

Causal Association of Type 2 Diabetes Mellitus and Glycemic Traits with Cardiovascular Events and Lipid Traits: A Mendelian Randomization Study

Supplementary Material

Mingkai Huang^{1,2†}, Loum-Davadi Laina-Nicaise^{1,2†}, Lingfeng Zha^{1,2†}, Tingting Tang^{1,2*}, Xiang Cheng^{1,2*}

¹Department of Cardiology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

²Key Laboratory of Biological Targeted Therapy of the Ministry of Education, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Figure S1 Study overview.

Table S1 Phenotype source and description.

Table S2 Genetic variants associated with exposures.

Table S3 Definition and sources for CVDs in FinnGen.

Table S4 The causal effect of genetically predicted type 2 diabetes mellitus on outcomes in different studies.

Table S5 The causal effect of genetically predicted FG on outcomes in different studies.

Table S6 The causal effect of genetically predicted FI on outcomes in different studies.

Table S7 The causal effect of genetically predicted HbA_{1c} on outcomes in different studies.

Table S8 HDL cholesterol as a mediator in the causal pathway between type 2 diabetes mellitus and risk of CVDs.

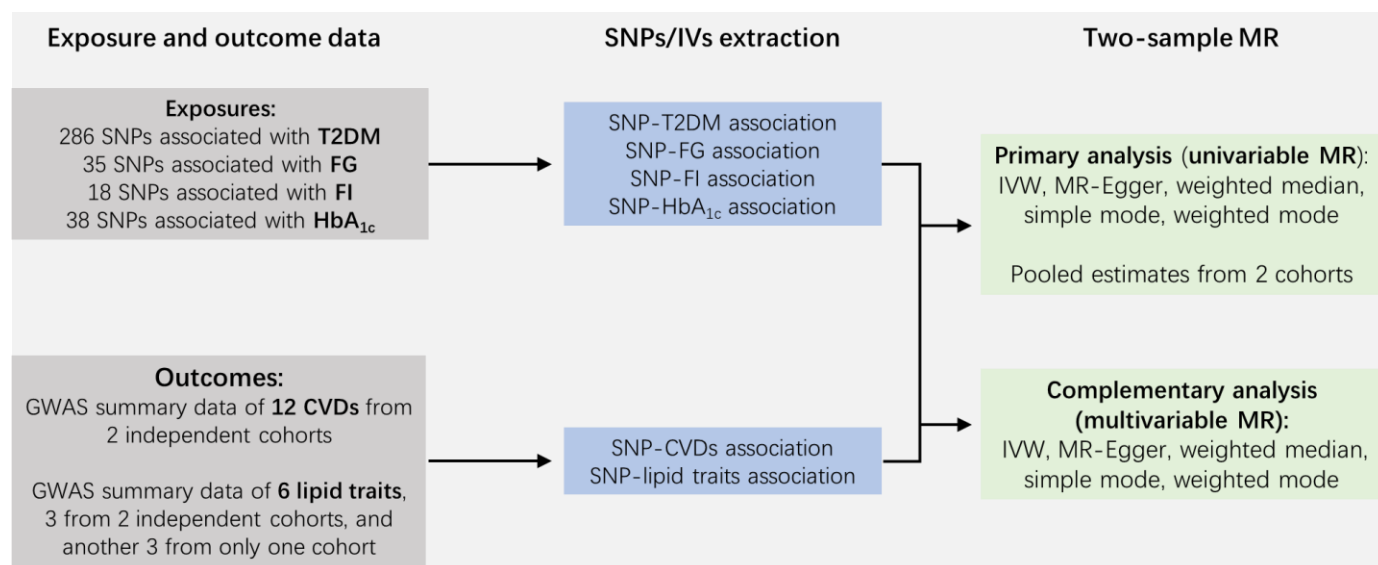
Table S9 Triglycerides as a mediator in the causal pathway between type 2 diabetes mellitus and risk of CVDs.

Table S10 Apolipoprotein A as a mediator in the causal pathway between type 2 diabetes mellitus and risk of CVDs.

Table S11 Multivariable Mendelian randomization using IVW method.

Supplementary Figure

Figure S1 Study Overview.



Supplementary Tables

Table S1 Phenotype source and description.

Phenotypes	Consortium or study	No. of cases	No. of controls	Data type	GWAS ID
Exposure					
Type 2 diabetes mellitus	DIAGRAM	74124	824006	Binary	NA
Fasting blood glucose	MAGIC	NA	NA	Continuous	NA
Fasting insulin	MAGIC	NA	NA	Continuous	NA
HbA _{1c}	MAGIC	NA	NA	Continuous	NA
CVDs					
Myocardial infarction	CARDIoGRAMplusC4D / FinnGen	43676/4065	128199/85760	Binary	ieu-a-798/finn-a-l9_MI
Heart failure	HERMES/ FinnGen	47309/8016	930014/75137	Binary	ebi-a-GCST009541/finn-a-HEARTFAIL

Ischemic heart disease	CARDIoGRAMplusC4D / FinnGen	60801/10739	123504/85760	Binary	ieu-a-7/finn-a-19_ISCHHEART
Coronary atherosclerosis	UKB/ FinnGen	14334/7661	34860/85760	Binary	ukb-d-19_CORATHER / finn-a-19_CORATHER
Major coronary heart disease event	UKB/ FinnGen	10157/7123	351037/89376	Binary	ukb-d-19_CHD/finn-a-19_CHD
Peripheral artery disease	BBJ/ FinnGen	7114/2398	475964/92349	Binary	bbj-a-144/finn-a-19_PAD
Essential hypertension	UKB/ FinnGen	54358/22142	408652/69160	Binary	ukb-b-12493/finn-a-19_HYPTENS
Stroke	MEGASTROKE/ FinnGen	40585/7144	406111/75420	Binary	ebi-a-GCST006906/finn-a-C_STROKE
Ischemic stroke	MEGASTROKE/ FinnGen	34217/4026	406111/90211	Binary	ebi-a-GCST006908/finn-a-19_STR_EXH
Intracerebral hemorrhage	UKB/ FinnGen	1253/1149	359941/90757	Binary	ukb-d-19_INTRACRA/finn-a-19_ICH
Atrial fibrillation and fluttering	Multi-cohorts ^a / FinnGen	62620/7244	970216/56378	Binary	ebi-a-GCST006414/finn-a-19_AF
Cardiovascular mortality	UKB/ FinnGen	1597/3480	359597/93019	Binary	ukb-d-19_K_CARDIA/finn-a-19_K_CARDIAC
Lipid traits					
HDL cholesterol	UKB/ GLGC	NA	NA	Continuous	ukb-d-30760_irnt/ieu-a-299
LDL cholesterol	UKB/ GLGC	NA	NA	Continuous	ukb-d-30780_irnt/ieu-a-300
Triglycerides	UKB/ GLGC	NA	NA	Continuous	ukb-d-30870_irnt/

					ieu-a-302
Apolipoprotein A	UKB	NA	NA	Continuous	ukb-d-30630_irnt
Apolipoprotein B	UKB	NA	NA	Continuous	ukb-d-30640_irnt
Lipoprotein A	UKB	NA	NA	Continuous	ukb-d-30790_irnt

^aFrom a meta-analysis of six contributing studies (The Nord-Trøndelag Health Study (HUNT), deCODE, the Michigan Genomics Initiative (MGI), DiscovEHR, UK Biobank, and the AFGen Consortium)

Table S2 Genetic variants associated with exposures.

SNP	Chromosome	Gene	Beta	SE	<i>p</i> value	F-statistics
Type 2 diabetes mellitus (286)						285.95
rs1005752	15	HMG20A	0.077	0.007	2.50E-29	323.76
rs10096633	8	LPL	0.068	0.010	1.10E-12	92.56
rs10097617	8	TP53INP1	0.039	0.007	3.30E-11	102.93
rs10193538	2	BNIP1	0.039	0.007	8.90E-09	97.99
rs10195252	2	GRB14/COBLL1	0.068	0.005	6.00E-25	424.22
rs10228066	7	DGKB	0.068	0.007	1.10E-28	311.11
rs10406431	19	GIPR	0.049	0.005	9.60E-14	224.32
rs1042725	12	HMG2	0.049	0.007	1.80E-13	162.49
rs1061810	11	HSD17B12	0.049	0.007	6.00E-13	133.88
rs10750397	11	ETS1	0.049	0.007	8.30E-13	131.08
rs10757283	9	CDKN2A/B	0.104	0.009	1.70E-41	558.65
rs10811660	9	CDKN2A/B	0.239	0.010	1.40E-115	1530.24
rs10830963	11	MTNR1B	0.095	0.007	4.80E-43	492.92
rs10842994	12	KLHDC5	0.077	0.007	4.10E-20	247.14
rs10882101	10	HHEX/IDE	0.058	0.010	1.40E-08	154.26
rs10893829	11	ETS1	0.058	0.010	1.30E-10	81.30
rs10937721	4	WFS1	0.058	0.010	1.50E-08	154.26
rs10938398	4	GNPDA2	0.049	0.007	3.60E-12	159.37
rs10954772	8	PURG	0.039	0.007	1.80E-09	88.10
rs10962	17	HNF1B	0.049	0.010	9.90E-10	80.60
rs10974438	9	GLIS3	0.049	0.007	1.50E-14	149.81

rs11042596	11	INS/IGF2	0.039	0.005	2.00E-08	127.50
rs11063028	12	CCND2	0.058	0.007	8.50E-11	134.46
rs11070332	15	LTK	0.049	0.005	1.10E-13	209.75
rs11137820	9	MTND2P8	0.039	0.007	2.90E-08	100.34
rs11202627	10	PTEN	0.058	0.010	4.70E-08	81.30
rs11257655	10	CDC123/CAMK1D	0.086	0.007	1.50E-32	343.78
rs1127215	1	PTGFRN	0.049	0.005	1.60E-13	221.77
rs11341409	2	CRYBA2	0.113	0.020	6.60E-09	57.48
3						
rs11496066	7	FBXL13	0.077	0.014	1.10E-08	118.49
rs11550561	5	PAM	0.174	0.015	1.30E-30	181.76
4						
rs11642430	16	FAM57B	0.039	0.005	2.20E-09	138.40
rs11680058	2	FAM49A	0.058	0.010	1.40E-08	76.77
rs11688682	2	GLI2	0.049	0.007	4.20E-09	128.16
rs11699802	20	CEBPB	0.039	0.007	1.80E-11	102.31
rs11700101	22	YWHAH	0.068	0.012	1.70E-08	59.82
3						
rs11708067	3	ADCY5	0.086	0.007	5.20E-32	354.80
rs11709077	3	PPARG	0.131	0.011	1.80E-36	312.37
rs11748389	15	TCF12	0.095	0.016	3.90E-08	41.06
4						
rs11759026	6	CENPW	0.068	0.007	2.40E-18	221.79
rs11820019	11	CCND1	0.148	0.020	5.10E-12	60.41
rs11842871	13	HMGBl	0.039	0.007	1.20E-08	79.25
rs11926707	3	KIF9	0.239	0.042	2.10E-08	601.28
rs12001437	9	UBAP2	0.039	0.007	2.80E-10	96.01
rs12140153	1	PATJ	0.068	0.012	1.30E-08	59.82
rs12454712	18	BCL2A	0.049	0.005	4.60E-13	216.58
rs1260326	2	GCKR	0.068	0.005	6.50E-25	417.20
rs12640250	4	LCORL	0.039	0.005	3.70E-08	116.25
rs12642790	4	SCD5	0.039	0.007	4.40E-10	92.43
rs12719778	8	BOP1	0.039	0.005	5.00E-09	143.24
rs12811407	12	FBRSL1	0.049	0.007	1.70E-12	143.76
rs12910825	15	PRC1	0.049	0.007	1.60E-15	149.81
rs12920022	16	SPG7	0.049	0.007	3.40E-09	87.38
rs1296328	4	PABPC4L	0.039	0.007	3.50E-08	101.94
rs13024606	2	GRB14/COBLL1	0.086	0.016	1.70E-08	41.62
rs13041756	20	NKX2.2	0.058	0.010	1.40E-08	62.43
rs13065698	3	MBNL1	0.049	0.007	8.10E-13	156.06
rs13085136	3	SHQ1	0.077	0.012	1.50E-08	60.97
rs1316776	5	DMGDH	0.049	0.007	2.60E-12	147.93
rs13262861	8	ANK1	0.068	0.010	4.00E-12	123.68

Supplementary Material

rs13426680	2	CYTIP	0.086	0.012	6.70E-10	65.89
rs1359790	13	SPRY2	0.086	0.007	2.40E-31	403.91
rs13737	15	PTPN9	0.049	0.007	5.60E-10	118.60
rs1377807	17	ZZEF1	0.049	0.007	4.20E-13	139.08
rs13833755	5	SLCO6A1	0.445	0.077	4.70E-09	17.49
6						
rs14024215	10	TCF7L2	0.307	0.056	2.20E-08	31.58
0						
rs1412234	9	LINGO2	0.039	0.007	1.90E-10	89.63
rs14152172	11	PDE3B	0.122	0.020	2.70E-08	27.65
1						
rs1421085	16	FTO	0.122	0.007	3.10E-84	982.82
rs1426371	12	WSCD2	0.049	0.007	8.20E-12	125.10
rs14567801	11	QSER1	0.104	0.016	2.00E-10	49.20
4						
rs14590438	1	FAM63A	0.174	0.030	2.60E-08	18.94
1						
rs14688610	5	ANKH	0.344	0.049	7.80E-13	45.32
8						
rs14936442	8	CPQ	0.239	0.034	1.80E-12	31.53
8						
rs1493694	1	NOTCH2	0.086	0.009	2.70E-16	152.51
rs1531583	4	PCGF3	0.122	0.016	3.50E-14	83.76
rs1561927	8	PVT1	0.039	0.007	1.50E-09	81.18
rs1562396	7	KLF14	0.058	0.007	9.90E-18	198.25
rs1580278	4	SLC9B1	0.039	0.005	2.20E-10	143.65
rs1641523	17	ATP1B2	0.049	0.007	1.20E-10	159.37
rs17013314	3	UBE2E2	0.104	0.018	8.40E-09	33.14
rs1708302	7	JAZF1	0.095	0.007	1.10E-48	611.10
rs17122772	14	SLC7A7	0.039	0.007	1.60E-08	72.94
rs17168486	7	DGKB	0.068	0.007	2.30E-17	184.84
rs17250977	5	ANKH	0.113	0.016	2.00E-11	58.09
rs17261179	5	ITGA1	0.039	0.007	1.30E-08	102.81
rs17522122	14	AKAP6	0.039	0.005	3.20E-09	143.65
rs17684074	18	WDR7	0.039	0.007	2.90E-08	79.25
rs17689007	8	MSRA	0.039	0.005	2.50E-09	143.65
rs177045	10	NEUROG3	0.068	0.007	6.60E-18	272.53
rs17772814	8	CASC11	0.077	0.014	5.40E-10	59.08
rs17791513	9	TLE4	0.095	0.012	3.10E-14	92.81
rs17802463	2	DTNB	0.039	0.005	2.90E-08	113.66
rs17819328	3	PPARG	0.058	0.007	4.80E-16	223.31
rs1783541	11	MAP3K11	0.058	0.007	2.00E-14	145.76

rs17836088	14	NRXN3	0.058	0.010	6.70E-14	109.43
rs1800574	12	HNF1A	0.131	0.020	1.70E-12	47.33
rs1800961	20	HNF4A	0.166	0.017	2.30E-22	117.99
rs1801645	22	PIM3	0.039	0.007	1.50E-08	83.03
rs18450920	10	TCF7L2	0.191	0.025	1.20E-13	54.21
1						
rs18466082	1	DENND2C	2.086	0.375	2.50E-08	4.40
9						
rs2028150	2	CEP68	0.049	0.007	2.30E-12	156.06
rs2066827	12	CDKN1B	0.049	0.007	4.20E-08	118.60
rs2102278	4	USP46	0.039	0.007	3.70E-08	89.63
rs2197973	12	USP44	0.039	0.007	3.60E-08	102.31
rs2237895	11	KCNQ1	0.113	0.007	6.00E-52	848.22
rs2237897	11	KCNQ1	0.207	0.017	8.40E-32	226.98
rs2238689	19	GIPR	0.039	0.005	5.40E-09	140.48
rs2249105	2	CEP68	0.095	0.012	2.20E-14	332.41
rs2258238	12	HMGA2	0.095	0.012	4.50E-21	128.31
rs2268078	20	RALY	0.039	0.007	2.30E-10	92.43
rs2272163	3	ROBO2	0.039	0.007	9.60E-09	97.04
rs2280141	10	PLEKHA1	0.049	0.007	1.40E-13	162.30
rs2283220	11	KCNQ1	0.049	0.007	1.40E-09	139.08
rs2307111	5	POC5	0.049	0.007	2.10E-16	154.69
rs231349	11	KCNQ1	0.068	0.012	2.30E-11	65.74
rs231361	11	KCNQ1	0.077	0.007	5.00E-25	308.98
rs234853	11	KCNQ1	0.077	0.009	6.80E-16	234.18
rs243024	2	BCL11A	0.058	0.005	2.50E-20	316.88
rs2431115	5	ANKRD55	0.039	0.007	3.90E-10	98.85
rs2456530	15	ONECUT1	0.058	0.010	5.40E-09	72.12
rs2581787	3	RFT1	0.039	0.007	2.40E-08	101.49
rs2642588	10	NEUROG3	0.049	0.007	2.20E-14	136.55
rs2767036	11	PDHX	0.039	0.007	3.30E-08	84.81
rs2796441	9	TLE1	0.068	0.007	4.40E-24	302.97
rs279744	5	ARL15	0.039	0.005	3.10E-08	123.35
rs2800733	6	SOGA3	0.049	0.007	6.00E-11	131.08
rs2820446	1	LYPLAL1	0.058	0.007	3.30E-16	187.59
rs28505901	9	GPSM1	0.086	0.009	6.70E-26	292.14
rs2872246	3	ABCC5	0.039	0.007	1.50E-08	101.94
rs28819812	4	PDGFC	0.039	0.007	2.20E-08	89.63
rs291367	1	GNG4	0.039	0.007	4.70E-10	96.01
rs2925979	16	CMIP	0.049	0.007	1.40E-14	136.55
rs2972144	2	IRS1	0.095	0.007	2.10E-46	563.38
rs2982521	6	MIR3668	0.049	0.007	1.30E-09	153.19
rs3111316	19	FARSA	0.049	0.007	6.30E-13	157.29

Supplementary Material

rs3217792	12	CCND2	0.113	0.011	2.60E-21	180.23
rs3217860	12	CCND2	0.049	0.007	3.90E-09	125.10
rs329122	5	PHF15	0.039	0.005	3.60E-09	141.34
rs340874	1	PROX1	0.068	0.007	1.60E-22	308.61
rs34298980	6	LRFN2	0.039	0.005	9.30E-10	144.17
rs34454109	20	TSHZ2	0.039	0.007	7.10E-09	72.94
rs34584161	13	RNF6	0.049	0.007	2.20E-10	118.60
rs34715063	15	RASGRP1	0.095	0.012	2.30E-19	150.56
rs348330	1	ABCB10	0.049	0.007	2.70E-14	149.81
rs34855406	17	MLX	0.049	0.007	2.30E-12	131.08
rs34855922	10	TCF7L2	0.049	0.007	5.50E-12	131.08
rs34965774	12	KSR2	0.058	0.010	2.00E-09	76.77
rs35352848	3	UBE2E2	0.068	0.010	1.30E-17	145.42
rs35895680	17	TLL6	0.058	0.007	2.50E-15	198.25
rs35913461	2	TMEM18	0.058	0.010	1.60E-11	89.98
rs35999103	2	PABPC1P2	0.049	0.010	9.70E-09	61.17
rs362307	4	HTT	0.077	0.012	1.10E-09	68.93
rs3751837	16	CLUAP1	0.039	0.007	1.40E-08	70.68
rs3768321	1	MACF1	0.086	0.007	2.60E-26	320.53
rs3772071	2	RBMS1	0.049	0.007	1.20E-11	133.88
rs3774723	3	PSMD6	0.068	0.010	1.60E-13	117.81
rs3798519	6	TFAP2B	0.058	0.010	2.60E-12	94.12
rs3802177	8	SLC30A8	0.104	0.007	1.10E-55	626.88
rs3810291	19	ZC3H4	0.049	0.007	8.90E-12	143.76
rs3811978	5	ITGA1	0.058	0.007	7.70E-11	128.54
rs3845281	5	ANKH	0.077	0.009	2.30E-11	112.39
rs3887925	3	ST6GAL1	0.068	0.007	3.10E-22	309.99
rs39328	7	RELN	0.039	0.007	3.70E-08	100.95
rs3934712	5	EBF1	0.049	0.010	3.20E-08	75.50
rs4148856	12	MPHOSPH9	0.049	0.010	1.70E-10	78.10
rs4238013	12	CCND2	0.058	0.007	3.20E-11	151.14
rs4279506	7	IGF2BP3	0.058	0.010	4.80E-08	151.71
rs4281707	16	FTO	0.039	0.005	3.20E-10	143.24
rs429358	19	TOMM40/APOE	0.077	0.009	2.60E-18	159.23
rs4457053	5	ZBED3	0.058	0.007	8.40E-18	191.32
rs465002	5	ANKRD55	0.104	0.007	6.10E-38	563.83
rs4686471	3	LPP	0.058	0.007	1.70E-20	216.75
rs4688760	3	RBM6	0.039	0.007	3.50E-10	89.63
rs4709746	6	QKI	0.058	0.010	5.80E-09	72.12
rs474513	6	SLC22A3	0.039	0.005	8.10E-10	143.94
rs4776970	15	MAP2K5	0.039	0.005	5.00E-09	132.86
rs4804833	19	MAP2K7	0.049	0.007	7.70E-13	154.69

rs4810426	20	HNF4A	0.086	0.012	3.10E-17	114.38
rs4923543	11	METTL15	0.039	0.007	4.50E-08	91.07
rs4925109	17	RAI1	0.049	0.007	2.80E-12	141.49
rs4929965	11	INS/IGF2	0.068	0.007	4.00E-26	295.08
rs4932265	15	AP3S2	0.068	0.007	4.20E-20	246.85
rs4946812	6	BEND3	0.039	0.005	8.20E-09	127.50
rs4976033	5	PIK3R1	0.049	0.007	1.00E-09	157.29
rs4977213	8	BOP1	0.049	0.007	9.10E-14	153.19
rs505922	9	ABO	0.049	0.007	3.90E-12	143.76
rs5213	11	KCNJ11	0.068	0.007	3.50E-27	288.56
rs523288	18	MC4R	0.049	0.007	7.60E-13	118.60
rs52835091	15	WDR72	0.239	0.042	2.10E-08	25.52
1						
rs53664341	10	TCF7L2	0.405	0.073	2.60E-08	42.16
8						
rs539515	1	SEC16B	0.049	0.007	1.60E-10	104.03
rs55540274	6	SLC25A51P1	1.3	0.239	4.60E-08	5.36
8						
rs55575934	11	INS/IGF2	0.322	0.059	3.60E-08	16.24
1						
rs55653563	9	ZNF169	0.039	0.007	2.20E-09	81.18
rs56238620	2	DDX18	1.163	0.213	4.20E-08	7.22
2						
rs56337234	4	MAEA	0.058	0.007	8.60E-18	227.78
rs56348580	12	HNF1A	0.049	0.007	2.30E-13	139.08
rs56951154	17	KIF2B	2.032	0.358	1.50E-08	4.37
1						
rs57235767	11	MTNR1B	0.039	0.007	5.90E-10	84.81
rs57327348	8	XKR6	0.039	0.010	4.50E-08	49.47
rs5758223	22	EP300	0.039	0.005	3.80E-08	116.25
rs576674	13	KL	0.049	0.007	8.30E-10	91.74
rs58432198	1	FAF1	0.068	0.010	2.10E-10	92.56
rs58730668	4	ACSL1	0.068	0.010	1.30E-13	105.53
rs59944054	20	TCEA2	0.058	0.010	1.50E-08	116.31
rs601945	6	MHC	0.058	0.010	4.70E-08	94.12
rs60276348	17	ACE	0.049	0.010	2.60E-08	54.80
rs6063048	20	EYA2	0.049	0.007	2.20E-11	128.16
rs62007683	14	MARK3	0.039	0.007	3.10E-08	93.70
rs62080313	18	COMMD9	0.058	0.010	1.00E-08	67.34
rs62107261	2	TMEM18	0.113	0.016	3.80E-12	71.86
rs62271373	3	TSC22D2	0.086	0.014	1.00E-09	56.48
rs62492368	7	AOC1	0.049	0.007	1.10E-10	139.08
rs6458354	6	VEGFA	0.049	0.007	2.10E-12	133.88

Supplementary Material

rs6459733	7	MNX1	0.058	0.005	2.40E-17	282.04
rs649961	3	SLC12A8	0.039	0.005	9.90E-10	143.65
rs6518681	22	MTMR3/ASCC2	0.086	0.012	1.10E-12	95.69
rs6545714	2	BNIP1	0.039	0.007	8.90E-09	97.99
rs6600191	16	ITFG3	0.058	0.007	9.30E-13	128.54
rs6708643	2	THADA	0.039	0.007	3.90E-08	102.97
rs67232546	11	ETS1	0.058	0.007	1.30E-11	151.14
rs67254669	11	KCNJ11	0.637	0.111	1.10E-08	7.61
rs6780171	3	IGF2BP2	0.131	0.009	9.00E-56	773.72
rs6821438	4	SMARCA1	0.039	0.007	4.00E-11	102.60
rs6884702	5	MRPS30	0.039	0.007	1.50E-10	97.99
rs6885132	5	ANKH	0.068	0.012	1.70E-08	65.74
rs6976111	7	CTTNBP2	0.039	0.007	1.20E-08	88.10
rs7022807	9	HAUS6	0.039	0.005	2.70E-10	138.40
rs702634	5	ARL15	0.049	0.007	7.70E-14	139.08
rs7115753	11	CRY2	0.039	0.005	3.80E-09	142.73
rs7124681	11	CELF1	0.039	0.005	5.10E-09	139.50
rs71372253	17	NF1	0.077	0.012	4.40E-08	52.82
rs7178762	15	USP3	0.039	0.005	5.40E-10	143.24
rs718314	12	ITPR2	0.049	0.007	8.40E-11	121.91
rs7222481	17	GLP2R	0.039	0.005	1.40E-08	125.48
rs7240767	18	LAMA1	0.039	0.007	1.60E-08	97.04
rs7249758	19	UHRF1	0.049	0.010	3.40E-09	72.82
rs72631105	10	WDR11	0.058	0.010	3.70E-09	98.14
rs72802342	16	BCAR1	0.157	0.013	4.00E-32	264.58
rs72926932	18	TCF4	0.086	0.012	1.00E-14	85.99
rs73226260	12	HNF1A	0.122	0.018	5.90E-11	45.61
rs738408	22	PNPLA3	0.049	0.010	1.40E-10	80.60
rs74452128	18	MC4R	0.14	0.022	1.00E-09	33.10
rs74653713	3	MBNL1	0.095	0.016	1.20E-08	41.06
rs75253922	19	INSR	0.049	0.007	2.70E-08	100.06
rs76263492	3	CACNA2D3	0.086	0.016	6.30E-09	41.62
rs7629630	3	EGFEM1P	0.049	0.010	2.50E-08	54.80
rs7645517	3	ST6GAL1	0.077	0.014	2.50E-08	45.27
rs76549217	5	ANKH	0.131	0.020	3.00E-10	47.33
rs7669833	4	TMEM154	0.058	0.007	1.20E-14	187.59
rs76895963	12	CCND2	0.482	0.027	1.40E-69	319.77
rs77136196	6	HMGA1	0.104	0.021	1.60E-08	37.49
rs7719891	5	RASA1	0.039	0.007	2.40E-08	79.25
rs77464186	11	CENTD2/ARAP1	0.104	0.009	4.70E-33	306.25
rs7756992	6	CDKAL1	0.14	0.009	2.40E-88	814.31
rs77864822	12	RMST	0.077	0.014	1.10E-08	52.26

rs78020297	16	FTO	0.086	0.014	6.50E-09	47.56
rs78408340	5	PAM	0.385	0.038	2.10E-24	73.20
rs7867635	9	FOCAD	0.039	0.007	4.00E-08	99.64
rs7903146	10	TCF7L2	0.315	0.007	5.8E-447	5677.77
rs79046683	2	TMEM127	0.85	0.154	3.00E-08	2.67
rs7918400	10	TCF7L2	0.058	0.007	2.00E-15	227.41
rs79687284	1	PROX1	0.148	0.020	2.60E-16	60.41
rs7978610	12	ZNF664	0.239	0.042	2.00E-08	570.31
rs7987740	13	IRS2	0.039	0.007	4.00E-08	97.99
rs8010382	14	SMEK1	0.039	0.005	6.50E-09	140.48
rs80147536	2	THADA	0.122	0.011	2.70E-29	230.88
rs8017808	14	CLEC14A	0.039	0.007	2.10E-08	79.25
rs8032939	15	RASGRP1	0.058	0.007	3.50E-14	170.82
rs8046545	16	ATP2A1	0.039	0.007	1.90E-08	94.90
rs8107974	19	TM6SF2	0.095	0.012	3.30E-15	104.93
rs862320	16	NFAT5	0.039	0.007	3.90E-11	100.34
rs878521	7	GCK	0.058	0.007	1.90E-13	170.82
rs917195	7	CRHR2	0.049	0.007	4.20E-11	115.15
rs9379084	6	RREB1	0.104	0.012	3.30E-21	167.28
rs9494624	6	SLC35D3	0.039	0.007	6.10E-09	84.81
rs9505097	6	RREB1	0.049	0.010	8.60E-10	72.82
rs9537803	13	PCDH17	0.039	0.007	4.60E-08	83.03
rs9563615	13	SRGAP2D	0.049	0.007	6.40E-11	133.88
rs963740	13	DLEU1	0.039	0.005	2.10E-08	118.73
rs9687832	5	ANKRD55	0.077	0.009	1.70E-20	199.83
rs9828772	3	TMCC1	0.058	0.010	4.20E-08	57.39
rs9860730	3	ADAMTS9	0.058	0.007	4.90E-15	191.32
rs9873618	3	SLC2A2	0.068	0.007	4.80E-21	257.87
rs9957145	18	GRP	0.049	0.010	8.10E-09	64.22
Fasting glucose (35)						47.79
rs10747083	12	P2RX2	0.013	0.002	7.57E-09	13.83
rs10811661	9	CDKN2B	0.024	0.003	5.65E-18	20.67
rs10830963	11	MTNR1B	0.078	0.002	0.00E+0	458.43
					0	
rs10885122	10	ADRA2A	0.027	0.003	6.32E-17	18.72
rs11071657	15	VPS13C/C2CD4A/B	0.01	0.002	2.96E-07	8.50
rs11558471	8	SLC30A8	0.029	0.002	7.80E-37	66.77
rs11603334	11	ARAP1	0.019	0.003	1.12E-11	12.39
rs11605924	11	CRY2	0.02	0.002	3.93E-19	36.47
rs11619319	13	PDX1	0.019	0.002	1.33E-15	23.32
rs11708067	3	ADCY5	0.023	0.003	1.30E-18	21.34

Supplementary Material

rs11715915	3	AMT	0.012	0.002	4.90E-08	11.43
rs11920090	3	SLC2A2	0.026	0.003	8.56E-18	19.79
rs16913693	9	IKBKAP	0.043	0.007	3.51E-11	5.61
rs174550	11	FADS1	0.019	0.002	1.34E-17	29.55
rs17762454	6	RREB1	0.014	0.002	9.57E-09	13.75
rs2191349	7	DGKB/TMEM195	0.029	0.002	0.00E+0	76.45
					0	
rs2657879	12	GLS2	0.016	0.003	3.94E-08	9.19
rs340874	1	PROX1	0.013	0.002	4.08E-10	15.39
rs3783347	14	WARS	0.017	0.003	1.32E-10	11.66
rs3829109	9	LOC728489	0.017	0.003	1.13E-10	14.47
rs4506565	10	TCF7L2	0.021	0.002	3.95E-19	33.78
rs4607517	7	GCK	0.057	0.003	0.00E+0	106.25
					0	
rs4869272	5	PCSK1	0.018	0.002	1.02E-15	25.28
rs560887	2	G6PC2	0.071	0.002	0.00E+0	387.20
					0	
rs576674	13	KL	0.017	0.003	2.26E-08	8.96
rs6072275	20	TOP1	0.016	0.003	1.66E-08	8.37
rs6113722	20	FOXA2	0.035	0.005	2.49E-11	6.86
rs6943153	7	GRB10	0.015	0.002	1.63E-12	18.42
rs7651090	3	IGF2BP2	0.013	0.002	1.75E-08	13.18
rs7708285	5	ZBED3	0.015	0.003	1.20E-08	10.78
rs780094	2	GCKR	0.027	0.002	2.58E-37	63.28
rs7867224	9	GLIS3	0.013	0.002	3.90E-09	15.40
rs7944584	11	MADD	0.023	0.002	4.82E-22	38.04
rs9368222	6	CDKAL1	0.014	0.002	1.00E-09	14.41
rs983309	8	PPP1R3B	0.026	0.003	6.29E-15	17.36
Fasting						16.52
insulin (18)						
rs10195252	2	GRB14	0.016	0.003	4.87E-10	15.06
rs1167800	7	HIP1	0.016	0.003	2.61E-09	15.46
rs1421085	16	FTO	0.02	0.003	1.87E-15	23.70
rs1530559	2	YSK4	0.015	0.003	3.37E-08	13.66
rs17036328	3	PPARG	0.021	0.003	3.59E-12	12.91
rs2126259	8	PPP1R3B	0.024	0.003	3.30E-13	13.71
rs2745353	6	RSPO3	0.014	0.002	5.48E-09	17.87
rs2943645	2	IRS1	0.019	0.002	2.26E-19	30.70
rs3822072	4	FAM13A1	0.012	0.002	1.80E-08	13.11
rs459193	5	ANKRD55	0.015	0.002	1.15E-10	16.18
rs4846565	1	LYPLAL1	0.013	0.002	1.76E-09	13.63
rs4865796	5	ARL15	0.015	0.003	2.09E-08	12.10

rs6912327	6	C6orf107	0.017	0.003	2.26E-08	11.24
rs731839	19	PEPD	0.015	0.003	5.13E-12	12.28
rs780094	2	GCKR	0.019	0.002	7.06E-14	31.33
rs7903146	10	TCF7L2	0.018	0.003	6.13E-11	15.88
rs860598	12	IGF1	0.018	0.003	1.64E-08	11.12
rs974801	4	TET2	0.014	0.002	3.27E-11	16.84
HbA _{1c} (38)						17.71
rs1046896	17	FN3KRP	0.028	0.002	4.00E-64	65.91
rs10774625	12	ATXN2	0.0088	0.003	1.00E-08	3.98
rs10823343	10	HK1	0.0325	0.003	2.00E-55	44.91
rs10830963	11	MTNR1B	0.0196	0.002	2.00E-23	23.23
rs11248914	16	FAM234A	0.0142	0.002	3.00E-14	13.42
rs11558471	8	SLC30A8/LOC1053757 16	0.015	0.002	1.00E-19	19.19
rs11603334	11	ARAP1	0.012	0.021	7.00E-09	0.62
rs11708067	3	ADCY5	0.0132	0.019	1.00E-12	1.02
rs11964178	6	CCDC162P	0.0096	0.016	6.00E-10	0.85
rs12621844	2	RN7SKP224	0.0099	0.018	2.00E-08	0.78
rs13134327	4	FREM3	0.0131	0.017	3.00E-15	1.31
rs1558902	16	FTO	0.0103	0.019	3.00E-08	0.81
rs17509001	2	ATAD2B	0.0181	0.002	2.00E-15	11.29
rs17533903	19	MYO9B	0.015	0.002	5.00E-12	12.06
rs17747324	10	TCF7L2	0.0149	0.002	6.00E-11	10.78
rs1800562	6	HFE/HFE-AS1	0.0398	0.003	5.00E-28	22.43
rs198846	6	H1-6	0.0218	0.002	1.00E-23	17.47
rs2110073	12	PHB2	0.0153	0.003	4.00E-08	4.84
rs2383208	9	CDKN2B-AS1	0.0142	0.002	7.00E-12	9.43
rs2408955	12	PFKM/SENP1	0.0124	0.002	1.00E-15	14.46
rs267738	1	CERS2	0.0111	0.019	3.00E-09	0.69
rs3782123	11	BET1L	0.0126	0.020	2.00E-10	1.03
rs3824065	7	YKT6	0.0192	0.002	4.00E-35	36.09
rs4607517	7	GCK	0.0306	0.002	9.00E-38	39.16
rs4745982	10	HK1	0.0954	0.006	3.00E-65	107.34
rs4820268	22	TMPRSS6	0.0162	0.002	1.00E-22	21.66
rs560887	2	G6PC2	0.0284	0.002	1.00E-58	57.91
rs579459	9	Y_RNA/ABO	0.0107	0.003	9.00E-09	3.55
rs592423	6	ATP5B/P6/LINC01625	0.0091	0.002	4.00E-08	7.27
rs6474359	8	ANK1	0.0436	0.005	2.00E-16	9.44
rs7040409	9	PCNPP2	0.0284	0.004	3.00E-14	11.74
rs7616006	3	SYN2/GSTM5P1	0.0103	0.003	5.00E-10	4.69
rs7756992	6	CDKAL1	0.0123	0.002	3.00E-12	10.27
rs8192675	3	SLC2A2	0.0112	0.002	1.00E-11	9.49

rs837763	16	LOC107984842	0.0172	0.002	2.00E-28	28.40
rs857691	1	SPTA1	0.0193	0.002	4.00E-25	24.47
rs9604573	13	GAS6/GAS6-AS1	0.0101	0.002	1.00E-08	6.74
rs9914988	17	ERAL1/FAM222B	0.0131	0.002	3.00E-11	9.86

Table S3 Definition and sources for CVDs in FinnGen.

CVDs	No. of cases	ICD-10 diagnosis for the first occurrence
Myocardial infarction	4065	I21, I22
Heart failure	8016	I11.0, I13.0, I13.2, I50
Ischemic heart disease	10739	I20-I25
Coronary atherosclerosis	7661	I24, I25, T82.2, Z95.1
Major coronary heart disease event	7123	I20.0, I21, I22; Including revascularizations
Peripheral artery disease	2398	E10.5, E10.5+I79.2, E11.5, E11.5, I79.2, E12.5, E13.5, E14.5, I70.2, I73.9
Essential hypertension	22142	I10
Stroke	7144	I60-I64, G45
Ischaemic stroke	4026	I63, I64
Intracerebral haemorrhage	1149	I61
Atrial fibrillation and fluttering	7244	I48
Cardiovascular mortality	3480	I00-I02, I05-I09, I10-I15, I20-I25, I26-I28, I30-I52, R96, R98, R99

Table S4 The causal effect of genetically predicted type 2 diabetes mellitus on outcomes in different studies.

ID of outcome	Outcome	Methods	No. of SNPs	Beta	SE	p value	OR	LCI	UCI	Heterogeneity p value	p value for intercept	p value for MR-PRESSO	Distortion test p value
ukb-d-19_K_CARDIAC	Cardiovascular mortality	MR Egger	273	0.000	0.000	0.130	1.000	1.000	1.000	0.367	0.399	0.379	

		Weighted median	273	0.00	0.00	0.017	1.00	1.00	1.00				
		Inverse variance weighted	273	0.00	0.00	0.000	1.00	1.00	1.00	0.372			
		Simple mode	273	0.00	0.00	0.038	1.00	1.00	1.00				
		Weighted mode	273	0.00	0.00	0.055	1.00	1.00	1.00				
		MR-PRESSO	273	0.00	0.00	0.000	1.00	1.00	1.00				
ieu-a-798	Myocardial infarction	MR Egger	268	0.02	0.03	0.485	1.02	0.96	1.08	0.000	0.000	<0.001	0.687
		Weighted median	268	0.079	0.024	0.001	1.083	1.032	1.135				
		Inverse variance weighted	268	0.118	0.016	0.000	1.126	1.092	1.161	0.000			
		Simple mode	268	0.095	0.055	0.087	1.099	0.987	1.225				
		Weighted mode	268	0.069	0.025	0.007	1.071	1.019	1.125				
		MR-PRESSO	268	0.120	0.016	0.000	1.127	1.094	1.162				
ukb-d-I9_INTRACRA A	Intracranial haemorrhage	MR Egger	271	0.00	0.00	0.213	1.000	0.999	1.000	0.099	0.065	0.121	
		Weighted median	271	0.000	0.000	0.860	1.000	0.999	1.001				
		Inverse variance weighted	271	-0.001	0.001	0.172	0.999	0.998	1.000	0.081			
		Simple mode	271	0.000	0.000	0.493	1.000	1.000	1.000				
		Weighted mode	271	0.000	0.000	0.177	1.000	0.999	1.000				
		MR-PRESSO	271	0.000	0.000	0.489	1.000	1.000	1.000				
ebi-a-GCST009541	Heart failure	MR Egger	232	-0.014	0.025	0.578	0.986	0.939	1.036	0.000	0.001	<0.001	0.511
		Weighted median	232	0.014	0.019	0.458	1.014	0.977	1.053				
		Inverse variance weighted	232	0.059	0.013	0.000	1.061	1.035	1.088	0.000			
		Simple mode	232	0.065	0.044	0.141	1.067	0.979	1.163				
		Weighted mode	232	0.014	0.019	0.464	1.014	0.977	1.054				
		MR-PRESSO	232	0.066	0.011	0.000	1.068	1.045	1.092				

Supplementary Material

ieu-a-7	Ischemic heart disease	MR Egger	269	0.03 1	0.02 8	0.27 6	1.03 1	0.97 6	1.09 0	0.000	0.000	<0.001	0.586
		Weighted median	269	0.10 6	0.02 3	0.00 0	1.11 1	1.06 3	1.16 2				
		Inverse variance weighted	269	0.12 8	0.01 5	0.00 0	1.13 7	1.10 5	1.17 0	0.000			
		Simple mode	269	0.17 9	0.05 1	0.00 1	1.19 6	1.08 2	1.32 3				
		Weighted mode	269	0.09 7	0.02 6	0.00 0	1.10 2	1.04 6	1.16 1				
ukb-d-I9_CORATHERR	Coronary atherosclerosis	MR Egger	277	0.00 3	0.00 1	0.00 8	1.00 3	1.00 1	1.00 6	0.000	0.096	<0.001	0.762
		Weighted median	277	0.00 5	0.00 1	0.00 0	1.00 5	1.00 4	1.00 7				
		Inverse variance weighted	277	0.00 5	0.00 1	0.00 0	1.00 5	1.00 4	1.00 7	0.000			
		Simple mode	277	0.00 8	0.00 3	0.00 2	1.00 8	1.00 3	1.01 3				
		Weighted mode	277	0.00 4	0.00 1	0.00 0	1.00 4	1.00 2	1.00 6				
ukb-d-I9_CHD	Major coronary heart disease event	MR Egger	276	0.00 2	0.00 1	0.10 1	1.00 2	1.00 0	1.00 4	0.000	0.047	<0.001	0.96
		Weighted median	276	0.00 3	0.00 1	0.00 0	1.00 3	1.00 2	1.00 5				
		Inverse variance weighted	276	0.00 3	0.00 1	0.00 0	1.00 3	1.00 2	1.00 4	0.000			
		Simple mode	276	0.00 3	0.00 2	0.12 5	1.00 3	0.99 9	1.00 6				
		Weighted mode	276	0.00 3	0.00 1	0.00 0	1.00 3	1.00 1	1.00 4				
bbj-a-144	Peripheral artery disease	MR Egger	217	0.12 0	0.05 1	0.02 0	1.12 8	1.02 0	1.24 7	0.059	0.075	0.039	NA*
		Weighted median	217	0.11 5	0.05 3	0.03 0	1.12 2	1.01 1	1.24 5				
		Inverse variance weighted	217	0.19 5	0.03 0	0.00 0	1.21 5	1.14 5	1.28 9	0.047			
		Simple mode	217	0.12 3	0.05 2	0.02 5	1.12 3	1.02 9	1.24 6				
		Weighted mode	217	0.11 3	0.05 1	0.03 0	1.12 3	1.01 1	1.24 4				

		Simple mode	217	0.099	0.110	0.366	1.105	0.891	1.370				
		Weighted mode	217	0.099	0.054	0.069	1.105	0.993	1.229				
		MR-PRESSO	217	0.190	0.029	0.000	1.209	1.141	1.280				
ukb-b-12493	Essential hypertension	MR Egger	276	0.002	0.002	0.431	1.002	0.997	1.006	0.000	0.000	<0.001	0.953
		Weighted median	276	0.006	0.002	0.000	1.006	1.003	1.009				
		Inverse variance weighted	276	0.012	0.001	0.000	1.012	1.010	1.014	0.000			
		Simple mode	276	0.006	0.004	0.122	1.006	0.998	1.014				
		Weighted mode	276	0.005	0.001	0.000	1.005	1.003	1.008				
		MR-PRESSO	276	0.012	0.001	0.000	1.012	1.010	1.014				
ebi-a-GCST006906	Stroke	MR Egger	268	0.050	0.023	0.033	1.051	1.004	1.100	0.000	0.224	0.001	0.619
		Weighted median	268	0.049	0.008	0.006	1.050	1.014	1.087				
		Inverse variance weighted	268	0.074	0.012	0.000	1.077	1.052	1.102	0.000			
		Simple mode	268	0.047	0.041	0.247	1.048	0.968	1.136				
		Weighted mode	268	0.051	0.020	0.013	1.052	1.011	1.095				
		MR-PRESSO	268	0.074	0.011	0.000	1.077	1.053	1.101				
ebi-a-GCST006908	Ischemic stroke	MR Egger	269	0.063	0.024	0.010	1.065	1.015	1.118	0.001	0.337	0.005	0.88
		Weighted median	269	0.067	0.020	0.001	1.069	1.028	1.112				
		Inverse variance weighted	269	0.084	0.012	0.000	1.087	1.061	1.114	0.001			
		Simple mode	269	0.063	0.051	0.212	1.065	0.965	1.176				
		Weighted mode	269	0.067	0.022	0.002	1.069	1.024	1.116				
		MR-PRESSO	269	0.083	0.012	0.000	1.087	1.061	1.112				
ebi-a-GCST006414	Atrial fibrillation and fluttering	MR Egger	283	-0.008	0.022	0.715	0.992	0.949	1.036	0.000	0.172	<0.001	0.097
		Weighted median	283	-0.022	0.015	0.147	0.978	0.950	1.008				

Supplementary Material

		Inverse variance weighted	283	0.018	0.012	0.117	1.018	0.995	1.042	0.000			
		Simple mode	283	-0.050	0.044	0.253	0.951	0.873	1.036				
		Weighted mode	283	-0.039	0.018	0.027	0.962	0.929	0.995				
		MR-PRESSO	283	0.018	0.011	0.121	1.018	0.995	1.041				
ukb-d-30760_irnt	HDL cholesterol	MR Egger	277	-0.016	0.008	0.051	0.985	0.969	1.000	0.000	0.010	<0.001	0.106
		Weighted median	277	-0.013	0.002	0.000	0.987	0.983	0.991				
		Inverse variance weighted	277	-0.033	0.004	0.000	0.967	0.960	0.975	0.000			
		Simple mode	277	-0.012	0.006	0.049	0.988	0.977	1.000				
		Weighted mode	277	-0.009	0.002	0.000	0.991	0.987	0.995				
		MR-PRESSO	277	-0.034	0.004	0.000	0.967	0.959	0.974				
ukb-d-30780_irnt	LDL cholesterol	MR Egger	277	-0.019	0.019	0.327	0.982	0.946	1.019	0.000	0.690	<0.001	0.013
		Weighted median	277	-0.015	0.004	0.000	0.985	0.977	0.993				
		Inverse variance weighted	277	-0.025	0.000	0.010	0.975	0.957	0.994	0.000			
		Simple mode	277	-0.017	0.012	0.172	0.983	0.960	1.007				
		Weighted mode	277	-0.017	0.006	0.006	0.983	0.972	0.995				
		MR-PRESSO	277	-0.034	0.004	0.000	0.967	0.959	0.974				
ukb-d-30870_irnt	Triglycerides	MR Egger	277	0.043	0.026	0.098	1.044	0.992	1.097	0.000	0.091	<0.001	0.118
		Weighted median	277	0.052	0.006	0.000	1.054	1.041	1.067				
		Inverse variance weighted	277	0.080	0.013	0.000	1.083	1.056	1.112	0.000			
		Simple mode	277	0.059	0.013	0.000	1.060	1.033	1.088				

		Weighted mode	277	0.042	0.007	0.000	1.043	1.029	1.057				
		MR-PRESSO	277	0.082	0.013	0.000	1.086	1.058	1.114				
ukb-d-30630_irnt	Apolipoprotein A	MR Egger	277	-0.008	0.005	0.137	0.992	0.982	1.002	0.000	0.021	<0.001	<0.001
		Weighted median	277	-0.006	0.001	0.000	0.994	0.992	0.997				
		Inverse variance weighted	277	-0.018	0.003	0.000	0.982	0.977	0.987	0.000			
		Simple mode	277	-0.006	0.003	0.107	0.994	0.988	1.001				
		Weighted mode	277	-0.006	0.002	0.002	0.994	0.991	0.998				
		MR-PRESSO	277	-0.018	0.003	0.000	0.982	0.977	0.987				
ukb-d-30640_irnt	Apolipoprotein B	MR Egger	277	-0.004	0.006	0.560	0.996	0.984	1.009	0.000	0.879	<0.001	0.081
		Weighted median	277	-0.001	0.002	0.524	0.999	0.996	1.002				
		Inverse variance weighted	277	-0.003	0.003	0.377	0.997	0.991	1.004	0.000			
		Simple mode	277	-0.006	0.004	0.188	0.994	0.986	1.003				
		Weighted mode	277	-0.006	0.002	0.002	0.994	0.991	0.998				
		MR-PRESSO	277	-0.003	0.003	0.416	0.997	0.991	1.004				
ukb-d-30790_irnt	Lipoprotein A	MR Egger	277	-0.030	0.029	0.299	0.971	0.917	1.027	0.000	0.215	<0.001	0.456
		Weighted median	277	-0.010	0.005	0.056	0.990	0.980	1.000				
		Inverse variance weighted	277	0.001	0.015	0.961	1.001	0.972	1.030	0.000			
		Simple mode	277	-0.003	0.001	0.776	0.997	0.975	1.019				
		Weighted mode	277	-0.003	0.006	0.606	0.997	0.985	1.009				
		MR-PRESSO	277	0.000	0.014	0.976	1.000	0.973	1.029				

FinnGen Study

Supplementary Material

finn-a-I9_K_CARDIA C	Cardiovascular mortality	MR Egger	231	0.03 4	0.04 2	0.42 2	1.03 5	0.95 2	1.12 5	0.142	0.546	0.022	NA*		
		Weighted median	231	0.06 2	0.03 7	0.09 1	1.06 4	0.99 0	1.14 3						
		Inverse variance weighted	231	0.05 6	0.02 2	0.01 1	1.05 8	1.01 3	1.10 4	0.148					
		Simple mode	231	0.01 4	0.07 7	0.86 1	1.01 4	0.87 1	1.17 9						
		Weighted mode	231	0.05 3	0.03 8	0.16 9	1.05 4	0.97 8	1.13 7						
		MR-PRESSO	231	0.05 8	0.02 1	0.00 5	1.06 0	1.01 8	1.10 4						
		finn-a-I9_MI	Myocardial infarction	MR Egger	231	0.10 2	0.04 2	0.01 6	1.10 8	1.02 0	1.20 3	0.000	0.383	0.016	NA*
				Weighted median	231	0.09 6	0.03 1	0.00 2	1.10 1	1.03 6	1.17 1				
		Inverse variance weighted	231	0.13 4	0.02 2	0.00 0	1.14 3	1.09 5	1.19 3	0.000					
		Simple mode	231	0.15 4	0.07 6	0.04 4	1.16 7	1.00 5	1.35 5						
		Weighted mode	231	0.11 1	0.03 1	0.00 0	1.11 7	1.05 2	1.18 7						
		MR-PRESSO	231	- 0.09 1	0.08 5	0.29 5	0.91 3	0.77 3	1.08 0						
finn-a-I9_ICH	Intracerebral hemorrhage	MR Egger	231	0.01 6	0.06 0	0.79 0	1.01 6	0.90 3	1.14 3	0.945	0.232	0.113			
		Weighted median	231	0.11 1	0.05 4	0.04 1	1.11 7	1.00 4	1.24 3						
		Inverse variance weighted	231	0.07 8	0.03 1	0.01 3	1.08 1	1.01 6	1.14 9	0.942					
		Simple mode	231	0.26 2	0.12 3	0.03 5	1.29 9	1.02 1	1.65 3						
		Weighted mode	231	0.10 0	0.06 4	0.12 2	1.10 5	0.97 4	1.25 4						
		MR-PRESSO	231	0.08 9	0.10 0	0.37 3	1.09 4	0.89 9	1.33 0						
		finn-a-HEARTFAIL	Heart failure	MR Egger	231	- 0.03 8	0.03 6	0.29 2	0.96 2	0.89 6	1.03 3	0.001	0.040	0.003	0.224
				Weighted median	231	- 0.01 1	0.02 9	0.71 1	0.98 9	0.93 5	1.04 7				
		Inverse variance weighted	231	0.02 6	0.01 9	0.17 8	1.02 6	0.98 8	1.06 5	0.000					
		Simple mode	231	0.16 6	0.06 9	0.01 8	1.18 1	1.03 0	1.35 3						

		Weighted mode	231	-0.021	0.032	0.516	0.979	0.920	1.043			
		MR-PRESSO	231	0.048	0.037	0.203	1.049	0.975	1.129			
finn-a-I9_ISCHHEART	Ischemic heart disease	MR Egger	231	0.106	0.032	0.001	1.112	1.045	1.183	0.000	0.784	0.051
		Weighted median	231	0.094	0.023	0.000	1.099	1.050	1.150			
		Inverse variance weighted	231	0.114	0.016	0.000	1.120	1.085	1.157	0.000		
		Simple mode	231	0.067	0.052	0.197	1.069	0.966	1.183			
		Weighted mode	231	0.083	0.024	0.001	1.086	1.036	1.138			
		MR-PRESSO	231	0.114	0.031	0.000	1.121	1.054	1.192			
finn-a-I9_CORATHERR	Coronary atherosclerosis	MR Egger	231	0.088	0.036	0.016	1.092	1.017	1.173	0.000	0.328	0.062
		Weighted median	231	0.078	0.027	0.003	1.082	1.026	1.140			
		Inverse variance weighted	231	0.118	0.019	0.000	1.126	1.085	1.168	0.000		
		Simple mode	231	0.101	0.062	0.104	1.106	0.980	1.248			
		Weighted mode	231	0.076	0.028	0.007	1.079	1.021	1.141			
		MR-PRESSO	231	0.128	0.036	0.001	1.136	1.058	1.220			
finn-a-I9_CHD	Major coronary heart disease event	MR Egger	231	0.082	0.037	0.029	1.085	1.009	1.168	0.000	0.509	0.130
		Weighted median	231	0.123	0.026	0.000	1.131	1.074	1.191			
		Inverse variance weighted	231	0.103	0.019	0.000	1.109	1.067	1.152	0.000		
		Simple mode	231	0.196	0.066	0.003	1.216	1.069	1.383			
		Weighted mode	231	0.108	0.031	0.001	1.114	1.048	1.184			
		MR-PRESSO	231	0.082	0.036	0.023	1.086	1.012	1.164			
finn-a-I9_PAD	Peripheral artery disease	MR Egger	231	0.113	0.049	0.022	1.120	1.017	1.232	0.000	0.093	0.073
		Weighted median	231	0.165	0.036	0.000	1.180	1.099	1.266			

		Inverse variance weighted	231	0.18 3	0.02 6	0.00 0	1.20 1	1.14 3	1.26 3	0.000			
		Simple mode	231	0.10 5	0.08 8	0.23 1	1.11 1	0.93 5	1.32 0				
		Weighted mode	231	0.13 4	0.03 7	0.00 0	1.14 3	1.06 3	1.23 0				
		MR-PRESSO	231	0.15 7	0.05 6	0.00 6	1.16 9	1.04 7	1.30 6				
finn-a-I9_HYPTENSE SS	Essential hypertension	MR Egger	231	0.02 5	0.03 0	0.40 2	1.02 6	0.96 7	1.08 8	0.000	0.000	<0.001	0.842
		Weighted median	231	0.06 3	0.02 3	0.00 6	1.06 5	1.01 8	1.11 4				
		Inverse variance weighted	231	0.12 2	0.01 6	0.00 0	1.13 0	1.09 5	1.16 6	0.000			
		Simple mode	231	0.02 3	0.05 8	0.69 2	1.02 3	0.91 3	1.14 7				
		Weighted mode	231	0.01 7	0.02 0	0.39 7	1.01 7	0.97 8	1.05 9				
		MR-PRESSO	231	0.05 9	0.03 1	0.05 8	1.06 1	0.99 9	1.12 6				
finn-a-C_STROKE	Stroke	MR Egger	231	0.04 9	0.02 9	0.09 1	1.05 0	0.99 2	1.11 1	0.134	0.044	0.788	
		Weighted median	231	0.09 5	0.02 5	0.00 0	1.10 0	1.04 7	1.15 6				
		Inverse variance weighted	231	0.09 9	0.01 5	0.00 0	1.10 4	1.07 1	1.13 7	0.105			
		Simple mode	231	0.08 6	0.05 7	0.13 5	1.09 0	0.97 4	1.21 9				
		Weighted mode	231	0.11 2	0.03 4	0.00 1	1.11 9	1.04 7	1.19 6				
		MR-PRESSO	231	0.05 6	0.03 1	0.07 0	1.05 8	0.99 6	1.12 3				
finn-a-I9_STR_EXH	Ischemic stroke	MR Egger	231	0.03 3	0.03 4	0.34 6	1.03 3	0.96 6	1.10 5	0.139	0.306	0.404	
		Weighted median	231	0.07 8	0.03 0	0.00 8	1.08 1	1.02 0	1.14 6				
		Inverse variance weighted	231	0.06 3	0.01 8	0.00 0	1.06 5	1.02 8	1.10 3	0.138			
		Simple mode	231	0.12 2	0.06 6	0.06 5	1.12 9	0.99 3	1.28 4				
		Weighted mode	231	0.10 5	0.04 2	0.01 3	1.11 0	1.02 3	1.20 4				
		MR-PRESSO	231	0.03 8	0.04 1	0.35 4	1.03 9	0.95 9	1.12 5				
finn-a-I9_AF	Atrial fibrillation	MR Egger	231	- 0.06 7	0.04 2	0.11 3	0.93 5	0.86 2	1.01 6	0.000	0.024	0.009	NA*

	and fluttering												
		Weighted median	231	-0.043	0.032	0.180	0.958	0.900	1.020				
		Inverse variance weighted	231	0.015	0.022	0.505	1.015	0.972	1.060	0.000			
		Simple mode	231	0.072	0.072	0.320	1.074	0.933	1.236				
		Weighted mode	231	-0.018	0.034	0.595	0.982	0.918	1.050				
		MR-PRESSO	231	0.035	0.043	0.418	1.036	0.952	1.127				
The Global Lipids Genetics Consortium													
ieu-a-299	HDL cholesterol	MR Egger	124	0.010	0.034	0.772	1.010	0.944	1.081	0.000	0.004	<0.001	0.019
		Weighted median	124	-0.008	0.011	0.460	0.992	0.971	1.013				
		Inverse variance weighted	124	-0.075	0.019	0.000	0.928	0.894	0.962	0.000			
		Simple mode	124	-0.029	0.021	0.171	0.971	0.932	1.012				
		Weighted mode	124	0.000	0.009	0.977	1.000	0.982	1.019				
		MR-PRESSO	124	-0.077	0.017	0.000	0.926	0.896	0.957				
ieu-a-300	LDL cholesterol	MR Egger	122	0.019	0.022	0.379	1.019	0.977	1.063	0.000	0.914	<0.001	0.554
		Weighted median	122	0.018	0.011	0.106	1.018	0.996	1.040				
		Inverse variance weighted	122	0.017	0.011	0.134	1.017	0.995	1.040	0.000			
		Simple mode	122	0.008	0.021	0.683	1.008	0.969	1.050				
		Weighted mode	122	0.018	0.010	0.054	1.019	1.000	1.038				
		MR-PRESSO	122	-0.077	0.017	0.000	0.926	0.896	0.957				
ieu-a-302	Triglycerides	MR Egger	123	-0.001	0.045	0.981	0.999	0.914	1.092	0.000	0.140	<0.001	0.442
		Weighted median	123	0.028	0.010	0.008	1.028	1.007	1.049				
		Inverse variance weighted	123	0.056	0.024	0.020	1.058	1.009	1.109	0.000			

	weighte d												
	Simple mode	123	0.03 1	0.02 3	0.18 0	1.03 2	0.98 6	1.08 0					
	Weight ed mode	123	0.01 5	0.01 0	0.11 4	1.01 5	0.99 7	1.03 5					
	MR- PRESSO	123	0.02 2	0.01 0	0.03 2	1.02 3	1.00 2	1.04 4					

*No significant outliers

Table S5 The causal effect of genetically predicted FG on outcomes in different studies.

ID of outcome	Outcome	Metho ds	No. of SNP s	Bet a	SE	ρ valu e	OR	LCI	UCI	Heterogene ity ρ value	ρ value for interce pt	ρ value for MR- PRESS O	Distorti on test ρ value
ukb-d- I9_K_CARDIA C	Cardiovascul ar mortality	MR Egger	35	0.00 3	0.00 2	0.11 5	1.00 3	0.99 9	1.00 7	0.978	0.990	0.993	
		Weight ed median	35	0.00 3	0.00 1	0.05 6	1.00 3	1.00 0	1.00 6				
		Inverse variance weighte d	35	0.00 3	0.00 1	0.00 4	1.00 3	1.00 1	1.00 5	0.984			
		Simple mode	35	0.00 2	0.00 3	0.37 4	1.00 2	0.99 7	1.00 8				
		Weight ed mode	35	0.00 3	0.00 1	0.05 7	1.00 3	1.00 0	1.00 6				
ieu-a-798	Myocardial infarction	MR Egger	35	0.05 1	0.17 9	0.77 7	1.05 3	0.74 1	1.49 6	0.005	0.282	0.01	NA*
		Weight ed median	35	0.20 8	0.11 5	0.07 1	1.23 1	0.98 2	1.54 4				
		Inverse variance weighte d	35	0.21 4	0.10 0	0.03 2	1.23 9	1.01 8	1.50 8	0.004			
		Simple mode	35	0.12 7	0.19 7	0.52 5	1.13 5	0.77 1	1.67 2				
		Weight ed mode	35	0.14 4	0.10 9	0.19 4	1.15 5	0.93 3	1.42 9				
ukb-d- I9_INTRACR A	Intracranial haemorrhag e	MR Egger	35	- 0.00 1	0.00 2	0.48 0	0.99 9	0.99 5	1.00 2	0.700	0.891	0.718	
		Weight ed median	35	- 0.00 1	0.00 1	0.45 2	0.99 9	0.99 6	1.00 2				

		Inverse variance weighted	35	-	0.00	0.14	0.99	0.99	1.00	0.635			
		Simple mode	35	-	0.00	0.36	0.99	0.99	1.00				
		Weighted mode	35	-	0.00	0.45	0.99	0.99	1.00				
		MR-PRESSO	35	-	0.00	0.12	0.99	0.99	1.00				
ebi-a-GCST009541	Heart failure	MR Egger	35	0.09	0.17	0.59	1.09	0.78	1.53	0.009	0.597	0.011	NA*
		Weighted median	35	0.20	0.10	0.04	1.22	1.00	1.50				
		Inverse variance weighted	35	0.17	0.08	0.05	1.18	0.99	1.40	0.011			
		Simple mode	35	0.24	0.17	0.18	1.27	0.89	1.80				
		Weighted mode	35	0.21	0.09	0.03	1.23	1.02	1.49				
		MR-PRESSO	35	0.11	0.07	0.12	1.12	0.97	1.30				
ieu-a-7	Ischemic heart disease	MR Egger	35	0.11	0.17	0.51	1.12	0.79	1.57	0.000	0.389	0.707	
		Weighted median	35	0.23	0.09	0.01	1.26	1.04	1.52				
		Inverse variance weighted	35	0.24	0.09	0.01	1.27	1.05	1.53	0.000			
		Simple mode	35	0.15	0.18	0.41	1.16	0.81	1.67				
		Weighted mode	35	0.20	0.08	0.02	1.22	1.03	1.45				
		MR-PRESSO	35	0.24	0.09	0.01	1.27	1.05	1.53				
ukb-d-I9_CORATHERR	Coronary atherosclerosis	MR Egger	35	0.01	0.00	0.12	1.01	0.99	1.03	0.000	0.932	<0.001	0.695
		Weighted median	35	0.01	0.00	0.00	1.01	1.00	1.02				
		Inverse variance weighted	35	0.01	0.00	0.00	1.01	1.00	1.02	0.000			
		Simple mode	35	0.02	0.01	0.06	1.02	0.99	1.04				
		Weighted mode	35	0.01	0.00	0.00	1.01	1.00	1.02				
		MR-PRESSO	35	0.01	0.00	0.00	1.01	1.00	1.02				

Supplementary Material

ukb-d-19_CHD	Major coronary heart disease event	MR Egger	35	0.00 6	0.00 7	0.37 8	1.00 6	0.99 2	1.02 1	0.097	0.784	0.092
		Weighted median	35	0.01 1	0.00 5	0.02 0	1.01 1	1.00 2	1.02 0			
		Inverse variance weighted	35	0.00 8	0.00 3	0.01 7	1.00 8	1.00 1	1.01 5	0.117		
		Simple mode	35	0.01 4	0.00 9	0.14 1	1.01 4	0.99 6	1.03 2			
bbj-a-144	Peripheral artery disease	MR Egger	32	- 0.78 3	0.55 6	0.17 0	0.45 7	0.15 4	1.36 0	0.421	0.004	0.126
		Weighted median	32	0.30 1	0.35 6	0.39 8	1.35 1	0.67 2	2.71 7			
		Inverse variance weighted	32	0.79 1	0.28 1	0.00 5	2.20 6	1.27 1	3.82 7	0.105		
		Simple mode	32	1.10 5	0.57 1	0.06 2	3.01 9	0.98 6	9.24 5			
ukb-b-12493	Essential hypertension	MR Egger	35	- 0.00 8	0.01 8	0.68 0	0.99 2	0.95 7	1.02 9	0.000	0.426	<0.001 0.616
		Weighted median	35	0.00 4	0.00 8	0.62 6	1.00 4	0.98 9	1.01 9			
		Inverse variance weighted	35	0.00 5	0.00 9	0.54 7	1.00 5	0.98 8	1.02 3	0.000		
		Simple mode	35	- 0.00 3	0.01 2	0.83 2	0.99 7	0.97 4	1.02 1			
ebi-a-GCST006906	Stroke	MR Egger	34	- 0.15 8	0.17 5	0.37 3	0.85 4	0.60 7	1.20 2	0.001	0.030	<0.001 0.801
		Weighted median	34	- 0.02 2	0.11 1	0.84 3	0.97 8	0.78 7	1.21 6			
		Inverse variance	34	0.17 2	0.10 3	0.09 5	1.18 7	0.97 0	1.45 3	0.000		
		Simple mode	34	- 0.00 3	0.01 2	0.83 2	0.99 7	0.97 4	1.02 1			

				weighte d									
		Simple mode	34	- 0.01 7	0.22 2	0.93 9	0.98 3	0.63 6	1.51 9				
		Weight ed mode	34	- 0.02 9	0.09 2	0.75 3	0.97 1	0.81 1	1.16 4				
		MR- PRESSO	34	0.17 2	0.10 3	0.10 5	1.18 7	0.97 0	1.45 3				
ebi-a- GCST006908	Ischemic stroke	MR Egger	35	- 0.21 2	0.18 0	0.24 6	0.80 9	0.56 9	1.15 0	0.005	0.009	<0.001	0.399
		Weight ed median	35	- 0.06 4	0.12 7	0.61 6	0.93 8	0.73 2	1.20 3				
		Inverse variance weighte d	35	0.20 6	0.10 9	0.05 8	1.22 8	0.99 3	1.52 0	0.000			
		Simple mode	35	0.01 3	0.25 5	0.95 9	1.01 3	0.61 5	1.67 1				
		Weight ed mode	35	- 0.04 5	0.10 2	0.65 9	0.95 6	0.78 3	1.16 6				
		MR- PRESSO	35	0.20 6	0.10 9	0.06 7	1.22 8	0.99 3	1.52 0				
ebi-a- GCST006414	Atrial fibrillation and fluttering	MR Egger	35	0.02 6	0.11 5	0.82 4	1.02 6	0.81 8	1.28 6	0.002	0.423	0.002	0.36
		Weight ed median	35	- 0.07 0	0.07 8	0.36 7	0.93 2	0.80 1	1.08 6				
		Inverse variance weighte d	35	- 0.05 2	0.06 4	0.42 0	0.95 0	0.83 7	1.07 7	0.003			
		Simple mode	35	- 0.08 5	0.15 6	0.58 7	0.91 8	0.06 4	1.24 6				
		Weight ed mode	35	0.00 4	0.07 5	0.95 6	1.00 4	0.86 6	1.16 4				
		MR- PRESSO	35	- 0.05 2	0.06 4	0.42 6	0.95 0	0.83 7	1.07 7				
ukb-d- 30760_irnt	HDL cholesterol	MR Egger	35	- 0.02 6	0.08 0	0.74 9	0.97 4	0.83 3	1.14 0	0.000	0.521	<0.001	0.096
		Weight ed median	35	0.01 3	0.01 2	0.28 6	1.01 3	0.98 9	1.03 8				
		Inverse variance weighte d	35	0.02 0	0.03 8	0.60 8	1.02 0	0.94 6	1.09 9	0.000			
		Simple mode	35	0.00 3	0.02 4	0.89 8	1.00 3	0.95 7	1.05 2				
		Weight ed mode	35	0.00 8	0.01 2	0.52 9	1.00 8	0.98 4	1.03 2				
		MR- PRESSO	35	0.00 2	0.01 0	0.86 1	1.00 2	0.98 3	1.02 1				

Supplementary Material

ukb-d-30780_irnt	LDL cholesterol	MR Egger	35	-0.050	0.108	0.650	0.952	0.769	1.177	0.000	0.899	<0.001	<0.001
		Weighted median	35	-0.010	0.021	0.640	0.990	0.951	1.032				
		Inverse variance weighted	35	-0.038	0.060	0.524	0.963	0.856	1.083	0.000			
		Simple mode	35	0.046	0.043	0.283	1.048	0.964	1.139				
		Weighted mode	35	0.001	0.019	0.969	1.001	0.963	1.039				
MR-PRESSO	35	-0.038	0.060	0.528	0.963	0.856	1.083						
ukb-d-30870_irnt	Triglycerides	MR Egger	35	0.050	0.251	0.844	1.051	0.642	1.720	0.000	0.485	<0.001	<0.001
		Weighted median	35	0.125	0.028	0.000	1.133	1.073	1.196				
		Inverse variance weighted	35	-0.097	0.140	0.488	0.907	0.690	1.194	0.000			
		Simple mode	35	0.079	0.067	0.247	1.083	0.949	1.236				
		Weighted mode	35	0.101	0.021	0.000	1.106	1.061	1.153				
MR-PRESSO	35	-0.097	0.140	0.493	0.907	0.690	1.194						
ukb-d-30630_irnt	Apolipoprotein A	MR Egger	35	-0.024	0.039	0.540	0.976	0.904	1.054	0.000	0.792	<0.001	0.452
		Weighted median	35	-0.017	0.007	0.012	0.983	0.970	0.996				
		Inverse variance weighted	35	-0.016	0.004	0.470	0.984	0.976	0.993	0.000			
		Simple mode	35	-0.017	0.014	0.235	0.983	0.957	1.011				
		Weighted mode	35	-0.011	0.006	0.082	0.989	0.977	1.001				
MR-PRESSO	35	-0.016	0.022	0.474	0.984	0.944	1.027						
ukb-d-30640_irnt	Apolipoprotein B	MR Egger	35	-0.015	0.037	0.686	0.985	0.915	1.060	0.000	0.749	<0.001	0.051
		Weighted median	35	0.003	0.006	0.580	1.003	0.992	1.015				
		Inverse variance weighted	35	-0.005	0.021	0.799	0.995	0.955	1.036	0.000			

				weighte d								
		Simple mode	35	0.01 1	0.01 2	0.36 9	1.01 1	0.98 7	1.03 6			
		Weight ed mode	35	0.00 4	0.00 5	0.38 5	1.00 4	0.99 5	1.01 4			
		MR- PRESSO	35	- 0.00 5	0.02 1	0.80 1	0.99 5	0.95 5	1.03 6			
ukb-d- 30790_irnt	Lipoprotein A	MR Egger	35	- 0.00 1	0.04 1	0.97 2	0.99 9	0.92 1	1.08 3	0.040	0.624	0.06
		Weight ed median	35	- 0.03 3	0.03 0	0.27 7	0.96 8	0.91 3	1.02 7			
		Inverse variance weighte d	35	- 0.01 8	0.02 3	0.42 3	0.98 2	0.93 9	1.02 7	0.048		
		Simple mode	35	- 0.07 7	0.05 4	0.15 9	0.92 6	0.83 3	1.02 8			
		Weight ed mode	35	- 0.01 9	0.02 7	0.49 7	0.98 2	0.93 1	1.03 5			
		MR- PRESSO	35	- 0.01 8	0.02 3	0.42 8	0.98 2	0.93 9	1.02 7			
FinnGen Study												
finn-a- I9_K_CARDIA C	Cardiovascul ar mortality	MR Egger	17	0.28 7	0.49 7	0.57 2	1.33 3	0.50 3	3.53 0	0.546	0.927	0.641
		Weight ed median	17	0.16 7	0.33 6	0.62 0	1.18 1	0.61 1	2.28 3			
		Inverse variance weighte d	17	0.08 0	0.28 5	0.77 9	1.08 3	0.62 0	1.89 2	0.598		
		Simple mode	17	- 0.22 5	0.75 1	0.76 9	0.79 9	0.18 3	3.48 0			
		Weight ed mode	17	0.19 9	0.34 0	0.56 6	1.22 0	0.62 7	2.37 4			
		MR- PRESSO	17	0.15 2	0.12 4	0.22 9	1.16 4	0.91 3	1.48 5			
finn-a-I9_MI	Myocardial infarction	MR Egger	17	0.19 2	0.31 4	0.54 7	1.21 1	0.65 4	2.24 3	0.063	0.938	0.098
		Weight ed median	17	0.26 2	0.19 8	0.18 6	1.29 9	0.88 2	1.91 5			
		Inverse variance weighte d	17	0.17 0	0.15 8	0.28 1	1.18 6	0.87 0	1.61 7	0.080		
		Simple mode	17	0.22 3	0.38 8	0.57 0	1.25 0	0.58 5	2.67 1			
		Weight ed mode	17	0.27 6	0.19 1	0.15 8	1.31 8	0.90 6	1.91 7			

		MR-PRESSO	17	0.22 0	0.12 8	0.09 6	1.24 6	0.96 9	1.60 2			
finn-a-I9_ICH	Intracranial haemorrhage	MR Egger	17	3.09 9	0.95 9	0.00 6	22.1 7	3.38 6	145. 2	0.249	0.842	0.105
		Weighted median	17	2.30 8	0.69 0	0.00 1	10.0 4	2.60 0	38.8 3			
		Inverse variance weighted	17	1.13 1	0.56 3	0.04 5	3.09 9	1.02 8	9.34 0	0.289		
		Simple mode	17	- 0.00 1	1.67 9	1.00 0	0.99 9	0.03 7	26.8 2			
		Weighted mode	17	2.28 5	0.72 7	0.00 6	9.82 7	2.36 4	40.8 4			
		MR-PRESSO	17	- 0.06 8	0.21 7	0.75 7	0.93 4	0.61 0	1.43 0			
finn-a-HEARTFAIL	Heart failure	MR Egger	17	- 0.41 5	0.28 2	0.15 2	0.66 0	0.38 0	1.14 7	0.101	0.519	0.058
		Weighted median	17	- 0.28 2	0.19 8	0.15 5	0.75 5	0.51 2	1.11 3			
		Inverse variance weighted	17	- 0.25 7	0.14 3	0.07 2	0.77 4	0.58 5	1.02 3	0.113		
		Simple mode	17	0.52 1	0.41 6	0.21 9	1.68 5	0.74 6	3.80 5			
		Weighted mode	17	- 0.24 4	0.20 9	0.25 2	0.78 3	0.52 0	1.18 0			
		MR-PRESSO	17	- 0.11 0	0.12 0	0.36 2	0.89 5	0.70 8	1.13 2			
finn-a-I9_ISCHHEART	Ischemic heart disease	MR Egger	17	- 0.10 7	0.20 9	0.61 2	0.89 8	0.59 6	1.35 4	0.166	0.295	0.077
		Weighted median	17	0.04 7	0.14 5	0.74 3	1.04 8	0.79 0	1.39 2			
		Inverse variance weighted	17	0.08 5	0.10 7	0.42 9	1.08 8	0.88 2	1.34 3	0.157		
		Simple mode	17	0.08 7	0.26 1	0.74 0	1.09 1	0.65 4	1.82 2			
		Weighted mode	17	0.05 4	0.13 8	0.69 9	1.05 5	0.80 5	1.38 3			
		MR-PRESSO	17	0.14 7	0.09 3	0.12 0	1.15 9	0.96 7	1.38 9			
finn-a-I9_CORATHERR	Coronary atherosclerosis	MR Egger	17	0.18 8	0.22 9	0.41 8	1.20 7	0.77 1	1.89 0	0.244	0.904	0.231
		Weighted median	17	0.22 4	0.16 9	0.18 6	1.25 1	0.89 8	1.74 3			

		Inverse variance weighted	17	0.164	0.115	0.154	1.178	0.940	1.477	0.286			
		Simple mode	17	0.446	0.318	0.171	1.563	0.837	2.917				
		Weighted mode	17	0.275	0.167	0.110	1.316	0.949	1.827				
		MR-PRESSO	17	0.224	0.097	0.027	1.250	1.034	1.512				
finn-a-I9_CHD	Major coronary heart disease event	MR Egger	17	0.098	0.265	0.715	1.103	0.656	1.854	0.048	0.655	0.022	NA*
		Weighted median	17	0.147	0.164	0.368	1.159	0.841	1.597				
		Inverse variance weighted	17	-0.005	0.134	0.969	0.995	0.765	1.293	0.057			
		Simple mode	17	-0.180	0.296	0.546	0.835	0.468	1.490				
		Weighted mode	17	0.084	0.154	0.590	1.087	0.804	1.471				
		MR-PRESSO	17	0.121	0.113	0.294	1.128	0.903	1.409				
finn-a-I9_PAD	Peripheral artery disease	MR Egger	17	0.405	0.527	0.449	1.499	0.533	4.213	0.000	0.801	<0.001	NA*
		Weighted median	17	0.325	0.244	0.183	1.383	0.858	2.231				
		Inverse variance weighted	17	0.520	0.265	0.050	1.682	1.000	2.831	0.000			
		Simple mode	17	0.819	0.461	0.086	2.267	0.918	5.599				
		Weighted mode	17	0.380	0.230	0.108	1.462	0.932	2.293				
		MR-PRESSO	17	0.441	0.212	0.045	1.555	1.027	2.353				
finn-a-I9_HYPTENSE SS	Essential hypertension	MR Egger	17	-0.500	0.212	0.025	0.606	0.400	0.918	0.002	0.081	<0.001	0.143
		Weighted median	17	-0.251	0.113	0.026	0.778	0.623	0.971				
		Inverse variance weighted	17	-0.172	0.113	0.127	0.842	0.675	1.050	0.001			
		Simple mode	17	-0.180	0.195	0.361	0.835	0.570	1.223				
		Weighted mode	17	-0.279	0.101	0.009	0.756	0.621	0.921				

		MR- PRESSO	17	- 0.08 5	0.09 5	0.38 2	0.91 9	0.76 2	1.10 8				
finn-a- C_STROKE	Stroke	MR Egger	17	- 0.32 9	0.22 4	0.15 3	0.72 0	0.46 4	1.11 6	0.300	0.029	0.149	
		Weight ed median	17	0.05 1	0.16 0	0.75 0	1.05 2	0.76 9	1.44 1				
		Inverse variance weighte d	17	0.11 2	0.12 2	0.35 9	1.11 9	0.88 0	1.42 2	0.141			
		Simple mode	17	0.10 6	0.30 4	0.72 9	1.11 2	0.61 3	2.01 8				
		Weight ed mode	17	- 0.09 9	0.16 5	0.55 1	0.90 5	0.65 6	1.25 1				
		MR- PRESSO	17	0.12 8	0.09 7	0.19 8	1.13 6	0.93 9	1.37 5				
finn-a- I9_STR_EXH	Ischemic stroke	MR Egger	17	0.04 4	0.29 4	0.88 2	1.04 5	0.58 7	1.86 0	0.102	0.866	0.165	
		Weight ed median	17	- 0.07 4	0.19 6	0.70 8	0.92 9	0.63 2	1.36 5				
		Inverse variance weighte d	17	0.08 7	0.14 8	0.55 7	1.09 1	0.81 6	1.45 9	0.126			
		Simple mode	17	0.30 0	0.38 2	0.43 9	1.34 9	0.63 8	2.85 4				
		Weight ed mode	17	- 0.01 9	0.20 4	0.92 5	0.98 1	0.65 8	1.46 3				
		MR- PRESSO	17	0.12 4	0.12 0	0.30 8	1.13 3	0.89 5	1.43 3				
finn-a-I9_AF	Atrial fibrillation and fluttering	MR Egger	17	- 0.16 4	0.29 3	0.57 9	0.84 8	0.47 8	1.50 6	0.089	0.719	0.014	NA*
		Weight ed median	17	- 0.21 6	0.19 4	0.26 6	0.80 6	0.55 2	1.17 8				
		Inverse variance weighte d	17	- 0.25 6	0.14 8	0.08 3	0.77 4	0.58 0	1.03 4	0.107			
		Simple mode	17	- 0.01 3	0.35 2	0.97 1	0.98 7	0.49 5	1.96 7				
		Weight ed mode	17	- 0.22 2	0.20 4	0.28 6	0.80 1	0.53 7	1.19 5				
		MR- PRESSO	17	- 0.05 7	0.13 2	0.66 9	0.94 5	0.73 0	1.22 3				
The Global Lipids Genetics Consortium													
ieu-a-299	HDL cholesterol	MR Egger	35	0.03 0	0.15 3	0.84 5	1.03 0	0.76 4	1.39 0	0.000	0.716	<0.001	0.915

		Weighted median	35	0.040	0.037	0.285	1.040	0.968	1.119				
		Inverse variance weighted	35	0.077	0.083	0.357	1.080	0.917	1.271	0.000			
		Simple mode	35	0.040	0.072	0.583	1.041	0.903	1.199				
		Weighted mode	35	0.040	0.033	0.238	1.041	0.975	1.111				
		MR-PRESSO	35	0.077	0.083	0.363	1.080	0.917	1.271				
ieu-a-300	LDL cholesterol	MR Egger	35	-0.070	0.169	0.680	0.932	0.670	1.297	0.000	0.423	<0.001	0.657
		Weighted median	35	0.017	0.043	0.685	1.018	0.935	1.107				
		Inverse variance weighted	35	0.044	0.092	0.635	1.045	0.872	1.253	0.000			
		Simple mode	35	0.027	0.091	0.765	1.028	0.860	1.228				
		Weighted mode	35	0.027	0.040	0.503	1.028	0.950	1.112				
		MR-PRESSO	35	0.044	0.092	0.638	1.045	0.872	1.253				
ieu-a-302	Triglycerides	MR Egger	35	-0.070	0.281	0.804	0.932	0.538	1.616	0.000	0.671	<0.001	<0.001
		Weighted median	35	0.023	0.036	0.536	1.023	0.952	1.099				
		Inverse variance weighted	35	-0.171	0.153	0.263	0.843	0.625	1.137	0.000			
		Simple mode	35	-0.004	0.065	0.946	0.996	0.876	1.131				
		Weighted mode	35	0.020	0.029	0.501	1.020	0.963	1.080				
		MR-PRESSO	35	-0.171	0.153	0.271	0.843	0.625	1.137				

*No significant outliers

Table S6 The causal effect of genetically predicted FI on outcomes in different studies.

ID of outcome	Outcome	Methods	No. of SNPs	Beta	SE	p value	OR	LCI	UCI	Heterogeneity p value	p value for intercept	p value for MR-PRESSO	Distortion test p value
ukb-d-I9_K_CARDIA C	Cardiovascular mortality	MR Egger	18	0.018	0.016	0.279	1.018	0.987	1.050	0.415	0.376	0.434	
		Weighted median	18	0.006	0.004	0.144	1.006	0.998	1.014				
		Inverse variance weighted	18	0.004	0.003	0.216	1.004	0.998	1.009	0.428			
		Simple mode	18	0.007	0.007	0.311	1.007	0.994	1.020				
		Weighted mode	18	0.005	0.006	0.417	1.005	0.993	1.018				
ieu-a-798	Myocardial infarction	MR Egger	17	-1.531	1.390	0.292	0.216	0.014	3.297	0.005	0.251	0.006	NA*
		Weighted median	17	0.529	0.295	0.073	1.697	0.953	3.024				
		Inverse variance weighted	17	0.596	0.271	0.028	1.815	1.068	3.085	0.003			
		Simple mode	17	0.358	0.587	0.552	1.431	0.453	4.525				
		Weighted mode	17	0.300	0.508	0.565	1.350	0.499	3.654				
ukb-d-I9_INTRACRA A	Intracranial haemorrhage	MR Egger	17	-0.006	0.019	0.763	0.994	0.959	1.031	0.016	0.824	0.022	0.507
		Weighted median	17	-0.005	0.003	0.117	0.995	0.989	1.001				
		Inverse variance weighted	17	-0.002	0.003	0.597	0.998	0.993	1.004	0.023			
		Simple mode	17	-0.005	0.005	0.315	0.995	0.985	1.005				
		Weighted mode	17	-0.005	0.005	0.258	0.995	0.986	1.004				
MR-PRESSO		17	-0.004	0.002	0.110	0.996	0.991	1.001					

ebi-a-GCST009541	Heart failure	MR Egger	18	1.54 8	1.25 4	0.23 5	4.70 2	0.40 2	54.92	0.000	0.285	<0.001	
		Weighted median	18	- 0.03 6	0.18 2	0.84 2	0.96 4	0.67 5	1.379				
		Inverse variance weighted	18	0.17 9	0.20 5	0.38 4	1.19 6	0.80 0	1.788	0.000			
		Simple mode	18	- 0.01 2	0.29 3	0.96 8	0.98 8	0.55 6	1.755				
		Weighted mode	18	- 0.04 0	0.27 9	0.88 9	0.96 1	0.55 7	1.660				
		MR-PRESSO	18	0.17 9	0.20 5	0.39 6	1.19 6	0.80 0	1.788				
ieu-a-7	Ischemic heart disease	MR Egger	18	- 1.18 0	1.45 2	0.42 8	0.30 7	0.01 8	5.294	0.001	0.203	0.002	0.459
		Weighted median	18	0.81 5	0.24 6	0.00 1	2.26 0	1.39 7	3.657				
		Inverse variance weighted	18	0.72 1	0.24 3	0.00 3	2.05 7	1.27 8	3.311	0.000			
		Simple mode	18	1.29 1	0.48 7	0.01 7	3.63 6	1.40 0	9.441				
		Weighted mode	18	1.29 1	0.50 3	0.02 0	3.63 6	1.35 8	9.738				
		MR-PRESSO	18	0.72 1	0.24 3	0.00 9	2.05 7	1.27 8	3.311				
ukb-d-I9_CORATHR	Coronary atherosclerosis	MR Egger	18	- 0.14 4	0.06 1	0.03 5	0.86 6	0.76 9	0.975	0.037	0.012	<0.001	0.484
		Weighted median	18	0.04 4	0.01 4	0.00 1	1.04 5	1.01 7	1.074				
		Inverse variance weighted	18	0.03 2	0.01 4	0.02 4	1.03 3	1.00 4	1.062	0.000			
		Simple mode	18	0.06 0	0.02 6	0.03 7	1.06 2	1.00 9	1.116				
		Weighted mode	18	0.05 8	0.02 3	0.02 6	1.06 0	1.01 3	1.108				
		MR-PRESSO	18	0.04 0	0.01 1	0.00 5	1.04 1	1.01 8	1.064				
ukb-d-I9_CHD	Major coronary heart disease event	MR Egger	18	- 0.10 0	0.04 4	0.04 1	0.90 5	0.83 0	0.985	0.209	0.015	0.016	NA*
		Weighted median	18	0.02 4	0.01 1	0.03 2	1.02 4	1.00 2	1.047				
		Inverse variance	18	0.02 1	0.01 0	0.03 9	1.02 1	1.00 1	1.041	0.017			

				e weighte d								
		Simple mode	18	0.02 9	0.02 2	0.22 0	1.02 9	0.98 5	1.076			
		Weighted mode	18	0.02 3	0.02 1	0.28 9	1.02 4	0.98 2	1.067			
		MR-PRESSO	18	0.02 1	0.01 0	0.06 0	1.02 1	1.00 1	1.041			
bbj-a-144	Peripheral artery disease	MR Egger	17	1.12 1	3.64 7	0.76 3	3.06 8	0.00 2	3901. 3	0.094	0.964	0.141
		Weighted median	17	1.96 9	0.64 1	0.00 2	7.16 3	2.03 9	25.16			
		Inverse variance	17	1.28 5	0.44 5	0.00 4	3.61 4	1.51 0	8.650	0.126		
				e weighte d								
		Simple mode	17	2.22 3	0.91 6	0.02 7	9.23 6	1.53 5	55.56			
		Weighted mode	17	2.16 0	0.91 3	0.03 1	8.67 5	1.44 9	51.93			
		MR-PRESSO	17	1.28 5	0.52 9	0.02 7	3.61 4	1.28 2	10.18			
ukb-b-12493	Essential hypertension	MR Egger	18	0.08 7	0.11 5	0.46 7	1.09 1	0.87 0	1.367	0.000	0.984	<0.001 0.326
		Weighted median	18	0.09 5	0.02 1	0.00 0	1.10 0	1.05 6	1.146			
		Inverse variance	18	0.08 9	0.02 1	0.00 0	1.09 3	1.05 0	1.138	0.000		
				e weighte d								
		Simple mode	18	0.13 8	0.03 7	0.00 3	1.14 8	1.06 7	1.235			
		Weighted mode	18	0.13 6	0.03 5	0.00 2	1.14 6	1.06 9	1.228			
		MR-PRESSO	18	0.11 1	0.01 8	0.00 0	1.11 7	1.07 8	1.158			
ebi-a-GCST006906	Stroke	MR Egger	17	0.12 1	1.10 6	0.91 5	1.12 8	0.12 9	9.868	0.084	0.931	0.123
		Weighted median	17	0.17 3	0.21 8	0.43 0	1.18 8	0.77 4	1.823			
		Inverse variance	17	0.19 6	0.18 8	0.29 8	1.21 6	0.84 1	1.759	0.113		
				e weighte d								
		Simple mode	17	0.34 4	0.34 6	0.33 6	1.41 0	0.71 5	2.781			
		Weighted mode	17	0.23 5	0.35 5	0.51 7	1.26 5	0.63 1	2.537			
		MR-PRESSO	17	0.02 4	0.18 2	0.89 7	1.02 4	0.71 7	1.464			

ebi-a-GCST006908	Ischemic stroke	MR Egger	17	-	1.16	0.89	0.85	0.08	8.445	0.356	0.945	0.155	
				0.15	6	8	9	7					
				1									
		Weighted median	17	0.25	0.22	0.24	1.29	0.84	1.991				
		Inverse variance weighted	17	0.14	0.18	0.43	1.15	0.80	1.670	0.434			
		Simple mode	17	0.47	0.36	0.20	1.60	0.79	3.267				
			6	1	7	9	2						
		Weighted mode	17	0.35	0.36	0.34	1.42	0.69	2.935				
				5	8	9	6	3					
		MR-PRESSO	17	0.01	0.19	0.93	1.01	0.69	1.479				
				7	1	1	7	9					
ebi-a-GCST006414	Atrial fibrillation and fluttering	MR Egger	17	0.33	1.13	0.77	1.40	0.15	12.95	0.000	0.720	<0.001	0.547
				7	5	1	1	1					
				Weighted median	17	-	0.17	0.41	0.86	0.61	1.219		
						0.14	4	2	7	7			
						3							
				Inverse variance weighted	17	-	0.18	0.70	0.93	0.64	1.339	0.000	
				0.07	5	1	1	8					
				1									
		Simple mode	17	-	0.30	0.28	0.71	0.39	1.291				
				0.33	1	3	6	7					
				4									
		Weighted mode	17	-	0.31	0.36	0.74	0.40	1.387				
				0.29	7	7	5	0					
				4									
		MR-PRESSO	17	-	0.18	0.70	0.93	0.64	1.339				
				0.07	5	6	1	8					
				1									
ukb-d-30760_irnt	HDL cholesterol	MR Egger	18	-	0.55	0.61	0.74	0.25	2.231	0.000	0.913	<0.001	0.746
				0.29	7	0	8	1					
				0									
		Weighted median	18	-	0.03	0.00	0.81	0.75	0.881				
					0.20	8	0	8	9				
					1								
		Inverse variance weighted	18	-	0.08	0.00	0.70	0.59	0.837	0.000			
				0.35	8	0	4	3					
				1									
		Simple mode	18	-	0.07	0.00	0.68	0.59	0.795				
				0.37	5	0	7	3					
				6									
		Weighted mode	18	-	0.09	0.07	0.83	0.69	1.002				
				0.18	5	0	3	2					
				3									
		MR-PRESSO	18	-	0.08	0.00	0.70	0.59	0.837				
				0.35	8	1	4	3					
				1									
ukb-d-30780_irnt	LDL cholesterol	MR Egger	18	-	0.89	0.02	0.10	0.01	0.578	0.000	0.030	<0.001	1
				2.29	2	0	1	8					
				5									

Supplementary Material

		Weighted median	18	-0.005	0.072	0.943	0.995	0.864	1.146	0.000			
		Inverse variance weighted	18	-0.204	0.164	0.213	0.816	0.592	1.124				
		Simple mode	18	0.044	0.123	0.724	1.045	0.821	1.331				
		Weighted mode	18	-0.003	0.092	0.977	0.997	0.832	1.195				
		MR-PRESSO	18	-0.204	0.164	0.230	0.816	0.592	1.124				
ukb-d-30870_irt	Triglycerides	MR Egger	18	-3.583	2.768	0.214	0.028	0.000	6.314	0.000	0.176	<0.001	1
		Weighted median	18	0.209	0.091	0.022	1.232	1.031	1.473				
		Inverse variance weighted	18	0.283	0.464	0.541	1.328	0.535	3.294	0.000			
		Simple mode	18	0.335	0.252	0.201	1.398	0.853	2.290				
		Weighted mode	18	0.064	0.065	0.343	1.066	0.938	1.211				
		MR-PRESSO	18	0.283	0.464	0.549	1.328	0.535	3.294				
ukb-d-30630_irt	Apolipoprotein A	MR Egger	18	-0.387	0.327	0.254	0.679	0.358	1.288	0.000	0.646	<0.001	0.343
		Weighted median	18	-0.109	0.028	0.000	0.896	0.849	0.947				
		Inverse variance weighted	18	-0.236	0.052	0.000	0.790	0.713	0.874	0.000			
		Simple mode	18	-0.294	0.051	0.000	0.746	0.674	0.824				
		Weighted mode	18	-0.065	0.039	0.111	0.937	0.868	1.011				
		MR-PRESSO	18	-0.236	0.052	0.000	0.790	0.713	0.874				
ukb-d-30640_irt	Apolipoprotein B	MR Egger	18	-0.638	0.317	0.041	0.528	0.284	0.983	0.000	0.068	<0.001	<0.001
		Weighted median	18	0.037	0.022	0.097	1.038	0.993	1.085				
		Inverse variance weighted	18	-0.025	0.056	0.655	0.975	0.874	1.088	0.000			

		weighte d											
		Simple mode	18	0.09 3	0.03 0	0.00 6	1.09 8	1.03 5	1.163				
		Weight ed mode	18	0.08 0	0.03 0	0.01 7	1.08 3	1.02 1	1.149				
		MR- PRESSO	18	- 0.02 5	0.05 6	0.66 1	0.97 5	0.87 4	1.088				
ukb-d- 30790_irnt	Lipoprotein A	MR Egger	18	0.14 1	0.36 0	0.70 1	1.15 1	0.56 9	2.331	0.017	0.448	0.017	NA*
		Weight ed median	18	- 0.08 1	0.06 6	0.22 4	0.92 3	0.81 0	1.051				
		Inverse varianc e weighte d	18	- 0.13 5	0.05 8	0.01 9	0.87 3	0.78 0	0.978	0.018			
		Simple mode	18	- 0.08 5	0.14 4	0.56 5	0.91 9	0.69 2	1.219				
		Weight ed mode	18	- 0.06 7	0.12 3	0.59 3	0.93 5	0.73 4	1.191				
		MR- PRESSO	18	- 0.13 5	0.05 8	0.03 2	0.87 3	0.78 0	0.978				
FinnGen Study													
finn-a- I9_K_CARDIA C	Cardiovascul ar mortality	MR Egger	18	1.57 2	1.77 5	0.38 9	4.81 7	0.14 9	156.1	0.384	0.498	0.420	
		Weight ed median	18	0.52 0	0.39 6	0.18 9	1.68 2	0.77 4	3.656				
		Inverse varianc e weighte d	18	0.35 9	0.29 4	0.22 1	1.43 2	0.80 6	2.546	0.419			
		Simple mode	18	0.54 6	0.82 8	0.51 8	1.72 7	0.34 1	8.742				
		Weight ed mode	18	0.74 4	0.73 0	0.32 2	2.10 4	0.50 3	8.793				
		MR- PRESSO	18	0.35 9	0.29 4	0.23 8	1.43 2	0.80 6	2.546				
finn-a-I9_MI	Myocardial infarction	MR Egger	18	- 1.22 0	2.11 8	0.57 3	0.29 5	0.00 5	18.73	0.005	0.331	0.003	0.111
		Weight ed median	18	0.70 3	0.37 1	0.05 8	2.01 9	0.97 6	4.174				
		Inverse varianc e weighte d	18	0.87 3	0.35 6	0.01 4	2.39 3	1.19 2	4.805	0.004			
		Simple mode	18	0.55 7	0.72 7	0.45 4	1.74 6	0.42 0	7.262				

		Weighted mode	18	0.576	0.728	0.440	1.779	0.427	7.411				
		MR-PRESSO	18	0.873	0.356	0.025	2.393	1.192	4.805				
finn-a-I9_ICH	Intracranial haemorrhage	MR Egger	18	-4.098	2.553	0.128	0.017	0.000	2.473	0.726	0.096	0.596	
		Weighted median	18	0.867	0.584	0.138	2.380	0.757	7.480				
		Inverse variance weighted	18	0.354	0.428	0.408	1.425	0.616	3.300	0.567			
		Simple mode	18	0.858	1.025	0.414	2.359	0.317	17.57				
		Weighted mode	18	0.878	0.999	0.392	2.406	0.339	100.6				
		MR-PRESSO	18	0.354	0.408	0.397	1.425	0.641	3.168				
finn-a-HEARTFAIL	Heart failure	MR Egger	18	1.518	1.579	0.351	4.563	0.207	100.6	0.131	0.591	0.167	
		Weighted median	18	0.574	0.338	0.089	1.775	0.916	3.441				
		Inverse variance weighted	18	0.665	0.259	0.010	1.945	1.170	3.234	0.155			
		Simple mode	18	0.846	0.691	0.237	2.330	0.602	9.018				
		Weighted mode	18	0.526	0.726	0.479	1.692	0.407	7.026				
		MR-PRESSO	18	0.665	0.259	0.020	1.945	1.170	3.234				
finn-a-I9_ISCHHEART	Ischemic heart disease	MR Egger	18	-1.985	1.948	0.324	0.137	0.003	6.261	0.000	0.186	<0.001	0.438
		Weighted median	18	0.577	0.294	0.049	1.781	1.002	3.167				
		Inverse variance weighted	18	0.669	0.336	0.046	1.952	1.011	3.771	0.000			
		Simple mode	18	0.984	0.733	0.197	2.674	0.636	11.25				
		Weighted mode	18	1.018	0.756	0.196	2.767	0.629	12.17				
		MR-PRESSO	18	0.669	0.336	0.063	1.952	1.011	3.771				
finn-a-I9_CORATHERR	Coronary atherosclerosis	MR Egger	18	-1.342	1.972	0.506	0.261	0.005	12.46	0.000	0.299	<0.001	0.305

		Weighted median	18	0.783	0.329	0.017	2.188	1.149	4.170				
		Inverse variance weighted	18	0.745	0.332	0.025	2.106	1.097	4.040	0.000			
		Simple mode	18	1.015	0.680	0.154	2.760	0.728	10.45				
		Weighted mode	18	1.120	0.641	0.099	3.066	0.873	10.76				
		MR-PRESSO	18	0.745	0.332	0.039	2.106	1.097	4.040				
finn-a-I9_CHD	Major coronary heart disease event	MR Egger	18	-2.990	1.935	0.142	0.050	0.001	2.233	0.000	0.085	<0.001	0.244
		Weighted median	18	0.608	0.337	0.071	1.837	0.949	3.554				
		Inverse variance weighted	18	0.517	0.347	0.137	1.676	0.849	3.309	0.000			
		Simple mode	18	1.261	0.722	0.099	3.527	0.857	14.52				
		Weighted mode	18	1.104	0.778	0.174	3.015	0.657	13.84				
		MR-PRESSO	18	0.517	0.347	0.155	1.676	0.849	3.309				
finn-a-I9_PAD	Peripheral artery disease	MR Egger	18	-1.732	2.180	0.438	0.177	0.002	12.67	0.052	0.246	0.048	NA*
		Weighted median	18	1.079	0.420	0.010	2.941	1.292	6.697				
		Inverse variance weighted	18	0.855	0.371	0.021	2.351	1.136	4.865	0.039			
		Simple mode	18	1.024	0.630	0.123	2.784	0.809	9.578				
		Weighted mode	18	1.044	0.588	0.094	2.840	0.897	8.987				
		MR-PRESSO	18	0.855	0.371	0.034	2.351	1.136	4.865				
finn-a-I9_HYPTENS ESS	Essential hypertension	MR Egger	18	-0.101	1.806	0.956	0.904	0.026	31.15	0.000	0.556	<0.001	0.364
		Weighted median	18	1.363	0.259	0.000	3.908	2.351	6.498				
		Inverse variance weighted	18	0.969	0.297	0.001	2.634	1.471	4.719	0.000			

		Simple mode	18	1.60 4	0.37 0	0.00 0	4.97 3	2.41 0	10.26				
		Weighted mode	18	1.60 4	0.49 3	0.00 5	4.97 3	1.89 1	13.07				
		MR-PRESSO	18	0.96 9	0.29 7	0.00 5	2.63 4	1.47 1	4.719				
finn-a-C_STROKE	Stroke	MR Egger	18	- 2.53 9	1.28 2	0.06 5	0.07 9	0.00 6	0.973	0.244	0.024	0.075	
		Weighted median	18	0.38 4	0.28 2	0.17 4	1.46 7	0.84 4	2.552				
		Inverse variance weighted	18	0.61 7	0.24 6	0.01 2	1.85 3	1.14 4	3.004	0.057			
		Simple mode	18	0.28 4	0.50 6	0.58 2	1.32 9	0.49 3	3.583				
		Weighted mode	18	0.23 8	0.49 2	0.63 5	1.26 8	0.48 4	3.326				
		MR-PRESSO	18	0.61 7	0.24 6	0.02 3	1.85 3	1.14 4	3.004				
finn-a-I9_STR_EXH	Ischemic stroke	MR Egger	18	0.13 6	1.39 6	0.92 3	1.14 6	0.07 4	17.67	0.645	0.648	0.703	
		Weighted median	18	0.79 1	0.32 1	0.01 4	2.20 5	1.17 6	4.134				
		Inverse variance weighted	18	0.77 7	0.23 4	0.00 1	2.17 5	1.37 4	3.441	0.696			
		Simple mode	18	0.97 0	0.56 7	0.10 5	2.63 8	0.86 8	8.016				
		Weighted mode	18	0.86 4	0.52 5	0.11 8	2.37 3	0.84 8	6.640				
		MR-PRESSO	18	0.77 7	0.20 9	0.00 2	2.17 5	1.44 3	3.278				
finn-a-I9_AF	Atrial fibrillation and fluttering	MR Egger	18	1.93 8	1.85 3	0.31 1	6.94 4	0.18 4	262.3	0.023	0.495	0.027	NA*
		Weighted median	18	0.62 4	0.35 9	0.08 2	1.86 6	0.92 3	3.774				
		Inverse variance weighted	18										
		Simple mode	18	0.63 6	0.67 7	0.36 1	1.88 8	0.50 1	7.114				
		Weighted mode	18	0.68 5	0.64 5	0.30 3	1.98 4	0.56 0	7.022				
		MR-PRESSO	18	0.66 1	0.30 6	0.04 6	1.93 7	1.06 2	3.531				

The Global Lipids

Genetics Consortium														
ieu-a-299	HDL cholesterol	MR Egger	18	-	1.33	0.66	0.55	0.04	7.603	0.000	0.772	<0.001	0.513	
				0.58	5	6	6	1						
				7										
		Weighted median	18	-	0.12	0.00	0.41	0.32	0.532					
				0.87	4	0	8	8						
				3										
		Inverse variance weighted	18	-	0.21	0.00	0.37	0.24	0.575	0.000				
		0.97	6	0	7	7								
		6												
Simple mode	18	-	0.23	0.00	0.33	0.21	0.528							
		1.09	4	0	3	0								
		9												
Weighted mode	18	-	0.23	0.00	0.43	0.27	0.697							
		0.82	9	3	7	4								
		9												
MR-PRESSO	18	-	0.21	0.00	0.37	0.24	0.575							
		0.97	6	0	7	7								
		6												
ieu-a-300	LDL cholesterol	MR Egger	18	-	1.22	0.03	0.06	0.00	0.681	0.000	0.046	<0.001	0.001	
				2.78	6	7	2	6						
				6										
		Weighted median	18	-	0.11	0.98	0.99	0.79	1.246					
				0.00	3	6	8	9						
				2										
		Inverse variance weighted	18	-	0.22	0.44	0.84	0.54	1.305	0.000				
		0.17	4	1	2	3								
		2												
Simple mode	18	0.12	0.17	0.46	1.13	0.81	1.591							
		7	2	9	6	1								
Weighted mode	18	0.09	0.13	0.50	1.09	0.84	1.414							
		0	1	1	4	7								
MR-PRESSO	18	-	0.22	0.45	0.84	0.54	1.305							
		0.17	4	2	2	3								
		2												
ieu-a-302	Triglycerides	MR Egger	18	-	2.85	0.35	0.06	0.00	18.01	0.000	0.306	<0.001	1	
				2.71	8	7	6	0						
				1										
		Weighted median	18	0.66	0.11	0.00	1.94	1.56	2.415					
				5	1	0	4	6						
		Inverse variance weighted	18	0.27	0.47	0.56	1.31	0.51	3.308	0.000				
		1	2	6	1	9								
Simple mode	18	0.69	0.27	0.02	1.99	1.16	3.407							
		1	3	2	5	8								
Weighted mode	18	0.52	0.21	0.02	1.68	1.11	2.536							
		0	0	4	1	5								
MR-PRESSO	18	0.27	0.47	0.57	1.31	0.51	3.308							
		1	2	4	1	9								

*No significant outliers

Table S7 The causal effect of genetically predicted HbA_{1c} on outcomes in different studies.

ID of outcome	Outcome	Methods	No. of SNPs	Beta	SE	ρ value	OR	LCI	UCI	Heterogeneity ρ value	ρ value for intercept	ρ value for MR-PRESSO	Distortion test ρ value
ukb-d-I9_K_CARDIAC	Cardiovascular mortality	MR Egger	34	-0.001	0.003	0.723	0.999	0.993	1.005	0.792	0.162	0.504	
		Weighted median	34	0.001	0.002	0.560	1.001	0.997	1.006				
		Inverse variance weighted	34	0.002	0.002	0.124	1.002	0.999	1.006	0.743			
		Simple mode	34	0.005	0.004	0.228	1.005	0.997	1.014				
		Weighted mode	34	0.000	0.002	0.973	1.000	0.995	1.005				
ieu-a-798	Myocardial infarction	MR Egger	34	0.531	0.511	0.306	1.701	0.625	4.627	0.000	0.520	<0.001	0.537
		Weighted median	34	0.389	0.169	0.021	1.475	1.059	2.055				
		Inverse variance weighted	34	0.222	0.110	0.043	1.249	1.007	1.550	0.000			
		Simple mode	34	0.271	0.279	0.338	1.311	0.759	2.266				
		Weighted mode	34	0.302	0.189	0.119	1.353	0.934	1.959				
ukb-d-I9_INTRACRAA	Intracranial haemorrhage	MR Egger	34	-0.001	0.003	0.604	0.999	0.994	1.004	0.783	0.885	0.811	
		Weighted median	34	0.000	0.002	0.910	1.000	0.996	1.004				
		Inverse variance weighted	34	-0.001	0.001	0.464	0.999	0.996	1.002	0.818			
		Simple mode	34	-0.003	0.003	0.310	0.997	0.990	1.003				
		Weighted mode	34	-0.001	0.002	0.696	0.999	0.995	1.003				
ebi-a-GCST009541	Heart failure	MR Egger	31	0.266	0.251	0.299	1.304	0.797	2.134	0.000	0.075	<0.001	0.839
		MR-PRESSO	34	-0.001	0.001	0.485	0.999	0.997	1.002				
		Weighted median	34	0.000	0.002	0.910	1.000	0.996	1.004				
		Inverse variance weighted	34	-0.001	0.001	0.464	0.999	0.996	1.002	0.818			
		Simple mode	34	-0.003	0.003	0.310	0.997	0.990	1.003				

		Weighted median	31	0.002	0.133	0.988	1.002	0.772	1.301				
		Inverse variance weighted	31	-0.120	0.145	0.408	0.887	0.667	1.179	0.000			
		Simple mode	31	-0.263	0.202	0.203	0.768	0.517	1.142				
		Weighted mode	31	-0.017	0.130	0.898	0.983	0.763	1.268				
		MR-PRESSO	31	-0.120	0.141	0.400	0.887	0.673	1.169				
ieu-a-7	Ischemic heart disease	MR Egger	34	0.533	0.241	0.055	1.704	1.062	2.733	0.625	0.286	<0.001	0.309
		Weighted median	34	0.319	0.127	0.012	1.376	1.072	1.765				
		Inverse variance weighted	34	0.283	0.099	0.004	1.327	1.094	1.611	0.590			
		Simple mode	34	0.294	0.196	0.165	1.342	0.913	1.973				
		Weighted mode	34	0.322	0.152	0.061	1.380	1.024	1.860				
		MR-PRESSO	34	0.353	0.195	0.079	1.423	0.970	2.087				
ukb-d-I9_CORATHE R	Coronary atherosclerosis	MR Egger	34	0.004	0.013	0.744	1.004	0.980	1.030	0.000	0.467	0.102	
		Weighted median	34	0.011	0.006	0.063	1.011	0.999	1.024				
		Inverse variance weighted	34	0.019	0.006	0.001	1.019	1.008	1.031	0.000			
		Simple mode	34	0.015	0.011	0.205	1.015	0.993	1.038				
		Weighted mode	34	0.012	0.006	0.068	1.012	1.000	1.025				
		MR-PRESSO	34	0.015	0.006	0.018	1.015	1.003	1.026				
ukb-d-I9_CHD	Major coronary heart disease event	MR Egger	34	-0.007	0.011	0.513	0.993	0.971	1.015	0.000	0.955	<0.001	0.305
		Weighted median	34	-0.012	0.006	0.059	0.988	0.976	1.000				
		Inverse variance weighted	34	-0.007	0.006	0.255	0.993	0.981	1.005	0.000			
		Simple mode	34	0.022	0.013	0.084	1.023	0.998	1.048				

		Weighted mode	34	-0.013	0.007	0.068	0.987	0.973	1.001				
		MR-PRESSO	34	-0.001	0.005	0.805	0.999	0.989	1.008				
bbj-a-144	Peripheral artery disease	MR Egger	28	0.911	1.184	0.449	2.486	0.244	25.32	0.027	0.522	0.021	NA*
		Weighted median	28	0.776	0.556	0.163	2.172	0.731	6.455				
		Inverse variance weighted	28	0.200	0.447	0.654	1.222	0.508	2.937	0.031			
		Simple mode	28	1.803	0.940	0.066	6.066	0.961	38.30				
		Weighted mode	28	1.020	0.618	0.110	2.773	0.826	9.310				
		MR-PRESSO	28	0.231	0.393	0.561	1.260	0.583	2.722				
ukb-b-12493	Essential hypertension	MR Egger	34	0.013	0.034	0.700	1.013	0.948	1.083	0.000	0.686	<0.001	0.562
		Weighted median	34	0.030	0.010	0.005	1.030	1.009	1.051				
		Inverse variance weighted	34	0.002	0.018	0.929	1.002	0.966	1.038	0.000			
		Simple mode	34	0.027	0.015	0.082	1.027	0.998	1.057				
		Weighted mode	34	0.027	0.010	0.012	1.027	1.007	1.047				
		MR-PRESSO	34	0.022	0.009	0.023	1.022	1.004	1.041				
ebi-a-GCST006906	Stroke	MR Egger	33	-0.173	0.302	0.571	0.841	0.465	1.521	0.000	0.920	<0.001	0.304
		Weighted median	33	-0.043	0.145	0.769	0.958	0.721	1.273				
		Inverse variance weighted	33	-0.148	0.162	0.362	0.863	0.628	1.185	0.000			
		Simple mode	33	-0.187	0.276	0.503	0.829	0.482	1.426				
		Weighted mode	33	-0.120	0.159	0.456	0.887	0.649	1.211				
		MR-PRESSO	33	-0.088	0.151	0.562	0.916	0.682	1.230				
ebi-a-GCST006908	Ischemic stroke	MR Egger	33	-0.141	0.345	0.686	0.869	0.442	1.708	0.000	0.946	<0.001	0.259

		Weighted median	33	-0.052	0.167	0.756	0.949	0.684	1.318				
		Inverse variance weighted	33	-0.161	0.185	0.384	0.851	0.593	1.223	0.000			
		Simple mode	33	-0.031	0.287	0.915	0.970	0.552	1.702				
		Weighted mode	33	-0.107	0.172	0.539	0.899	0.642	1.258				
		MR-PRESSO	33	-0.092	0.172	0.597	0.912	0.651	1.278				
ebi-a-GCST006414	Atrial fibrillation and fluttering	MR Egger	33	-0.043	0.176	0.810	0.958	0.679	1.352	0.002	0.883	0.008	0.733
		Weighted median	33	-0.096	0.105	0.358	0.908	0.739	1.115				
		Inverse variance weighted	33	-0.064	0.093	0.490	0.938	0.781	1.126	0.003			
		Simple mode	33	-0.148	0.177	0.410	0.862	0.609	1.221				
		Weighted mode	33	-0.102	0.115	0.384	0.903	0.721	1.132				
		MR-PRESSO	33	-0.091	0.085	0.295	0.913	0.773	1.080				
ukb-d-30760_irt	HDL cholesterol	MR Egger	34	0.070	0.060	0.252	1.072	0.953	1.206	0.000	0.204	<0.001	0.894
		Weighted median	34	0.023	0.015	0.114	1.024	0.994	1.054				
		Inverse variance weighted	34	0.005	0.033	0.885	1.005	0.941	1.072	0.000			
		Simple mode	34	0.033	0.023	0.154	1.034	0.989	1.081				
		Weighted mode	34	0.025	0.014	0.081	1.025	0.998	1.053				
		MR-PRESSO	34	0.000	0.030	0.997	1.000	0.943	1.061				
ukb-d-30780_irt	LDL cholesterol	MR Egger	34	0.307	0.184	0.104	1.360	0.949	1.949	0.000	0.436	<0.001	<0.001
		Weighted median	34	0.171	0.037	0.000	1.186	1.102	1.276				
		Inverse variance weighted	34	0.186	0.021	0.000	1.205	1.157	1.255	0.000			
		Simple mode	34	0.048	0.072	0.514	1.049	0.910	1.209				

Supplementary Material

		Weighted mode	34	0.140	0.034	0.000	1.150	1.076	1.230				
		MR-PRESSO	34	0.169	0.095	0.085	1.184	0.982	1.426				
ukb-d-30870_irtt	Triglycerides	MR Egger	34	-0.129	0.126	0.315	0.879	0.686	1.126	0.000	0.069	<0.001	<0.001
		Weighted median	34	-0.023	0.039	0.564	0.978	0.906	1.056				
		Inverse variance weighted	34	0.070	0.072	0.329	1.073	0.932	1.235	0.000			
		Simple mode	34	0.051	0.064	0.436	1.052	0.928	1.193				
		Weighted mode	34	-0.009	0.032	0.779	0.991	0.930	1.056				
		MR-PRESSO	34	0.121	0.076	0.121	1.129	0.972	1.310				
ukb-d-30630_irtt	Apolipoprotein A	MR Egger	34	0.037	0.041	0.364	1.038	0.959	1.124	0.000	0.150	<0.001	0.791
		Weighted median	34	0.005	0.011	0.670	1.005	0.983	1.026				
		Inverse variance weighted	34	-0.013	0.023	0.573	0.987	0.944	1.032	0.000			
		Simple mode	34	0.001	0.018	0.935	1.001	0.967	1.037				
		Weighted mode	34	0.001	0.010	0.881	1.001	0.983	1.021				
		MR-PRESSO	34	-0.012	0.021	0.575	0.988	0.949	1.030				
ukb-d-30640_irtt	Apolipoprotein B	MR Egger	34	0.071	0.042	0.097	1.074	0.990	1.165	0.000	0.637	<0.001	<0.001
		Weighted median	34	0.045	0.010	0.000	1.046	1.025	1.067				
		Inverse variance weighted	34	0.055	0.022	0.015	1.056	1.011	1.104	0.000			
		Simple mode	34	0.033	0.020	0.096	1.034	0.995	1.074				
		Weighted mode	34	0.040	0.009	0.000	1.041	1.022	1.060				
		MR-PRESSO	34	0.051	0.022	0.024	1.053	1.009	1.099				
ukb-d-30790_irtt	Lipoprotein A	MR Egger	34	0.018	0.055	0.749	1.018	0.913	1.134	0.195	0.713	0.005	0.072
		Weighted median	34	0.017	0.043	0.690	1.017	0.935	1.107				
		Inverse variance	34	0.001	0.030	0.983	1.001	0.944	1.061	0.225			

				weighte									
				d									
		Simple	34	-	0.07	0.76	0.97	0.84	1.12				
		mode		0.02	3	3	8	7	9				
				2									
		Weight	34	0.02	0.04	0.62	1.02	0.94	1.10				
		ed		0	2	8	1	0	8				
		mode											
		MR-	34										
		PRESSO											
FinnGen													
Study													
finn-a-	Cardiovascul	MR	31	0.01	0.39	0.97	1.01	0.46	2.19	0.829		0.466	0.486
I9_K_CARDIA	ar mortality	Egger		4	4	1	4	9	4				
C													
		Weight	31	-	0.29	0.69	0.89	0.50	1.58				
		ed		0.11	5	8	2	1	9				
		median		4									
		Inverse	31	-	0.20	0.26	0.79	0.52	1.19	0.842			
		variance		0.23	8	4	3	7	2				
		weighte		2									
		d											
		Simple	31	-	0.47	0.79	0.88	0.34	2.23				
		mode		0.12	5	0	0	7	2				
				8									
		Weight	31	0.02	0.32	0.93	1.02	0.54	1.92				
		ed		7	1	3	8	8	6				
		mode											
		MR-	31	-	0.19	0.53	0.88	0.60	1.29				
		PRESSO		0.12	3	3	5	6	4				
				2									
finn-a-I9_MI	Myocardial	MR	31	0.46	0.45	0.32	1.58	0.64	3.87	0.002		0.338	0.001
	infarction	Egger		0	6	1	5	8	7				0.108
		Weight	31	0.29	0.25	0.25	1.34	0.81	2.22				
		ed		6	8	1	5	1	9				
		median											
		Inverse	31	0.08	0.24	0.72	1.08	0.67	1.74	0.002			
		variance		4	2	9	7	7	6				
		weighte											
		d											
		Simple	31	0.23	0.41	0.57	1.26	0.56	2.85				
		mode		5	5	5	5	1	3				
		Weight	31	0.32	0.26	0.23	1.38	0.81	2.33				
		ed		5	8	5	3	9	7				
		mode											
		MR-	31	0.00	0.22	0.97	1.00	0.65	1.56				
		PRESSO		8	4	0	9	1	3				
finn-a-	Intracranial	MR	31	-	0.58	0.41	0.61	0.19	1.93	0.819		0.712	0.741
I9_ICH	haemorrhage	Egger		0.48	2	3	7	7	1				
				3									
		Weight	31	-	0.47	0.46	0.70	0.27	1.80				
		ed		0.34	8	7	6	7	3				
		median		8									
		Inverse	31	-	0.30	0.33	0.74	0.40	1.35	0.847			
		variance		0.29	9	2	2	5	8				
		weighte		9									
		d											
		Simple	31	-	0.85	0.29	0.40	0.07	2.13				
		mode		0.90	0	4	3	6	3				
				9									
		Weight	31	-	0.51	0.53	0.72	0.26	1.98				
		ed		0.32	7	1	1	2	5				
		mode		8									

		MR-PRESSO	31	-	0.26	0.28	0.75	0.44	1.26				
				0.28	3	6	2	9	0				
				5									
finn-a-HEARTFAIL	Heart failure	MR Egger	31	0.11	0.39	0.78	1.11	0.51	2.41	0.012	0.349	0.005	0.173
				0	3	3	6	6	2				
		Weighted median	31	0.11	0.23	0.64	1.11	0.70	1.77				
				0	8	4	6	1	8				
		Inverse variance weighted	31	-	0.20	0.31	0.81	0.54	1.22	0.011			
				0.20	9	9	2	0	2				
				8									
		Simple mode	31	0.26	0.37	0.48	1.30	0.62	2.72				
				5	5	6	3	4	0				
		Weighted mode	31	0.09	0.24	0.71	1.09	0.67	1.77				
				1	6	5	5	6	5				
		MR-PRESSO	31	-	0.19	0.32	0.82	0.55	1.21				
				0.19	9	7	0	5	2				
				8									
finn-a-I9_ISCHHEART	Ischemic heart disease	MR Egger	31	0.16	0.36	0.66	1.17	0.57	2.38	0.000	0.853	<0.001	0.151
				0	3	3	3	6	8				
		Weighted median	31	0.10	0.17	0.54	1.11	0.79	1.56				
				6	3	0	2	2	2				
		Inverse variance weighted	31	0.10	0.18	0.59	1.10	0.76	1.60	0.000			
				2	9	0	8	4	5				
		Simple mode	31	0.24	0.29	0.40	1.28	0.72	2.27				
				9	2	0	2	4	1				
		Weighted mode	31	0.20	0.17	0.24	1.22	0.87	1.72				
				4	3	9	6	3	2				
		MR-PRESSO	31	0.03	0.17	0.85	1.03	0.72	1.46				
				3	9	5	3	8	8				
finn-a-I9_CORATHERR	Coronary atherosclerosis	MR Egger	31	0.25	0.44	0.57	1.28	0.54	3.05	0.000	0.604	<0.001	0.065
				0	2	6	4	0	5				
		Weighted median	31	0.13	0.20	0.50	1.14	0.76	1.71				
				7	5	5	7	7	5				
		Inverse variance weighted	31	0.05	0.23	0.81	1.05	0.67	1.66	0.000			
				4	2	7	5	0	2				
		Simple mode	31	0.26	0.32	0.42	1.30	0.68	2.49				
				7	9	3	6	5	0				
		Weighted mode	31	0.18	0.19	0.35	1.20	0.81	1.77				
				5	7	4	4	8	0				
		MR-PRESSO	31	-	0.22	0.97	0.99	0.64	1.52				
				0.00	0	0	2	5	5				
				8									
finn-a-I9_CHD	Major coronary heart disease event	MR Egger	31	0.40	0.40	0.32	1.49	0.67	3.27	0.000	0.412	<0.001	0.739
				0	2	8	2	9	9				
		Weighted median	31	0.39	0.21	0.06	1.48	0.98	2.24				
				7	1	0	7	3	9				

		Inverse variance weighted	31	0.116	0.212	0.583	1.123	0.741	1.702	0.000			
		Simple mode	31	0.288	0.339	0.402	1.334	0.687	2.591				
		Weighted mode	31	0.312	0.216	0.158	1.366	0.895	2.085				
		MR-PRESSO	31	0.013	0.205	0.952	1.013	0.678	1.513				
finn-a-I9_PAD	Peripheral artery disease	MR Egger	31	0.525	0.550	0.347	1.691	0.576	4.965	0.001	0.424	0.003	0.081
		Weighted median	31	0.241	0.299	0.419	1.273	0.709	2.286				
		Inverse variance weighted	31	0.148	0.290	0.610	1.160	0.657	2.048	0.001			
		Simple mode	31	0.403	0.465	0.393	1.496	0.602	3.718				
		Weighted mode	31	0.294	0.301	0.336	1.342	0.744	2.422				
		MR-PRESSO	31	0.167	0.260	0.525	1.182	0.710	1.966				
finn-a-I9_HYPTENSE SS	Essential hypertension	MR Egger	31	-0.038	0.473	0.936	0.963	0.381	2.433	0.000	0.701	<0.001	0.422
		Weighted median	31	-0.128	0.191	0.504	0.880	0.605	1.280				
		Inverse variance weighted	31	-0.194	0.248	0.435	0.824	0.507	1.339	0.000			
		Simple mode	31	-0.064	0.293	0.827	0.938	0.528	1.664				
		Weighted mode	31	-0.090	0.199	0.656	0.914	0.619	1.351				
		MR-PRESSO	31	-0.216	0.238	0.371	0.806	0.505	1.286				
finn-a-C_STROKE	Stroke	MR Egger	31	-0.423	0.424	0.326	0.655	0.285	1.503	0.000	0.451	<0.001	0.487
		Weighted median	31	-0.316	0.242	0.192	0.729	0.453	1.172				
		Inverse variance weighted	31	-0.149	0.224	0.506	0.862	0.555	1.336	0.000			
		Simple mode	31	0.649	0.522	0.223	1.914	0.688	5.318				
		Weighted mode	31	-0.452	0.216	0.045	0.637	0.417	0.972				

		MR-PRESSO	31	-0.09	0.20	0.65	0.91	0.61	1.36				
				1	3	6	3	3	0				
finn-a-I9_STR_EXH	Ischemic stroke	MR Egger	31	-0.32	0.41	0.45	0.72	0.32	1.64	0.008	0.803	0.010	0.279
				1	8	0	6	0	7				
		Weighted median	31	-0.34	0.27	0.21	0.70	0.41	1.21				
				5	6	1	8	2	6				
		Inverse variance weighted	31	-0.23	0.21	0.29	0.79	0.51	1.21	0.011			
				1	9	0	4	7	8				
		Simple mode	31	-0.45	0.47	0.34	0.63	0.25	1.60				
				1	0	5	7	3	2				
		Weighted mode	31	-0.40	0.26	0.14	0.66	0.39	1.13				
				3	8	3	8	5	0				
		MR-PRESSO	31	-0.13	0.19	0.49	0.87	0.59	1.28				
				6	6	2	2	4	2				
finn-a-I9_AF	Atrial fibrillation and fluttering	MR Egger	31	0.24	0.51	0.63	1.27	0.46	3.50	0.000	0.193	<0.001	0.84
				4	5	9	7	5	5				
		Weighted median	31	0.21	0.25	0.40	1.23	0.75	2.02				
				1	3	3	5	3	6				
		Inverse variance weighted	31	-0.33	0.27	0.22	0.71	0.41	1.23	0.000			
				7	7	4	4	5	0				
		Simple mode	31	0.34	0.44	0.45	1.40	0.58	3.39				
				2	9	2	7	4	2				
		Weighted mode	31	0.19	0.24	0.43	1.21	0.74	1.97				
				5	8	7	6	8	5				
		MR-PRESSO	31	-0.40	0.26	0.13	0.66	0.40	1.11				
				5	1	0	7	0	3				
The Global Lipids and Genetics Consortium													
ieu-a-299	HDL cholesterol	MR Egger	33	0.24	0.19	0.20	1.28	0.88	1.86	0.000	0.266	<0.001	0.584
				8	1	5	1	0	4				
		Weighted median	33	0.14	0.05	0.00	1.16	1.03	1.29				
				8	6	8	0	9	4				
		Inverse variance weighted	33	0.05	0.09	0.53	1.06	0.88	1.28	0.000			
				9	6	4	1	0	0				
		Simple mode	33	0.13	0.07	0.07	1.14	0.99	1.32				
				7	5	7	7	0	8				
		Weighted mode	33	0.14	0.05	0.01	1.16	1.04	1.29				
				8	6	2	0	0	3				
		MR-PRESSO	33	0.04	0.09	0.66	1.04	0.87	1.24				
				0	1	2	1	1	3				
ieu-a-300	LDL cholesterol	MR Egger	33	0.24	0.32	0.45	1.27	0.67	2.40	0.000	0.969	<0.001	0.748
				5	3	3	8	9	8				

	Weighted median	33	0.185	0.069	0.007	1.204	1.052	1.378				
	Inverse variance weighted	33	0.234	0.158	0.137	1.264	0.928	1.721	0.000			
	Simple mode	33	0.062	0.118	0.602	1.064	0.844	1.341				
	Weighted mode	33	0.146	0.072	0.052	1.157	1.004	1.333				
	MR-PRESSO	33	0.188	0.142	0.196	1.206	0.913	1.595				
ieu-a-302	Triglycerides	MR Egger	-0.235	0.145	0.117	0.791	0.595	1.052	0.000	0.121	<0.001	0.314
	Weighted median	33	-0.109	0.059	0.062	0.896	0.799	1.006				
	Inverse variance weighted	33	-0.034	0.075	0.646	0.966	0.834	1.119	0.000			
	Simple mode	33	-0.066	0.099	0.512	0.936	0.771	1.138				
	Weighted mode	33	-0.104	0.060	0.095	0.902	0.801	1.014				
	MR-PRESSO	33	0.014	0.076	0.853	1.014	0.874	1.178				

*No significant outliers

Table S8 HDL-C as a mediator in the causal pathway between T2DM and risk of CVDs

Outcome	Total effect	Direct effect	Mediation effect	Mediation proportion (95% CI)
Cardiovascular mortality	0.056	0.049	0.0071	12.8% (-0.4%, 39.3%)
Myocardial infarction	0.134	0.138	-0.0044	7.4% (0.8%, 20.6%)
Intracerebral hemorrhage	0.078	0.077	0.0003	0.4% (-9.2%, 29.0%)
Ischemic heart disease	0.114	0.113	0.0003	0.2% (-6.3%, 19.1%)
Coronary atherosclerosis	0.118	0.103	0.0152	12.8% (2.4%, 31.0%)
Major coronary heart disease event	0.103	0.089	0.0139	13.5% (2.4%, 33.2%)
Peripheral artery disease	0.183	0.164	0.0195	10.6% (2.4%, 24.6%)
Essential hypertension	0.122	0.115	0.0072	5.9% (0.2%, 17.3%)
Stroke	0.099	0.093	0.006	6.1% (-0.5%, 19.6%)
Ischemic stroke	0.063	0.057	0.0052	8.4% (-1.8%, 30.2%)

Table S9 Triglycerides as a mediator in the causal pathway between T2DM and risk of CVDs

Outcome	Total effect	Direct effect	Mediation effect	Mediation proportion (95% CI)
---------	--------------	---------------	------------------	-------------------------------

Cardiovascular mortality	0.056	0.056	0.0004	0.7% (-1.9%, 24.2%)
Myocardial infarction	0.134	0.118	0.0158	11.9% (1.1%, 31.2%)
Intracerebral hemorrhage	0.078	0.075	0.0026	3.3% (-1.9%, 35.0%)
Ischemic heart disease	0.114	0.105	0.0084	7.4% (-19.0%, 53.0%)
Coronary atherosclerosis	0.118	0.108	0.0100	8.5% (-21.6%, 60.5%)
Major coronary heart disease event	0.103	0.093	0.0095	9.2% (-6.2%, 35.5%)
Peripheral artery disease	0.183	0.171	0.0122	6.7% (0.2%, 21.6%)
Essential hypertension	0.122	0.113	0.0089	7.3% (0.4%, 22.2%)
Stroke	0.099	0.095	0.0033	3.4% (-0.3%, 15.8%)
Ischemic stroke	0.063	0.064	-0.0013	-2.0% (-1.9%, 15.3%)

Table S10 ApoA as a mediator in the causal pathway between T2DM and risk of CVDs

Outcome	Total effect	Direct effect	Mediation effect	Mediation proportion (95% CI)
Cardiovascular mortality	0.056	0.054	0.0017	3.0% (-5.9%, 18.3%)
Myocardial infarction	0.134	0.125	0.0088	6.6% (1.2%, 14.9%)
Intracerebral hemorrhage	0.078	0.081	-0.0038	-4.9% (-14.0%, 12.8%)
Ischemic heart disease	0.114	0.104	0.0097	8.5% (2.3%, 17.8%)
Coronary atherosclerosis	0.118	0.108	0.0104	8.8% (2.2%, 18.8%)
Major coronary heart disease event	0.103	0.093	0.0103	10.0% (2.6%, 21.0%)
Peripheral artery disease	0.183	0.173	0.01	5.5% (1.0%, 12.3%)
Essential hypertension	0.122	0.121	0.0016	1.3% (-1.9%, 6.8%)
Stroke	0.099	0.092	0.0064	6.5% (1.0%, 14.9%)
Ischemic stroke	0.063	0.057	0.0054	8.5% (-0.2%, 22.5%)

Table S11 Multivariable Mendelian randomization using IVW method.

Outcome	Exposure	No. of SNPs	Beta	SE	OR	LCI	UCI	<i>p</i> value
Cardiovascular mortality	T2DM	80	0.001	0.000	1.001	1.000	1.001	0.031
	HbA _{1c}	6	0.000	0.001	1.000	0.997	1.002	0.779
	FG	27	0.003	0.001	1.003	1.001	1.005	0.006
	FI	11	0.002	0.002	1.002	0.997	1.007	0.374
Myocardial infarction	T2DM	80	0.135	0.038	1.144	1.062	1.233	0.000
	HbA _{1c}	6	0.193	0.244	1.213	0.752	1.957	0.428
	FG	27	-	0.174	0.916	0.651	1.289	0.615
	FI	11	0.109	0.311	1.115	0.606	2.052	0.727

Intracranial haemorrhage	T2DM	80	0.000	0.000	1.000	0.999	1.000	0.707
	HbA _{1c}	6	0.001	0.002	1.001	0.998	1.004	0.606
	FG	27	-	0.001	0.998	0.996	1.000	0.107
			0.002					
	FI	11	0.002	0.002	1.002	0.998	1.007	0.351
Heart failure	T2DM	75	0.037	0.023	1.037	0.991	1.086	0.114
	HbA _{1c}	5	-	0.142	0.835	0.631	1.104	0.205
			0.181					
	FG	26	0.206	0.115	1.228	0.980	1.540	0.075
	FI	11	-	0.188	0.795	0.550	1.150	0.224
			0.229					
Ischemic heart disease	T2DM	80	0.160	0.038	1.173	1.089	1.263	0.000
	HbA _{1c}	6	0.119	0.242	1.127	0.702	1.809	0.621
	FG	27	-	0.172	0.966	0.689	1.354	0.842
			0.034					
	FI	11	0.248	0.308	1.281	0.701	2.343	0.421
Coronary atherosclerosis	T2DM	80	0.006	0.002	1.006	1.002	1.009	0.002
	HbA _{1c}	6	0.011	0.011	1.011	0.990	1.033	0.310
	FG	27	0.003	0.008	1.003	0.987	1.019	0.698
	FI	11	0.002	0.015	1.002	0.973	1.032	0.902
Major coronary heart disease event	T2DM	80	0.006	0.002	1.006	1.002	1.009	0.002
	HbA _{1c}	6	0.011	0.011	1.011	0.990	1.033	0.310
	FG	27	0.003	0.008	1.003	0.987	1.019	0.698
	FI	11	0.002	0.015	1.002	0.973	1.032	0.902
Peripheral artery disease	T2DM	75	0.300	0.067	1.350	1.184	1.540	0.000
	HbA _{1c}	4	0.537	0.446	1.712	0.714	4.102	0.228
	FG	25	-	0.348	0.717	0.363	1.418	0.339
			0.332					
	FI	11	1.092	0.496	2.980	1.128	7.871	0.028
Essential hypertension	T2DM	80	0.013	0.002	1.013	1.009	1.017	0.000
	HbA _{1c}	6	0.015	0.013	1.015	0.989	1.042	0.250
	FG	27	-	0.010	0.982	0.963	1.001	0.063
			0.018					
	FI	11	0.071	0.018	1.074	1.036	1.113	0.000
Stroke	T2DM	80	0.122	0.022	1.129	1.082	1.179	0.000

	HbA _{1c}	6	-	0.134	0.882	0.678	1.148	0.351
			0.125					
	FG	27	-	0.099	0.948	0.781	1.151	0.588
			0.054					
	FI	11	-	0.178	0.969	0.683	1.374	0.861
			0.031					
Ischemic stroke	T2DM	80	0.130	0.022	1.139	1.090	1.190	0.000
	HbA _{1c}	6	-	0.136	0.838	0.642	1.095	0.196
			0.176					
	FG	27	-	0.102	0.989	0.809	1.208	0.911
			0.011					
	FI	11	-	0.183	0.886	0.619	1.269	0.509
			0.121					
Atrial fibrillation and fluttering	T2DM	80	0.003	0.022	1.003	0.961	1.047	0.891
	HbA _{1c}	6	-	0.136	0.924	0.707	1.208	0.564
			0.079					
	FG	27	0.023	0.099	1.023	0.842	1.243	0.818
	FI	11	-	0.180	0.841	0.591	1.197	0.336
			0.173					
HDL cholesterol	T2DM	80	-	0.010	0.960	0.941	0.979	0.000
			0.041					
	HbA _{1c}	6	0.065	0.062	1.067	0.946	1.204	0.290
	FG	27	0.028	0.045	1.029	0.941	1.124	0.534
	FI	11	-	0.084	0.673	0.570	0.793	0.000
			0.397					
LDL cholesterol	T2DM	80	-	0.015	0.965	0.936	0.994	0.017
			0.036					
	HbA _{1c}	6	0.219	0.092	1.244	1.040	1.489	0.017
	FG	27	-	0.068	0.915	0.802	1.044	0.188
			0.089					
	FI	11	-	0.125	0.820	0.642	1.048	0.113
			0.198					
Triglycerides	T2DM	80	0.090	0.037	1.094	1.018	1.175	0.014
	HbA _{1c}	6	0.079	0.222	1.083	0.701	1.673	0.720
	FG	27	-	0.164	0.779	0.565	1.074	0.128
			0.250					
	FI	11	0.197	0.304	1.218	0.671	2.212	0.516
Apolipoprotein A	T2DM	80	-	0.006	0.979	0.968	0.990	0.000
			0.021					
	HbA _{1c}	6	0.042	0.035	1.043	0.974	1.117	0.227

	FG	27	-	0.026	0.995	0.946	1.046	0.831
			0.005					
	FI	11	-	0.048	0.758	0.690	0.832	0.000
			0.278					
Apolipoprotein B	T2DM	80	-	0.005	0.995	0.986	1.005	0.301
			0.005					
	HbA _{1c}	6	0.059	0.029	1.061	1.001	1.124	0.046
	FG	27	-	0.022	0.975	0.935	1.018	0.248
			0.025					
	FI	11	-	0.040	0.970	0.897	1.050	0.453
			0.030					
Lipoprotein A	T2DM	80	0.013	0.047	1.013	0.924	1.110	0.781
	HbA _{1c}	6	0.363	0.283	1.437	0.825	2.502	0.200
	FG	27	-	0.209	0.832	0.552	1.254	0.380
			0.184					
	FI	11	-	0.388	0.540	0.252	1.156	0.112
			0.616					