Diabetology & Metabolic Syndrome

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Association of lipid-lowering drugs with the risk of type 2 diabetes and its complications: a mendelian randomized study

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Abstract

Background The pathogenesis of type 2 diabetes mellitus is somewhat associated with lipid metabolism. We aim to assess the impact of lipid-lowering drugs (*HMGCR* inhibitors, *PCSK9* inhibitors, and *NPC1L1* inhibitors) on type 2 diabetes mellitus and its complications through a two-sample Mendelian randomization (MR) study.

Method We identified suitable genetic instruments from the GWAS database that represent the expression levels of three genes, interpreting reduced genetically proxied gene expression as indicative of lipid-lowering drug use. We evaluated the causal relationships among these variables employing a two-sample Mendelian randomization approach, with the Inverse Variance Weighted (IVW) analysis serving as the primary method. Coronary artery disease was utilized as a positive control to validate the reliability of the selected genetic instruments.

Result Increased genetically proxied *HMGCR* expression is significantly associated with a reduced risk of type 2 diabetes mellitus (OR = 0.64, 95%CI = 0.55–0.74), which was replicated in the FinnGen study with consistent results (OR = 0.65, 95%CI = 0.53–0.80). Increased genetically proxied *HMGCR* expression is associated with a reduced risk of diabetic retinopathy (OR = 0.23, 95%CI = 0.12–0.44) and diabetic nephropathy (OR = 0.35, 95%CI = 0.17–0.71). In contrast, increased genetically proxied *PCSK9* expression is associated with a decreased risk of diabetic coma (OR = 0.70, 95%CI = 0.50–0.98), diabetic neuropathy (OR = 0.24, 95%CI = 0.14–0.42), diabetic retinopathy (OR = 0.67, 95%CI = 0.48–0.96), diabetic cardiovascular diseases (OR = 0.62, 95%CI = 0.38–0.99), and diabetic nephropathy (OR = 0.62, 95%CI = 0.41–0.95).

Conclusions This Mendelian randomization study suggests an association between *HMGCR* and the pathogenesis of type 2 diabetes mellitus, with increased genetically proxied *HMGCR* expression reducing the risk of type 2 diabetes mellitus, while *PCSK9* and *NPC1L1* show no significant association with type 2 diabetes mellitus. These findings may offer more reasonable lipid-lowering drug options for patients with dyslipidemia.

Highlights

- Many studies have found that certain lipid-lowering drugs increase the risk of some diseases.
- Observational study finds *HMGCR* inhibitors increase the risk of type 2 diabetes mellitus.
- *HMGCR* inhibitor use increased the risk of type 2 diabetes in both of two different populations.

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Keywords Lipid-lowering drugs, Type 2 diabetes Mellitus, Mendelian randomization, Complications of type 2 diabetes, *HMGCR*

Introduction

Type 2 diabetes is a prevalent endocrine system metabolic disorder characterized by either absolute or relative insufficient insulin secretion and reduced sensitivity of target organs to insulin, resulting in disturbances in lipid metabolism, water, and electrolytes, among other aspects [1, 2]. According to the "IDF Diabetes Atlas (10th edition)" report released in 2021, approximately 537 million adults aged 20 to 79 worldwide are afflicted with diabetes, with projections suggesting this figure will rise to 643 million by 2030 [3]. This represents a 46% increase in the number of diabetes cases during this period [4]. Furthermore, medical expenses for individuals with diabetes are three times higher than those for the general population without diabetes [5]. Conservative estimates by the International Diabetes Federation indicate that in 2015, the cost of managing diabetes and its related complications amounted to $673 billion, constituting 12% of global health expenditure [6]. Undoubtedly, these trends underscore the escalating social burden attributable to diabetes [7]. As type 2 diabetes progresses, various organs and tissues of patients suffer damage, which stands as the primary cause of mortality among individuals with type 2 diabetes [8–10]. Reports indicate that in the United States, 53% of medical expenses incurred over the lifetimes of type 2 diabetes patients are allocated towards managing major late complications such as nephropathy, neuropathy, retinopathy, and cardiovascular complications [11].

Given the elusive nature of the specific pathogenesis underlying Type 2 Diabetes Mellitus, prevailing observational studies hint at a potential slight elevation in the risk of type 2 diabetes mellitus development among individuals utilizing 3-hydroxy-3-methylglutaryl-CoA reductase(*HMGCR*) inhibitors (statins) [12, 13], although the establishment of a causal relationship remains elusive. Similarly, a dearth of research exists concerning the potential risks of type 2 diabetes mellitus and its associated complications concerning Proprotein convertase subtilisin/kexin type 9(*PCSK9*) inhibitors and NPC1 like intracellular cholesterol transporter 1(*NPC1L1*) inhibitors. These pharmaceutical agents are designed to lower circulating LDL-c levels to attain lipid-lowering objectives.

Mendelian randomization(MR) studies are recognized as a method for establishing causality between exposure and outcome, utilizing SNPs as proxy instruments for exposure factors to minimize the influence of confounding factors [14]. According to Mendelian genetics, genetic variation is randomly allocated at conception and remains randomly distributed before the onset of disease, thereby minimizing confounding factors and reverse causation [15]. While randomized controlled trials (RCTs) are regarded as the gold standard for establishing causal relationships, their limitations—including high workload, complexity, and limited sample sizes—pose significant challenges for conducting large-scale studies. MR is recognized as a robust alternative to RCTs, with a growing body of research utilizing MR to explore potential causal associations [16]. Therefore, in this study, we conducted a two-sample Mendelian randomization analysis to examine the relationship between lipid-lowering drugs (*HMGCR* inhibitors, *PCSK9* inhibitors, and *NPC1L1* inhibitors) and type 2 diabetes mellitus and its complications.

Method

Data sources

In this drug-targeted Mendelian randomization analysis, all data sources are publicly available, as outlined in Table 1. All participants in the GWAS provided informed consent, obtained appropriate ethical approvals, and underwent rigorous quality control procedures. Since the data utilized in this study are summary-level GWAS data, no additional ethical approval is required. Figure 1 delineates the fundamental design framework of this study.

Genetic proxy tools for lipid-lowering drugs

According to FDA reports, three approved lipid-lowering drugs were selected for corresponding studies: *HMGCR* inhibitors, *PCSK9* inhibitors, and *NPC1L1* inhibitors.

In this study, LDL-c was chosen as the downstream biomarker because *HMGCR* inhibitors, *PCSK9* inhibitors, and *NPC1L1* inhibitors have demonstrated efficacy in reducing human LDL-c levels (refer to Fig. 2). Subsequently, we screened SNPs with genome-wide significance for LDL-c within a±100 kb range of the *HMGCR* gene (build GRCh37.p13; chromosome 5: 74632993.74657941), *PCSK9* gene (build GRCh37.p13; chromosome 1: 55505221.55530525), and *NPC1L1* gene (build GRCh37.p13; chromosome 7: 44552134.44580929), with a significance threshold of $p<5\times10^{-8}$. SNPs with low linkage disequilibrium ($r^2<0.3$) among them were then selected to maximize the instrumental strength of each drug.

Furthermore, considering existing observational studies on lipids and type 2 diabetes mellitus, we simultaneously investigated the causal relationship between genetically predicted LDL-c (rather than through lipid-lowering drug targets) and type 2 diabetes mellitus.

Table 1 Summary of the GWAS data used in the MR analysis

Phenotype	No of participants	Ethnicity	Consortium/ Cohort	Year of publication	PubMed ID / GWAS ID
LDL-c	440,546	European	UK Biobank	2020	32,203,549
T2DM	61,714cases/ 1,178controls	European	NA	2018	30,054,458
	32,469cases/ 183,185controls	European	FinnGen	2021	finn-b-E4_DM2
CAD	60,801cases/ 123,504controls	European	CARDIoGRAMplusC4D	2015	26,343,387
Type 2 diabetes with coma	2,247cases/16,380,337controls	European	FinnGen	2021	finn-b-E4_DM2COMA
Type 2 diabetes with ketoacidosis	183,185cases/ 16,380,334 controls	European	FinnGen	2021	finn-b-E4_DM2KETO
Type 2 diabetes with neurological complications	183,185cases/ 16,380,335 controls	European	FinnGen	2021	finn-b-E4_DM2NEU
Type 2 diabetes with ophthalmic complications	183,185cases/ 16,380,340 controls	European	FinnGen	2021	finn-b-E4_DM2OPTH
Type 2 diabetes with peripheral circulatory complications	183,185cases/ 16,380,336 controls	European	FinnGen	2021	finn-b-E4_DM-2PERIPH
Type 2 diabetes with renal complications	183,185cases/ 16,380,337 controls	European	FinnGen	2021	finn-b-E4_DM2REN

MR, Mendelian randomisation; LDL-c, Low-density lipoprotein cholesterol; T2DM, type 2 diabetes mellitus; CAD, coronary artery disease; GWAS, genome-wide association studies.

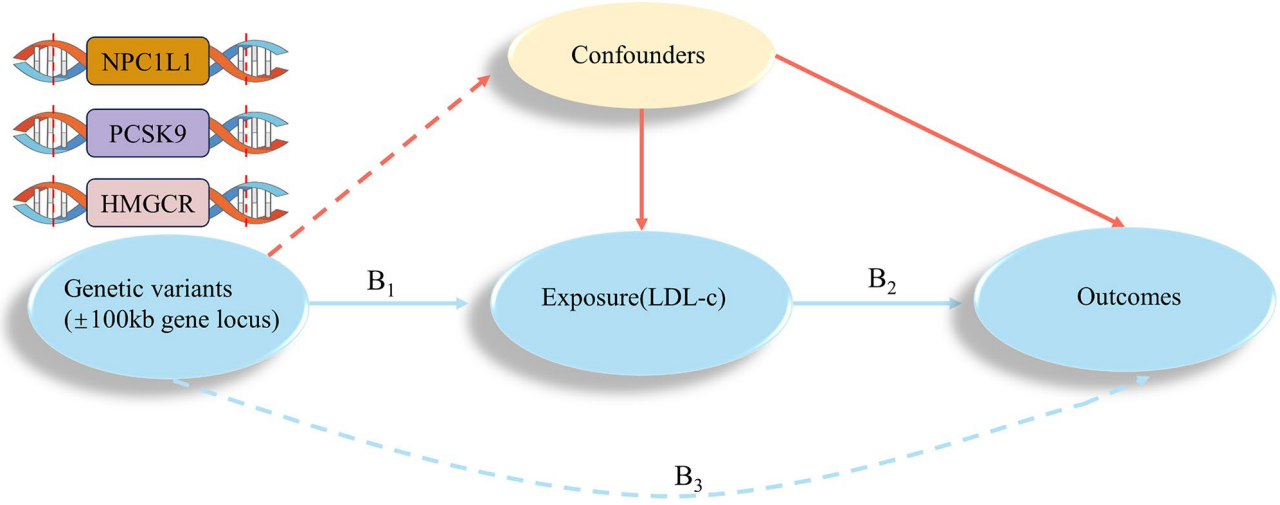

Fig. 1 Single nucleotide polymorphisms (SNPs) were extracted from GWASs on low-density lipoprotein (LDL) cholesterol levels (i.e., 3-ydroxy-3-methylglutaryl-coenzyme A reductase [*HMGCR*], proprotein convertase subtilisin/kexin type 9 [*PCSK9*] and niemann-pick c1-like 1[*NPC1L1*] SNPs 100 kilobases of gene base-pair boundaries) surpassing genome-wide significance ($P < 5 \times 10–8$)

Independent SNPs with genome-wide significance for LDL-c were selected from the initial pool of 12,321,875 SNPs, with a linkage disequilibrium (LD) threshold of $r^2 < 0.001$ and a distance threshold greater than 10,000 kb as instrumental variables.

Source of outcomes

To bolster the credibility of our findings, we employed genetic instruments sourced from two distinct sample repositories: Ebi for the discovery phase and the FinnGen study for validation. In our investigation, we delved into the relationship between genetically predicted lipid-lowering drug targets and type 2 diabetes mellitus. The data obtained from Ebi originated from a meta-analysis conducted by Angli Xue et al. [17], wherein they amalgamated data from the DIAbetes Genetics Replication and Meta-analysis (DIAGRAM) [18], Genetic Epidemiology Research on Aging (GERA) [19], and the full cohort release of the UK Biobank (UKB) to maximize statistical power [20]. The FinnGen study, on the other hand, constitutes a nationwide genome-wide meta-analysis from Finland [21], with minimal overlap with Ebi and low-density lipoprotein cholesterol (LDL-c) genome-wide association study (GWAS) data. To serve as positive controls for our study, coronary artery disease (CAD) data were acquired from the Coronary ARtery DIsease Genome wide Replication and Meta-analysis (CARDIoGRAM) plus The Coronary Artery Disease (C4D) Genetics (CARDIoGRAMplusC4D). Furthermore, all GWAS data about type 2 diabetes mellitus complications were

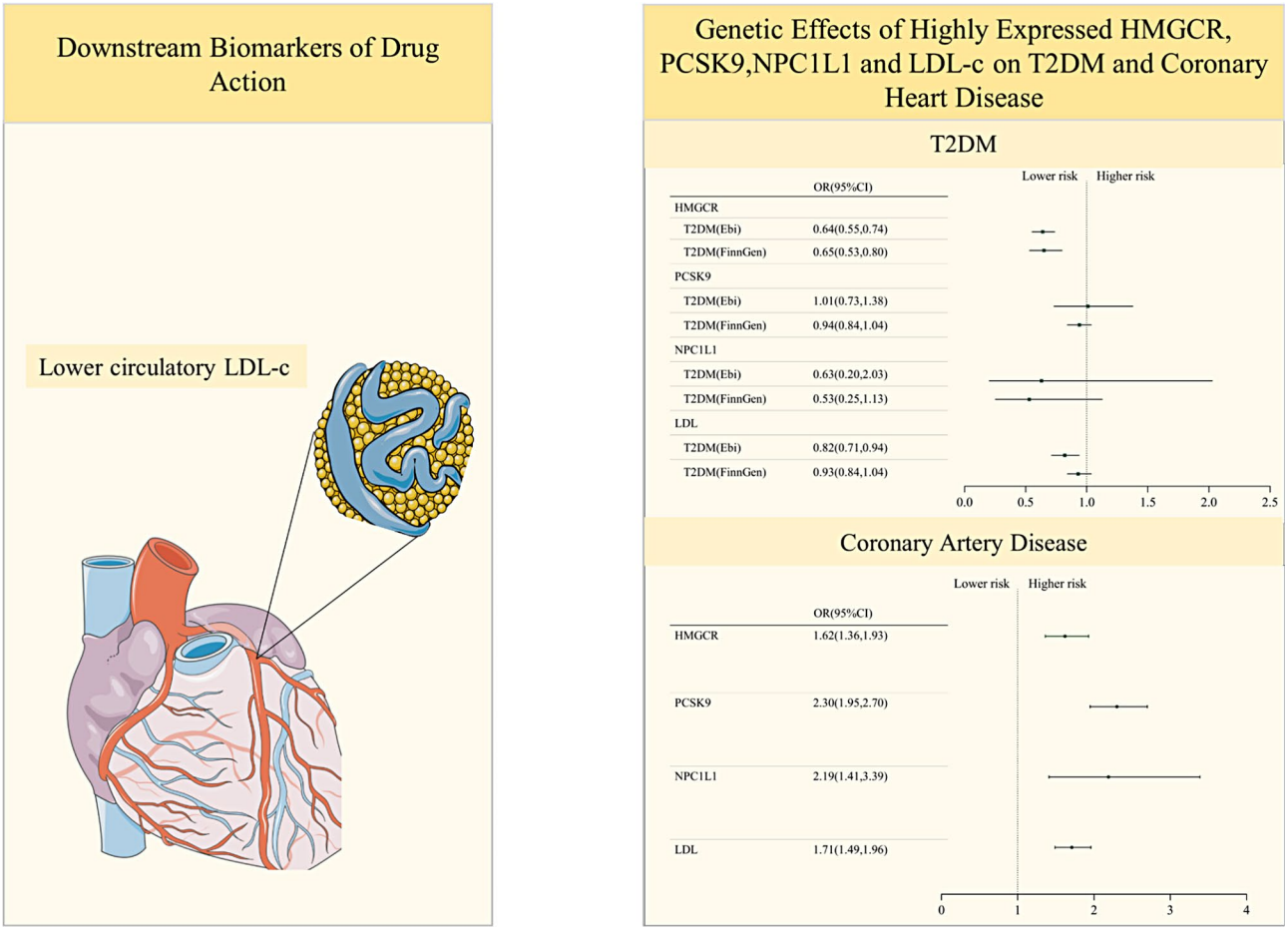

Fig. 2 Drug-target Mendelian randomization (MR) was performed on T2DM and coronary heart disease. Data shown are standardized MR effect estimates and 95% CIs corresponding to elevation of LDL cholesterol by drug-targeted genes

extracted from the FinnGen study [21]. According to the ICD-11 disease codes, type 2 diabetes is designated as 5A11, CAD is classified as the composite event L1-BA8, and type 2 diabetes-related complications are delineated by the FinnGen study.

Statistical analysis

Primary analysis

The present investigation predominantly adopts the inverse variance–weighted (IVW) methodology, leveraging multiple random effects to derive the weighted mean of individual factor estimates [22]. Ensuring robustness, all Mendelian randomization (MR) analyses adhere rigorously to three fundamental assumptions delineated within the literature. Firstly, genetic instruments must exhibit a robust association with the exposure under scrutiny. Secondly, instrumental variables (IVs) are postulated to solely influence the outcome through their effect on the exposure, excluding any alternative causal pathways. Lastly, single nucleotide polymorphisms (SNPs) employed for both exposure and outcome variables should ideally be drawn from distinct populations, mitigating potential biases stemming from population stratification. Effect estimates are articulated in terms of odds ratios (ORs), β coefficients, or proportions, accompanied by their corresponding 95% confidence intervals (CIs) to elucidate the precision of the estimates. Furthermore, Cochran's Q test is employed to gauge the presence of heterogeneity amongst the included studies, where a significance level of $p<0.05$ indicates the presence of substantial heterogeneity warranting further exploration. To address potential sources of pleiotropy, MR-Egger regression analyses are deployed, providing a robust assessment of the horizontal pleiotropy levels exhibited by the SNPs serving as instrumental variables. Specifically, the intercept term within MR-Egger regression serves as a pivotal indicator, with a significance threshold set at $p<0.05$, denoting evidence suggestive of horizontal pleiotropy. This comprehensive methodological framework ensures the integrity and reliability of the ensuing findings, facilitating a nuanced understanding of the interplay between genetic variants, exposures, and outcomes within the realms of Mendelian randomization analysis.

Supplementary analysis

To ensure the robustness and comprehensiveness of our findings, we undertook a series of supplementary analyses aimed at reinforcing the validity of our primary investigation while offering comparative insights. Initially, we employed coronary artery disease (CAD) as a positive control outcome to scrutinize the efficacy of the genetic instruments utilized in our study. Leveraging data from a genomic analysis comprising 60,801 clinically diagnosed cases of CAD, juxtaposed against 123,504 control subjects, we evaluated the genetic associations pertinent to this cardiovascular pathology [23]. Subsequently, mirroring the methodology employed in our principal analysis, we reiterated the MR analysis employing the same genetic instruments utilized in our primary investigation.

Furthermore, recognizing the clinical significance of elucidating the interplay between lipid-lowering drugs and associated complications of type 2 diabetes mellitus, we conducted additional analyses exploring the causal relationships between various type 2 diabetes mellitus complications and the genetic proxies of lipid-lowering medications. All MR analyses, including both primary and supplementary investigations, were meticulously executed utilizing the "TwoSampleMR" and "MendelianRandomization" R packages within the R statistical environment version 4.3.1, ensuring adherence to best practices in MR methodology and facilitating reproducibility and transparency in our analytical approach. A significance threshold of $p<0.05$ was employed, with a rigorous two-tailed statistical testing standard applied for evaluation.

Result

Primary analysis

Preliminary analysis was conducted separately on type 2 diabetes mellitus data from Ebi and FinnGen, resulting in the identification of 19 SNPs each for promoting *HMGCR* expression to represent LDL-c elevation, 28 and 29 for *PCSK9*, and 6 for *NPC1L1*. In Ebi's type 2 diabetes mellitus data, increased genetically proxied *HMGCR* expression was significantly associated with a reduced risk of type 2 diabetes mellitus (OR=0.64, 95% CI=0.55–0.74). This analysis was replicated using data from the FinnGen study, yielding consistent results (OR=0.65, 95% CI=0.53–0.80) (refer to Fig. 2 and Supplementary Table 1), with various sensitivity analyses corroborating the estimates. Cochran's Q test revealed heterogeneity only between *NPC1L1* and LDL, with no evidence of heterogeneity found for *HMGCR* and *PCSK9* ($p>0.05$; Supplementary Table 2). Except for *PCSK9*, intercept terms in MR-Egger regression did not suggest bias from horizontal pleiotropy (all $p>0.05$; Supplementary Table 3). Across both datasets, there was little statistical evidence indicating an association between *PCSK9* and *NPC1L1* with type 2 diabetes mellitus (see Fig. 2 and Supplementary Table 1). Notably, in Ebi's data, genetically proxied LDL-c elevation was associated with a reduced risk of type 2 diabetes mellitus (OR=0.82, 95% CI=0.71–0.94), but this association vanished in the analysis of FinnGen data.

Supplementary analysis

Increased genetically proxied of the three-drug target genes expression and elevation of LDL-c are correlated with an increased risk of coronary heart disease (refer to Fig. 2 and Supplementary Table 4), aligning with actual clinical observations. Table 2 presents the associations between various complications of type 2 diabetes and LDL-c mediated by genetic proxies of the three lipid-lowering drugs. Increased genetically proxied *HMGCR* expression is linked to a reduced risk of type 2 diabetes with ophthalmic complications (OR=0.23, 95% CI=0.12–0.44) and type 2 diabetes with renal complications (OR=0.35, 95% CI=0.17–0.71). Conversely, increased genetically proxied *PCSK9* expression is associated with a decreased risk of type 2 diabetes with coma (OR=0.70, 95% CI=0.50–0.98), neurological complications (OR=0.24, 95% CI=0.14–0.42), ophthalmic complications (OR=0.67, 95% CI=0.48–0.96), peripheral circulatory complications (OR=0.62, 95% CI=0.38–0.99), and renal complications (OR=0.62, 95% CI=0.41–0.95). Various sensitivity analysis methods consistently produced similar results. Besides the horizontal pleiotropy bias observed in the effect of *PCSK9* on type 2 diabetes with ocular disease, no significant horizontal pleiotropy bias was detected in other analyses. Unfortunately, a causal relationship between genetically proxied *NPC1L1* and complications of type 2 diabetes was not identified. Additionally, Table S5 presents the β(SE) for single SNPs of the genetically proxied lipid-lowering drug target genes associated with type 2 diabetes.

Discussion

This drug-targeted MR study substantiates the nexus between increased genetically proxied *HMGCR* expression and the ensuing elevation in LDL-c levels, a phenomenon primarily mediated by *HMGCR*. Additionally, it delineates a mitigated risk of type 2 diabetes mellitus, particularly concerning type 2 diabetes mellitus with ocular disease and nephropathy, concomitant with such elevation. Conversely, the study elucidates that increased genetically proxied *PCSK9* expression and the resultant LDL-c elevation, mediated by *PCSK9*, are comparably associated with a reduced susceptibility to severe type 2 diabetes mellitus complications, including coma, neuropathy, ocular disease, cardiovascular disease, and nephropathy. However, it posits that these associations exhibit diminished correlation with circulating LDL-c

Table 2 Associations between genetically proxied exposures (drug targets) and complications of type 2 diabetes

Gene	Method	OR(95%CI)	*P* value	Egger intercept	SE	*P* value
Type 2 diabetes with coma						
HMGCR	IVW	1.01(0.58,1.78)	0.97	0.01	0.04	0.78
	MR Egger	1.01(0.16,6.39)	0.99			
	Weighted median	0.89(0.41,1.95)	0.77			
	Weighted mode	0.93(0.47,1.85)	0.85			
PCSK9	IVW	0.70(0.50,0.98)	0.04	-0.009	0.01	0.49
	MR Egger	0.78(0.50,1.22)	0.29			
	Weighted median	0.73(0.47,1.13)	0.16			
	Weighted mode	0.73(0.49,1.08)	0.13			
NPC1L1	IVW	3.17(0.84,11.98)	0.09	0.09	0.05	0.16
	MR Egger	0.10(0.002,6.04)	0.34			
	Weighted median	1.22(0.25,5.90)	0.81			
	Weighted mode	1.31(0.22,7.82)	0.78			
Type 2 diabetes with ketoacidosis						
HMGCR	IVW	0.59(0.09,3.77)	0.58	0.05	0.13	0.70
	MR Egger	0.19(0.004,84.93)	0.60			
	Weighted median	0.70(0.11,4.28)	0.69			
	Weighted mode	0.62(0.10,3.88)	0.62			
PCSK9	IVW	1.53(0.70,3.35)	0.29	0.02	0.03	0.50
	MR Egger	1.20(0.42,3.43)	0.74			
	Weighted median	1.38(0.47,4.00)	0.56			
	Weighted mode	1.39(0.53,3.67)	0.51			
NPC1L1	IVW	19.82(0.91,429.69)	0.06	0.039	0.12	0.77
	MR Egger	4.39(0.003,76644.55)	0.78			
	Weighted median	19.41(0.47,797.57)	0.12			
	Weighted mode	8.32(0.12,600.00)	0.38			
Type 2 diabetes with neurological complications						
HMGCR	IVW	0.46(0.17,1.25)	0.13	0.12	0.07	0.09
	MR Egger	0.03(0.001,0.67)	0.04			
	Weighted median	0.31(0.08,1.14)	0.08			
	Weighted mode	0.21(0.05,0.87)	0.05			
PCSK9	IVW	0.24(0.14,0.42)	4.50e-07	-0.03	0.02	0.11
	MR Egger	0.36(0.18,0.75)	1.05e-02			
	Weighted median	0.33(0.17,0.64)	1.12e-03			
	Weighted mode	0.33(0.18,0.64)	2.36e-03			
NPC1L1	IVW	3.09(0.24,40.02)	0.39	0.16	0.08	0.11
	MR Egger	0.005(9.89e-06,2.98)	0.18			
	Weighted median	2.42(0.20,29.59)	0.49			
	Weighted mode	0.32(2.31e-02,4.31)	0.43			
Type 2 diabetes with ophthalmic complications						
HMGCR	IVW	0.23(0.12,0.44)	1.06e-05	0.0003	0.05	0.99
	MR Egger	0.22(0.02,2.03)	2.01e-01			
	Weighted median	0.20(0.10,0.44)	3.96e-05			
	Weighted mode	0.23(0.11,0.48)	1.10e-03			
PCSK9	IVW	0.67(0.48,0.96)	0.03	0.03	0.01	0.04
	MR Egger	0.48(0.30,0.76)	0.004			
	Weighted median	0.6p0(0.38,0.94)	0.03			
	Weighted mode	0.58(0.37,0.89)	0.02			
NPC1L1	IVW	0.43(0.11,1.60)	0.21	-0.03	0.05	0.57
	MR Egger	1.51(0.02,97.76)	0.86			
	Weighted median	0.42(0.09,2.08)	0.29			
	Weighted mode	0.41(0.07,2.53)	0.38			
Type 2 diabetes with peripheral circulatory complications						

Table 2 (continued)

Gene	Method	OR(95%CI)	*P* value	Egger intercept	SE	*P* value
HMGCR	IVW	0.58(0.26,1.29)	0.18	-0.02	0.06	0.72
	MR Egger	0.93(0.07,13.08)	0.96			
	Weighted median	0.52(0.17,1.55)	0.24			
	Weighted mode	0.50(0.17,1.49)	0.23			
PCSK9	IVW	0.62(0.38,0.99)	0.04	-0.003	0.02	0.84
	MR Egger	0.65(0.34,1.23)	0.19			
	Weighted median	0.62(0.32,1.18)	0.14			
	Weighted mode	0.61(0.34,1.07)	0.10			
NPC1L1	IVW	1.02(0.16,6.39)	0.98	-0.03	0.07	0.66
	MR Egger	3.87(0.01,1300.93)	0.67			
	Weighted median	0.79(0.09,7.28)	0.84			
	Weighted mode	0.79(0.07,9.22)	0.85			
Type 2 diabetes with renal complications						
HMGCR	IVW	0.35(0.17,0.71)	0.004	-0.03	0.04	0.61
	MR Egger	0.63(0.06,6.17)	0.69			
	Weighted median	0.33(0.13,0.87)	0.02			
	Weighted mode	0.37(0.15,0.95)	0.05			
PCSK9	IVW	0.62(0.41,0.95)	0.03	0.02	0.02	0.38
	MR Egger	0.52(0.29,0.93)	0.04			
	Weighted median	0.65(0.37,1.16)	0.14			
	Weighted mode	0.55(0.32,0.93)	0.03			
NPC1L1	IVW	0.86(0.17,4.47)	0.86	0.06	0.06	0.43
	MR Egger	0.09(0.0004,17.06)	0.42			
	Weighted median	0.68(0.09,4.95)	0.70			
	Weighted mode	0.50(0.06,4.32)	0.56			

MR, Mendelian randomization ; IVW, inverse variance weighted; OR, odds ratio; CI, confidence interval.

levels. This assertion is corroborated by the absence of a discernible link between LDL-c levels and type 2 diabetes mellitus within the FinnGen population.

In individuals with type 2 diabetes mellitus, *HMGCR* levels exhibit elevation compared to those in the healthy control cohort, conceivably linked to pathways mediated by LDL-c receptors. Numerous studies have investigated the potential associations between various risk factors and the development of type 2 diabetes. For example, individuals who engage in more than 7 h of exercise per week exhibit a reduced relative risk of developing type 2 diabetes (Relative Risk=0.71, 95% CI=0.56–0.90), while those who smoke over 15 cigarettes daily face an increased relative risk (Relative Risk=1.34, 95% CI=1.20–1.50) [24]. Moreover, first-degree relatives of individuals with type 2 diabetes have a 40% increased likelihood of developing the disease, in contrast to an incidence rate of just 6% in the general population [25]. In comparison with these established risk factors for type 2 diabetes, the pathogenic effect of genetically proxied *HMGCR* inhibitor use identified in this study warrants significant attention. While several biological mechanisms have been postulated to elucidate this association [26], the precise mechanism remains elusive. Genetic evidence has implicated that *HMGCR* inhibitors may induce mild impairment in glucose tolerance among patients, thereby heightening the susceptibility to type 2 diabetes mellitus [12]. Furthermore, some investigations posit that *HMGCR* inhibitors might augment the risk of type 2 diabetes mellitus by modulating endogenous cholesterol synthesis [27]. Notably, certain studies propose that heightened internalization of cholesterol within pancreatic β-cells could culminate in compromised insulin secretion [28, 29], a proposition substantiated by murine experimental models [30]. Moreover, it is suggested that *HMGCR* gene variants linked to reduced LDL-c levels correlate with elevated fasting insulin levels and body mass index, indicative of mechanisms intertwined with insulin resistance [31]. Additionally, Vergeer et al. [32] postulate that perturbations in intracellular cholesterol homeostasis attributed to ABCA1 defects might engender impaired insulin secretion in human physiology. These lines of evidence are consonant with the findings of another observational study, which implies a lower incidence of diabetes in individuals with familial hypercholesterolemia compared to their unaffected relatives [33]. In essence, this body of evidence aligns with the outcomes of our study, affirming a discernible relationship between the reduction of circulating LDL-c via *HMGCR* inhibitors and the mitigation of type 2 diabetes mellitus risk.

Fortunately, our investigation did not uncover a causal relationship between *PCSK9* and type 2 diabetes mellitus. This finding aligns with the outcomes of a prior small-scale observational study and is further corroborated by existing evidence indicating that *PCSK9* inhibitors do not heighten the risk of type 2 diabetes mellitus [34–36]. Carugo et al. [37] proposed that the utilization of *PCSK9* inhibitors merely induces transient blood sugar elevation without concomitantly increasing the risk of type 2 diabetes mellitus. However, Lotta et al. [38] identified an association between the p.R46L variant in *PCSK9* (rs11591147) and an augmented susceptibility to type 2 diabetes. Additionally, some observational inquiries suggest a positive correlation between plasma *PCSK9* levels and type 2 diabetes mellitus incidence [39]. Presently, these contradictory findings pose challenges to rational explication and underscore the necessity for further mechanistic investigations to validate such assertions.

Concurrently, our investigation did not reveal a causal relationship between *NPC1L1* and type 2 diabetes mellitus, contrary to existing research findings. Results from a randomized controlled trial by Takeshita et al. [40] demonstrate that the use of *NPC1L1* inhibitors can significantly elevate patients' HbA1c levels. Moreover, a study conducted on mice indicates that *NPC1L1* inhibitors may mitigate diet-induced hyperglycemia and insulin resistance [41].

Furthermore, there remains a dearth of research regarding the association between these three lipid-lowering drugs and complications arising from type 2 diabetes mellitus. Consequently, our findings may be ascribed to the potential protective effects of the *HMGCR*, *PCSK9*, and *NPC1L1* genes against type 2 diabetes via multiple pathways. It is crucial to emphasize, however, that while our results indicate a potential risk of type 2 diabetes associated with *HMGCR* and *PCSK9* inhibitors, these agents, as key lipid-lowering drugs in contemporary clinical practice, may confer cardiovascular benefits that outweigh the diabetes risk in hyperlipidemic patients. Observational studies have demonstrated that the use of *PCSK9* inhibitors is linked to a 15% reduction in cardiovascular event risk and a corresponding 15% decrease in all-cause mortality [42]. Thus, we hope that our findings contribute valuable evidence and insights to the development and clinical application of lipid-lowering drugs, assisting clinicians in selecting safer and more effective therapies.

Strengths and limitations

The primary strength of this study lies in its utilization of genetic instruments to proxy drug exposure, thereby mitigating bias stemming from confounding factors. Additionally, the iterative analysis employing two-sample Mendelian randomization and the application of diverse sensitivity methodologies serve to bolster the credibility of the study findings.

However, the study also harbors several limitations. Firstly, the applicability of the results is confined to the realm of type 2 diabetes mellitus prevention, as opposed to treatment, owing to the distinction between risk factors for disease onset and progression. Secondly, the use of genetic proxies for lipid-lowering drugs may not fully encapsulate the effects of these pharmaceutical agents on the human body, given that genetic factors entail lifelong exposure, whereas drug administration may be transient. Thirdly, the selected instrumental variables lack validation through clinical experience, thereby potentially introducing bias from pleiotropy or confounding, despite the study's endeavors to address these sources of bias. Fourthly, the utilization of aggregated-level GWAS data precludes the characterization of baseline population traits or the execution of subgroup analyses. Fifthly, the study cohort comprises solely individuals of European ancestry, necessitating future investigations within other ethnic cohorts to ascertain the generalizability of the present study outcomes.

Abbreviations

GWAS	Genome-wide association studies
HMGCR	3-hydroxy-3-methylglutaryl-CoA reductase
IVW	Inverse variance weighting
MR	Mendelian randomization
NPC1L1	NPC1 like intracellular cholesterol transporter 1
PCSK9	Proprotein convertase subtilisin/kexin type 9
SNP	Single nucleotide polymorphisms

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13098-024-01477-8.

Supplementary Material 1

Supplementary Material 2

Acknowledgements

We are grateful to the authors and participants of all GWASs for the summary statistics used.

Author contributions

YYZ and BXC made equal contributions to this work performing the statistical analysis, interpreting the results, writing the paper, and they share the first authorship. QW proposed the ideas. All authors contributed to the article and approved the submitted version.

Funding

The Ministry of Science and Technology of China provided funding for this study through grants 2016YFC0901200.

Data availability

All data sources can be found in Table 1. Original data generated and analyzed during this study are included in this published article or in the data repositories listed in References.

Declarations

Ethics approval and consent to participate

This study is based on publicly available summarized data. Ethical approval and informed consent had been obtained in all original studies.

Competing interests

The authors declare no competing interests.

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Received: 4 June 2024 / Accepted: 23 September 2024
Published online: 04 October 2024

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