

Original Article

Cholecystectomy and blood lipid/glucose traits: insights from a population-based cross-sectional and Mendelian randomization study

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Abstract: Objectives: Cholecystectomy is noted for potentially impacting blood lipid/glucose levels, yet causal links remain unclear. Methods: Cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) 2017-2018 were employed to explore the relationship between cholecystectomy and blood lipid/glucose traits. Propensity-score matching (PSM) was performed to equalize baseline differences. Genome-wide association study (GWAS) data from the UK Biobank, FinnGen, Global Lipids Genetics Consortium (GLGC), and the Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC) were analyzed by Mendelian randomization (MR) to infer causality. Combination of MR results was achieved with meta-analysis. Results: Based on the NHANES database, significantly decreased levels of total cholesterol (TC) ($P = 0.021$), low-density lipoprotein cholesterol (LDL-C) ($P = 0.036$), high-density lipoprotein cholesterol (HDL-C) ($P = 0.017$) and augmented triglyceride (TG) ($P = 0.021$) were found in patients with gallbladder removal after PSM. No difference was observed in fasting glucose, fasting insulin and hemoglobin A1c (HbA1c). In MR analysis, significant associations were found between cholecystectomy and lower TC ($P = 0.002$), especially LDL-C ($P = 0.002$) and HDL-C ($P = 0.044$). No significant associations were observed with TG, fasting glucose, fasting insulin or HbA1c. Conclusions: Cholecystectomy has specific impacts on serum lipid profiles instead of glucose traits.

Keywords: Cholecystectomy, cross-sectional study, Mendelian randomization, blood lipids, blood glucose, causality analysis

Introduction

Cholecystectomy is the gold-standard treatment for gallbladder diseases [1-3]. It has become one of the most frequently performed abdominal surgeries worldwide, with millions undergoing the procedure annually [4, 5]. In addition, cholecystectomy has attracted attention for its potential influence on lipid and glucose metabolism [6].

Several contradictory studies have suggested associations between cholecystectomy and changes in lipid and glucose traits. A longitudinal study conducted in South Korea found that patients who underwent cholecystectomy had a 21% higher risk of developing incident metabolic syndrome (as indicated by hyperlipidemia) and hyperglycemia, compared with those who

did not receive the surgery [7]. However, other observational studies [8-10] reported a reduction in cardio-cerebrovascular diseases among patients who underwent cholecystectomy, which was associated with improvements in lipid or glucose metabolism. These conflicting studies have suggested uncertain associations between cholecystectomy and metabolic profiles, especially lipid and glucose metabolism. Additionally, the coexistence of dyslipidemia and hyperglycemia in individuals predisposed to gallbladder diseases complicates the elucidation of the causal relationship between cholecystectomy and metabolic outcomes [11]. Investigating the impact is crucial for enhancing our understanding of the metabolic repercussions of cholecystectomy, potentially altering the indications of cholecystectomy in patients with dyslipidemia and pathoglycemia.

Mendelian randomization (MR) has been considered as a powerful tool for inferring causal correlations between risk factors and health outcomes [12, 13]. In contrast to conventional observational studies, which are susceptible to confounding and reverse causation biases, MR employs genetic variants as instrumental variables to infer causality more robustly. By leveraging germline genetic variants randomly apportioned during meiosis, the MR design effectively minimizes confounding components and remains unaffected by environmental or self-adopted factors, thereby enhancing causal inference [14, 15]. By utilizing selected genetic variants associated with the exposure (cholecystectomy) but unaffected by confounders (blood lipid and glucose traits), MR facilitates the emulation of randomized controlled trials in observational settings, thereby providing valuable insights into causal associations.

In this study, we firstly analyzed cross-sectional data from the United States National Health and Nutrition Examination Survey (NHANES) to explore the associations between cholecystectomy and blood lipid/glucose traits. To balance the baseline parameters, propensity score matching (PSM) analyses were conducted to ensure changes in serum lipids/glucose after cholecystectomy. Furthermore, unlike previous observational studies which were only able to infer ambiguous correlations, MR analyses were applied in this study to address whether cholecystectomy has causal effects on blood lipids/glucose by utilizing genome-wide association study (GWAS) data from the Global Lipids Genetics Consortium (GLGC), the Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC), as well as the UK Biobank and FinnGen.

Materials and methods

Study design

In the present study, we investigated the impact of cholecystectomy on the blood lipid and glucose traits in a cross-sectional study based on the NHANES database. PSM analyses were performed to adjust the observed bias due to the baseline differences. We then performed two-sample MR analyses to evaluate the causal relationships. The results of the MR analyses from the different databases were combined in a meta-analysis.

Cross-sectional study

Data source: The data for the observational cross-sectional study were from the 2017-2018 NHANES. A total of 5,566 participants with complete data regarding whether they received cholecystectomy or not were included. Ultimately, after removing the patients with incomplete records for blood lipid/glucose, body mass index (BMI) data, diabetes or cholesterol-regulating agent usage, a total of 1,721 patients were enrolled (**Figure 1A**). Informed consents were acquired from all the individuals analyzed in this study, and ethical approval was awarded by the National Center for Health Statistics (NCHS) Ethical Review Board.

Statistical analysis: Continuous variables were recorded as means \pm standard deviations or medians with interquartile ranges (IQRs). Student's *t*-test or the Mann-Whitney *U* test was utilized for comparisons of two groups of continuous variables. The Chi-squared test or the Kruskal-Wallis test was applied to compare categorical variables that were reported as weighted counts and percentages. PSM was performed using the MatchIt package to balance baseline factors between the patients who underwent cholecystectomy and those who did not. We matched the patients for age, sex, BMI, history of diabetes, and lipid-regulating agent usage, which were predisposed to affect the blood lipid/glucose traits. The PSM analysis employs a nearest-neighbor method with a no-replacement strategy at a 1:2 ratio and a caliper width of 0.2, using logit distance to estimate the matching extent. R software version 4.3.2 was applied.

Mendelian randomization

Cholecystectomy was used as the exposure factor and blood lipids and glucose were used as the outcome factors. The prerequisite for conducting the two-sample MR analysis is to meet three core assumptions: (1) the selected single-nucleotide polymorphisms (SNPs) as instrument variables are significantly related with exposure (i.e., cholecystectomy); (2) the selected SNPs are independent to confounding factors; and (3) the selected SNPs should be connected to the outcome only through exposure (**Figure 1B**). The flowchart of the MR analyses is shown in **Figure 1C**. Summary data from public databases (NHANES, UK Biobank,

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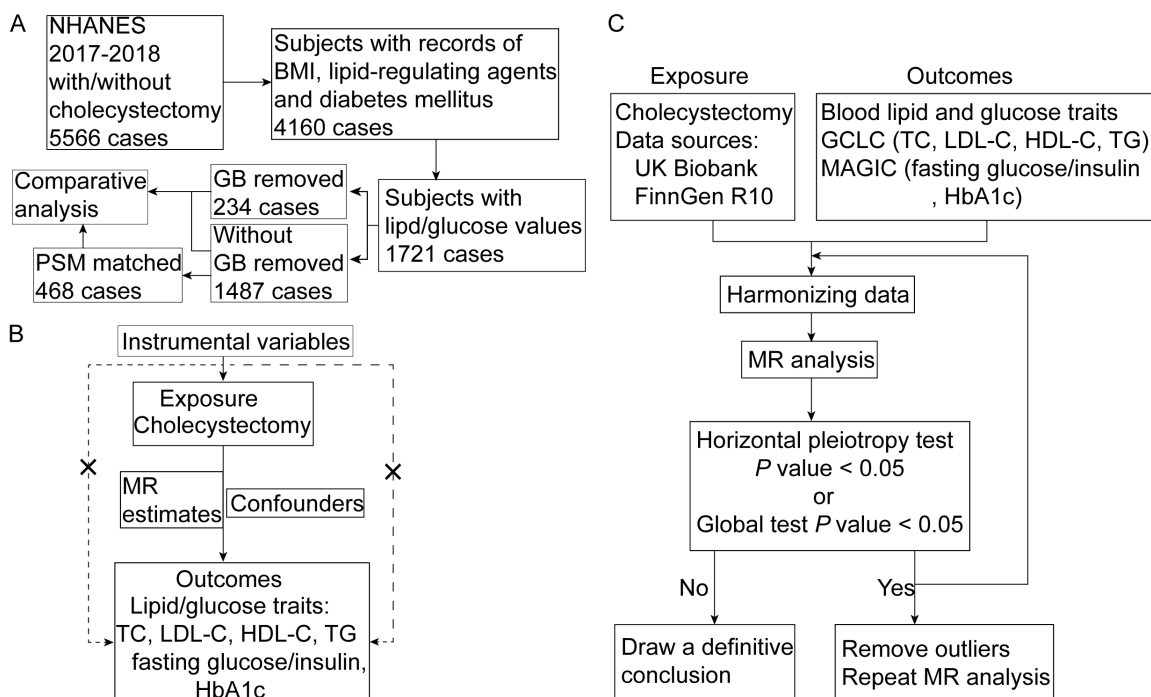


Figure 1. Graphical overview of the whole study design. A. Workflow of propensity score matching (PSM) analysis using National Health and Nutrition Examination Survey (NHANES) database; B. Assumptions of MR analysis; C. Flow-chart of the MR analysis. Abbreviations: BMI, body mass index; GB, gallbladder; PSM, propensity score matching; MR, Mendelian randomization; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; HbA1c, hemoglobin A1c; GLGC, Global Lipids Genetics Consortium; MAGIC, Meta-Analyses of Glucose and Insulin-related traits Consortium.

FinnGen, GLGC and MAGIC) which had acquired individual consent and ethical approval were analyzed.

Data sources: SNPs associated with cholecystectomy were extracted from the UK Biobank dataset, which consisted of 18,319 cases and 444,614 controls (total sample size: 462,933) of European ancestry, as well as from the FinnGen R10 dataset, which included 29,157 cases and 383,024 controls. SNPs for blood lipid traits (high-density lipid cholesterol [HDL-C], low-density lipid cholesterol [LDL-C], total cholesterol [TC], and triglycerides [TG]) were extracted from a GWAS dataset in the GLGC database that included 1.32 million cases of European ancestry [16]. Summary statistic data for blood glucose were obtained from the MAGIC database of European ancestry [17, 18]. Specific brief information is exhibited in **Table 1**.

Selection criteria for instrumental variables (IVs): The following criteria were adopted to screen independent and significant SNPs as IVs

for exposure factors (cholecystectomy): (1) SNPs were considered significant if they met the genome-wide association threshold of $P < 5 \times 10^{-6}$. (2) All selected SNPs were required to be independent, with a linkage disequilibrium (LD) threshold of $r^2 < 0.01$, using a clumping window of 10,000 kb. (3) SNPs with F-statistics below 10 were excluded to minimize weak instrument bias. The F-statistic was calculated using the formula $F = [(N-K-1)/K] \times [R^2/(1-R^2)]$, where R^2 represents the cumulative variance explained by the selected SNPs for the exposure, N is the sample size of the exposure dataset, and K is the number of SNPs included in the analysis. An F-statistic greater than 10 indicates a reduced risk of weak instrument bias. (4) SNPs containing palindromic sequences were excluded from the analysis. (5) SNPs that showed significant associations ($P < 1 \times 10^{-5}$) with known confounding factors, such as lipid and glucose metabolism, were also removed.

Sensitivity analysis: Heterogeneity was detected using Cochran's Q-test [20], applying the inverse-variance weighted (IVW) method [21]. A

Table 1. Characteristics of data used in the Mendelian randomization study

Exposure/Outcome	Participants	Resource
Cholecystectomy	18,319 cases and 444,614 non-cases of European ancestry	UK Biobank
Cholecystectomy	29,157 cases and 383,024 non-cases of European ancestry	FinnGen R10
TC	1.32 million individuals of European ancestry	GLGC
LDL-C	1.32 million individuals of European ancestry	GLGC
HDL-C	1.32 million individuals of European ancestry	GLGC
TG	1.32 million individuals of European ancestry	GLGC
Fasting Glucose	58,074 individuals of European ancestry	MAGIC
Fasting Insulin	51,750 individuals of European ancestry	MAGIC
HbA1c	46,368 individuals of European ancestry	MAGIC

Abbreviations: TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; HbA1c, hemoglobin A1c; GLGC, Global Lipids Genetics Consortium; MAGIC, Meta-Analyses of Glucose and Insulin-related traits Consortium.

significance threshold of $P < 0.05$ was interpreted as evidence of heterogeneity. In the presence of heterogeneity, the random-effects IVW method was employed. The MR Pleiotropy Residual Sum and Outlier (MR-PRESSO) method was employed to mitigate the influence of horizontal pleiotropy [22]. If the MR-PRESSO global test or the pleiotropy test indicated significance, it suggested the presence of horizontal pleiotropy; therefore, all outlier IVs were removed before conducting further MR analysis. Additionally, a leave-one-out sensitivity analysis was performed to validate the robustness of the results by systematically removing each SNP with iterations. Scatter and funnel plots were created to visually assess the outcomes of the MR analyses.

MR analyses: Two-sample MR analyses were conducted to investigate the potential causal associations between cholecystectomy and blood lipid and glucose traits. A variety of statistical methods were employed, including MR Egger (MRE), IVW, Weighted Median (WMed), weighted Mode (WMod), and Simple Mode (SMod) methods. The main results were based on the IVW analysis. Common-effect or random-effect models were conducted to combine MR estimates from different data sources based on heterogeneity testing. The heterogeneity test results were evaluated according to I^2 statistic or the Q statistic. TwoSampleMR [23] and MR-PRESSO [22] packages were used to perform all the analyses. If the horizontal pleiotropy was detected, all the outliers were removed using the RadialMR package, and further repeated MR analyses were performed. R software version 4.3.2 was utilized.

Results

Effects of cholecystectomy on serum lipids and glucose before and after PSM analyses by using NHANES data

As analyzed in **Table 2**, before PSM, patients who underwent cholecystectomy were more likely to be older (55.1% vs. 38.7%, $P < 0.001$), female sex (76.1% vs. 49.6%, $P < 0.001$), and have higher BMI (33.2 ± 8.2 vs. 29.6 ± 7.2 , $P < 0.001$) compared with those who did not undergo cholecystectomy. Moreover, subjects with cholecystectomy had higher comorbidity rates of hypertension (57.3% vs. 41.6%, $P < 0.001$), diabetes mellitus (32.5% vs. 18.2%, $P < 0.001$), and usage of lipid-regulating agents (45.7% vs. 38.1%, $P < 0.001$) and reduced TC (median, 177.0 vs. 184.0, $P = 0.020$), LDL-C (median, 101.0 vs. 109.0, $P = 0.006$), and TG (median, 129.0 vs. 110.0, $P < 0.001$) levels. Elevated levels of fasting glucose (median, 110.0 vs. 105.0, $P < 0.001$), fasting insulin (median, 12.8 vs. 9.7, $P < 0.001$), and HbA1c (median, 5.8% vs. 5.6%, $P < 0.001$) were observed in cholecystectomized patients. No changes in HDL-C (median, 50.0 vs. 52.0, $P = 0.212$) were detected after cholecystectomy.

Given the baseline difference, we performed PSM to match age, sex, BMI, history of diabetes, and lipid-regulating agent usage, which was predisposed to affect the blood lipid/glucose traits. After balancing baseline values by PSM, no differences in age, sex, BMI values, hypertension rate, diabetes mellitus rate, or use of lipid-regulating agents were found in the matched patients. Notably, decreased concen-

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Table 2. Overview of demographic parameters from NHANES database before/after PSM analyses

	Before PSM			After PSM		
	With cholecystectomy (n = 234)	Without cholecystectomy (n = 1487)	P	With cholecystectomy (n = 234)	Without cholecystectomy (n = 468)	P
Age (> 60, (%))	129 (55.1)	575 (38.7)	< 0.001*	129 (55.1)	244 (52.1)	0.504
Sex (Female, (%))	178 (76.1)	737 (49.6)	< 0.001*	178 (76.1)	365 (78.0)	0.633
Education level (%)			0.058			0.418
< 9th grade	20 (8.5)	105 (7.1)		20 (8.5)	40 (8.5)	
9-11th grade	29 (12.4)	155 (10.4)		29 (12.4)	50 (10.7)	
High school	64 (27.4)	329 (22.1)		64 (27.4)	103 (22.0)	
Some college or AA degree	79 (33.8)	492 (33.1)		79 (33.8)	172 (36.8)	
College graduate or above	42 (17.9)	405 (27.2)		42 (17.9)	103 (22.0)	
Don't Know	0 (0.0)	1 (0.1)		/	/	
BMI (mean (SD))	33.2 (8.2)	29.6 (7.2)	< 0.001*	33.2 (8.2)	32.7 (8.8)	0.406
Hypertension (%)	134 (57.3)	618 (41.6)	< 0.001*	134 (57.3)	231 (49.4)	0.058
Diabetes mellitus (%)	76 (32.5)	271 (18.2)	< 0.001*	76 (32.5)	139 (29.7)	0.506
Lipid-regulating agents (%)	107 (45.7)	566 (38.1)	0.031*	107 (45.7)	201 (42.9)	0.536
TC (mg/dL, median [IQR])	177.0 [152.2, 207.5]	184.0 [160.0, 215.0]	0.020*	177.0 [152.3, 207.5]	184.0 [161.0, 217.0]	0.021*
LDL-C (mg/dL, median [IQR])	101.0 [78.0, 127.8]	109.0 [87.0, 135.0]	0.006*	101.0 [78.0, 127.8]	108.0 [86.8, 136.0]	0.036*
HDL-C (mg/dL, median [IQR])	50.0 [42.0, 61.0]	52.0 [43.0, 63.0]	0.212	50.0 [42.0, 61.0]	53.0 [44.0, 65.0]	0.017*
TG (mg/dL, median [IQR])	129.0 [91.0, 167.8]	110.0 [78.0, 155.0]	< 0.001*	129.0 [91.0, 167.8]	114.0 [84.0, 158.0]	0.021*
Fasting glucose (mg/dL, median [IQR])	110.0 [100.0, 129.0]	105.0 [97.0, 117.0]	< 0.001*	110.0 [100.0, 129.0]	107.0 [97.8, 127.0]	0.061
Fasting insulin (uU/dL, median [IQR])	12.8 [8.8, 20.4]	9.7 [6.1, 15.8]	< 0.001*	12.8 [8.8, 20.4]	11.7 [7.3, 20.2]	0.071
HbA1c (% , median [IQR])	5.8 [5.4, 6.4]	5.6 [5.3, 6.0]	< 0.001*	5.8 [5.4, 6.4]	5.8 [5.4, 6.5]	0.860

*, $P < 0.05$. Abbreviations: BMI, body mass index; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; HbA1c, hemoglobin A1c; IQR, interquartile range.

trations of TC (median, 177.0 vs. 184.0, $P = 0.021$), LDL-C (median, 101.0 vs. 108.0, $P = 0.036$), and HDL-C (median, 50.0 vs. 53.0, $P = 0.017$) but increased levels of TG (median, 129.0 vs. 114.0, $P = 0.021$) were noted in those with cholecystectomy. Although exhibiting increasing trends, no significance was detected for fasting glucose (median, 110.0 vs. 107.0, $P = 0.061$), fasting insulin (median, 12.8 vs. 11.7, $P = 0.071$), or HbA1c (median, 5.8% vs. 5.8%, $P = 0.860$) between individuals with and without cholecystectomy. To clarify the effects of cholecystectomy on serum lipid and glucose traits, we further conducted MR analyses to simulate random clinical trials to explore the causality.

Primary MR results of lipid and glucose traits

In the primary MR analysis, 52 genome-wide significant SNPs from UK Biobank and 108 SNPs from FinnGen were selected as IVs, excluding palindromic SNPs and those associated with cholesterol, lipid, and glucose metabolism. All selected SNPs had F-statistics greater than 10, demonstrating the strong validity of the genetic instruments. Comprehensive

details of the SNPs employed as instrumental variables can be found in [Tables S1](#) and [S2](#).

Based on the data from the UK Biobank, we observed a decreasing trend towards a lower odds ratio (odds ratio [OR]: 0.635, 95% confidence interval [CI]: 0.408-0.988, $P = 0.044$) between cholecystectomy and LDL-C. No significant associations were found with other lipid or glucose parameters (**Table 3**). In the analysis of the FinnGen data, cholecystectomy demonstrated a significant association with TC levels (OR: 0.983, 95% CI: 0.972-0.994, $P = 0.002$). Furthermore, regarding specific cholesterol types, cholecystectomy showed significant associations with LDL-C levels (OR: 0.983, 95% CI: 0.972-0.994, $P = 0.004$). A significant association was observed between cholecystectomy and HDL-C levels (OR: 0.990, 95% CI: 0.982-0.999, $P = 0.022$). There were no significant associations between cholecystectomy and TG, fasting glucose, fasting insulin, and HbA1c levels. Heterogeneity was detected in the analysis of lipid traits and fasting insulin; therefore, the random-effect IVW method was performed. However, in the MR test of the lipid traits, significant heterogeneity and horizontal

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Table 3. Primary MR analyses of cholecystectomy and blood lipid/glucose traits before outlier removal

	Source	UK Biobank			FinnGen		
		OR	95% CI	P value	OR	95% CI	P value
TC	GLGC	0.767	(0.490; 1.201)	0.246 [#]	0.983	(0.972; 0.994)	0.002 ^{*,#}
LDL-C	GLGC	0.635	(0.408; 0.988)	0.044 ^{*,#}	0.983	(0.972; 0.994)	0.004 ^{*,#}
HDL-C	GLGC	0.628	(0.339; 1.161)	0.138 [#]	0.990	(0.982; 0.999)	0.022 ^{*,#}
TG	GLGC	1.912	(0.890; 4.107)	0.097 [#]	1.006	(0.997; 1.015)	0.182 [#]
Fasting Glucose	MAGIC	1.658	(0.804; 3.417)	0.171	1.023	(0.999; 1.048)	0.066
Fasting Insulin	MAGIC	1.123	(0.454; 2.778)	0.802 [#]	1.006	(0.982; 1.031)	0.607
HbA1c	MAGIC	0.970	(0.490; 1.921)	0.930	1.001	(0.972; 1.032)	0.929

* $P < 0.05$, [#]calculated by random-effect IVW method. Abbreviations: TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; HbA1c, hemoglobin A1c; GLGC, Global Lipids Genetics Consortium; MAGIC, Meta-Analyses of Glucose and Insulin-related traits Consortium; OR, odds ratio; CI, confidence interval.

pleiotropy were observed, suggesting that the causal relationship may lack robustness (Table S3). Therefore, we removed outlier SNPs using RadialMR, and performed a further two-sample MR for the lipid traits.

Replicated MR analysis of lipid traits

As significant heterogeneity and horizontal pleiotropy were detected in the primary lipid-associated MR analysis, replicated MR analyses were performed after excluding all outlier SNPs (see Tables S4 and S5). In the replicated MR analysis, neither the MR-PRESSO global test nor the pleiotropy tests showed evidence of horizontal pleiotropy (Table S6). Moreover, no heterogeneity was observed in the subsequent MR analysis (Table S6).

In the repeated MR analysis, genetically predicted cholecystectomy was significantly associated with lower TC levels in the FinnGen data (OR: 0.991, 95% CI: 0.985-0.996, $P = 0.002$). While not statistically significant, a consistent trend for total cholesterol (TC) was noted in the UK Biobank dataset (OR: 0.875, 95% CI: 0.674-1.137, $P = 0.319$). Regarding specific cholesterol levels, genetically predicted cholecystectomy was significantly associated with lower LDL-C levels in the FinnGen cohort (OR: 0.990, 95% CI: 0.984-0.996, $P = 0.002$), and a similar trend was observed in the UK Biobank dataset (OR: 0.757, 95% CI: 0.585-0.979, $P = 0.034$). However, there was no significant association between genetically predicted cholecystectomy and HDL-C levels in the FinnGen data (OR: 0.994, 95% CI: 0.989-1.000, $P = 0.051$), and lower HDL-C levels were observed in the UK Biobank database (OR: 0.771, 95% CI: 0.620-

0.958, $P = 0.019$). TG levels showed inconsistency between the UK Biobank (OR: 1.679, 95% CI: 1.351-2.087, $P < 0.001$) and FinnGen datasets (OR: 1.007, 95% CI: 0.998-1.016, $P = 0.146$) (Figure 2A and 2B). The results of the IVW, MRE, WMed, WMod, and SMod methods for the lipid traits (repeated MR results) and glucose traits (primary MR results) are shown in Tables S7, S8, S9, S10. Scatter plots, funnel plots and forest plots of these outcomes are presented in Figures S1, S2, S3. Sensitivity analysis using the leave-one-out method demonstrated the robustness of the results (see Figure S4).

Combined results of lipid and glucose traits by meta-analysis

Based on the repeated MR analyses in both the UK Biobank and FinnGen cohorts, we conducted a meta-analysis to combine the two sets of results and derive a more generalized conclusion. Specific model selection of the meta-analysis was based on the I^2 statistic and Q statistics generated by the heterogeneity test (Table S11). The meta-analysis of the UK Biobank and FinnGen data (see Figure 2C) demonstrated a significant reduction in TC levels associated with cholecystectomy (OR: 0.996, 95% CI: 0.993-0.998, $P = 0.002$). Similarly, the meta-analysis revealed significant decreases in LDL-C levels (OR: 0.996, 95% CI: 0.993-0.998, $P = 0.002$) and HDL-C levels (OR: 0.998, 95% CI: 0.995-1.000, $P = 0.044$) levels associated with cholecystectomy. However, there were no significant associations found between genetically predicted cholecystectomy and TG levels ($P = 0.099$), fasting glucose ($P = 0.060$), fasting insulin ($P = 0.603$), and HbA1c ($P = 0.932$).

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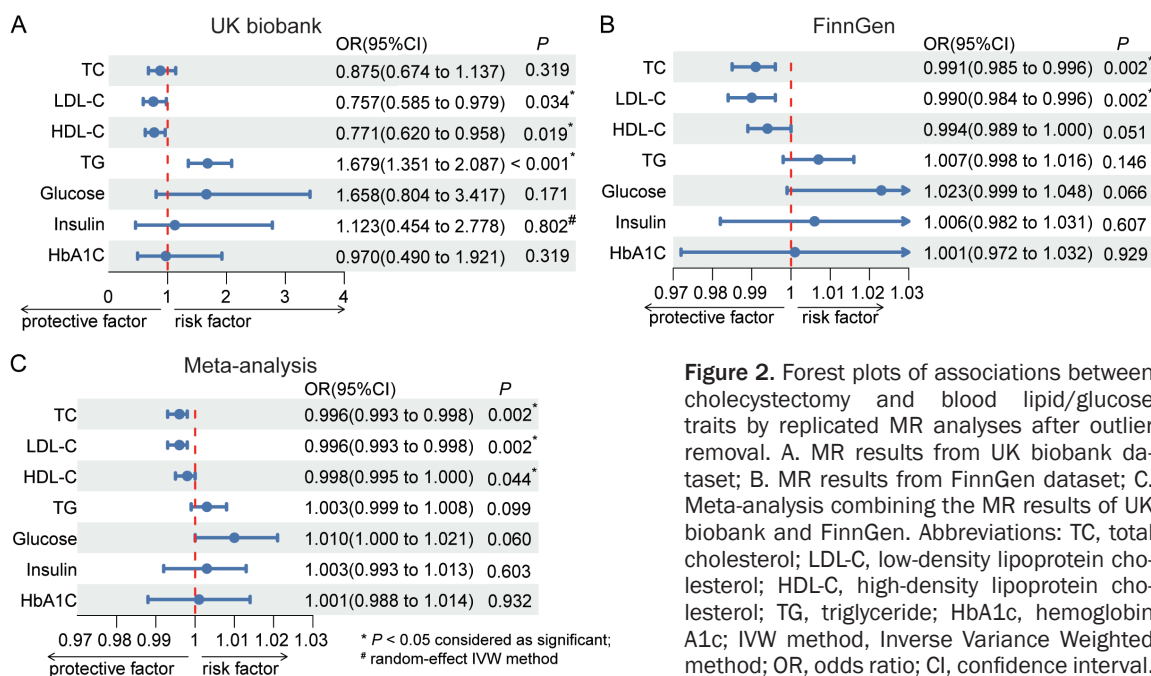


Figure 2. Forest plots of associations between cholecystectomy and blood lipid/glucose traits by replicated MR analyses after outlier removal. A. MR results from UK biobank dataset; B. MR results from FinnGen dataset; C. Meta-analysis combining the MR results of UK biobank and FinnGen. Abbreviations: TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; HbA1c, hemoglobin A1c; IVW method, Inverse Variance Weighted method; OR, odds ratio; CI, confidence interval.

Discussion

In this study, we first employed population-based cross-sectional data from NHANES to infer associations between cholecystectomy and serum lipid/glucose levels. Then, we conducted PSM analyses to avoid baseline differences. Moreover, we performed MR analyses on multiple large-sample cohorts to investigate the associations between cholecystectomy and blood lipid/glucose profiles. Our findings revealed the causal relationship between cholecystectomy and reduced TC levels, specifically LDL-C and HDL-C, with no notable changes in TG and glucose metabolic indices.

Previous studies have reported varied findings regarding the impact of cholecystectomy on blood lipid profiles. Malik et al. found significant reductions in serum TC and LDL-C among patients who underwent cholecystectomy [24], in agreement with our results. Similarly, Walmesley et al. reported a maximum reduction of 30-36% in serum cholesterol levels [25]. Conversely, although TC and LDL-C levels declined on the 3rd day after gallbladder removal, Juvonen et al. reported that these values quickly returned to preoperative levels [26]. Gill et al. described increased HDL-C concentrations and stable LDL-C concentrations after cholecystectomy [27]. Nervi revealed that serum levels of TC, LDL-C, HDL-C, and TG

remained unchanged. However, an accumulation of apolipoprotein B (apoB) lipoprotein, which is the main component of LDL, was observed in cholecystectomized patients compared with controls [28]. Discrepancies among these findings may be attributed to factors such as preoperative lipid status and dietary habits [29, 30]. Additionally, predisposed disorders in lipid metabolism leading to gallbladder disease and dietary restrictions, particularly fat intake post-operation, may contribute to the diverse findings. Advantageously, our study effectively utilized GWAS data from large cohorts and applied MR analysis, providing fresh perspectives on the metabolic effects of cholecystectomy. By judiciously excluding lipid/glucose-related SNPs during instrumental variable selection, we ensured a robust reduction of potential biases, thereby enhancing our understanding of the metabolic implications of cholecystectomy.

As antecedently reported [11, 25], cholecystectomy alters the storage and reabsorption of bile acids (BAs). These acids dissolve triglycerides, thereby ameliorating the predisposition to cholesterol accumulation. Additionally, this process affects metabolites such as bile salts, which play a crucial role in lowering serum cholesterol levels. Cholecystectomy exonerates the concentrated effect of the gallbladder on BAs and promotes BA entering the intestine

rapidly, thereby impairing BA homeostasis. BA, as hormonal signaling molecules, can interact with nuclear farnesoid X receptor (FXR) through activating small heterodimer partner (SHP) and peroxisome proliferator-activated receptor α (PPAR α) to decrease lipogenesis and to increase lipolysis. Also, the BA-FXR axis is associated with reduced accumulation of intrahepatic cholesterol [31], whose main effect is transporting intrinsic cholesterol. Meanwhile, BA-FXR axis activates fibroblast growth factor 19 (FGF19) and the downstream receptor FGFR4 inhibits lipogenesis by suppressing synthesis of fatty acids and sterol and activities of lipogenic enzymes [31, 32]. Moreover, cholecystectomy also disturbs gut microbiota homeostasis, which in turn affects generation and reabsorption of secondary BA, exerting a regulatory impact on lipid metabolism [33, 34]. These results could elucidate our findings from a mechanistic perspective.

No significant differences were observed in fasting blood glucose, fasting insulin levels, or HbA1c levels between individuals who underwent cholecystectomy and those who did not in either the cross-sectional study or the MR analysis. Similar to our findings, Park *et al.* reported no significant changes in serum fasting serum glucose concentrations in patients who underwent cholecystectomy compared with those who did not undergo gallbladder resection [10]. However, in a pilot study assessing Hispanic patients, serum insulin levels increased from 8.1 ± 0.7 to 10.0 ± 1.9 $\mu\text{U/ml}$ 24 months after cholecystectomy in non-obese patients [28]. Moreover, cholecystectomized patients exhibited elevated serum fasting glucagon and postprandial glucose levels compared with controls [35]. The risk of higher blood glucose increased by 1.21-fold in individuals who underwent cholecystectomy compared with those who did not [7]. Nevertheless, our study did not find comparable effects on insulin sensitivity after cholecystectomy. The findings of previous studies may be influenced by dietary control after the operation, resulting in improved blood glucose management, and surgical stress, which could lead to insulin resistance following cholecystectomy [36-38]. Importantly, our study mitigated these biases by excluding glucose- and insulin-related SNPs during instrumental variable selection, potentially explaining the biases of previous studies. Our findings enrich the exist-

ing literature by offering insights into the glucose metabolic consequences of cholecystectomy and underscore the necessity for additional studies to clarify the underlying mechanisms.

The present study possesses several advantages, including the utilization of MR analysis and large-scale GWAS data. MR analysis allows us to infer causal relationships by leveraging genetic variants as instrumental variables, mimicking a randomized controlled study. This methodological approach bolsters the robustness and validity of our findings minimizing the bias from the observational cross-sectional study. Despite these strengths, we should acknowledge several limitations. First, our study predominantly focused on populations of European ancestry, thereby limiting the generalizability of our findings to other ethnic groups. In particular, Asian populations may present different etiologies of cholelithiasis, as these populations have less predominant lipid metabolism disorder compared with Western populations. Second, the retrospective nature of the GWAS data introduced selection bias, as individuals who undergo cholecystectomy may systematically differ from those who do not.

In conclusion, our study elucidated the association between cholecystectomy and blood lipid and glucose profiles. The cross-sectional study with PSM showed significant associations between cholecystectomy and decreased TC, LDL-C, and HDL-C levels and increased TG levels. The meta-analysis combining the MR results of the UK Biobank and FinnGen cohorts unveiled the causal relationship between cholecystectomy and lower TC levels, especially lower LDL-C levels. No causal impacts of cholecystectomy on HDL-C and TG levels and glucose metabolic indices were observed. Therefore, blood cholesterol levels in patients who have undergone cholecystectomy should be monitored diligently; thus, the indications for cholecystectomy in individuals with high cholesterol levels might be expanded.

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Disclosure of conflict of interest

None.

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Table S1. 52 genome-wide significant SNPs In UK Biobank were used as IVs to investigate the causal relationship between cholecystectomy and blood lipid and glucose traits

SNPs	CHR*	Position	EA*	OA*	Beta	EAF	SE*	F-Stat	P value
rs10199034	2	235935809	C	G	0.002441	0.226825	0.000486	25.24066	5.10E-07
rs10799476	1	228603029	A	C	-0.00209	0.302419	0.000443	22.28211	2.40E-06
rs10882890	10	99048262	A	G	-0.00221	0.622812	0.000417	28.15487	1.10E-07
rs112634731	12	109292973	G	A	-0.00382	0.068792	0.000796	23.05946	1.60E-06
rs113525652	1	95604674	C	T	-0.00354	0.083063	0.000731	23.43042	1.30E-06
rs11603634	11	1136478	G	A	-0.0022	0.503905	0.000405	29.49634	5.60E-08
rs116468765	2	43908318	G	A	0.008453	0.02494	0.00129	42.92637	5.70E-11
rs11686966	2	44047651	G	C	-0.00634	0.024779	0.001355	21.9242	2.80E-06
rs1201467	6	105432994	C	G	-0.00386	0.104519	0.00066	34.2879	4.80E-09
rs1208280	6	134165237	G	A	-0.00216	0.398265	0.000412	27.44448	1.60E-07
rs12369071	12	115789029	T	G	0.002065	0.27809	0.000453	20.82569	5.00E-06
rs13061117	3	181186466	C	T	0.003365	0.090209	0.000712	22.3161	2.30E-06
rs138776098	2	54903555	C	T	0.005121	0.038771	0.001066	23.09568	1.50E-06
rs146652454	7	535398	T	C	0.006885	0.031145	0.001243	30.66692	3.10E-08
rs150844304	15	43726625	C	A	0.007165	0.025812	0.00127	31.81152	1.70E-08
rs17138478	17	36073320	A	C	0.003928	0.128841	0.000602	42.61232	6.70E-11
rs1811515	2	44325917	C	G	0.003244	0.400945	0.000413	61.82773	3.70E-15
rs2107944	7	141053519	G	A	-0.00195	0.34061	0.000426	20.91754	4.80E-06
rs2470048	8	120295405	T	C	0.002543	0.708173	0.000444	32.87017	9.90E-09
rs28378706	2	224685334	C	T	0.002143	0.380942	0.000417	26.47262	2.70E-07
rs28517482	2	44101538	T	C	-0.00259	0.530457	0.000436	35.39392	2.70E-09
rs2978388	8	146154001	T	C	-0.00343	0.101031	0.000678	25.62795	4.10E-07
rs3094509	17	36062299	G	A	0.002392	0.639268	0.000424	31.79174	1.70E-08
rs332981	4	172854531	G	T	-0.00194	0.567975	0.000407	22.81022	1.80E-06
rs3793770	10	102116914	T	G	-0.00214	0.352954	0.000423	25.55033	4.30E-07
rs3862794	11	72538600	C	T	0.003246	0.256545	0.000462	49.42266	2.10E-12
rs41276920	15	90347920	A	G	-0.00475	0.087572	0.000713	44.41727	2.70E-11
rs41281265	22	40720704	G	A	0.002348	0.349041	0.000424	30.59838	3.20E-08
rs4150336	13	103519251	T	C	0.005126	0.048579	0.000936	29.98734	4.30E-08
rs4331955	6	93579401	A	G	-0.00245	0.183614	0.000522	22.14301	2.50E-06
rs4346434	2	44219746	T	C	-0.00598	0.736536	0.000459	170.1353	6.90E-39
rs4681516	3	149212125	C	G	-0.00492	0.561695	0.000407	146.3147	1.10E-33
rs4881744	11	1399402	G	A	0.002365	0.201577	0.000504	22.04437	2.70E-06
rs55780704	3	149185633	T	C	0.006634	0.042285	0.001008	43.30119	4.70E-11
rs55971546	13	103718308	T	C	0.00541	0.0427	0.000997	29.46966	5.70E-08
rs580477	2	45071428	T	C	0.005049	0.03738	0.001069	22.29988	2.30E-06
rs62090594	18	42383005	A	G	0.003516	0.079869	0.000751	21.89845	2.90E-06
rs698838	2	44738763	T	C	0.002004	0.625104	0.000416	23.2453	1.40E-06
rs714583	7	107473153	A	T	-0.00455	0.230102	0.000488	87.09168	1.00E-20
rs72931779	11	69833580	G	C	0.00481	0.098516	0.000677	50.44449	1.20E-12
rs73192932	7	85881867	C	T	-0.00505	0.037413	0.001062	22.5883	2.00E-06
rs7337432	13	52422211	G	A	-0.00212	0.674786	0.000432	24.10879	9.10E-07
rs7564733	2	235958802	C	T	0.002439	0.238176	0.000475	26.36381	2.80E-07
rs76818081	15	57640005	A	G	0.007874	0.028962	0.001337	34.7021	3.80E-09
rs76862077	3	59188684	T	C	0.005456	0.032275	0.001155	22.30086	2.30E-06
rs7993414	13	103371810	G	A	-0.00192	0.484552	0.000403	22.56577	2.00E-06

Serum lipid/glucose traits after cholecystectomy from observational and MR study

rs8077886	17	70058020	C	T	-0.0035	0.108272	0.00065	29.03423	7.10E-08
rs932784	13	103866575	A	T	0.007651	0.022017	0.001376	30.9293	2.70E-08
rs9371004	6	17601853	C	T	-0.00314	0.46429	0.000406	59.84855	1.00E-14
rs9471953	6	12508653	G	A	0.003903	0.061084	0.000843	21.4398	3.70E-06
rs9544535	13	36095039	G	A	-0.00188	0.57346	0.000411	20.93839	4.70E-06
rs9790309	3	149183177	A	G	-0.00284	0.856098	0.000582	23.81479	1.10E-06

*CHR chromosome, EA effect allele, OA other allele, EAF effect allele frequency, SE standard error.

Table S2. 108 genome-wide significant SNPs In FinnGen were used as IVs to investigate the causal relationship between cholecystectomy and blood lipid and glucose traits

SNPs	CHR*	Position	EA*	OA*	Beta	EAF	SE*	F-Stat	P value
rs12135720	1	75672495	G	T	-0.46254	0.003305	0.085608	29.19235	6.55E-08
rs263462	1	86723238	A	G	0.109198	0.036616	0.022852	22.83394	1.77E-06
rs3790843	1	200041696	T	C	0.052812	0.423614	0.008877	35.39149	2.70E-09
rs1629928	1	245606061	G	A	0.045664	0.287025	0.009707	22.13201	2.55E-06
rs76592665	2	39984226	T	G	-0.06093	0.128652	0.013169	21.40315	3.72E-06
rs12470367	2	41464133	A	G	0.046046	0.722491	0.009799	22.07934	2.62E-06
rs62140201	2	41987058	A	G	0.149783	0.017889	0.032284	21.52589	3.49E-06
rs186890864	2	42406199	C	T	0.240167	0.026876	0.026017	85.21425	2.68E-20
rs143949742	2	42410653	C	G	0.213898	0.011876	0.038163	31.4147	2.08E-08
rs139199716	2	42506512	C	T	0.193654	0.028373	0.024993	60.03565	9.32E-15
rs79693383	2	42826986	A	G	0.070977	0.107902	0.014015	25.64803	4.10E-07
rs12615717	2	42878079	G	A	0.106407	0.223779	0.010408	104.5296	1.55E-24
rs11690947	2	43050237	C	G	-0.09894	0.112933	0.014229	48.34467	3.58E-12
rs730803	2	43056600	T	G	0.28261	0.016495	0.031775	79.104	5.89E-19
rs13414085	2	43118875	A	G	0.074633	0.255252	0.009887	56.9837	4.39E-14
rs2011896	2	43192747	G	A	-0.0737	0.360721	0.009263	63.30147	1.77E-15
rs75841075	2	43959696	A	G	-0.18737	0.03149	0.026357	50.5337	1.17E-12
rs61614759	2	43966363	A	G	-0.13221	0.147441	0.012604	110.0422	9.60E-26
rs55935092	2	44020807	G	T	0.089062	0.233584	0.010185	76.46271	2.24E-18
rs75120545	2	44044357	T	C	0.131326	0.044953	0.0204	41.44326	1.21E-10
rs71420083	2	44047252	A	G	0.096803	0.087747	0.015235	40.37519	2.10E-10
rs11691443	2	44094498	T	A	0.074906	0.09175	0.014908	25.24652	5.04E-07
rs187779008	2	44590590	G	T	0.395597	0.024937	0.02567	237.4875	1.39E-53
rs163520	2	44904012	A	C	-0.13662	0.051948	0.020461	44.58357	2.44E-11
rs112266464	2	44951472	T	C	0.178239	0.047991	0.019874	80.43393	3.01E-19
rs2921987	2	45027388	G	A	0.098801	0.832726	0.01193	68.59219	1.21E-16
rs576479048	2	45038193	A	G	0.230446	0.010449	0.039855	33.43347	7.37E-09
rs13399179	2	45186147	T	C	0.088389	0.060733	0.017873	24.45603	7.60E-07
rs72799962	2	45194235	A	G	0.129805	0.085649	0.015202	72.90904	1.36E-17
rs10208775	2	45228585	G	A	0.116584	0.051961	0.019115	37.19805	1.07E-09
rs582384	2	45669298	A	C	0.049829	0.604457	0.008986	30.74902	2.94E-08
rs34997129	2	45708906	T	C	0.180582	0.027376	0.025577	49.84979	1.66E-12
rs145048510	2	46089233	C	G	0.149561	0.032959	0.024104	38.49948	5.48E-10
rs150212157	2	61808494	A	G	-0.05912	0.155672	0.012257	23.26222	1.41E-06
rs871962	3	148860828	A	G	0.047148	0.382407	0.008985	27.53758	1.54E-07
rs79348616	3	149287571	T	C	0.127869	0.078752	0.016113	62.97795	2.09E-15
rs76733846	3	149433851	G	T	0.071208	0.142828	0.01249	32.50198	1.19E-08
rs79478006	3	149462775	T	C	-0.1158	0.098232	0.0151	58.81295	1.73E-14

Serum lipid/glucose traits after cholecystectomy from observational and MR study

rs62272019	3	149478444	T	C	0.238694	0.092667	0.014488	271.4314	5.54E-61
rs78815523	3	149580110	T	C	-0.08383	0.108285	0.014453	33.64538	6.61E-09
rs66498012	3	149680106	A	G	-0.05569	0.271609	0.009898	31.65586	1.84E-08
rs79469600	3	150067426	G	A	0.097206	0.044549	0.021056	21.31196	3.90E-06
rs4681199	3	150277525	G	A	0.046922	0.45868	0.008932	27.59618	1.49E-07
rs843372	3	184278425	T	C	-0.04947	0.717723	0.009651	26.2785	2.96E-07
rs6448619	4	28970411	T	C	0.043375	0.318083	0.009366	21.44589	3.64E-06
rs13126112	4	94918869	T	C	0.057621	0.158958	0.011865	23.58535	1.19E-06
rs13104082	4	115022856	G	A	-0.08689	0.943807	0.018729	21.52174	3.50E-06
rs2016239	4	166098443	C	G	-0.04357	0.491819	0.008818	24.4102	7.79E-07
rs16891958	5	33933857	T	C	0.484143	0.001452	0.10247	22.32307	2.30E-06
rs1320308	5	76875427	C	A	0.044883	0.67384	0.009403	22.78335	1.81E-06
rs181090787	5	82866204	T	A	-0.18289	0.015269	0.038635	22.40855	2.20E-06
rs375844484	5	114274349	A	G	-0.12947	0.028078	0.027544	22.09382	2.60E-06
rs9396788	6	17676239	G	A	-0.06873	0.367114	0.009116	56.84143	4.72E-14
rs182978364	6	29754228	A	G	-0.17821	0.018013	0.035047	25.85708	3.68E-07
rs735286	6	43776884	T	C	0.050626	0.232783	0.010271	24.29688	8.26E-07
rs4629659	6	84683238	T	C	-0.04255	0.495475	0.008731	23.74789	1.10E-06
rs375716154	6	102757915	C	T	-0.06599	0.158104	0.012223	29.15184	6.69E-08
rs78956178	6	105041334	G	T	-0.10474	0.058193	0.019308	29.42864	5.80E-08
rs9487939	6	112644625	C	A	0.0524	0.271382	0.009868	28.19629	1.10E-07
rs78686882	7	6743309	T	C	0.070123	0.090573	0.015104	21.55417	3.44E-06
rs75128707	7	27869731	T	C	-0.1198	0.033	0.025352	22.32987	2.30E-06
rs73135307	7	74455527	G	C	-0.09258	0.061309	0.018799	24.25437	8.44E-07
rs60851079	7	87017091	T	C	-0.08359	0.112321	0.014113	35.08268	3.16E-09
rs116979197	7	87359731	G	A	-0.12237	0.040236	0.023094	28.07916	1.16E-07
rs12154319	7	87559241	A	G	-0.30817	0.009651	0.048505	40.36354	2.11E-10
rs2188251	7	88574992	C	G	0.082791	0.912697	0.015881	27.17812	1.86E-07
rs73194916	7	88617367	T	C	-0.07655	0.080299	0.016423	21.72978	3.14E-06
rs75741381	7	101166177	G	C	-0.06547	0.15219	0.012343	28.13546	1.13E-07
rs714582	7	107832881	A	G	-0.08385	0.295045	0.009707	74.62879	5.68E-18
rs193067613	7	119273716	A	T	-0.06696	0.126165	0.013498	24.60706	7.03E-07
rs117920913	8	1043637	C	A	0.46571	0.001701	0.093693	24.70677	6.68E-07
rs117018004	8	11298452	A	G	-0.13669	0.02507	0.029237	21.85926	2.93E-06
rs74707612	8	23383264	T	C	0.168733	0.014761	0.034835	23.46191	1.27E-06
rs75745670	8	58145023	T	G	-0.08244	0.085982	0.016199	25.89843	3.60E-07
rs16894137	8	95934063	C	T	0.080856	0.130545	0.012803	39.88651	2.69E-10
rs2468191	8	119222029	A	G	0.040684	0.583063	0.008896	20.91532	4.80E-06
rs113828886	9	7384055	T	C	-0.14886	0.024132	0.030248	24.21887	8.60E-07
rs7039251	9	133025870	A	T	0.041543	0.463642	0.008804	22.268	2.37E-06
rs11012722	10	21483238	G	A	0.046759	0.290648	0.009617	23.64108	1.16E-06
rs147037994	10	29737565	T	C	0.165288	0.015178	0.034759	22.613	1.98E-06
rs6584349	10	100182799	G	A	0.061531	0.126047	0.013075	22.14611	2.53E-06
rs1502593	10	100349445	A	G	-0.04628	0.470589	0.008792	27.70291	1.41E-07
rs7104956	11	993745	G	C	-0.0611	0.19195	0.011371	28.87821	7.71E-08
rs35779873	11	1197482	T	C	0.046456	0.242253	0.010177	20.83888	5.00E-06
rs10831930	11	12971602	T	C	0.047218	0.309277	0.009877	22.85428	1.75E-06
rs11023658	11	15624182	G	A	-0.17443	0.017996	0.034887	24.99914	5.74E-07
rs61898562	11	61909033	T	C	-0.14976	0.02612	0.029028	26.61474	2.48E-07

Serum lipid/glucose traits after cholecystectomy from observational and MR study

rs17421328	11	70017223	T	C	0.107614	0.072358	0.01647	42.6903	6.41E-11
rs76726250	11	70189554	T	G	0.098054	0.046827	0.020383	23.14224	1.50E-06
rs556153	11	107802902	C	T	0.049348	0.463267	0.00876	31.73485	1.77E-08
rs75497660	12	14984781	T	A	0.061232	0.156109	0.011881	26.56336	2.55E-07
rs2146990	13	102814632	C	G	-0.07753	0.65365	0.009137	72.00915	2.14E-17
rs16961281	13	103066474	A	G	-0.10946	0.09983	0.014948	53.61946	2.43E-13
rs862135	14	56783060	A	G	-0.04424	0.710884	0.009618	21.16086	4.22E-06
rs62041381	16	52831633	C	A	0.158127	0.018939	0.031273	25.56644	4.27E-07
rs7193671	16	85201484	C	G	0.045923	0.712696	0.009755	22.16238	2.51E-06
rs75532121	17	56047927	A	G	-0.14775	0.023983	0.030414	23.60008	1.19E-06
rs28537992	17	79927531	T	G	0.072358	0.119478	0.013341	29.41557	5.84E-08
rs140864352	18	14396062	C	T	0.136064	0.028486	0.025608	28.2307	1.08E-07
rs554790528	18	26973074	C	T	0.099073	0.043397	0.021188	21.86389	2.93E-06
rs1032916	18	77767543	G	A	0.045234	0.282091	0.009665	21.90601	2.86E-06
rs9676730	19	32176163	A	G	0.044932	0.487821	0.008774	26.2247	3.04E-07
rs7246984	19	33077764	T	C	-0.06331	0.130289	0.013185	23.05669	1.57E-06
rs67165745	19	47420724	A	C	-0.124	0.03661	0.024379	25.87005	3.65E-07
rs117549631	19	47988536	T	C	-0.12964	0.034536	0.025164	26.54045	2.58E-07
rs2425622	20	44149792	G	A	0.04584	0.574535	0.008908	26.48287	2.66E-07
rs374283213	20	44672053	T	C	0.130455	0.026024	0.028225	21.36318	3.80E-06
rs117296576	20	44697510	A	T	0.124031	0.035328	0.023284	28.37537	9.99E-08

*CHR chromosome, EA effect allele, OA other allele, EAF effect allele frequency, SE standard error.

Table S3. Heterogeneity and pleiotropy test in the primary MR analysis

	UK Biobank			FinnGen		
	Cochran's Q test for IVW	Pleiotropy test	Global Test from MR-PRESSO results	Cochran's Q test for IVW	Pleiotropy test	Global Test from MR-PRESSO results
LDL	1.55E-44	0.6794916	< 0.001	4.60E-56	0.8970017	< 0.001
HDL	7.71E-113	0.4352173	< 0.001	9.94E-18	0.01004672	0.085
TC	1.04E-53	0.4356993	< 0.001	2.27E-52	0.9150016	< 0.001
TG	2.62E-192	0.6036673	< 0.001	2.10E-25	0.01152794	< 0.001
Fasting Glucose	0.1258829	0.5840239	0.241	0.1941064	0.06259374	0.706
Fasting Insulin	0.003960247	0.8520083	0.107	0.6700269	0.2420156	0.726
HbA1C	0.5202533	0.2311212	0.435	0.1941064	0.06259374	0.278

Value in bold means significant.

Serum lipid/glucose traits after cholecystectomy from observational and MR study

Table S4. IVs and Outliers in UK Biobank for lipid traits detected via RadialMR package

	SNP	TC	LDL-C	HDL-C	TG
1	rs10199034	Outlier	Outlier	Variant	Outlier
2	rs10799476	Variant	Variant	Outlier	Variant
3	rs10882890	Outlier	Variant	Variant	Variant
4	rs112634731	Variant	Variant	Variant	Variant
5	rs113525652	Outlier	Outlier	Variant	Outlier
6	rs11603634	Outlier	Outlier	Outlier	Variant
7	rs116468765	Outlier	Outlier	Variant	Variant
8	rs11686966	Outlier	Outlier	Outlier	Outlier
9	rs1201467	Variant	Variant	Variant	Variant
10	rs1208280	Outlier	Outlier	Variant	Outlier
11	rs12369071	Variant	Variant	Variant	Variant
12	rs13061117	Variant	Variant	Variant	Variant
13	rs138776098	Variant	Variant	Outlier	Variant
14	rs146652454	Outlier	Variant	Variant	Variant
15	rs150844304	Outlier	Variant	Outlier	Outlier
16	rs17138478	Variant	Variant	Variant	Variant
17	rs1811515	Outlier	Outlier	Variant	Variant
18	rs2107944	Outlier	Outlier	Variant	Variant
19	rs2470048	Variant	Variant	Variant	Outlier
20	rs28378706	Variant	Variant	Outlier	Variant
21	rs28517482	Outlier	Outlier	Variant	Outlier
22	rs2978388	Variant	Variant	Variant	Variant
23	rs3094509	Variant	Variant	Variant	Variant
24	rs332981	Variant	Variant	Variant	Variant
25	rs3793770	Outlier	Outlier	Variant	Variant
26	rs3862794	Variant	Variant	Variant	Variant
27	rs41276920	Outlier	Outlier	Outlier	Outlier
28	rs41281265	Variant	Variant	Outlier	Outlier
29	rs4150336	Outlier	Outlier	Outlier	Variant
30	rs4331955	Variant	Variant	Variant	Variant
31	rs4346434	Outlier	Outlier	Outlier	Outlier
32	rs4681516	Outlier	Outlier	Variant	Outlier
33	rs4881744	Variant	Variant	Variant	Variant
34	rs55780704	Outlier	Outlier	Outlier	Outlier
35	rs55971546	Variant	Variant	Variant	Variant
36	rs580477	Outlier	Outlier	Variant	Variant
37	rs62090594	Variant	Variant	Variant	Variant
38	rs698838	Outlier	Variant	Outlier	Variant
39	rs714583	Variant	Variant	Variant	Variant
40	rs72931779	Outlier	Outlier	Outlier	Outlier
41	rs73192932	Outlier	Outlier	Variant	Variant
42	rs7337432	Variant	Variant	Variant	Variant
43	rs7564733	Variant	Variant	Variant	Variant
44	rs76818081	Variant	Variant	Outlier	Variant
45	rs76862077	Variant	Variant	Variant	Variant
46	rs7993414	Outlier	Outlier	Variant	Outlier
47	rs8077886	Variant	Variant	Outlier	Outlier
48	rs932784	Variant	Variant	Outlier	Variant
49	rs9371004	Variant	Variant	Variant	Variant
50	rs9471953	Variant	Variant	Variant	Variant
51	rs9544535	Variant	Variant	Outlier	Outlier
52	rs9790309	Variant	Variant	Outlier	Outlier

Serum lipid/glucose traits after cholecystectomy from observational and MR study

Table S5. IVs and Outliers in FinnGen for lipid traits detected via RadialMR package

	SNP	TC	LDL	HDL	TG
1	rs10208775	Variant	Variant	Variant	Variant
2	rs1032916	Variant	Variant	Variant	Variant
3	rs10831930	Variant	Variant	Variant	Variant
4	rs11012722	Variant	Variant	Outlier	Outlier
5	rs11023658	Variant	Variant	Variant	Outlier
6	rs112266464	Variant	Variant	Variant	Variant
7	rs113828886	Variant	Variant	Variant	Variant
8	rs11690947	Outlier	Outlier	Variant	Variant
9	rs11691443	Outlier	Outlier	Variant	Variant
10	rs116979197	Variant	Variant	Variant	Variant
11	rs117018004	Variant	Variant	Variant	Variant
12	rs117296576	Outlier	Variant	Outlier	Variant
13	rs117549631	Outlier	Variant	Variant	Variant
14	rs117920913	Variant	Variant	Outlier	Variant
15	rs12135720	Variant	Variant	Variant	Variant
16	rs12154319	Variant	Outlier	Variant	Variant
17	rs12470367	Variant	Variant	Outlier	Outlier
18	rs12615717	Variant	Variant	Variant	Variant
19	rs13104082	Variant	Outlier	Outlier	Variant
20	rs13126112	Variant	Variant	Variant	Variant
21	rs1320308	Variant	Variant	Variant	Variant
22	rs13399179	Variant	Variant	Outlier	Variant
23	rs13414085	Outlier	Outlier	Variant	Variant
24	rs139199716	Variant	Variant	Variant	Variant
25	rs140864352	Variant	Variant	Variant	Variant
26	rs143949742	Variant	Variant	Variant	Variant
27	rs145048510	Variant	Variant	Variant	Variant
28	rs147037994	Variant	Variant	Variant	Variant
29	rs150212157	Variant	Variant	Variant	Variant
30	rs1502593	Outlier	Outlier	Variant	Variant
31	rs1629928	Variant	Variant	Variant	Variant
32	rs163520	Variant	Variant	Variant	Variant
33	rs16891958	Variant	Variant	Variant	Variant
34	rs16894137	Variant	Variant	Outlier	Variant
35	rs16961281	Outlier	Outlier	Variant	Outlier
36	rs17421328	Outlier	Outlier	Outlier	Outlier
37	rs181090787	Variant	Variant	Variant	Variant
38	rs182978364	Variant	Variant	Variant	Variant
39	rs186890864	Outlier	Outlier	Variant	Variant
40	rs187779008	Variant	Variant	Variant	Variant
41	rs193067613	Variant	Variant	Variant	Variant
42	rs2011896	Outlier	Outlier	Variant	Variant
43	rs2016239	Variant	Variant	Variant	Variant
44	rs2146990	Outlier	Outlier	Variant	Outlier
45	rs2188251	Outlier	Outlier	Variant	Outlier
46	rs2425622	Variant	Variant	Outlier	Variant
47	rs2468191	Variant	Variant	Variant	Outlier

Serum lipid/glucose traits after cholecystectomy from observational and MR study

48	rs263462	Variant	Variant	Variant	Variant
49	rs28537992	Outlier	Outlier	Variant	Variant
50	rs2921987	Variant	Variant	Outlier	Variant
51	rs34997129	Variant	Variant	Variant	Variant
52	rs35779873	Variant	Variant	Variant	Variant
53	rs374283213	Variant	Variant	Variant	Variant
54	rs375716154	Variant	Variant	Variant	Variant
55	rs375844484	Variant	Variant	Variant	Variant
56	rs3790843	Variant	Variant	Variant	Variant
57	rs4629659	Variant	Variant	Variant	Variant
58	rs4681199	Variant	Variant	Outlier	Outlier
59	rs554790528	Variant	Variant	Variant	Variant
60	rs556153	Variant	Variant	Variant	Variant
61	rs55935092	Outlier	Outlier	Outlier	Outlier
62	rs576479048	Variant	Outlier	Variant	Variant
63	rs582384	Variant	Variant	Variant	Variant
64	rs60851079	Outlier	Outlier	Variant	Variant
65	rs61614759	Outlier	Outlier	Variant	Variant
66	rs61898562	Variant	Variant	Outlier	Outlier
67	rs62041381	Variant	Variant	Variant	Variant
68	rs62140201	Variant	Variant	Variant	Variant
69	rs62272019	Outlier	Outlier	Variant	Outlier
70	rs6448619	Outlier	Variant	Variant	Outlier
71	rs6584349	Outlier	Variant	Outlier	Outlier
72	rs66498012	Outlier	Outlier	Variant	Outlier
73	rs67165745	Variant	Variant	Outlier	Variant
74	rs7039251	Variant	Variant	Variant	Variant
75	rs7104956	Outlier	Outlier	Variant	Variant
76	rs71420083	Outlier	Outlier	Outlier	Variant
77	rs714582	Variant	Variant	Variant	Variant
78	rs7193671	Variant	Variant	Variant	Outlier
79	rs7246984	Outlier	Outlier	Variant	Variant
80	rs72799962	Variant	Variant	Variant	Outlier
81	rs730803	Variant	Variant	Variant	Variant
82	rs73135307	Variant	Variant	Variant	Outlier
83	rs73194916	Outlier	Variant	Variant	Variant
84	rs735286	Variant	Variant	Variant	Variant
85	rs74707612	Variant	Variant	Variant	Variant
86	rs75120545	Outlier	Outlier	Variant	Outlier
87	rs75128707	Variant	Variant	Variant	Variant
88	rs75497660	Variant	Variant	Variant	Variant
89	rs75532121	Variant	Variant	Variant	Variant
90	rs75741381	Variant	Variant	Outlier	Outlier
91	rs75745670	Outlier	Outlier	Variant	Outlier
92	rs75841075	Outlier	Outlier	Variant	Variant
93	rs76592665	Variant	Variant	Variant	Variant
94	rs76726250	Variant	Variant	Variant	Outlier
95	rs76733846	Variant	Outlier	Variant	Variant
96	rs78686882	Variant	Variant	Variant	Variant

Serum lipid/glucose traits after cholecystectomy from observational and MR study

97	rs78815523	Variant	Variant	Variant	Variant
98	rs78956178	Variant	Outlier	Variant	Variant
99	rs79348616	Variant	Variant	Variant	Variant
100	rs79469600	Variant	Variant	Variant	Variant
101	rs79478006	Variant	Variant	Variant	Variant
102	rs79693383	Variant	Variant	Variant	Variant
103	rs843372	Outlier	Outlier	Outlier	Outlier
104	rs862135	Variant	Variant	Variant	Variant
105	rs871962	Variant	Variant	Variant	Variant
106	rs9396788	Variant	Variant	Variant	Variant
107	rs9487939	Variant	Variant	Variant	Outlier
108	rs9676730	Variant	Variant	Variant	Variant

Table S6. Heterogeneity and pleiotropy test in the repeated MR analysis for lipid traits after outlier removal

	UK Biobank			FinnGen		
	Cochran's Q test for IVW	Pleiotropy test	Global Test from MR-PRESSO results	Cochran's Q test for IVW	Pleiotropy test	Global Test from MR-PRESSO results
LDL-C	0.09579939	0.571592	0.102	0.6165756	0.3583751	0.458
HDL-C	0.5505367	0.5941352	0.0575	0.4749689	0.2541208	0.431
TC	0.08498349	0.4487776	0.104	0.6365185	0.8969529	0.564
TG	0.3341356	0.4445664	0.375	0.8091941	0.1992355	0.355

Serum lipid/glucose traits after cholecystectomy from observational and MR study

Table S7. Association between genetically predicted cholecystectomy and blood lipid traits in UK Biobank

exposure	outcome	method	nsnp	b	se	pval	lo_ci	up_ci	or	or_lci95	or_uci95
cholecystectomy	TC	MR Egger	29	0.162857	0.407652	0.692668	-0.63614	0.961855	1.176868	0.529331	2.616545
cholecystectomy	TC	Weighted median	29	-0.0382	0.171731	0.823978	-0.37479	0.298395	0.962522	0.687433	1.347694
cholecystectomy	TC	Inverse variance weighted	29	-0.13296	0.133421	0.318985	-0.39447	0.128545	0.8755	0.67404	1.137173
cholecystectomy	TC	Simple mode	29	0.41667	0.401746	0.308541	-0.37075	1.204093	1.516902	0.690215	3.333733
cholecystectomy	TC	Weighted mode	29	0.272529	0.368446	0.465655	-0.44962	0.994683	1.313282	0.637868	2.703868
cholecystectomy	LDL-C	MR Egger	32	-0.07519	0.380244	0.844579	-0.82047	0.670088	0.927566	0.440225	1.954409
cholecystectomy	LDL-C	Weighted median	32	-0.17723	0.17479	0.310595	-0.51982	0.165356	0.837585	0.594627	1.179813
cholecystectomy	LDL-C	Inverse variance weighted	32	-0.27896	0.131508	0.033903	-0.53671	-0.0212	0.756573	0.584668	0.979022
cholecystectomy	LDL-C	Simple mode	32	0.085182	0.352448	0.810615	-0.60562	0.77598	1.088915	0.545738	2.17272
cholecystectomy	LDL-C	Weighted mode	32	-0.0551	0.37583	0.884391	-0.79173	0.681527	0.946391	0.453062	1.976895
cholecystectomy	HDL-C	MR Egger	33	-0.43975	0.351313	0.220031	-1.12832	0.248824	0.644198	0.323575	1.282516
cholecystectomy	HDL-C	Weighted median	33	-0.27597	0.158023	0.080747	-0.58569	0.033759	0.758838	0.55672	1.034336
cholecystectomy	HDL-C	Inverse variance weighted	33	-0.26024	0.11074	0.018773	-0.47729	-0.04319	0.770866	0.620462	0.95773
cholecystectomy	HDL-C	Simple mode	33	-0.41373	0.32258	0.208862	-1.04598	0.218531	0.661182	0.351346	1.244248
cholecystectomy	HDL-C	Weighted mode	33	-0.37801	0.259028	0.154217	-0.88571	0.129683	0.685222	0.412422	1.138467
cholecystectomy	TG	MR Egger	35	0.740345	0.307647	0.021866	0.137356	1.343334	2.096658	1.147237	3.831796
cholecystectomy	TG	Weighted median	35	0.611595	0.160558	0.000139	0.296902	0.926288	1.843369	1.345683	2.525119
cholecystectomy	TG	Inverse variance weighted	35	0.518493	0.110892	2.93E-06	0.301144	0.735842	1.679494	1.351404	2.087238
cholecystectomy	TG	Simple mode	35	0.775825	0.336486	0.027358	0.116313	1.435337	2.172384	1.123348	4.20106
cholecystectomy	TG	Weighted mode	35	0.727329	0.303211	0.022082	0.133035	1.321622	2.069544	1.14229	3.749499

Serum lipid/glucose traits after cholecystectomy from observational and MR study

Table S8. Association between genetically predicted cholecystectomy and blood lipid traits in FinnGen

exposure	outcome	method	nsnp	b	se	pval	lo_ci	up_ci	or	or_lci95	or_uci95
cholecystectomy	TC	MR Egger	78	-0.01007	0.005483	0.070091	-0.02082	0.000673	0.989978	0.979397	1.000674
cholecystectomy	TC	Weighted median	78	-0.00505	0.00518	0.329495	-0.0152	0.005101	0.994962	0.984912	1.005114
cholecystectomy	TC	Inverse variance weighted	78	-0.00948	0.003045	0.001849	-0.01545	-0.003512	0.990565	0.984671	0.996494
cholecystectomy	TC	Simple mode	78	0.00987	0.011596	0.39732	-0.01286	0.032597	1.009919	0.987225	1.033134
cholecystectomy	TC	Weighted mode	78	-0.0017	0.007792	0.828125	-0.01697	0.013574	0.998304	0.983174	1.013667
cholecystectomy	LDL-C	MR Egger	77	-0.01434	0.00582	0.016065	-0.02574	-0.002928	0.985767	0.974586	0.997076
cholecystectomy	LDL-C	Weighted median	77	-0.0034	0.005264	0.517786	-0.01372	0.006912	0.996602	0.986373	1.006936
cholecystectomy	LDL-C	Inverse variance weighted	77	-0.00986	0.003224	0.00223	-0.01618	-0.003539	0.990191	0.983954	0.996467
cholecystectomy	LDL-C	Simple mode	77	0.002975	0.011985	0.804656	-0.02052	0.026466	1.002979	0.979692	1.026819
cholecystectomy	LDL-C	Weighted mode	77	0.00116	0.008651	0.893708	-0.0158	0.018116	1.00116	0.984328	1.018281
cholecystectomy	HDL-C	MR Egger	88	-0.00025	0.005546	0.964164	-0.01112	0.01062	0.99975	0.988942	1.010676
cholecystectomy	HDL-C	Weighted median	88	-0.00252	0.004391	0.565337	-0.01113	0.006082	0.997479	0.988931	1.0061
cholecystectomy	HDL-C	Inverse variance weighted	88	-0.00567	0.002906	0.050862	-0.01137	2.14E-05	0.994342	0.988694	1.000021
cholecystectomy	HDL-C	Simple mode	88	0.000406	0.009707	0.966748	-0.01862	0.019431	1.000406	0.981553	1.019621
cholecystectomy	HDL-C	Weighted mode	88	-0.00161	0.007697	0.835045	-0.01669	0.013479	0.998394	0.983444	1.01357
cholecystectomy	TG	MR Egger	78	-0.00789	0.008372	0.349189	-0.0243	0.008523	0.992144	0.975996	1.00856
cholecystectomy	TG	Weighted median	78	-0.00434	0.00501	0.386159	-0.01416	0.005478	0.995668	0.985939	1.005493
cholecystectomy	TG	Inverse variance weighted	78	0.006904	0.004754	0.146367	-0.00241	0.016221	1.006928	0.99759	1.016354
cholecystectomy	TG	Simple mode	78	-0.00989	0.011363	0.38686	-0.03216	0.012383	0.99016	0.96835	1.01246
cholecystectomy	TG	Weighted mode	78	-0.00865	0.007863	0.274712	-0.02406	0.006762	0.991387	0.976224	1.006785

Serum lipid/glucose traits after cholecystectomy from observational and MR study

Table S9. Association between genetically predicted cholecystectomy and blood glucose traits in UK Biobank

exposure	outcome	method	n SNP	b	se	pval	lo_ci	up_ci	or	or_lci95	or_uci95
cholecystectomy	Fasting Glucose	MR Egger	19	1.022421	0.999849	0.320841	-0.93728	2.982125	2.779917	0.391691	19.72969
cholecystectomy	Fasting Glucose	Weighted median	19	0.364355	0.475288	0.443321	-0.56721	1.29592	1.439585	0.567105	3.654356
cholecystectomy	Fasting Glucose	Inverse variance weighted	19	0.5054	0.369058	0.170864	-0.21795	1.228754	1.657649	0.804162	3.416971
cholecystectomy	Fasting Glucose	Simple mode	19	-0.05876	0.857526	0.94613	-1.73951	1.621996	0.942938	0.175607	5.063187
cholecystectomy	Fasting Glucose	Weighted mode	19	0.24792	0.556778	0.661429	-0.84337	1.339205	1.281357	0.43026	3.81601
cholecystectomy	Fasting Insulin	MR Egger	19	0.338647	1.26738	0.792528	-2.14542	2.822711	1.403048	0.117019	16.8224
cholecystectomy	Fasting Insulin	Weighted median	19	0.343181	0.491155	0.484725	-0.61948	1.305844	1.409424	0.538223	3.690804
cholecystectomy	Fasting Insulin	Inverse variance weighted	19	0.116074	0.46202	0.801635	-0.78949	1.021634	1.123079	0.454078	2.777729
cholecystectomy	Fasting Insulin	Simple mode	19	0.446577	1.103343	0.690431	-1.71597	2.609129	1.562953	0.179788	13.58721
cholecystectomy	Fasting Insulin	Weighted mode	19	0.380697	0.560213	0.505431	-0.71732	1.478715	1.463304	0.488058	4.387304
cholecystectomy	HbA1c	MR Egger	19	1.013599	0.910318	0.281009	-0.77062	2.797822	2.755501	0.462725	16.40886
cholecystectomy	HbA1c	Weighted median	19	0.233157	0.503369	0.643226	-0.75345	1.21976	1.26258	0.470742	3.386374
cholecystectomy	HbA1c	Inverse variance weighted	19	-0.03074	0.348675	0.929749	-0.71414	0.652663	0.969728	0.489612	1.92065
cholecystectomy	HbA1c	Simple mode	19	-1.29551	0.919072	0.175705	-3.09689	0.505868	0.273757	0.045189	1.658424
cholecystectomy	HbA1c	Weighted mode	19	0.421642	0.590219	0.484153	-0.73519	1.578472	1.524463	0.479415	4.847542

Table S10. Association between genetically predicted cholecystectomy and blood glucose traits in FinnGen

exposure	outcome	method	n SNP	b	se	pval	lo_ci	up_ci	or	or_lci95	or_uci95
cholecystectomy	Fasting Glucose	MR Egger	26	0.045313	0.034417	0.200406	-0.02214	0.112769	1.046355	0.9781	1.119374
cholecystectomy	Fasting Glucose	Weighted median	26	0.023215	0.017837	0.193079	-0.01175	0.058176	1.023487	0.988323	1.059902
cholecystectomy	Fasting Glucose	Inverse variance weighted	26	0.022497	0.01224	0.066064	-0.00149	0.046488	1.022752	0.998508	1.047585
cholecystectomy	Fasting Glucose	Simple mode	26	0.050603	0.037215	0.186053	-0.02234	0.123544	1.051905	0.977909	1.1315
cholecystectomy	Fasting Glucose	Weighted mode	26	0.052287	0.035195	0.149878	-0.0167	0.121269	1.053678	0.983443	1.128929
cholecystectomy	Fasting Insulin	MR Egger	26	0.045187	0.034652	0.204604	-0.02273	0.113105	1.046223	0.977524	1.11975
cholecystectomy	Fasting Insulin	Weighted median	26	0.001597	0.01769	0.928048	-0.03308	0.036271	1.001599	0.967465	1.036936
cholecystectomy	Fasting Insulin	Inverse variance weighted	26	0.00632	0.012288	0.607033	-0.01776	0.030404	1.00634	0.982392	1.030871
cholecystectomy	Fasting Insulin	Simple mode	26	0.002309	0.033902	0.946233	-0.06414	0.068756	1.002312	0.937876	1.071175
cholecystectomy	Fasting Insulin	Weighted mode	26	0.010934	0.026711	0.685768	-0.04142	0.063287	1.010994	0.959427	1.065332
cholecystectomy	HbA1c	MR Egger	24	0.075444	0.040394	0.075181	-0.00373	0.154616	1.078363	0.996279	1.167209
cholecystectomy	HbA1c	Weighted median	24	0.020503	0.018968	0.279749	-0.01668	0.057681	1.020714	0.983463	1.059377
cholecystectomy	HbA1c	Inverse variance weighted	24	0.001359	0.015184	0.928699	-0.0284	0.031119	1.00136	0.971998	1.031608
cholecystectomy	HbA1c	Simple mode	24	0.01519	0.034903	0.667465	-0.05322	0.083601	1.015306	0.948171	1.087195
cholecystectomy	HbA1c	Weighted mode	24	0.020044	0.027626	0.475447	-0.0341	0.074191	1.020246	0.966471	1.077012

Serum lipid/glucose traits after cholecystectomy from observational and MR study

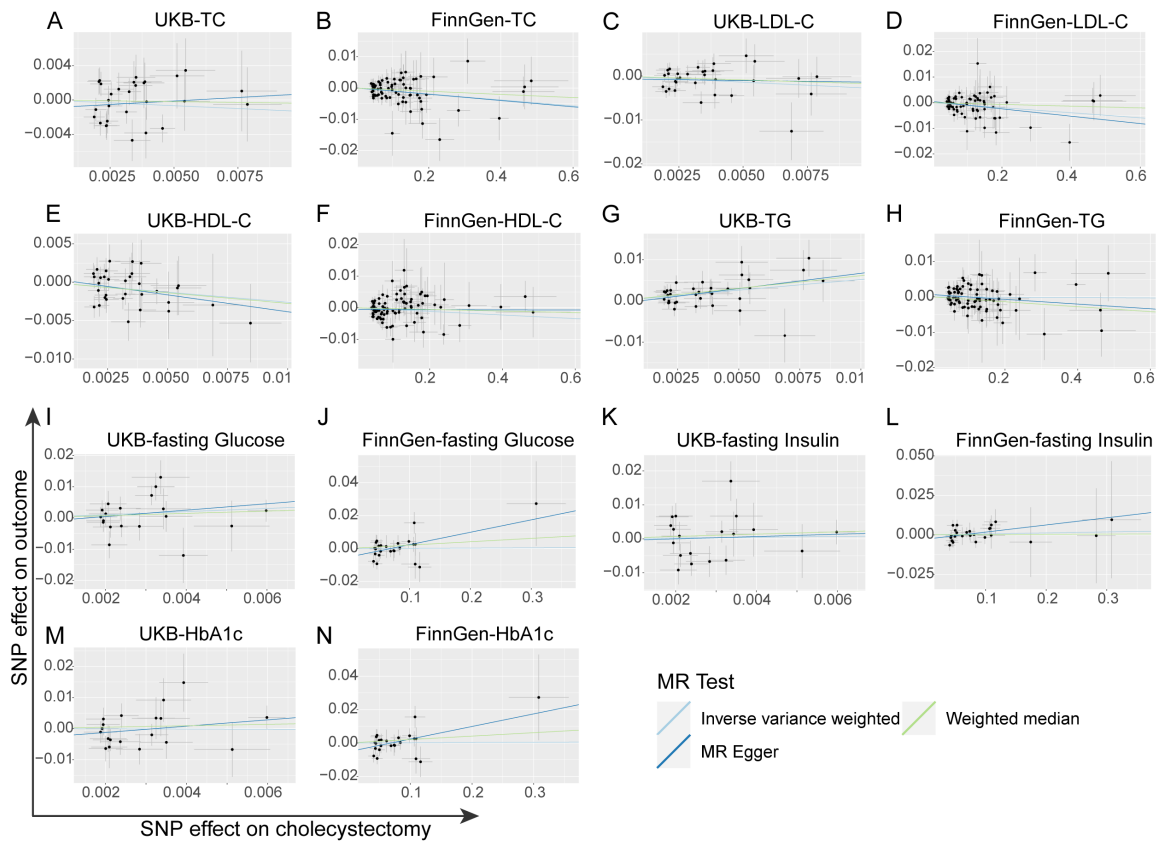
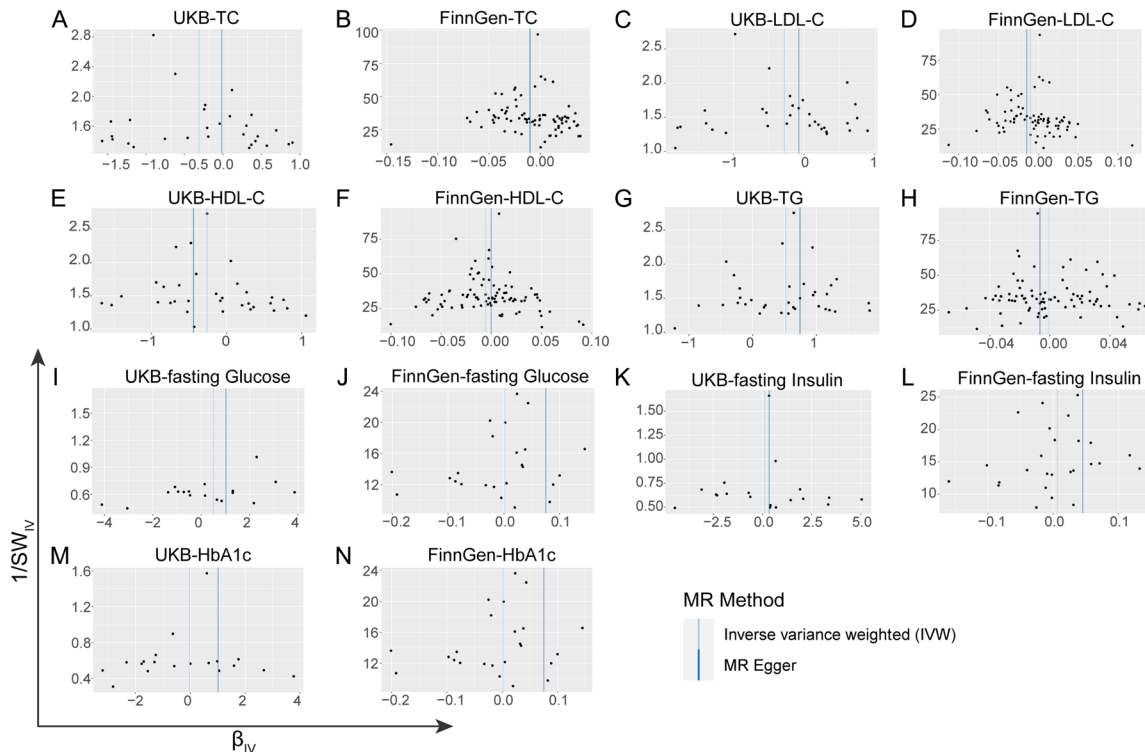


Figure S1. Scatter plots of MR results from UK biobank and FinnGen datasets. Abbreviations: UKB, UK biobank; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; HbA1c, hemoglobin A1c; IVW method, Inverse Variance Weighted method; MR, Mendelian randomization; SNP, single nucleotide polymorphism.



Serum lipid/glucose traits after cholecystectomy from observational and MR study

Figure S2. Funnel plots of MR results from UK biobank and FinnGen datasets. Abbreviations: UKB, UK biobank; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; HbA1c, hemoglobin A1c; IVW method, Inverse Variance Weighted method; MR, Mendelian randomization; SNP, single nucleotide polymorphism.

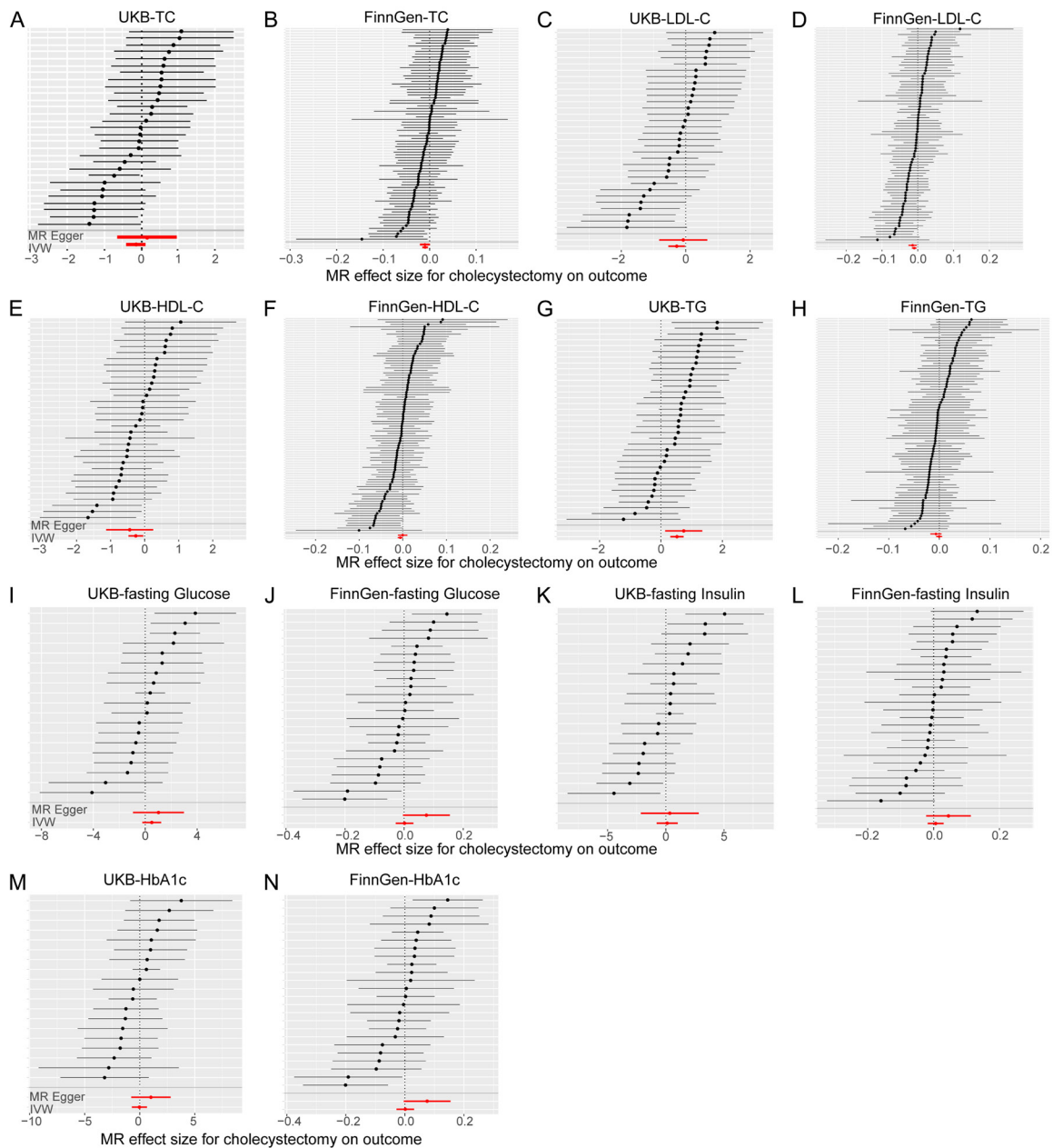


Figure S3. Forest plots of MR results from UK biobank and FinnGen datasets. Abbreviations: UKB, UK biobank; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; HbA1c, hemoglobin A1c; IVW method, Inverse Variance Weighted method; MR, Mendelian randomization; SNP, single nucleotide polymorphism.

Serum lipid/glucose traits after cholecystectomy from observational and MR study

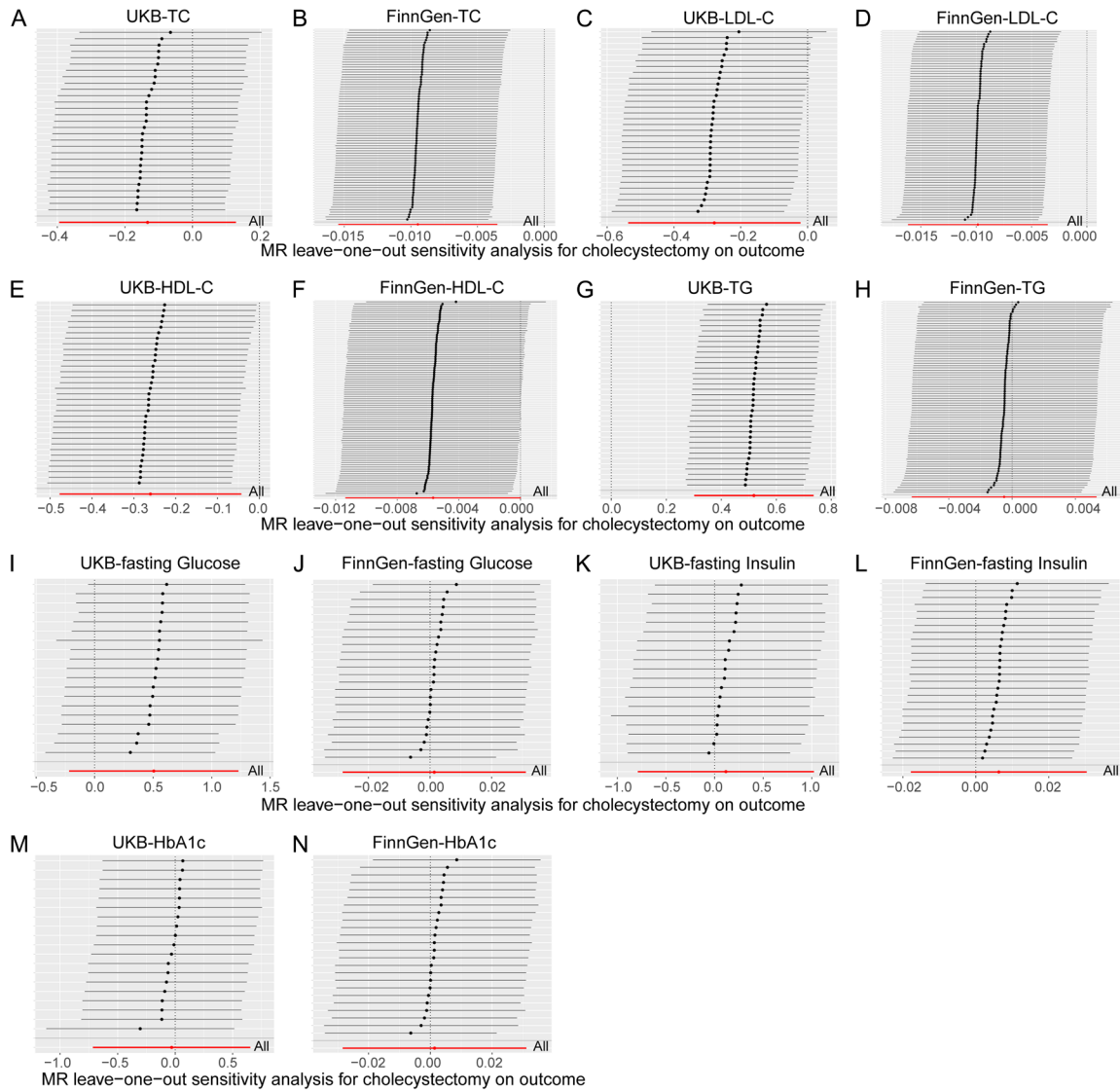


Figure S4. Leave-one-out plots of MR results from UK biobank and FinnGen datasets. Abbreviations: UKB, UK biobank; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; HbA1c, hemoglobin A1c; IVW method, Inverse Variance Weighted method; MR, Mendelian randomization; SNP, single nucleotide polymorphism.

Table S11. Results of heterogeneity test to combine Mendelian randomization estimates.

Source	Estimates	I ² statistic	Q statistic	Specific Model
GCLC	LDL	0.761	0.0408	Random-effect model
GCLC	HDL	0.811	0.0216	Random-effect model
GCLC	TC	0	0.3548	Common-effect model
GCLC	TG	0.953	< 0.0001	Random-effect model
MAGIC	Fasting Glucose	0.415	0.191	Common-effect model
MAGIC	Fasting Insulin	0	0.8123	Common-effect model
MAGIC	HbA1C	0	0.9267	Common-effect model