

Genetically Proxied Therapeutic Effect of Lipid-Lowering Drugs Use, Breast Cancer, and Endometrial Cancer's Risk: A Drug Target-Based Mendelian Randomization Study

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Background: Observational studies have investigated the association between lipid-lowering drugs and breast cancer (BC) and endometrial cancer (EC), but some controversy remains.

Objective: This paper aims to explore the causal relationship between genetic proxies for lipid-lowering drugs and breast and endometrial cancers using drug-target Mendelian randomization (MR).

Methods: Analyses were mainly performed using inverse variance weighted (IVW), heterogeneity and horizontal pleiotropy tests, and sensitivity analysis to assess the robustness of the results and causal relationship.

Results: HMGCR, APOB, and NPC1L1 increased the risk of breast cancer, LPL increased the risk of endometrial cancer, and APOC3 decreased the risk of breast and endometrial cancer. No heterogeneity or horizontal pleiotropy was detected, and nor was there any evidence of an association between other lipid-lowering drugs and breast and endometrial cancer.

Conclusion: Our study demonstrated genetically that HMGCR inhibition, APOB inhibition, and NPC1L1 inhibition decrease the risk of breast cancer, LPL agonist increases the risk of endometrial cancer, and APOC3 inhibition decreases the risk of breast cancer and endometrial cancer, and these findings provide genetic insights into the potential risks of lipid-lowering drug therapy.

Keywords: lipid-lowering drugs, breast cancer, endometrial cancer, drug-target Mendelian randomization

Introduction

Breast cancer (BC) is the most common malignancy among women worldwide and the annual incidence continues to increase.¹ According to the 2020 estimates by International Agency for Research on Cancer (IARC), female breast cancer has surpassed lung cancer as the leading cause of cancer incidence worldwide, with approximately 2.3 million new cases, accounting for 11.7% of all cancer cases.² Endometrial cancer (EC) is the seventh most common malignant disease in the world and the most common gynecological malignancy in developed countries.³ Although 75% of patients with EC can be diagnosed at an early stage, the prognosis of patients with advanced disease remains poor.⁴ Due to limited therapeutic measures (eg, surgery, radiotherapy, and hormonal therapy) and the poor prognosis of BC & EC,^{5,6} primary prevention may become the least costly strategy for controlling BC & EC, which can effectively reduce the burden of the disease.

Reprogramming of lipid metabolism is one of the hallmarks of cancer,^{7,8} and cholesterol, an important component of blood lipids, is thought to underlie the proliferation and survival of cancer cells.⁹ Several studies have shown a negative correlation between serum cholesterol levels and cancer risk.¹⁰ Cholesterol is thought to increase the risk of BC & EC

because it is a precursor for steroid hormone synthesis and endogenous steroid hormones, which are directly associated with BC risk.^{11,12} Dyslipidaemia is characterized by elevated levels of triglycerides (TG), small and dense low-density lipoprotein cholesterol (LDL-C), as well as reduced levels of high-density lipoprotein cholesterol (HDL-C).¹³ Higher levels of TG, HDL-C, and lower levels of LDL-C have been found to be associated with a reduced risk of BC, while higher levels of TG and HDL-C have been associated with an increased risk of EC.^{14–16} Recent studies^{17,18} have confirmed the close relationship between dyslipidaemia and BC & EC, and there is also increasing interest in the role of lipid-lowering drugs in BC & EC. Evidence from preclinical studies suggests that statins may have anticancer properties by inducing apoptosis and inhibiting tumour growth, angiogenesis and cancer metastasis.^{19,20} Observational studies have shown no evidence of the effect of statins on BC risk.²¹ These studies have produced inconsistent results, which may be due to the varying study populations, methodologies and outcome definitions, as well as unavoidable confounding factors. Therefore, further studies are needed to clarify whether there is a causal association between lipid-lowering drugs and BC & EC.

Mendelian randomization (MR) study uses single nucleotide polymorphisms (SNPs) as instrumental variables (IVs) to infer the causal relationships between exposure and outcome. Since alleles are subject to the law of “random assignment of parental alleles to offspring”, similar to the randomization process in clinical trials, confounding bias and reverse causation can be better avoided and the causal relationship can be effectively elucidated.²² Drug-target MR was developed based on classical MR, which uses genetic variants located within or near drug target genes as instrumental variables to infer causal relationships between drugs and diseases, and it can be used to predict drug development and repurposing prospects.²³ Therefore, we used drug-target MR for the first time to assess the causal effects of lipid-lowering drugs on BC & EC based on the publicly available large-scale Genome-Wide Association Study (GWAS) database.

Material and Methods

Research Design

Our drug-target MR study was based on the GWAS database, and the study design is shown in Figure 1. Since lipid-lowering drugs mainly act on LDL-C, TG, and apolipoprotein B (ApoB),²⁴ we utilized the association of the drug target genes with the above three to proxy for the drug-targeting effect (correlation hypothesis). The selected instrumental variables were not associated with other confounders (independence assumption) and did not influence the outcome

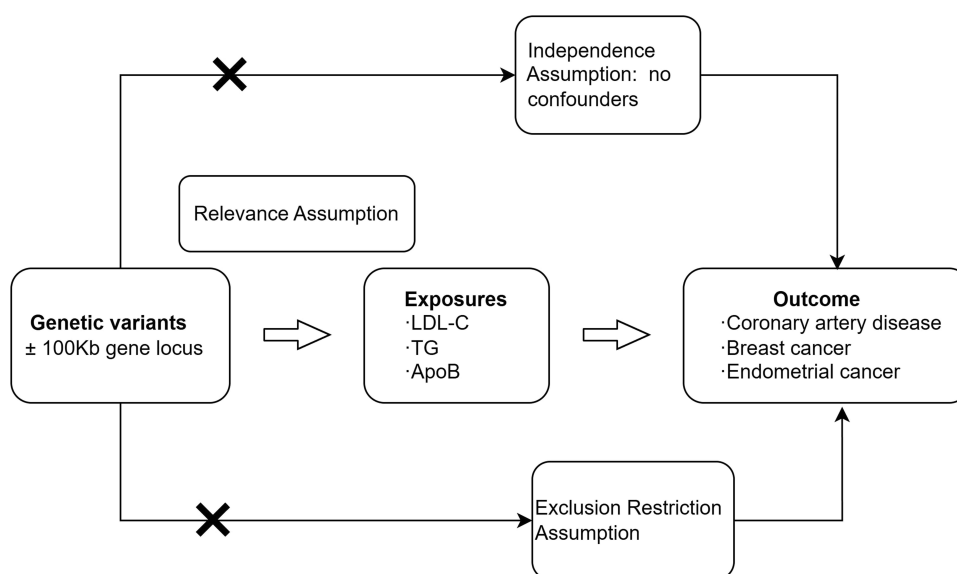


Figure 1 Instrumental variable screening flow chart for drug-target MR analysis.

Abbreviations: SNP, single nucleotide polymorphism; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; ApoB, apolipoprotein B.

through other pathways (exclusivity assumption). Subsequently, MR was applied and inverse variance weighted (IVW) was used as the main analytical method to determine causality, and Cochran's Q-test and MR-Egger intercept test were adopted to assess the heterogeneity and horizontal multivariate validity so as to determine the robustness of the results. Since lipid-lowering drugs are commonly used to control dyslipidaemia and treat cardiovascular disease, we performed a positive control analysis using coronary artery disease in order to increase the confidence in the causal effect of genetic variants, where the existence of a significant causal association indicated that our instrumental variables and causal effects have a high level of confidence. It is worth noting that according to item 1 and 2 of Article 32 of "the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects", this study is exempt from ethical review and approval.

Data Source

Pooled data for LDL-C and TG were obtained from a study by Willer CJ et al,²⁵ which included 173,082 (LDL-C) and 177,861 (TG) participants, respectively. Pooled data for ApoB were obtained from a study by Richardson TG et al, which included 439,214 participants.²⁶ The SNPs of drug target genes for LDL-C, TG, and ApoB were obtained as instrumental variables to model the effects of lipid-lowering drugs. BC was used in the study by Michailidou K et al,²⁷ which included 139,274 participants. EC was used in the study by Sakaue S et al,²⁸ which included 240,027 participants. It should be noted that none of the data included more detailed cohort data such as age and pathological stage grading to allow for further subgroup analyses, as detailed in [Table 1](#). All GWAS pooled data are of European origin.

Instrumental Variable Selection

To replace lipid-lowering drugs, we identified information on pharmacologically active protein targets and their encoding genes in lipid-lowering drugs based on a previous study,²⁹ including 4 LDL-C lowering drug targets: Apolipoprotein B (APOB), 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), Niemann-Pick C1-Like 1 (NPC1L1) and Proprotein convertase subtilisin/kexin type 9 (PCSK9), 5 TG-lowering drug targets: Angiopoietin-like 3 (ANGPTL3), APOB, Apolipoprotein C3 (APOC3), Peroxisome Proliferator Activated Receptor Alpha (PPARA) and Lipoprotein Lipase (LPL), six drug targets that reduce ApoB: ANGPTL3, APOB, APOC3, LPL, PPARA, and PCSK9. Firstly, genome-wide significant SNPs ($p\text{-value} < 5 \times 10^{-8}$) associated with LDL-C, TG, and ApoB were selected, respectively. Second, a linkage disequilibrium (LD) screen was performed ($r^2 < 0.3$). Finally, SNPs within a 100 kb window above and below the drug target gene were selected as instrumental variables for lipid-lowering drugs (minor allele frequency $> 1\%$). SNPs may be in low LD, so we estimated the F-value for each instrumental variable and excluded the weak instrumental variables with $F < 10$.³⁰ The results of the screening of target genes and instrumental variables for lipid-lowering drugs are presented in [Supplementary Excel 1](#).

Mendelian Randomization Analysis

Lipid-lowering drugs have been widely used in the treatment of coronary artery disease. Therefore, we used the GWAS pooled data for coronary artery disease as a positive control for the results to verify the validity of the instrumental variables. IVW³¹ was used as the primary analytical method to determine causality. The method involves weighting the

Table 1 Description of Included Traits

Trait	ID	Number of SNPs	Population	Sample size	Case/Control
LDL cholesterol	leu-A-300	2,437,752	European	173,082	/
Triglycerides	leu-A-302	2,439,433	European	177,861	/
Apolipoprotein B	leu-b-108	12,321,875	European	439,214	/
Breast cancer	Ebi-A-GCST004988	11,069,665	European	139,274	76,192/63,082
Endometrial cancer	Ebi-A-GCST90018838	24,135,295	European	240,027	2188/237839
Coronary artery disease	Ebi-A-GCST005195	7,934,254	European	547,261	122,733/424,528

inverse of the variance of all instrumental variables as weights, provided that they are valid. The test efficacy is highest in the absence of heterogeneity and horizontal pleiotropy. MR Egger regression, weighted median method (WME), etc. were used as a supplement to IVW results. Heterogeneity was assessed using the p-value of Cochran's Q-test,³² with $p < 0.05$ representing the presence of heterogeneity, then potential outliers were assessed using the MR pleiotropy residual sum and outlier test (MR-PRESSO),³³ which were eliminated and re-analyzed. The MR-Egger intercept was used to test for horizontal multiplicity to verify the reliability of the MR analysis results,³⁴ and the "leave-one-out" (LOO) method to assess the robustness of the results.³⁵ Considering multiple testing, the Bonferroni correction was used to modify the threshold for the significance level, with a p-value greater than the threshold and not exceeding 0.05 indicating a suggestive association.

Results

Genetic Instrument Selection

During the selection of IVs, PPARG had no suitable genetic surrogate and was excluded from the subsequent analyses. In addition, ANGPTL3, a target under TG and ApoB, and ApoB, a target under TG, were also excluded from the corresponding subsequent analyses because they were not statistically significant in the positive control analyses. The remaining genetic proxies for lipid-lowering drugs were associated with the risk of developing coronary artery disease, demonstrating the validity of these instrumental variables ([Supplementary Excel 2](#)). For LDL-C, we identified a total of 4 pharmacological target genes and 42 SNPs, including 7 for HMGCR, 20 for APOB, 3 for NPC1L1, and 12 for PCSK9. For TG, a total of 2 pharmacological target genes and 34 SNPs were identified, including 10 for APOC3 and 24 for LPL. For ApoB, a total of 4 pharmacological target genes with 91 SNPs were identified, of which 16 were for APOC3, 37 for APOB, 11 for LPL, and 27 for PCSK9. The F-statistics of all these instrumental SNPs exceeded 10, indicating that weak instrumental bias is not expected to affect the results ([Supplementary Excel 3](#)).

Causal Effects of Lipid-Lowering Drugs on Breast Cancer

Since there was no heterogeneity and horizontal pleiotropy among the lipid-lowering drugs, the results of IVW analysis were used as the main reference index. As shown in [Table 2](#), genetically predicted HMGCR ($OR=1.20$, 95% CI 1.08–1.33, $P=5.12 \times 10^{-4}$) was associated with an increased risk of BC, NPC1L1 ($OR=1.39$, 95% CI 1.11–1.74, $P=4.55 \times 10^{-3}$) was associated with an increased BC risk, APOB increased BC risk through LDL-C ($OR=1.07$, 95% CI 1.02–1.13, $p = 8.59 \times 10^{-3}$) and ApoB ($OR=1.06$, 95% CI 1.01–1.11, $p = 1.00 \times 10^{-2}$), and PCSK9 increased BC risk through LDL-C ($OR=1.11$, 95% CI 1.03–1.19, $p = 4.55 \times 10^{-3}$), PCSK9 under ApoB had a suggestive association with BC risk ($OR=1.11$, 95% CI 1.01–1.21, $p =$

Table 2 The Causal Effects of Genetic Proxies for Lipid-Lowering Drug Classes on Risk of BC

Drug-Target Gene	nSNP	OR (95% CI)	Pval
LDL-C			
HMGCR	7	1.20 (1.08,1.33)	5.12×10^{-4}
APOB	20	1.07 (1.02,1.13)	8.59×10^{-3}
NPC1L1	3	1.39 (1.11,1.74)	4.55×10^{-3}
PCSK9	12	1.11 (1.03,1.19)	4.55×10^{-3}
TG			
APOC3	8	0.91 (0.86,0.98)	9.40×10^{-3}
LPL	24	0.93 (0.88,0.99)	2.00×10^{-2}
ApoB			
APOC3	15	0.74 (0.64,0.85)	2.35×10^{-5}
APOB	37	1.06 (1.01,1.11)	1.00×10^{-2}
LPL	11	0.91 (0.74,1.12)	3.80×10^{-1}
PCSK9	29	1.11 (1.01,1.21)	2.00×10^{-2}

Abbreviations: SNP, single nucleotide polymorphism; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; ApoB, apolipoprotein B.

Table 3 The Causal Effects of Genetic Proxies for Lipid-Lowering Drug Classes on Risk of EC

Drug-target Gene	nSNP	OR (95% CI)	Pval
LDL-C			
HMGCR	7	1.15 (0.77, 1.72)	4.90×10^{-1}
APOB	20	0.85 (0.68, 1.06)	1.50×10^{-1}
NPC1L1	3	2.38 (0.56, 10.03)	2.40×10^{-1}
PCSK9	12	1.03 (0.78, 1.34)	8.50×10^{-1}
TG			
APOC3	10	0.60 (0.47, 0.78)	1.16×10^{-4}
LPL	24	1.64 (1.35, 2.00)	8.77×10^{-7}
ApoB			
APOC3	18	0.30 (0.18, 0.52)	1.30×10^{-5}
APOB	36	0.87 (0.70, 1.07)	1.90×10^{-1}
LPL	11	6.24 (2.63, 14.82)	3.29×10^{-5}
PCSK9	29	0.80 (0.56, 1.13)	2.10×10^{-1}

Abbreviations: SNP, single nucleotide polymorphism; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; ApoB, apolipoprotein B.

2.00×10^{-2}), APOC3 reduced BC risk through both TG (OR = 0.91, 95% CI 0.86–0.98, $p = 9.40 \times 10^{-3}$) and ApoB (OR = 0.74, 95% CI 0.64–0.85, $p = 2.35 \times 10^{-5}$), LPL at either TG (OR = 0.93, 95% CI 0.88–0.99, $p = 2.00 \times 10^{-2}$) or ApoB (OR = 0.91, 95% CI 0.74–1.12, $p = 3.80 \times 10^{-1}$) was not causally associated with risk of BC, suggesting that there is no causal association between LPL and BC. The results of all MR analyses of lipid-lowering drugs are presented in [Supplementary Excel 4](#). Cochran's Q test showed that there was no heterogeneity in any of the SNPs, and horizontal pleiotropy test showed that the MR-Egger regression term intercepts were all less than 0.05 and p-values were all greater than 0.05, suggesting no horizontal pleiotropy. LOO analyses showed that reanalyzing the results after removing one SNP in turn had little effect on the results, indicating robust results, see [Supplementary Excel 5](#) and [Supplementary Figure 1](#).

Causal Effects of Lipid-Lowering Drugs on Endometrial Cancer

Since none of the lipid-lowering drugs were heterogeneous and horizontally pleiotropic, the results of the IVW analysis were used as the main reference index. As shown in [Table 3](#), the genetic prediction of APOC3 reduced the risk of EC through TG (OR = 0.60, 95% CI 0.47–0.78, $p = 1.16 \times 10^{-4}$) and ApoB (OR = 0.30, 95% CI 0.18–0.52, $p = 1.30 \times 10^{-5}$), and LPL increased the risk of EC through TG (OR = 1.64, 95% CI 1.35–2.00, $p = 8.77 \times 10^{-7}$) and ApoB (OR = 6.24, 95% CI 2.63–14.82, $p = 3.29 \times 10^{-5}$), and none of the remaining lipid-lowering drugs were causally associated with the risk of developing EC. The results of all MR analyses of lipid-lowering drugs are presented in [Supplementary Excel 6](#). Cochran's Q test showed that there was no heterogeneity in any of the SNPs, and the horizontal pleiotropy test showed that the MR-Egger regression term intercepts were all less than 0.05 and p-values were all greater than 0.05, suggesting the absence of horizontal pleiotropy. LOO analyses showed that reanalyzing the results after removing one SNP in turn had little effect on the results, indicating robust results, see [Supplementary Excel 5](#) and [Supplementary Figure 2](#).

Discussion

A comprehensive MR analysis of drug targets was performed to infer the potential pathogenic effects of lipid-lowering agents on BC & EC. The results showed that the genetic proxies for APOC3 were associated with lower risk of BC & EC, the genetic proxies for LPL were associated with higher risk of EC, and the genetic proxies for APOB, HMGCR, and NPC1L1 were associated with higher BC risk. In addition, LDL-C-mediated PCSK9 was associated with higher BC risk, and ApoB-mediated PCSK9 had suggestive causal associations with higher BC risk. Unlike previous observational studies, which are susceptible to multiple confounding factors such as genetics and immunity, as well as the disadvantage of being difficult to conduct a large number of RCTs in the clinic, MR analysis avoids the influence generated by racial factors, and minimizes the

inherent bias caused by confounding factors or reverse causality. Moreover, the heterogeneity test, horizontal pleiotropy test, and sensitivity analysis ensured the credibility of the study.

Although the exact etiology of BC has still not been fully understood, there are several risk factors that may simultaneously contribute to the initiation and/or promotion of BC. Among these risk factors, elevated LDL-C and very low-density lipoprotein cholesterol (VLDL-C) have been confirmed to be directly associated with the development of BC.^{36,37} HMGCR (target of statins), NPC1L1 (target of ezetimibe), and PCSK9 are LDL-C-lowering cholesterol drugs were found to be common targets for the prevention of cardiovascular disease.³⁸ However, statins are liver-specific because cholesterol is mainly produced in the liver, whereas less than 5% of some statins taken orally reach the peripheral circulation.³⁹ Thus, even if statins are beneficial in experimental models, their effects may not be applicable to humans. In addition, estradiol has been shown to counteract the antiproliferative effects of statins *in vitro*.⁴⁰ Therefore, the hormonal environment of the mammary gland may also counteract the beneficial effects of statins if they reach the breast tissue.

Cholesterol is the initiating biosynthetic precursor for steroidogenesis and synthesises 17 β -estradiol, an estrogen receptor agonist, which activates multiple signalling pathways in hormone-dependent BC. Ezetimibe inhibits exogenous cholesterol uptake.⁴¹ The inhibition of NPC1L1, a target of ezetimibe, promotes the uptake of exogenous cholesterol, thereby promoting angiogenesis in breast tumors. As a result of altered cholesterol acquisition, efflux, and/or transport in BC cells, cholesterol levels are increased in BC cells compared to normal human mammary epithelial cells, many of which overexpress PCSK9.⁴² Circulating PCSK9 prevents the recirculation of this receptor by binding to LDL and targets the receptor in the lysosomal compartment, leading to its degradation, increasing cholesterol levels, and promoting angiogenesis in breast tumors.⁴³ Targeting HMGCR expression reduces cellular cholesterol and lipid synthesis, which leads to the decrease of autocrine hormone production within the tumor and promotes BC cell apoptosis by inducing nitric oxide synthase expression.^{44,45} Thus, the inhibition of HMGCR protein expression enhances the risk of BC development. Studies have demonstrated that elevated triglyceride-glucose (TyG) indices are associated with an increased risk of breast cancer, which may be related to stimulating signaling pathways (Ras/MAPK and PI3K/Akt/mTOR) and gene transcription of cancer-related genes.⁴⁶ It also inhibits the synthesis of hepatic sex hormone-binding globulin, leading to elevated estrogen bioactivity, which promotes BC progression.⁴⁷ It is worth mentioning that studies have found that the incidence of female breast cancer decreases with increased intake of polyunsaturated fatty acids⁴⁸. This is because that polyunsaturated fatty acids often act synergistically with B vitamins,⁴⁹ leading to a reduction in oestrogen-stimulated cell growth, which consequently affects the process of oestrogen metabolism⁵⁰ and decreases the incidence of hormone-dependent cancers such as BC & EC. Future studies may consider focusing on the role of B vitamins and polyunsaturated fatty acids in the metabolic pathways related to BC & EC.

Abnormalities in lipid metabolism are closely associated with the development and progression of EC, and elevated TG levels increase the risk of death from EC by 1.19-fold.⁵¹ High levels of TG accumulate in adipocytes and produce large amounts of aromatase, which converts androstenedione to estradiol.⁵² At the same time, high levels of TG also inhibit the production of sex hormone-binding globulin, which reduces the binding status of estrogen. Elevated estrogen levels not only promote EC cell proliferation and angiogenesis, but also inhibit their apoptosis, which ultimately leads to BC and EC progression.^{53–55} The inhibition of APOC3, a commonly used target for the regulation of lipid homeostasis, can significantly reduce TG levels in patients and thus decrease the risk of BC & EC.^{56,57} LPL activity favors TG accumulation in adipose tissue,⁵⁸ thereby raising the risk of EC.

Our study is different from previous studies in several aspects. For example, in a population-based prospective cohort study involving men,⁵⁹ we found that ApoB was positively associated with cancer risk, whereas breast cancer risk in women was negatively associated with ApoB. This discrepancy highlights the importance of considering cancer type, patient demographics, and potential confounders in analyses. The observation of opposite effects of the same target depending on cancer subtype and patient gender suggests that hormonal and tissue-specific factors may be involved in modulation, whereas MR analyses cannot address specific biological mechanisms. Therefore, in practical studies, detailed grouping according to gender, age, and different subtypes of BC & EC is recommended to further validate our findings. Undeniably, our study has some advantages in genetic epidemiology and clinical practice. For genetic epidemiology, it demonstrates the utility of Mendelian randomization in elucidating the causality of complex diseases, overcomes the limitations of observational studies, and highlights the need for subtype-specific analyses. In addition, our findings identify

potential therapeutic targets for BC & EC, offering the prospect of personalized medicine. Future directions include evaluating drug efficacy and safety by targeting these proteins, conducting prospective cohort studies to assess risk prediction and intervention outcomes, enabling risk stratification and prevention strategies, and ultimately informing public health policies to reduce BC & EC morbidity and mortality through novel prevention and treatment approaches.

At the same time, there are some limitations to our study: (1) The efficacy of lipid-lowering drugs may vary by subgroup. However, as the data we obtained did not have more detailed cohort data such as age and gender, further subgroup analyses could not be performed. (2) Human behaviour is complex, and although understanding the genetic risk of a disease can help prevent its occurrence to some extent, environmental factors themselves also play a role in the development of the disease, and MR can only eliminate the interference of confounding factors such as the environment to a certain extent. (3) Our findings are primarily related to the incidence of BC & EC, rather than the potential of these drug targets to mitigate the progression of BC & EC in cases. (4) The data used in the study came from a European population and, given the differences in the emergence of particular characteristics in different racial and ethnic groups, caution should be exercised in generalising the results to other populations with different lifestyles and cultural backgrounds.

Conclusions

This study provides evidence for a causal relationship between lipid-lowering drugs, BC, and EC. These findings suggest a correlation between genetically predicted levels of lipid profiles (elevated LDL-C, TG, or ApoB, or decreased HDL-C) and BC, EC, and identify three lipid-modulating drug targets that may decrease the risk of BC development (HMGCR inhibition, APOB inhibition, and NPC1L1 inhibition), a lipid-modulating drug target that increases the risk of EC development (LPL agonist), and a lipid-modulating drug target that increases the risk of BC and EC development (APOC3 inhibition). Our study provides a useful lipid-modulating drug regimen for clinical practice in patients with BC, and EC, but further studies are still needed to test the observed relationships due to the co-existence of drug-target genes that increase and decrease the risk of morbidity.

Abbreviations

MR, Mendelian randomization; BC, breast cancer; EC, endometrial cancer; SNPs, single nucleotide polymorphisms; IVs, instrumental variables; GWAS, genome wide association study; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; LD, linkage disequilibrium; IVW, inverse variance weighted; WME, weighted median; LOO, leave-one-out.

Data Sharing Statement

All data generated or analysed during this study are included in this published article and its [Supplementary Information Files](#).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflict of interest.

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