Genetic association of lipid-lowering drugs with functional gastrointestinal disorders: a drug-target Mendelian randomization study

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Abstract

Introduction: The effect of lipid-lowering drugs on functional gastrointestinal disorders (FGIDs) remains unclear, and the assessment of their relationship is always confounded by extraneous factors.

Material and methods: We detected genetic variants linked to LDL cholesterol (LDL-C) levels in or near the lipid-lowering drug targets (HMGCR, PPARG, PCSK9, and NPC1L1), using data from the Global Lipids Genetics Consortium (GLGC) genome-wide association study. Outcome data for FGIDs including seven disorders were extracted from genome-wide association studies (GWAS) datasets. Inverse-variance-weighted Mendelian randomization (IVW-MR) was conducted to identify the causal effect between four genetically proxied lipid-lowering drugs and FGIDs, and mediation Mendelian randomization (MR) was performed to investigate potential mediators. We employed several sensitivity analyses to validate the robustness of the results.

Results: Seven variants were identified as proxies for LDL-C lowering through HMGCR inhibitors, 3 for PPARG inhibitors, 12 for PCSK9 inhibitors, and 3 for NPC1L1 inhibitors. IVW-MR analysis revealed that genetically proxied HMGCR-mediated LDL-C elevation significantly increased the risk of several gastrointestinal outcomes. These included functional constipation (OR = 1.258, 95% CI: 1.043–1.517), functional dyspepsia (OR = 1.438, 95% CI: 1.014–2.036), nausea and vomiting (OR = 1.536, 95% CI: 1.070–2.207), and disorders of the gallbladder, biliary tract and pancreas (OR = 1.664, 95% CI: 1.392–1.989). Furthermore, mediation analysis identified mood swings as a significant mediator. It accounted for 6.23% of the total effect on functional dyspepsia (OR = 1.023, 95% CI: 1.001–1.058) and for 2.62% of the effect on disorders of the gallbladder, biliary tract, and pancreas (OR = 1.013, 95% CI: 1.001–1.033).

Conclusions: Our study suggested a potential protective effect of HMGCR inhibitors on FGIDs, which may be mediated by a reduced risk of mood swings.

Key words: lipid-lowering-drug, FGIDs, Mendelian randomization, drug target.

Introduction

Functional gastrointestinal disorders (FGIDs), characterized by chronic digestive symptoms in the absence of detectable structural abnormalities, represent a group of highly prevalent conditions. According to the Rome IV criteria, FGIDs encompass various subtypes such as functional bowel disorders and gastroduodenal disorders, affecting over 40% of the global population and imposing a substantial burden on healthcare systems and patients' quality of life [1]. The pathogenesis of FGIDs is complex and is widely recognized as resulting from the interplay of multiple factors, including gastrointestinal dysmotility, visceral hypersensitivity, altered mucosal immune function, intestinal dysbiosis, and dysfunction of the gut-brain axis [2, 3]. Notably, disruption of the gut-brain axis has received particular attention, as it provides the pathophysiological basis for the frequent co-occurrence of FGIDs with psychiatric comorbidities such as anxiety, depression, and mood instability. However, the current therapeutic approaches fall short because of limited evidence and are also burdened with substantial side effects [4]. Therefore, there has been significant interest in identifying drug candidates.

Lipid-lowering drugs are well established in the prevention and management of cardiovascular diseases [5]. Emerging evidence suggests that these agents may influence gastrointestinal function and the central nervous system through pleiotropic effects [6, 7]. For instance, observational studies have reported that statins (HMGCR inhibitors) may be associated with an increased risk of constipation and abdominal pain [8–10], while other studies have indicated their potential protective role in conditions such as irritable bowel syndrome or constipation [6, 11–13]. Meanwhile, PCSK9 inhibitors have been suggested to be potentially linked to mood instability [14, 15]. These conflicting findings are likely attributable to inherent limitations of conventional observational studies, including residual confounding such as comorbidities and concomitant medications. Therefore, it remains to be clarified whether a causal relationship exists between lipid-lowering drugs and FGIDs, and whether psychological factors such as mood swings mediate this relationship.

Drug-target Mendelian randomization (MR) analysis, which uses genetic variants in or near genes encoding drug targets as instrumental variables, provides a powerful tool for assessing causal effects of drug targets on clinical outcomes while minimizing confounding and reverse causation [16]. To systematically address the above questions, this study employed a two-sample MR framework. Using genetic proxies for four lipid-lowering drug targets (HMGCR, PCSK9, NPC1L1, and PPARG), we investigated their causal as-

Table I. Details of GWAS summary data for exposure and outcome in the study

Phenotype	Resource	Sex	Population ancestry	Sample size (case/control)	Data
Exposure					
LDL cholesterol	Global Lipids Genetics Consortium	Males and females	European	173,082	http://csg.sph.umich.edu/willer/public/lipids2013/
Outcome					
Irritable bowel syndrome	FinnGen	Males and females	European	187,028 (4,605/182,423)	https://gwas.mrcieu.ac.uk/datasets/finn-b-K11_IBS/
Functional constipation	FinnGen	Males and females	European	218,792 (17,246/201,546)	https://gwas.mrcieu.ac.uk/datasets/finn-b-K11_CONSTIPATION/
Functional dysphagia	FinnGen	Males and females	European	165,465 (3,497/161,968)	https://gwas.mrcieu.ac.uk/datasets/finn-b-R18_DYSPHAGIA/
Functional dyspepsia	FinnGen	Males and females	European	194,071 (4,376/189,695)	https://gwas.mrcieu.ac.uk/datasets/finn-b-K11_FUNCDYSP/
Nausea and vomiting	FinnGen	Males and females	European	166,077 (4,109/161,968)	https://gwas.mrcieu.ac.uk/datasets/finn-b-R18_NAUSEA_VOMITI/
Functional abdominal pain	UK Biobank	Males and females	European	463,010 (11,925/451,085)	https://gwas.mrcieu.ac.uk/datasets/ukb-b-6223/
Disorders of gallbladder, biliary tract and pancreas	FinnGen	Males and females	European	218,792 (23,648/195,144)	https://gwas.mrcieu.ac.uk/datasets/finn-b-K11_GALLBILPANC/

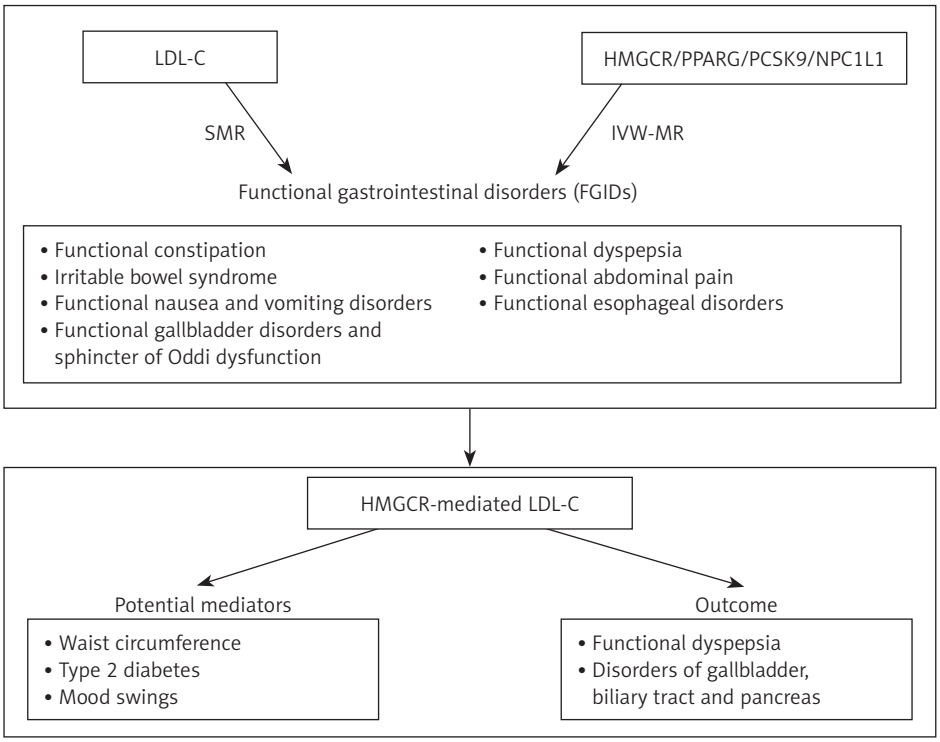

Figure 1. Flowchart of the study design

HMGCR – HMG-CoA reductase, IVW-MR – inverse-variance-weighted Mendelian randomization, LDL-C – low-density lipoprotein, NPC1L1 – Niemann-Pick C1-like protein 1, PCSK9 – proprotein convertase subtilisin/kexin type 9, PPARG – peroxisome proliferator activated receptor γ, SMR – summary-data-based MR.

sociations with seven common FGIDs according to the Rome IV criteria [1]: irritable bowel syndrome (IBS), functional constipation, functional dysphagia, functional dyspepsia, nausea and vomiting, functional abdominal pain, and disorders of the gallbladder, biliary tract, and pancreas. Furthermore, we evaluated the potential mediating role of mood swings in these associations.

Material and methods

Data sources

After reviewing the relevant literature on specific lipid-lowering drug targets [17], four lipid-regulating drugs were ultimately included in the study: HMGCR inhibitors, PCSK9 inhibitors, PPARG inhibitors, and NPC1L1 inhibitors.

Publicly accessible summary-level data derived from genome-wide association studies (GWAS) (Table I) and expression quantitative trait loci (eQTLs) studies were used in this work (Supplementary Table SI). Detailed information on eQTLs and corresponding analysis a shown in supplementary materials. The flowchart of this study is shown in Figure 1.

Genetic instrument selection

As demonstrated in Table I, the selection of genetic instruments for the targeted drug genes was derived from the Global Lipids Genetics Consortium (GLGC) genome-wide association study on LDL cholesterol (LDL-C) levels (n = 173,082) [18]. We sought to propose an alternative instrument by selecting single nucleotide polymorphisms (SNPs) located within 100 kb windows surrounding the target gene of each lipid-lowering drug. These SNPs were identified based on their significant association with LDL-C levels at a genome-wide level of significance ($p < 5.0 \times 10^{-8}$), and low pairwise linkage disequilibrium ($r^2 < 0.30$) to ensure independence between variants. We specifically focused on common SNPs with MAF > 1%. SNPs with an F-statistic below 10 were excluded to mitigate weak instrument bias. Finally, SNPs located within 100 kb of the target gene were chosen.

FGID outcome

In our study, we investigated 7 functional gastrointestinal disorder outcomes, which were publicly available and obtained from the Integrative Epidemiology Unit (IEU) Open GWAS project [19]. These seven outcomes correspond to the categories defined by the Rome IV criteria, which represent the internationally accepted classification for FGIDs. The UK Biobank [20] and FinnGen GWAS data [21] used in our study for FGIDs comprised a sizable sample of individuals, 187,028 from FinnGen for irritable bowel syndrome, 218,792 from

FinnGen for functional constipation, 165,465 from FinnGen for functional dysphagia, 194,071 from FinnGen for functional dyspepsia, 166,077 from FinnGen for nausea and vomiting, 463,010 from UK Biobank for functional abdominal pain, and 218,792 from FinnGen for disorders of the gallbladder, biliary tract, and pancreas (Table I).

Statistical analysis

The drug target two-sample MR study was conducted to assess the relationship between genetically proxied levels of LDL-C in whole blood and the risk of functional gastrointestinal disorders [22]. Additionally, summary-data-based MR (SMR) analysis was carried out to investigate the association of the genetically proxied lipid-lowering drug targets HMGCR, PPARG, PCSK9, and NPC1L1 with the risk of FGIDs (Supplementary Table SII). Mediation analysis was further performed to explore the potential mechanism.

Firstly, inverse-variance-weighted Mendelian randomization (IVW-MR) was performed to obtain the MR estimates for the causal effect by using genetic variants associated with LDL-C levels as instrumental variables [23]. Cochran's Q test was employed to evaluate the heterogeneity of effects, and a significance level of $p < 0.05$ was considered as evidence of heterogeneity. Additionally, we conducted several sensitivity analyses, including the weighted median, MR-Egger regression and Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MRPRESSO), to validate the findings obtained from the IVW-MR method [23–27]. The estimates of the weighted median and MR-Egger were applied to determine the causal direction. The *p* values for the MR-Egger intercept and MR-PRESSO Global test were used to assess potential horizontal pleiotropy [28]. Results with $p < 0.05$ were interpreted as evidence of horizontal pleiotropy and were excluded from the analysis.

Secondly, in order to ascertain whether the observed association between drug targets and FGIDs represents a direct relationship, we conducted MR analysis to examine the association between genetically determined LDL-C levels and potential risk factors for FGIDs, including waist circumference, type 2 diabetes, and mood swings [29–31]. If significant associations were identified, it suggests the presence of potential mediation effects through the exposure-mediator-outcome pathway. Then we employed two-step MR to evaluate the direct impact of the lipid-lowering drug on the risks of FGIDs while accounting for mediator variables [32]. After performing the above analysis, we applied the delta method and the propagation of error method to further estimate the mediated effects and mediated proportions [33]. All procedures were carried out using R software version 4.1.3 (https://www.npackd.org/p/r/4.1.3). All statistical analyses were conducted using the TwoSampleMR, tidyverse, and RMediation packages.

Results

The number of independent SNPs serving as genetic instruments for each drug target is summarized in Table II. Specifically, 7 variants were identified as proxies for LDL-C lowering through HMGCR inhibitors, 3 for PPARG inhibitors, 12 for PCSK9 inhibitors, and 3 for NPC1L1 inhibitors. The F-statistics for all instruments were substantially greater than 10, indicating a low risk of weak instrument bias.

To validate the robustness and biological relevance of these genetic instruments, we first confirmed their strong association with LDL-C levels. As shown in Table II, the genetically proxied inhibition of all four targets (HMGCR, PPARG, PCSK9, and NPC1L1) was significantly associated with LDL-C (per unit SD increase) [34]. Subsequently, we performed a positive control analysis using coronary artery disease as the outcome, given the well-established causal role of LDL-C in CAD pathogenesis. Consistent with expectation, the genetic proxies for all four lipid-lowering targets demonstrated a significant protective effect against CAD risk (Table III).

IVW-MR analysis

The primary causal estimates from the IVW MR analysis are summarized in Table IV and Figure 2. Our analysis revealed distinct causal profiles for the four lipid-lowering drug targets in relation to FGID risk. Genetically proxied HMGCR inhibition was associated with a reduced risk of several FGIDs. Specifically, a one-standard-deviation increase in LDL-C mediated by HMGCR was associated with higher odds of functional constipation (OR = 1.257, 95% CI: 1.043–1.517, $p = 0.016$), functional dyspepsia (OR = 1.437, 95% CI: 1.014–2.036, $p = 0.042$), nausea and vomiting (OR = 1.536, 95% CI: 1.070–2.207, $p = 0.020$), and disorders of the gallbladder, biliary tract, and pancreas (OR = 1.663, 95% CI: 1.392–1.989, $p < 0.001$). Conversely, HMGCR-mediated LDL-C showed a subtle adverse impact on functional abdominal pain (OR = 0.992, 95% CI: 0.986–0.997, $p = 0.003$).

Genetically proxied inhibition of NPC1L1 (the target of ezetimibe) was associated with an increased risk of functional constipation (OR = 0.485 per SD increase in LDL-C mediated by NPC1L1, 95% CI: 0.321–0.732, $p = 0.001$). For PCSK9 inhibition, genetically lowered LDL-C was associated with an increased risk of disorders of the gallbladder, biliary tract, and pancreas (OR = 0.914,

Table II. Information of genetic instrumental variants associated with LDL cholesterol located within 100 kb windows from gene *HMGCR, PPARG, PCSK9* or *NPC1L1*

Gene	SNP	SNP chromosome	Base pair	Effect_allele	Other_allele	Effect_allele frequence	Beta	Se	*P*-value	*F*-statistic
HMGCR	rs3857388	5	74620377	C	T	0.128	0.042	0.006	< 0.001	50.917
	rs10515198	5	74641560	A	G	0.103	0.060	0.006	< 0.001	96.426
	rs12659791	5	74757758	C	T	0.156	0.043	0.005	< 0.001	74.996
	rs72633962	5	74569028	C	T	0.141	0.060	0.007	< 0.001	69.444
	rs3804231	5	74696779	A	G	0.132	0.064	0.005	< 0.001	146.730
	rs10066707	5	74560579	A	G	0.417	0.050	0.005	< 0.001	84.708
	rs12916	5	74656539	C	T	0.431	0.073	0.004	< 0.001	372.084
PPARG	rs2959273	3	12442731	G	A	0.616	0.027	0.004	< 0.001	52.857
	rs17819328	3	12489342	G	T	0.426	0.024	0.004	< 0.001	38.571
	rs9875338	3	12296469	A	G	0.388	–0.027	0.004	< 0.001	53.251
PCSK9	rs2495495	1	55496556	C	T	0.865	–0.0342	0.006	< 0.001	33.601
	rs2479409	1	55504650	A	G	0.668	–0.0642	0.004	< 0.001	245.190
	rs12067569	1	55528629	A	G	0.034	0.089	0.010	< 0.001	78.323
	rs10493176	1	55538552	G	T	0.115	–0.0776	0.010	< 0.001	57.879
	rs11591147	1	55505647	T	G	0.017	–0.497	0.018	< 0.001	762.373
	rs4927193	1	55509872	C	T	0.131	–0.0352	0.006	< 0.001	39.510
	rs11583974	1	55551718	A	G	0.030	0.065	0.012	< 0.001	30.485
	rs2479394	1	55486064	A	G	0.715	–0.0386	0.004	< 0.001	88.635
	rs11206510	1	55496039	C	T	0.154	–0.0831	0.005	< 0.001	276.224
	rs572512	1	55517344	T	C	0.346	0.048	0.005	< 0.001	103.433
	rs11206514	1	55516004	A	C	0.611	0.051	0.004	< 0.001	152.914
	rs585131	1	55524116	T	C	0.815	0.064	0.005	< 0.001	162.308
NPC1L1	rs7791240	7	44602589	C	T	0.091	0.043	0.007	< 0.001	42.751
	rs2073547	7	44582331	G	A	0.194	0.049	0.005	< 0.001	97.970
	rs217386	7	44600695	A	G	0.408	–0.0363	0.004	< 0.001	91.253

Table III. IVW-MR association between LDL cholesterol mediated by gene *HMGCR*, *PPARG*, *PCSK9*, or *NPC1L1* and coronary heart disease

Genes	Outcome	Resource	PMID/GWAS ID	Beta	Se	*P*-value
HMGCR	Coronary heart disease	UK Biobank	ukb-d-I9_ CORATHER	0.017	0.004	< 0.001
PPARG				0.022	0.010	0.029
PCSK9				0.020	0.002	< 0.001
NPC1L1				0.028	0.011	0.013

95% CI: 0.836–1.000, p = 0.049). This finding, consistent with supplementary SMR analysis, suggests a potential adverse effect of PCSK9 inhibitors on this specific FGID. No statistically significant causal associations were found between genetically proxied inhibition of PPARG and the risk of any investigated FGID (all $p > 0.05$).

Sensitivity analysis

The robustness of the primary IVW-MR estimates was assessed through a series of sensitivity analyses, with detailed results presented in Table V. Cochran's Q test indicated no significant heterogeneity for the majority of the analyses (all $p > 0.05$), except for the association between PCSK9-mediated LDL-C and functional dyspepsia ($p < 0.05$). Results from the MR-Egger intercept test and weighted median method showed no evidence of significant horizontal pleiotropy (all MR-Egger intercept $p > 0.05$). These analyses collectively supported the robustness and reliability of our primary findings, with the noted exception suggesting caution in interpreting the PCSK9-functional dyspepsia association (Table V).

Mediation analysis

Given the significant associations observed between genetically proxied HMGCR inhibition and several FGIDs, we sought to explore potential mediating pathways. We selected three candidate mediators – waist circumference, type 2 diabetes, and mood swings – based on their established or plausible associations with both lipid metabolism and FGID pathophysiology. Waist circumference serves as a marker of central obesity and metabolic status, type 2 diabetes represents a state of systemic inflammation like FGIDs, and mood swings are a key manifestation of psychological distress implicated in the gut-brain axis dysfunction common in FGIDs. First, we evaluated the causal effects of HMGCR-mediated LDL-C reduction on these potential mediators. The results indicated that all three mediators were significantly associated with LDL-C ($p < 0.05$). (Table VI). Subsequently, we assessed the causal relationships of these mediators with the FGID outcomes (Table VII). Among the three candidates, only mood swings demonstrated a consistent and stable pattern of association suitable for further mediation testing with the FGIDs linked to HMGCR inhibition. A two-step MR mediation analysis was then performed, focusing on mood swings as the mediator. The results are summarized in Figure 3 and Table VIII. We identified a significant indirect effect of HMGCR-mediated LDL-C reduction on the risk of functional dyspepsia through mood swings (indirect effect OR = 1.023, 95% CI: 1.001–1.058), which accounted for 6.23% of the total effect. Similarly, a significant indirect pathway was found for disorders of the gallbladder, biliary tract, and pancreas (indirect effect OR = 1.013, 95% CI: 1.001–1.033), with a mediated proportion of 2.62%. No significant mediation by mood swings was detected for the other FGIDs associated with HMGCR inhibition.

Discussion

This drug-target MR analysis provided robust genetic evidence supporting a positive causal association between HMGCR-mediated LDL-C levels and the risk of most FGIDs, including functional constipation, functional dyspepsia, nausea and vomiting, and disorders of the gallbladder, biliary tract and pancreas. A two-step MR analysis further suggested that the protective effect may partially be mediated through a reduced risk of mood swings. In contrast, analyses targeting three other lipid-lowering drug targets (PCSK9, NPC1L1, and PPARG) did not reveal clear associations with the risk of FGIDs. To our knowledge, this is the first genetic study to systematically and comprehensively evaluate the causal relationships between multiple lipid-lowering drug targets and FGIDs classified according to the Rome IV criteria. Our findings not only offer potential additional benefits to consider when choosing lipid-lowering therapy for patients with cardiovascular disease, suggesting that preference for statins may help reduce the risk of comorbid FGIDs, but also open new pharmacological avenues for the prevention and treatment of FGIDs.

Previous evidence on the association between lipid-lowering drugs and FGIDs primarily stems from observational cohort studies, which have yielded inconsistent conclusions and carry methodological limitations. For instance, a prospective

Table IV. IVW–MR association between LDL cholesterol mediated by gene *HMGCR*, *PCSK9*, *NPC1L1*, *PPARG* and the risk of FDIGs

Exposure	Outcome	Number of SNPs	MR Egger			Weighted median			IVW				
			Beta	Se	*P*-value	Beta	Se	*P*-value	Beta	Se	*P*-value	OR	OR (95%CI)
HMGCR	Irritable bowel syndrome	7	0.188	0.945	0.850	0.206	0.218	0.345	0.203	0.175	0.245	1.226	(0.870, 1.727)
	Functional constipation	7	0.237	0.517	0.666	0.281	0.117	0.017	0.229	0.096	0.016	1.258	(1.043, 1.517)
	Functional dysphagia	7	–0.850	1.334	0.552	0.380	0.270	0.159	0.316	0.243	0.193	1.372	(0.853, 2.207)
	Functional dyspepsia	7	1.005	0.961	0.344	0.326	0.217	0.133	0.363	0.178	0.042	1.437	(1.014, 2.036)
	Nausea and vomiting	7	0.577	0.998	0.588	0.454	0.228	0.047	0.430	0.185	0.020	1.537	(1.070, 2.207)
	Functional abdominal pain	7	–0.004	0.014	0.790	–0.007	0.004	0.053	–0.008	0.003	0.003	0.992	(0.986, 0.997)
	Disorders of gallbladder, biliary tract and pancreas	7	0.133	0.511	0.806	0.533	0.117	< 0.001	0.509	0.091	< 0.001	1.664	(1.392, 1.989)
PCSK9	Irritable bowel syndrome	12	0.197	0.129	0.158	0.101	0.108	0.349	–0.042	0.106	0.692	0.959	(0.779, 1.180)
	Functional constipation	12	–0.097	0.079	0.245	–0.061	0.059	0.306	–0.044	0.055	0.426	0.957	(0.858, 1.067)
	Functional dysphagia	12	0.077	0.149	0.618	0.010	0.125	0.939	–0.055	0.105	0.602	0.947	(0.770, 1.163)
	Functional dyspepsia	12	–0.096	0.201	0.642	–0.124	0.113	0.272	–0.201	0.139	0.148	0.818	(0.623, 1.074)
	Nausea and vomiting	12	–0.041	0.137	0.772	–0.080	0.116	0.494	–0.159	0.097	0.099	0.853	(0.706, 1.031)
	Functional abdominal pain	12	0.010	0.008	0.267	–0.003	0.003	0.303	–0.003	0.002	0.157	0.997	(0.992, 1.001)
	Disorders of gallbladder, biliary tract and pancreas	12	–0.012	0.065	0.853	–0.048	0.055	0.386	–0.090	0.046	0.049	0.914	(0.836, 1.000)
NPC1L1	Irritable bowel syndrome	3	–1.639	4.651	0.784	–0.633	0.394	0.108	–0.413	0.438	0.346	0.662	(0.280, 1.562)
	Functional constipation	3	1.556	1.461	0.480	–0.682	0.228	0.003	–0.724	0.210	0.001	0.485	(0.321, 0.732)
	Functional dysphagia	3	5.157	3.176	0.351	0.683	0.473	0.149	0.558	0.511	0.276	1.746	(0.641, 4.759)
	Functional dyspepsia	3	–1.789	2.707	0.628	0.254	0.383	0.507	0.205	0.348	0.557	1.227	(0.620, 2.429)
	Nausea and vomiting	3	–1.321	2.817	0.721	–0.496	0.406	0.222	–0.446	0.363	0.219	0.640	(0.314, 1.303)
	Functional abdominal pain	3	–0.019	0.044	0.740	–0.008	0.007	0.203	–0.009	0.006	0.097	0.991	(0.980, 1.002)
	Disorders of gallbladder, biliary tract and pancreas	3	0.948	1.333	0.607	–0.195	0.196	0.320	–0.240	0.172	0.162	0.787	(0.562, 1.101)
PPARG	Irritable bowel syndrome	3	1.156	7.979	0.908	–0.982	0.573	0.086	–0.812	0.490	0.098	0.444	(0.170, 1.161)
	Functional constipation	3	2.662	4.379	0.652	–0.169	0.319	0.597	–0.180	0.269	0.503	0.835	(0.492, 1.416)
	Functional dysphagia	3	12.645	9.124	0.398	0.845	0.703	0.230	0.648	0.564	0.250	1.911	(0.633, 5.768)
	Functional dyspepsia	3	3.859	11.889	0.800	–0.568	0.649	0.382	–0.145	0.546	0.790	0.865	(0.296, 2.523)
	Nausea and vomiting	3	–14.455	8.423	0.336	–0.897	0.670	0.181	–0.368	0.614	0.550	0.692	(0.208, 2.309)
	Functional abdominal pain	3	–0.098	0.123	0.570	–0.007	0.009	0.392	–0.006	0.008	0.403	0.994	(0.979, 1.008)
	Disorders of gallbladder, biliary tract and pancreas	3	–2.038	5.534	0.775	0.327	0.314	0.297	0.103	0.258	0.688	1.109	(0.669, 1.837)

Gene	Outcome	95% CI	*P*	Cochran Q test *p*	MR-Egger intercept *p*
	Irritable bowel syndrome	1.23 (0.87–1.73)	0.245	0.964	0.987
	Functional constipation	1.26 (1.04–1.52)	0.016	0.79	0.989
	Functional dysphagia	1.37 (0.85–2.21)	0.193	0.185	0.414
HMGCR	Functional dyspepsia	1.44 (1.01–2.04)	0.042	0.815	0.527
	Nausea and vomiting	1.54 (1.07–2.21)	0.020	0.84	0.886
	Functional abdominal pain	0.99 (0.99–1.00)	0.003	0.728	0.781
	Disorders of gallbladder, biliary tract and pancreas	1.66 (1.39–1.99)	< 0.001	0.368	0.487
	Irritable bowel syndrome	0.96 (0.78–1.18)	0.692	0.19	0.026
	Functional constipation	0.96 (0.86–1.07)	0.426	0.265	0.364
	Functional dysphagia	0.95 (0.77–1.16)	0.602	0.979	0.241
PCSK9	Functional dyspepsia	0.82 (0.62–1.07)	0.148	0.011	0.48
	Nausea and vomiting	0.85 (0.71–1.03)	0.099	0.777	0.249
	Functional abdominal pain	1.00 (0.99–1.00)	0.157	0.453	0.136
	Disorders of gallbladder, biliary tract and pancreas	0.91 (0.84–1.00)	0.049	0.488	0.12
	Irritable bowel syndrome	0.66 (0.28–1.56)	0.346	0.196	0.835
	Functional constipation	0.49 (0.32–0.73)	0.001	0.287	0.36
	Functional dysphagia	1.75 (0.64–4.76)	0.276	0.184	0.382
NPC1L1	Functional dyspepsia	1.23 (0.62–2.43)	0.557	0.693	0.593
	Nausea and vomiting	0.64 (0.31–1.30)	0.219	0.951	0.807
	Functional abdominal pain	0.99 (0.98–1.00)	0.097	0.816	0.863
	Disorders of gallbladder, biliary tract and pancreas	0.79 (0.56–1.10)	0.162	0.575	0.534
	Irritable bowel syndrome	0.44 (0.17–1.16)	0.098	0.876	0.846
	Functional constipation	0.84 (0.49–1.42)	0.503	0.755	0.633
	Functional dysphagia	1.91 (0.63–5.77)	0.250	0.365	0.413
PPARG	Functional dyspepsia	0.87 (0.30–2.52)	0.790	0.301	0.793
	Nausea and vomiting	0.69 (0.21–2.31)	0.550	0.245	0.343
	Functional abdominal pain	0.99 (0.98–1.01)	0.403	0.707	0.59
	Disorders of gallbladder, biliary tract and pancreas	1.11 (0.67–1.84)	0.688	0.333	0.765

$p < 0.05$ was considered statistically significant

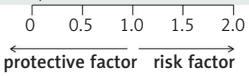

Figure 2. Association between LDL-C mediated by *HMGCR*, *PCSK9*, *NPC1L1*, and *PPARG* genes and the risk of FGIDs

p – p value for IVW-MR, Cochran Q test p – p value for Cochran's Q test MR-Egger intercept p – p value for MR-Egger intercept. HMGCR – HMG-CoA reductase, PCSK9 – proprotein convertase subtilisin/kexin type 9, NPC1L1 – Niemann-Pick C1-like protein 1, PPARG – peroxisome proliferator activated receptor γ.

cohort study of 477,293 participants from the UK Biobank by Zhang *et al.* reported that regular statin use was associated with a reduced risk of IBS in males [6]. Another propensity score-matched cohort analysis involving 12,684 patients indicated that statin use was associated with a lower risk of diarrhea without increasing the risk of other FGIDs such as constipation or abdominal pain [12]. While these studies offer partial support for our findings, several large cohort and meta-analyses have found no significant association between lipid-lowering drug use and the incidence of constipation, gallbladder disorders, or abdominal pain [35–38]. Such inconsistencies likely arose from inherent limitations of observational designs. It was challenging to rigorously control for key confounders such as dietary patterns, lifestyle, comorbidities, and concomitant medications. In addition, the absence of placebo controls or inadequate documentation of gastrointestinal adverse events in some studies may introduce bias. And finally, since FGID symptoms can significantly influence medication adherence, disentangling causality from reverse causation remained difficult.

In contrast, the drug-target MR design employed in this study offered distinct advantages. First, by using genetic instruments strongly associated with variations in the drug target gene to mimic lifelong inhibition of the target, this approach substantially minimized confounding and reverse causality inherent in conventional epidemiological studies. Second, our study simultaneously evaluated four major lipid-lowering targets, clearly distinguishing the effect of HMGCR inhibition from those of other targets and suggesting potential specificity. Third, our analysis comprehensively covered multiple FGID subtypes according to the Rome IV criteria. Thus, the work methodologically addressed the gaps left by prior observational evidence and provided higher-level support for the causal hypothesis that statins may reduce the risk of specific FGIDs.

The potential protective effects of statins against FGIDs may be explained by the following mechanisms. Lipid-lowering drugs have the potential to impact the diversity and abundance of gut microbiota, thereby holding significant promise beyond their lipid-lowering effects, particu-

Table V. Sensitivity analysis association between LDL cholesterol mediated by gene *HMGCR*, *PCSK9*, *NPC1L1*, *PPARG* and the risk of FDIGs

Exposure	Outcome	*P*-value for Cochran *Q* test	*P*-value for MR-Egger intercept	*P*-value for MR-PRESSO Global test
HMGCR	Irritable bowel syndrome	0.964	0.987	0.968
	Functional constipation	0.790	0.989	0.809
	Functional dysphagia	0.185	0.414	0.246
	Functional dyspepsia	0.815	0.527	0.850
	Nausea and vomiting	0.840	0.886	0.846
	Functional abdominal pain	0.728	0.781	0.793
	Disorders of gallbladder, biliary tract and pancreas	0.368	0.487	0.430
PCSK9	Irritable bowel syndrome	0.190	0.026	0.250
	Functional constipation	0.265	0.364	0.376
	Functional dysphagia	0.979	0.241	0.933
	Functional dyspepsia	0.011	0.480	0.085
	Nausea and vomiting	0.777	0.249	0.742
	Functional abdominal pain	0.453	0.136	0.518
	Disorders of gallbladder, biliary tract and pancreas	0.488	0.120	0.516
NPC1L1	Irritable bowel syndrome	0.196	0.835	N/A
	Functional constipation	0.287	0.360	N/A
	Functional dysphagia	0.184	0.382	N/A
	Functional dyspepsia	0.693	0.593	N/A
	Nausea and vomiting	0.951	0.807	N/A
	Functional abdominal pain	0.816	0.863	N/A
	Disorders of gallbladder, biliary tract and pancreas	0.575	0.534	N/A
PPARG	Irritable bowel syndrome	0.876	0.846	N/A
	Functional constipation	0.755	0.633	N/A
	Functional dysphagia	0.365	0.413	N/A
	Functional dyspepsia	0.301	0.793	N/A
	Nausea and vomiting	0.245	0.343	N/A
	Functional abdominal pain	0.707	0.590	N/A
	Disorders of gallbladder, biliary tract and pancreas	0.333	0.765	N/A

N/A – because of not enough intrumental variables

larly in gastrointestinal disorders and cancer [7, 39–42]. Studies have shown a lower prevalence of the Bacteroides 2 (Bact2) enterotype, which is associated with dysbiosis and low-grade inflammation among statin users [7]. Animal and human studies also indicated that atorvastatin treatment increased the abundance of beneficial bacteria such as *Lactobacillus reuteri* [42]. Given that *L. reuteri* has been shown to improve intestinal barrier function, reduce inflammation, and modulate visceral sensitivity [43–45], statin-induced favorable shifts in gut microbiota may contribute to alleviating FGID symptoms.

Chronic low-grade inflammation and immune dysregulation are considered part of the pathophysiology of FGIDs [46, 47]. Beyond lipid lowering, statins are well established for their pleiotropic effects, including suppression of proinflammatory cytokines and modulation of immune cell function [48, 49]. Therefore, statins may im-

Table VI. Association between LDL cholesterol mediated by gene *HMGCR* and potential risk factors for FGIDs

Risk factor	Resource	PMID/GWAS ID	Beta	Se	*P*-value
Waist circumference	UK Biobank	ukb-b-9405	–0.228	0.036	< 0.001
Type 2 diabetes	DIAGRAM/GERA/UKB	ebi-a-GCST006867	–0.349	0.068	< 0.001
Mood swings	UK Biobank	ukb-b-14180	0.020	0.009	0.025

Table VII. IVW-MR association between potential risk factors for FGIDs and the risk of FGIDs

Potential risk factor	Outcome	Beta	Se	*P*-value
Waist circumference	Functional constipation	–3.369E-02	5.234E-02	0.520
	Functional dyspepsia	7.219E-02	9.307E-02	0.438
	Nausea and vomiting	–4.079E-02	9.356E-02	0.663
	Functional abdominal pain	4.274E-03	1.443E-03	0.003
	Disorders of gallbladder, biliary tract and pancreas	5.204E-01	5.120E-02	< 0.001
Type 2 diabetes	Functional constipation	2.204E-02	1.876E-02	0.240
	Functional dyspepsia	8.561E-03	3.297E-02	0.795
	Nausea and vomiting	1.497E-02	3.610E-02	0.678
	Functional abdominal pain	3.040E-04	4.832E-04	0.529
	Disorders of gallbladder, biliary tract and pancreas	4.952E-02	2.006E-02	0.014
Mood swings	Functional constipation	2.421E-01	2.924E-01	0.408
	Functional dyspepsia	1.135E+00	4.680E-01	0.015
	Nausea and vomiting	9.290E-01	4.796E-01	0.053
	Functional abdominal pain	3.976E-02	7.351E-03	< 0.001
	Disorders of gallbladder, biliary tract and pancreas	6.706E-01	2.479E-01	0.007

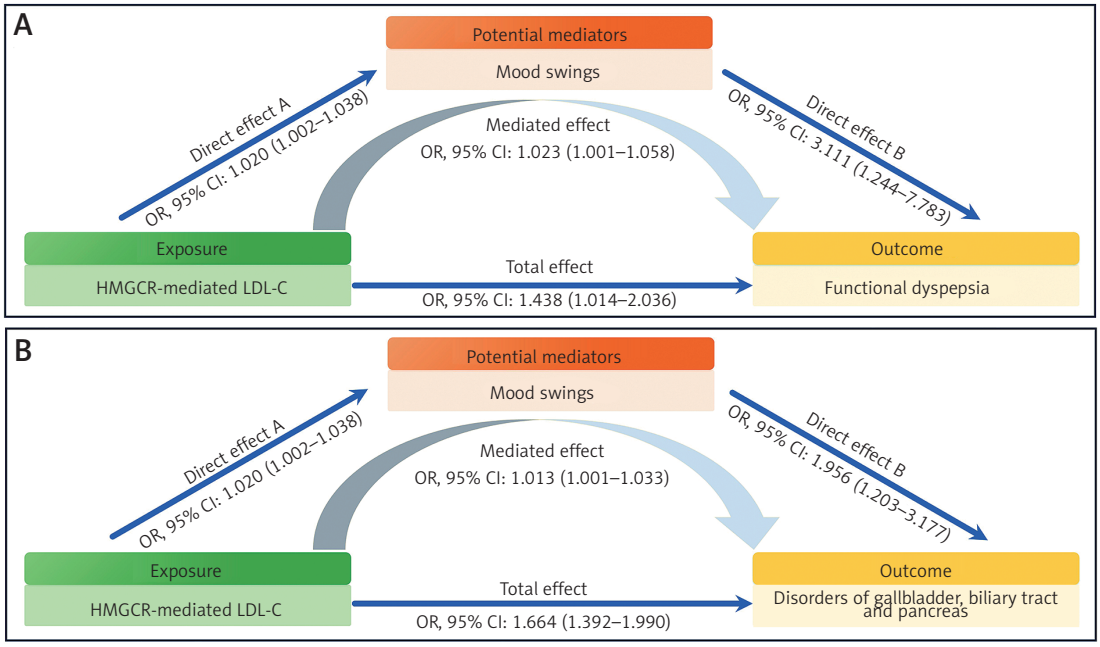

Figure 3. Mediation analysis of the effect of HMGCR-mediated LDL-C on the risk of FGIDs via potential mediators with two-step Mendelian randomization analysis. **A** – Mediation analysis of the effect of HMGCR-mediated LDL-C on the risk of functional dyspepsia. **B** – Mediation analysis of the effect of HMGCR-mediated LDL-C on the risk of disorders of the gallbladder, biliary tract and pancreas

Total effect – the effect of HMGCR-mediated LDL-C on FGIDs, direct effect A – the effect of HMGCR-mediated LDL-C on mediator (mood swings), direct effect B – the effect of mediator (mood swings) on FGIDs, mediation effect – the effect of HMGCR-mediated LDL-C on FGID risk through the mediator (mood swings).

prove FGID symptoms through systemic and local anti-inflammatory and immunomodulatory actions, thereby attenuating the underlying microinflammatory state.

The mediation analysis in this study suggests that mood swings partially mediate the protective effect of statins against FGIDs, strongly pointing to a central role of the gut-brain axis in this association. Substantial evidence links cholesterol homeostasis to neurotransmitter function [50–52]. Statins may influence neurotransmitter levels in the central and enteric nervous systems or modulate the secretion and signaling of gut-brain peptides, thereby simultaneously improving mood and gastrointestinal function. For example, studies suggested that statins can affect brain cholesterol metabolism and reestablish homeostasis, maintaining normal synaptic integrity and serotonin function, and subsequently regulating both mood and gastrointestinal motility [50]. However, key questions remained regarding specific neurotransmitter alterations and long-term outcomes. Notably, the choice of statin, such as lipophilic atorvastatin or hydrophilic rosuvastatin, significantly affects blood-brain barrier penetration and tissue distribution, implying that effects on neurotransmission may vary considerably among agents. Consequently, there is currently no validated method to predict which statin or which patients would benefit most in the context of FGID management.

A notable strength of our study lies in our use of genetic instruments as proxies for lipid-lowing drugs. However, the study also has some limitations. First, the primary analysis relied on blood-based eQTL data as a proxy for HMGCR expression, rather than using tissue-specific data from more relevant sites such as the liver or intestine. Second, MR estimates reflected lifelong target perturbation, which may differ from the effects of time-limited pharmacological treatment. Third, drug-target MR cannot distinguish potential heterogeneous effects among different compounds acting on the same target. Finally, the exclusive use of European ancestry data limited the generalizability of the findings. Accordingly, future studies should focus on several key directions. Mechanistically, experimental models and prospective clinical trials are needed to directly measure the dynamic effects of statins on neurotransmitters, gut microbiota, and inflammatory markers, thereby clarifying specific pathways. For clinical translation, prospective studies comparing different statins should be conducted, combined with pharmacogenomic analyses to evaluate the potential for personalized treatment. Additionally, future analyses should incorporate tissue-specific eQTL or pQTL data to improve the precision of genetic

Table VIII. Mood swings in mediating the relationship between HMGCR-mediated LDL-C and the risk of FGIDs

Exposure	Mediator	Outcome	Total effect		Direct effect A		Direct effect B		Mediation effect		Mediated proportion (%)
			Beta (95%CI)	OR (95%CI)	Beta (95%CI)	OR (95%CI)	Beta (95%CI)	OR (95%CI)	Beta (95%CI)	OR (95%CI)	(95%CI)
HMGCR-mediated LDL-C	Mood swings	Functional dyspepsia	0.363 (0.014, 0.711)	1.438 (1.014, 2.036)	0.020 (0.002, 0.037)	1.020 (1.002, 1.038)	1.135 (0.218, 2.052)	3.111 (1.244, 7.783)	0.023 (0.001, 0.056)	1.023 (1.001, 1.058)	6.23% (3.30%, 9.20%)
		Disorders of gallbladder, biliary tract and pancreas	0.509 (0.331, 0.688)	1.664 (1.392, 1.990)	0.020 (0.002, 0.037)	1.020 (1.002, 1.038)	0.671 (0.185, 1.156)	1.956 (1.203, 3.177)	0.013 (0.001, 0.032)	1.013 (1.001, 1.033)	2.62% (−2.10%, 7.40%)

proxies. Together, these efforts will help elucidate the specific mechanisms of lipid-lowering drugs in FGIDs and advance their clinical application.

In summary, this study provided novel and robust genetic evidence supporting a causal role of HMGCR inhibition in reducing the risk of multiple FGIDs, with mood swings identified as a potential partial mediator. These findings implied its possible benefits in the realm of gut-brain interaction disorders. While future research is needed to clarify the underlying molecular mechanisms, validate clinical efficacy, and explore personalized application strategies, this work offers an important theoretical foundation and direction for understanding the etiology of FGIDs and developing novel therapeutic approaches.

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Ethical approval

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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