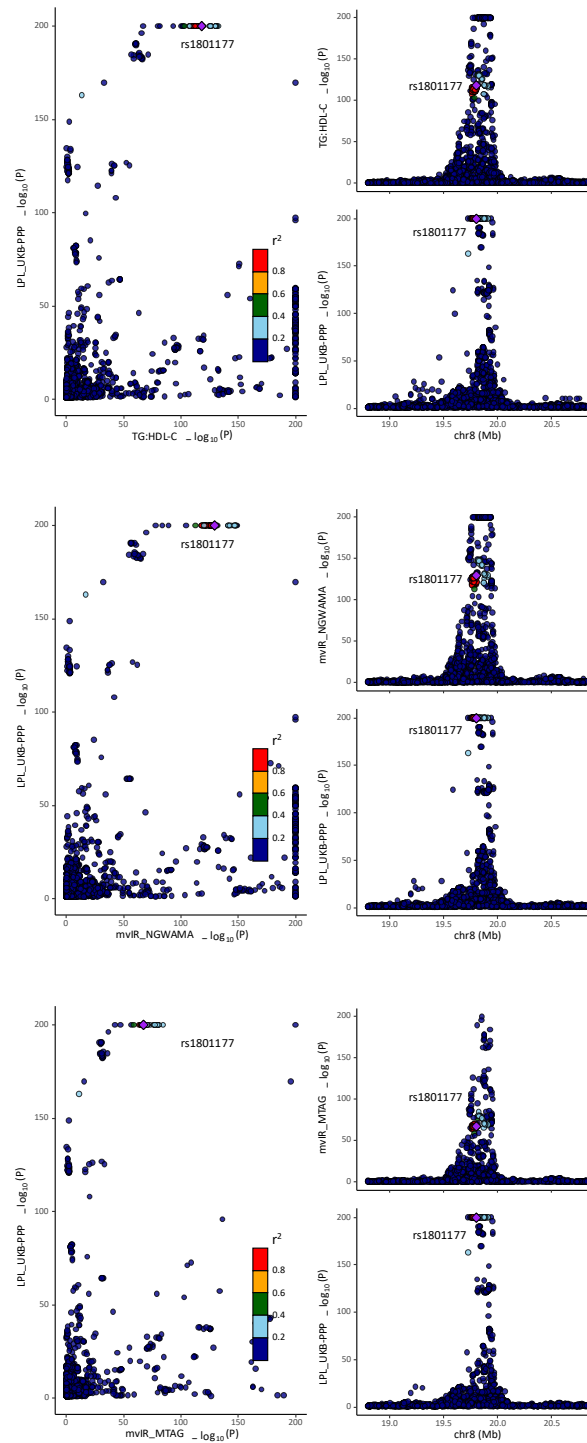
Abbreviations: MTAG, multi-trait analysis of genome-wide association study; SNP, single nucleotide polymorphism.



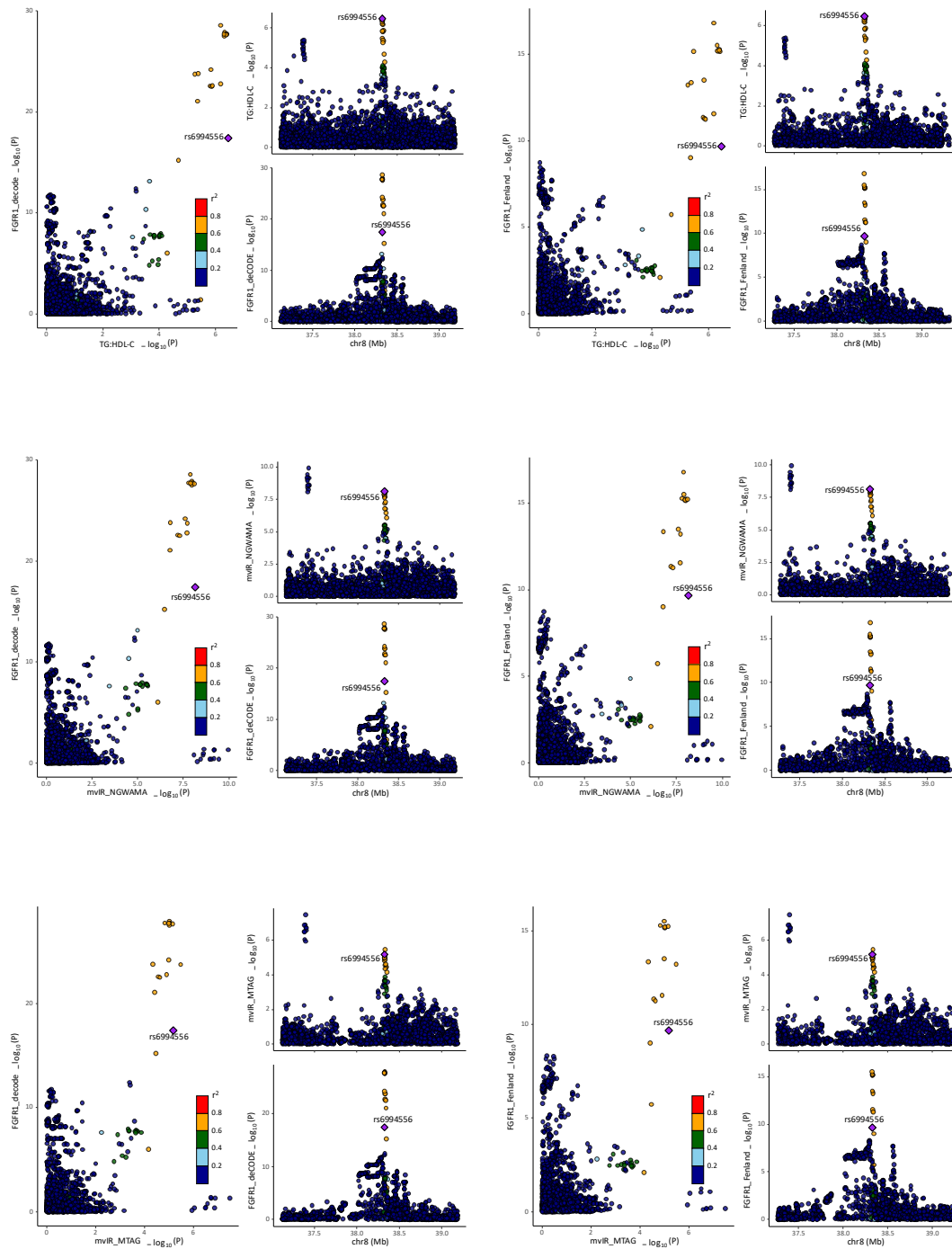
Supplementary Fig. 1. Overview of the processes for identifying therapeutic targets for IR. Abbreviations: eQTL, expression quantitative trait loci; FDR, false discovery rate; Fins, fasting insulin; HOMA-IR, homeostasis model assessment of insulin resistance; IR, insulin resistance; ISI, insulin sensitivity index; IV, instrumental variable; MAGIC, Meta-Analyses of Glucose and Insulin-Related Traits Consortium; MR, Mendelian randomization; pQTL, protein quantitative trait loci; TG:HDL-C, ratio of triglycerides to high-density lipoprotein cholesterol; UKB-PPP, UK Biobank Pharma Proteomics Project.



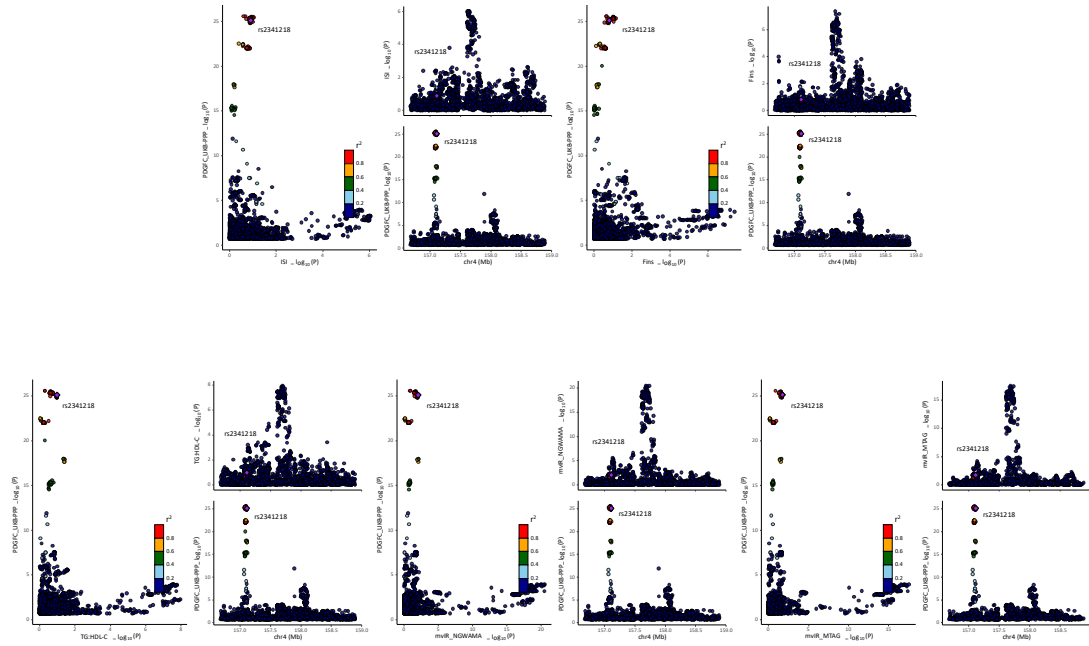
Supplementary Fig. 2. Regional plot of colocalization evidence of *ERBB3* with TG:HDL-C and mvIR. Abbreviation: TG:HDL-C, ratio of triglycerides to high-density lipoprotein cholesterol.



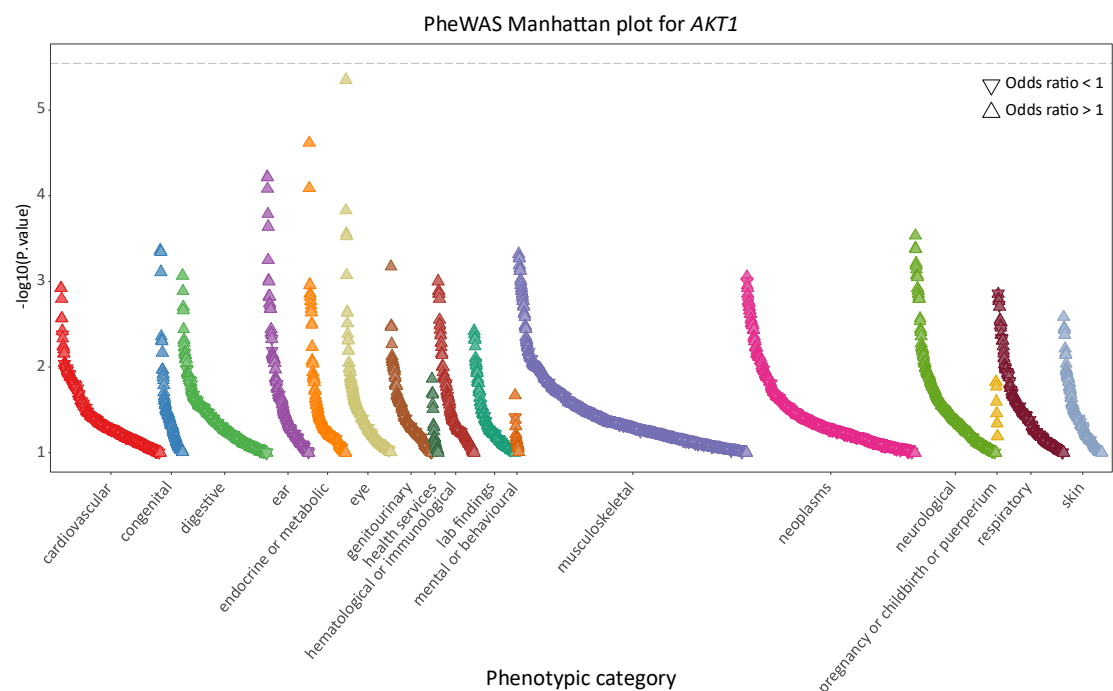
Supplementary Fig. 3. Regional plot of colocalization evidence of *LPL* with TG:HDL-C and mvIR. Abbreviation: TG:HDL-C, ratio of triglycerides to high-density lipoprotein cholesterol.



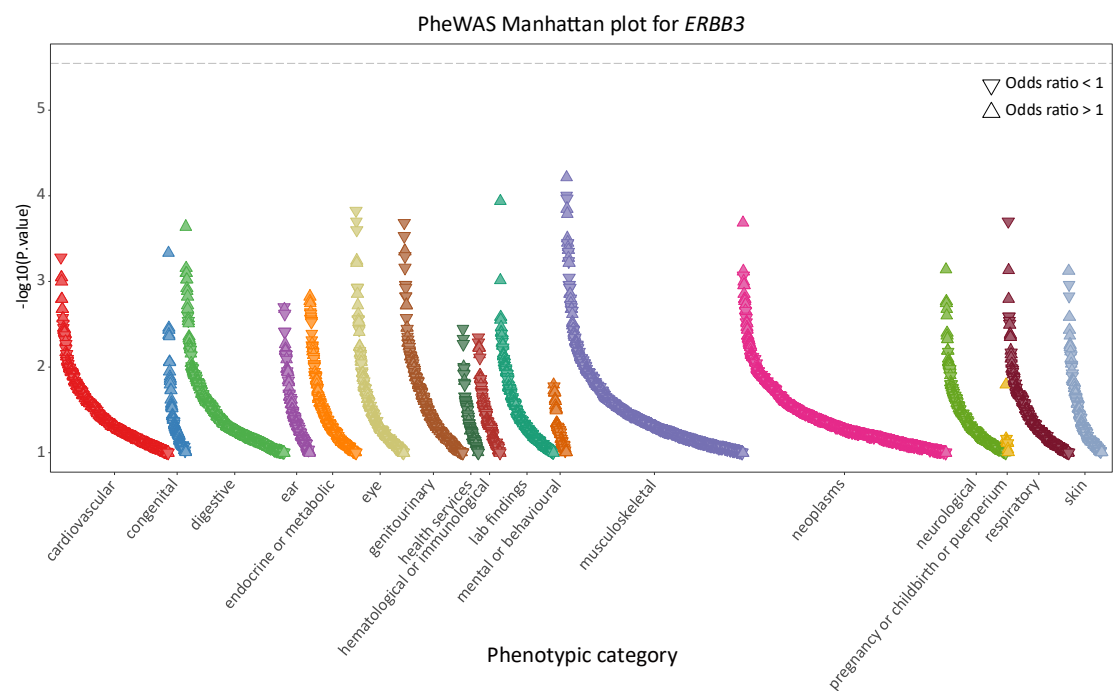
Supplementary Fig. 4. Regional plot of colocalization evidence of *FGFR1* with TG:HDL-C and mvIR. Abbreviation: TG:HDL-C, ratio of triglycerides to high-density lipoprotein cholesterol.



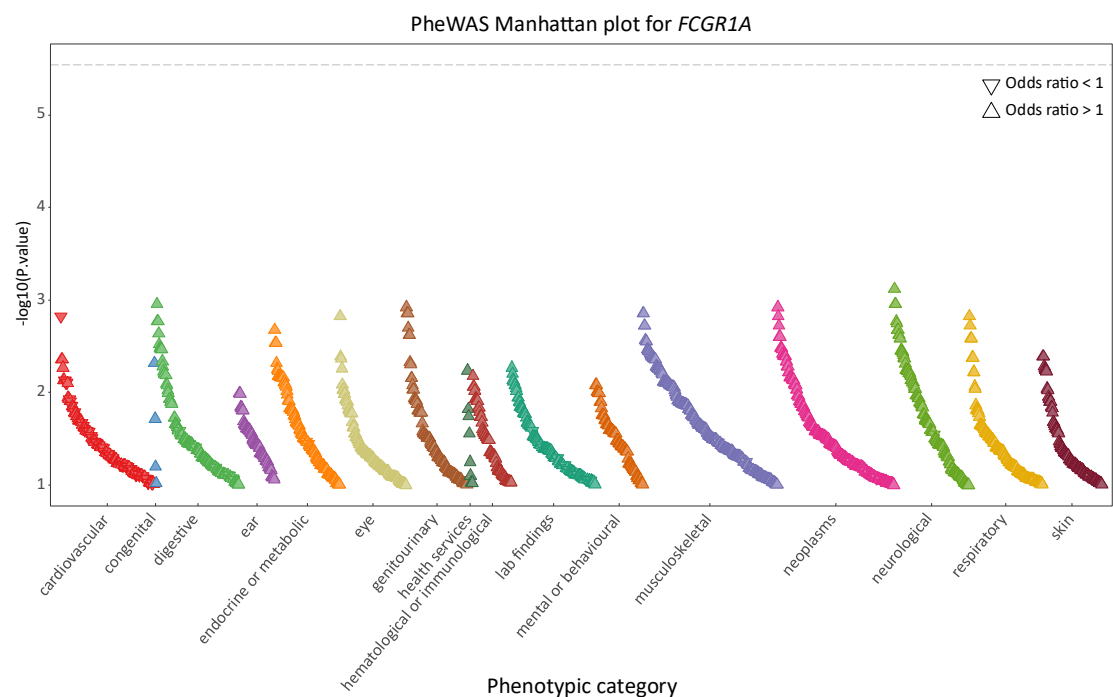
Supplementary Fig. 5. Regional plot of colocalization evidence of *PDGFC* with ISI, Fins, TG:HDL-C and mvIR. Abbreviations: Fins, fasting insulin; ISI, insulin resistance index; TG:HDL-C, ratio of triglycerides to high-density lipoprotein cholesterol.



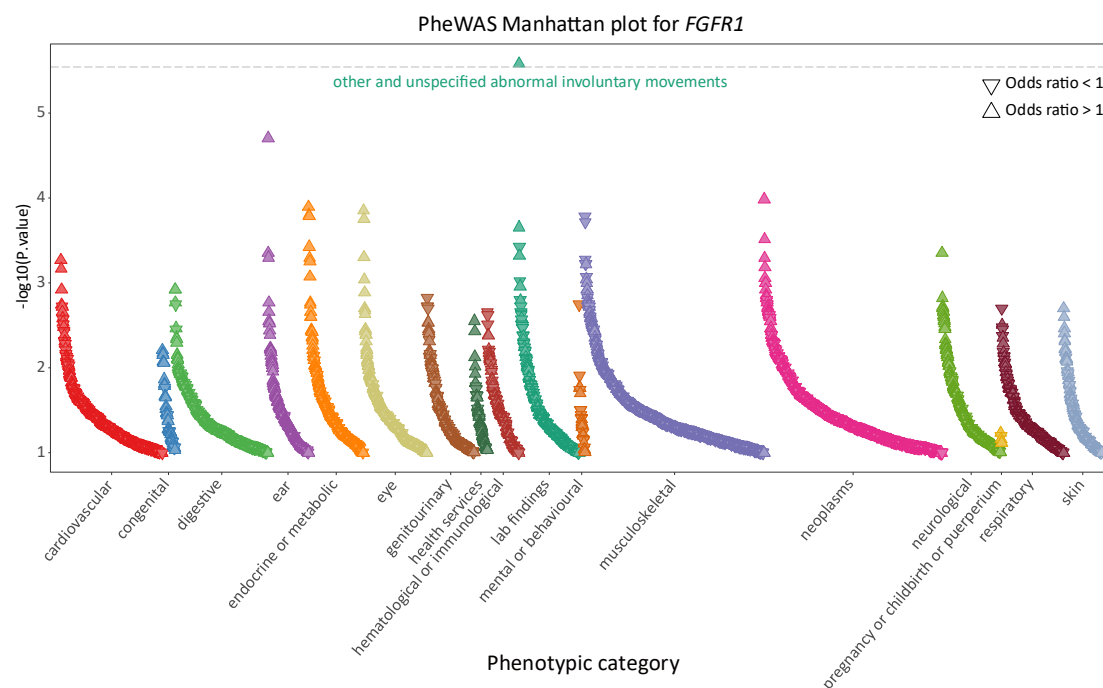
Supplementary Fig. 6. Results of PheWAS analysis for *AKT1*. The top dashed line is the significant line ($P \text{ value} < 2.88 \times 10^{-6}$, $0.05/17,361$). No significant association with disease traits at the gene level was observed for *AKT1*, suggesting that the potential side effects of drugs targeting this target and the presence of horizontal pleiotropy in this gene were likely to be minimal. Abbreviation: PheWAS, phenome-wide association study.



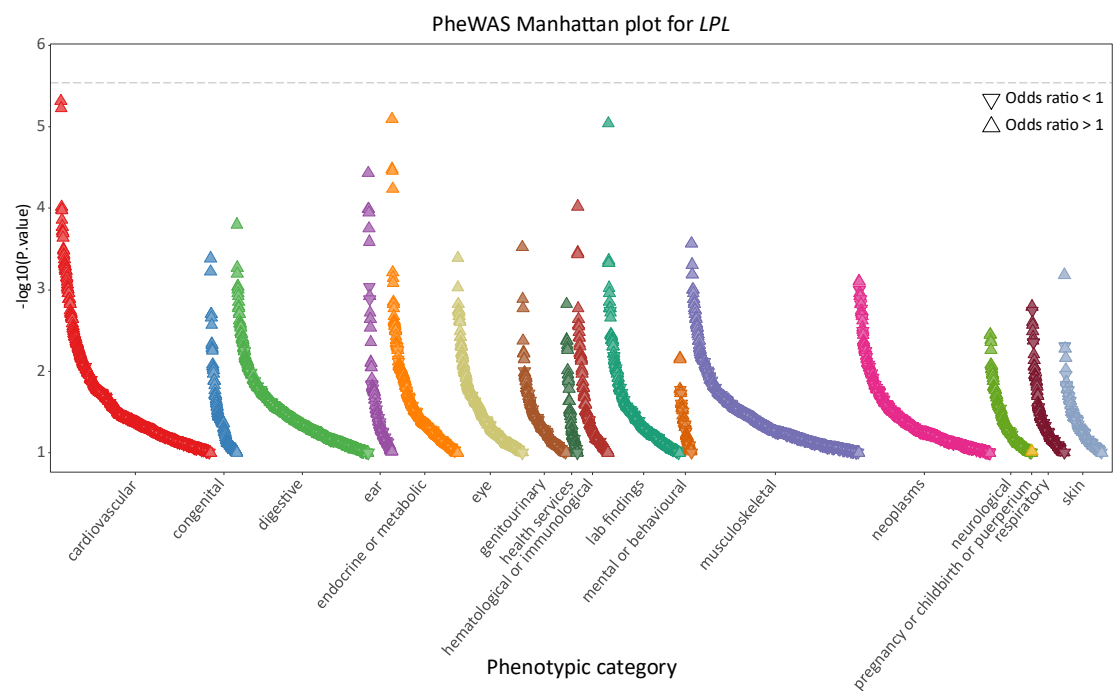
Supplementary Fig. 7. Results of PheWAS analysis for *ERBB3*. The top dashed line is the significant line ($P \text{ value} < 2.88 \times 10^{-6}$, $0.05/17,361$). No significant association with disease traits at the gene level was observed for *ERBB3*, suggesting that the potential side effects of drugs targeting this target and the presence of horizontal pleiotropy in this gene were likely to be minimal. Abbreviation: PheWAS, phenome-wide association study.



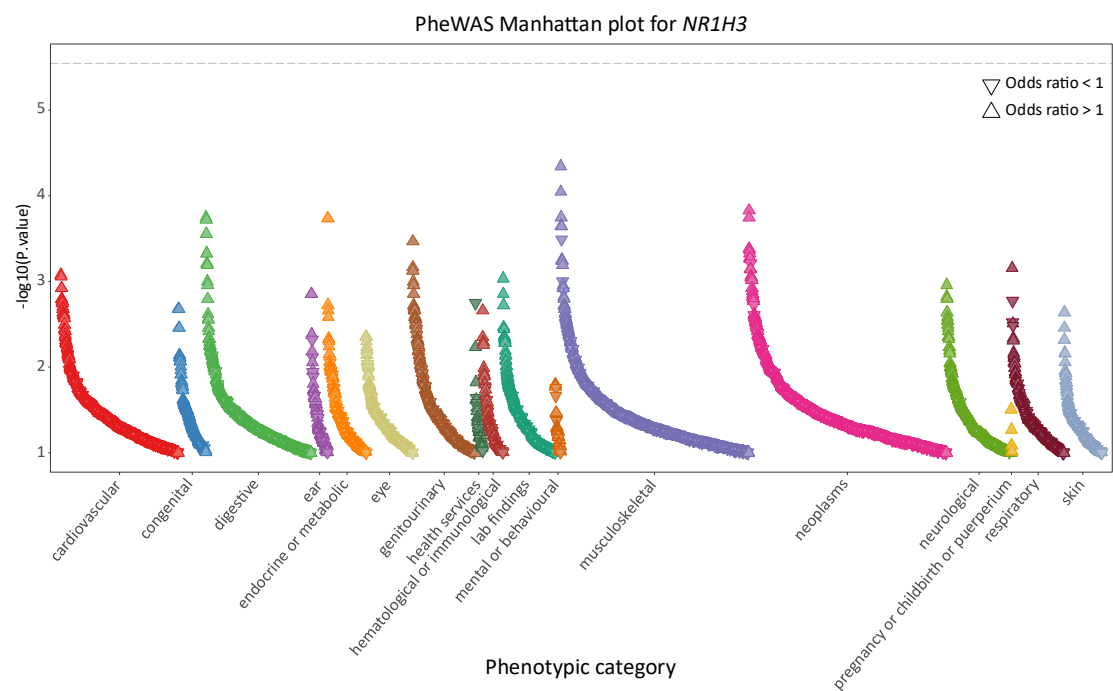
Supplementary Fig. 8. Results of PheWAS analysis for *FCGR1A*. The top dashed line is the significant line ($P \text{ value} < 2.88 \times 10^{-6}$, $0.05/17,361$). No significant association with disease traits at the gene level was observed for *FCGR1A*, suggesting that the potential side effects of drugs targeting this target and the presence of horizontal pleiotropy in this gene were likely to be minimal. Abbreviation: PheWAS, phenome-wide association study.



Supplementary Fig. 9. Results of PheWAS analysis for *FGFR1*. The top dashed line is the significant line (P value $< 2.88 \times 10^{-6}$, 0.05/17,361). The other and unspecified abnormal involuntary movements were marginally significantly associated with the *FGFR1* gene (P value $= 2.59 \times 10^{-6}$). Since the association between *FGFR1* and insulin resistance and the association between *FGFR1* and other and unspecified abnormal involuntary movements follow the same direction, it suggests that *FGFR1* encodes targets for drugs that have consistent effects in alleviating insulin resistance and reducing the risk of other and unspecified abnormal involuntary movements. Therefore, the PheWAS results for *FGFR1* did not indicate any significant potential side effects related to the induction of disease risks. Abbreviation: PheWAS, phenome-wide association study.



Supplementary Fig. 10. Results of PheWAS analysis for *LPL*. The top dashed line is the significant line ($P \text{ value} < 2.88 \times 10^{-6}$, $0.05/17,361$). No significant association with disease traits at the gene level was observed for *LPL*, suggesting that the potential side effects of drugs targeting this target and the presence of horizontal pleiotropy in this gene were likely to be minimal. Abbreviation: PheWAS, phenome-wide association study.



Supplementary Fig. 11. Results of PheWAS analysis for *NR1H3*. The top dashed line is the significant line ($P \text{ value} < 2.88 \times 10^{-6}$, $0.05/17,361$). No significant association with disease traits at the gene level was observed for *NR1H3*, suggesting that the potential side effects of drugs targeting this target and the presence of horizontal pleiotropy in this gene were likely to be minimal. Abbreviation: PheWAS, phenome-wide association study.