Genetic instrument selection for SMR analysis

As demonstrated in Supplementary Table SI, we utilized publicly available eQTLs data for the targeted genes of lipid-lowering drugs, to serve as a proxy for exposure to each respective drug. The eQTLs summary-level data for HMGCR and PPARG were obtained from eQTLGen Consortium (whole blood, https://www.eqtlgen.org/), while eQTLs for PCSK9 and NPC1L1 were from GTEx Consortium V8 (including 49 tissues, https://gtexportal.org/) [1]. Detailed information regarding these data sources can be found in Supplementary Table SI. We specifically identified independent and eligible single-nucleotide polymorphisms (SNPs) with stringent quality control protocols (minor allele frequencies (MAF) > 1% and $p < 5.0 \times 10^{-8}$) associated with each phenotype, including the expression of HMGCR, PPARG or PCSK9 in whole blood. Similarly, for NPC1L1, due to an absence of relevant eQTLs in blood or other tissues, we focused on adipose subcutaneous tissue. In constructing the instrumental variables for this study, only cis-eQTLs were considered, which encompassed eQTLs located within a 1 Mb region surrounding the target gene and on the same chromosome.

FGID Outcome for SMR analysis

In our study, we investigated 7 functional gastrointestinal disorders outcomes, which were publicly available and obtained from UKBiobank. All detailed information and data sources were shown in Supplementary Table SI.

SMR analysis

The whole procedures for SMR analysis were carried out with SMR software version 1.3.1 (https://cnsgenomics.com/software/smr/). SMR method utilizes eQTLs for 4 lipid-lowering drug target genes as instrumental variables to examine the association between gene expression levels and the risk of FGIDs. We additionally conducted the heterogeneity in dependent instrument (HEIDI) test, to evaluate whether there exists linkage disequilibrium with each other. *P* value of HEIDI-global test less than 0.05 was excluded to prevent potential bias.

Results for SMR analysis

The most statistically significant cis-eQTL SNP was selected as the instrumental variable to represent the target gene for 4 drugs (Supplementary Table SII). SMR analysis show that increased PCSK9 gene expression (corresponding to an increase of one standard deviation) with a slightly higher risk of irritable bowel syndrome (odds ratio [OR] = 1.001, 95% confidence interval (CI), 1.000–1.002, $p = 0.049$) and slightly lower risk of disorders of gallbladder biliary tract and pancreas (OR = 0.994, 95% CI = 0.989–0.999, $p = 0.031$). No other significant causal effect was found in the other three target genes. The results of the HEIDI global test indicated that none of the observed associations were attributable to a linkage ($p > 0.05$).

References

1. Battle A, Brown CD, Engelhardt BE, Montgomery SB. Genetic effects on gene expression across human tissues. Nature 2017;550:204-213.

Supplementary Table SI. Details of eQTL and GWAS summary data in the study

Phenotype	**Resource**	**Sex**	**Population ancestry**	**Sample size (case/control)**	**Tissue**	**Data**
eQTL data						
eQTL for HMGCR/PPARG	eQTLGen Consortium	Males and females	European	31684	Whole blood	https://www.gtexportal.org/home/datasets
eQTL in PCSK9	GTExV8	Males and females	European	755	Whole blood	https://www.gtexportal.org/home/datasets
eQTL in NPC1L1	GTExV8	Males and females	European	663	Adipose Subcutaneous	https://www.gtexportal.org/home/datasets
GWAS summary data						
LDL cholesterol	Global Lipids Genetics Consortium	Males and females	European	173,082	N/A	http://csg.sph.umich.edu/willer/public/lipids2013/
Irritable bowel syndrome	UK Biobank	Males and females	European	463,010 (1,047/461,963)	N/A	https://gwas.mrcieu.ac.uk/datasets/ukb-b-17961/
Functional constipation	UK Biobank	Males and females	European	459,682 (3,328/459,682)	N/A	https://gwas.mrcieu.ac.uk/datasets/ukb-b-6779/
Functional dysphagia	UK Biobank	Males and females	European	463,010 (3,012/459,998)	N/A	https://gwas.mrcieu.ac.uk/datasets/ukb-b-7073/
Functional dyspepsia	UK Biobank	Males and females	European	463,010 (7,662/455,348)	N/A	https://gwas.mrcieu.ac.uk/datasets/ukb-b-14814/
Nausea and vomiting	UK Biobank	Males and females	European	463,010 (2,143/460,867)	N/A	https://gwas.mrcieu.ac.uk/datasets/ukb-b-19419/
Functional abdominal pain	UK Biobank	Males and females	European	463,010 (11,925/451,085)	N/A	https://gwas.mrcieu.ac.uk/datasets/ukb-b-6223/
Disorders of gallbladder, biliary tract and pancreas	UK Biobank	Males and females	European	361,194 (13,922/347,272)	N/A	https://gwas.mrcieu.ac.uk/datasets/ukb-d-K11_GALLBILPANC/

Supplementary Table SII. SMR association between expression of gene *HMGCR, PPARG, PCSK9*, or *NPC1L1* and FDIGs

Gene	**Gene chromosome**	**Probe**	**Probe_bp**	**top eQTL SNP**	**SNP chromosome**	**topSNP_bp**	**Effect allele**	**Other allele**	**Effect allele frequency**	**GWAS association**			
										Outcome	**Beta**	**Se**	***P*-value**
HMGCR	5	ENSG00000113161	74645041	rs3846662	5	74651084	G	A	0.43047	Irritable bowel syndrome	0.00000915	0.0000998	0.93
	5	ENSG00000113161	74645041	rs6453133	5	74692776	G	A	0.286299	Functional constipation	0.0000832	0.00019357	0.67
	5	ENSG00000113161	74645041	rs6453133	5	74692776	G	A	0.286299	Functional dysphagia	–0.000110647	0.000184266	0.55
	5	ENSG00000113161	74645041	rs6453133	5	74692776	G	A	0.286299	Functional dyspepsia	–0.0000968	0.000292307	0.74
	5	ENSG00000113161	74645041	rs6453133	5	74692776	G	A	0.286299	Nausea and vomiting	–0.0000986	0.000155572	0.53
	5	ENSG00000113161	74645041	rs6453133	5	74692776	G	A	0.286299	Functional abdominal pain	–0.000609574	0.00036289	0.093
	5	ENSG00000113161	74645041	rs6453133	5	74692776	G	A	0.286299	Disorders of gallbladder biliary tract and pancreas	–0.000202661	0.000498978	0.685
PPARG	3	ENSG00000132170	12402361	rs1699346	3	12504295	C	A	0.429448	Irritable bowel syndrome	-0.00000255	0.000100926	0.98
	3	ENSG00000132170	12402361	rs1699346	3	12504295	C	A	0.429448	Functional constipation	-0.0000799	0.000179468	0.66
	3	ENSG00000132170	12402361	rs1699346	3	12504295	C	A	0.429448	Functional dysphagia	-0.0000426	0.000170842	0.8
	3	ENSG00000132170	12402361	rs1699346	3	12504295	C	A	0.429448	Functional dyspepsia	0.000437599	0.000271012	0.11
	3	ENSG00000132170	12402361	rs1699346	3	12504295	C	A	0.429448	Nausea and vomiting	0.0000573	0.000144239	0.69
	3	ENSG00000132170	12402361	rs1699346	3	12504295	C	A	0.429448	Functional abdominal pain	-0.000406343	0.000336459	0.23
	3	ENSG00000132170	12402361	rs1699346	3	12504295	C	A	0.429448	Disorders of gallbladder biliary tract and pancreas	-0.000145792	0.000462543	0.753
	1	ENSG00000169174	55505221	rs472495	1	55521313	T	G	0.627812	Irritable bowel syndrome	0.000211466	0.000103581	0.041
	1	ENSG00000169175	55505221	rs472495	1	55521313	T	G	0.627812	Functional constipation	-0.000221174	0.000184187	0.23

PCSK9	1	ENSG00000169176	55505221	rs472495	1	55521313	T	G	0.627812	Functional dysphagia	-0.000143408	0.000175333	0.41
	1	ENSG00000169177	55505221	rs472495	1	55521313	T	G	0.627812	Functional dyspepsia	-0.000108713	0.000278139	0.7
	1	ENSG00000169178	55505221	rs472495	1	55521313	T	G	0.627812	Nausea and vomiting	-0.00019117	0.00014803	0.2
	1	ENSG00000169179	55505221	rs472495	1	55521313	T	G	0.627812	Functional abdominal pain	-0.00000077	0.000345297	1
	1	ENSG00000169180	55505221	rs472495	1	55521313	T	G	0.627812	Disorders of gallbladder biliary tract and pancreas	-0.00107077	0.000474466	0.024
NPC1L1	7	ENSG00000015520	44552134	rs41279633	7	44580876	T	G	0.144172	Functional constipation	0.00000869	0.000243133	0.97
	7	ENSG00000015521	44552134	rs41279633	7	44580876	T	G	0.144172	Functional dysphagia	-0.0000171	0.000231448	0.94
	7	ENSG00000015522	44552134	rs41279633	7	44580876	T	G	0.144172	Functional dyspepsia	0.000117657	0.00036715	0.75
	7	ENSG00000015523	44552134	rs73107473	7	44577622	A	G	0.153374	Nausea and vomiting	-0.000150549	0.000191146	0.43
	7	ENSG00000015524	44552134	rs41279633	7	44580876	T	G	0.144172	Functional abdominal pain	-0.000489979	0.000455801	0.28
	7	ENSG00000015525	44552134	rs41279633	7	44580876	T	G	0.144172	Disorders of gallbladder biliary tract and pancreas	-0.0000396	0.000625283	0.95

Continued Table

eQTL association				**SMR association**					**HEIDI Test**	
Tissue	**Beta**	**Se**	***P*-value**	**Beta**	**Se**	***P*-value**	**OR**	**OR (95%CI)**	***P*-value**	**Number of SNPs**
Blood	0.103642	0.00800374	2.37E-38	0.0000882	0.000963256	0.927	1.000	(0.998,1.002)	0.613	20
Blood	0.127763	0.00853654	1.21E-50	0.000651592	0.0015157	0.667	1.001	(0.998,1.004)	0.0678	20
Blood	0.127763	0.00853654	1.21E-50	–0.000866033	0.00144341	0.549	0.999	(0.996,1.002)	0.541	20
Blood	0.127763	0.00853654	1.21E-50	–0.000757481	0.00228844	0.741	0.999	(0.995,1.004)	0.279	20
Blood	0.127763	0.00853654	1.21E-50	–0.0007716	0.00121875	0.527	0.999	(0.997,1.002)	0.75	20
Blood	0.127763	0.00853654	1.21E-50	–0.00477113	0.00285817	0.0951	0.995	(0.990,1.001)	0.626	20
Blood	0.127763	0.00853654	1.21E-50	–0.00158623	0.00390693	0.685	0.998	(0.991,1.006)	0.431	20

Blood	0.252822	0.00794678	4.09E-222	–0.0000101	0.000399198	0.98	1.000	(0.999,1.001)	0.974	20
Blood	0.252822	0.00794678	4.09E-222	–0.000316152	0.000709929	0.656	1.000	(0.998,1.001)	0.836	20
Blood	0.252822	0.00794678	4.09E-222	–0.000168436	0.000675761	0.803	1.000	(0.999,1.001)	0.15	20
Blood	0.252822	0.00794678	4.09E-222	0.00173086	0.00107333	0.107	1.002	(1.000,1.004)	0.529	20
Blood	0.252822	0.00794678	4.09E-222	0.00022667	0.00057056	0.691	1.000	(0.999,1.001)	0.57	20
Blood	0.252822	0.00794678	4.09E-222	–0.00160723	0.00133177	0.227	0.998	(0.996,1.001)	0.99	20
Blood	0.252822	0.00794678	4.09E-222	–0.000576659	0.00182961	0.753	0.999	(0.996,1.003)	0.697	20
Blood	0.187357	0.0251221	8.79E-14	0.00112868	0.000573194	0.0489	1.001	(1.000,1.002)	0.162	6
Blood	0.187357	0.0251221	8.79E-14	–0.0011805	0.000995742	0.236	0.999	(0.997,1.001)	0.468	7
Blood	0.187357	0.0251221	8.79E-14	–0.000765426	0.000941434	0.416	0.999	(0.997,1.001)	0.759	7
Blood	0.187357	0.0251221	8.79E-14	–0.000580245	0.00148658	0.696	0.999	(0.997,1.002)	0.655	7
Blood	0.187357	0.0251221	8.79E-14	–0.00102035	0.000801854	0.203	0.999	(0.997,1.001)	0.865	7
Blood	0.187357	0.0251221	8.79E-14	–0.00000411	0.00184299	0.998	1.000	(0.996,1.004)	0.719	7
Blood	0.187357	0.0251221	8.79E-14	–0.00571513	0.00264582	0.0308	0.994	(0.989,0.999)	0.364	8
Adipose Subcutaneous	0.473374	0.0539375	1.69E-18	0.0000184	0.000513621	0.971	1.000	(0.999,1.001)	0.777	5
Adipose Subcutaneous	0.473374	0.0539375	1.69E-18	–0.0000362	0.00048895	0.941	1.000	(0.999,1.001)	0.688	5
Adipose Subcutaneous	0.473374	0.0539375	1.69E-18	0.00024855	0.000776119	0.749	1.000	(0.999,1.002)	0.845	5
Adipose Subcutaneous	0.392971	0.053888	3.05E-13	–0.000383105	0.000489241	0.434	1.000	(0.999,1.001)	0.604	4
Adipose Subcutaneous	0.473374	0.0539375	1.69E-18	–0.00103508	0.000970073	0.286	0.999	(0.997,1.001)	0.931	5
Adipose Subcutaneous	0.473374	0.0539375	1.69E-18	–0.0000836	0.00132094	0.95	1.000	(0.997,1.003)	0.361	5

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