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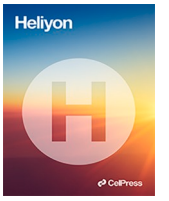

Research article

Genetic association of lipid and lipid-lowing drug targets with uterine fibroids

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ABSTRACT

Objective: Observational studies suggest that blood lipids are a risk factor for uterine fibroids (UFs) and that lipid-lowering drugs are beneficial for the treatment and prevention of UF; however, the conclusions are inconsistent. We aimed to determine the causal effects of lipids and lipid-lowering drugs on UFs using Mendelian randomization (MR).

Methods: Genetic variants from genome-wide association studies (GWAS) of lipid traits and variants in genes encoding lipid-lowering drug targets were extracted, and two independent UF GWAS were set as the outcome. Their effects on UF risk and related traits were estimated using the inverse variance weighted method.

Results: The MR analysis revealed that high density lipoprotein cholesterol (HDL-C, OR = 0.88, 95 % CI: 0.83–0.93, P = 3.58E-6) and triglycerides (TG, OR = 1.14, 95 % CI: 1.07–1.21, P = 6.83E-5) were protective factors and risk factors for UF, respectively. Drug-targeted MR analysis results indicated that genetically predicted inhibition of cholesteryl ester transfer protein (CETP) was associated with a lower UF risk (OR = 0.95, 95 % CI: 0.92–0.98, P = 7.83E-4), as well as reduced levels or risk of other UF-associated clinical traits, including estradiol level, excessive menstruation, abdominal and pelvic pain, myomectomy, and miscarriage.

Conclusions: Our study provides evidence that HDL-C and TG levels were causally associated with UF risk. Genetically proxied CETP inhibition may have a protective effect against UF, which warrants further investigation.

1. Background

Uterine fibroids (UFs) are one of the most prevalent health issues among women globally, with serious adverse effects on their health, quality of life, and socio-economic well-being [1]. The exact prevalence of UFs varies according to the diagnostic criteria and the population investigated; for example, the prevalence in women of childbearing age ranges from 5.4 to 77 percent [2]. Although many women with fibroids have no obvious symptoms, approximately 30 % will experience serious symptoms, including abnormal uterine bleeding, pelvic pain, infertility, and poor obstetric prognosis, requiring clinical intervention [3].

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These fibroids are the primary causes of hysterectomy; however, the risk of recurrence has been estimated to be 11 % for the removal of a single fibroid and even higher for the removal of multiple fibroids [4]. In addition, hysterectomy is not the ideal treatment option for women who wish to preserve their fertility or who are unsuitable candidates for surgery. Therefore, alternative treatments such as medication are more beneficial for treating fibroids [1,5]. The use of some medications, such as hormonal contraceptives, tranexamic acid, and non-steroidal anti-inflammatory drugs, can reduce symptoms such as menstrual bleeding [6]. Despite their effectiveness in alleviating dysmenorrhea and reducing blood loss, these agents have not been demonstrated to dissolve the aberrant extracellular matrix of leiomyomas or significantly reduce the overall disease burden; they only provide short-term relief [4]. In addition, associated adverse effects, including hot flashes, vaginitis, sweating, and bone loss, hinder the long-term use of these drugs [5,7].

Several observational studies have confirmed the association between dyslipidemia, metabolic syndrome, and UF risk; for example, elevated levels of low density lipoprotein cholesterol (LDL-C) and triglycerides (TG) significantly increase the risk of UFs [8–10]. Other studies have found a strong correlation between TG levels, number of UFs, and high lipid expression in recurrent UF tissues; thus, monitoring lipid levels is crucial in the management and follow-up of patients with UF [11]. In addition to their well-known lipid-lowering properties, some lipid-lowering drugs exhibit a wide range of in vivo effects, including antitumor activity. For instance, statins not only lower cholesterol but have also been shown to inhibit tumor proliferation in various cancers, such as breast, ovarian, leukemia, and lung cancers [12]. Inspired by these studies, research has explored the effects of lipid-lowering drugs on UF, finding that simvastatin and atorvastatin can reduce the number and size of endometrial implants in animal models of endometriosis [13,14]. Simvastatin reduces the proliferation and invasive capacity of human endometrial cells in vitro [15,16]. A nested case-control study conducted in a hyperlipidemic cohort found that statin use reduces the risk of UFs, associated clinical complications, and likelihood of myomectomy [12]. Although these preliminary studies showed promise, they were based on a hyperlipidemic population. Thus, there is a lack of relevant studies specifically examining the effects of lipid-lowering drugs on UFs [17].

Mendelian randomization (MR) is a genome-wide association study (GWAS)-based epidemiological analysis that explores the causal associations between exposures and outcomes, using genetic instrumental variables (IVs) derived from exposures that are not confounded by confounders [18]. Drug-target MR analyses, which utilize genetic IVs to model pharmacological perturbations of drug gene targets along with regression estimations of the effects of long-term drug use, are essential analytical tools for strengthening causal inferences regarding the impact of drug target genes on related diseases [19]. Therefore, drug-targeted MR can efficiently screen the effectiveness of drug candidates for relevant diseases and their associated side effects using genetic methods, thereby reducing time and economic costs. In particular, it can assess the efficacy of existing drugs for other diseases by identifying potential new uses of old drugs. For example, some lipid-lowering drugs such as statins have been approved by the U.S. Food and Drug Administration, and their safety has been well explored [12]. In this study, we employed MR to investigate the effects of genetically proxied, commonly used lipid-lowering drug target genes on UF risk and to explore their potential for treating UF from a genetic perspective.

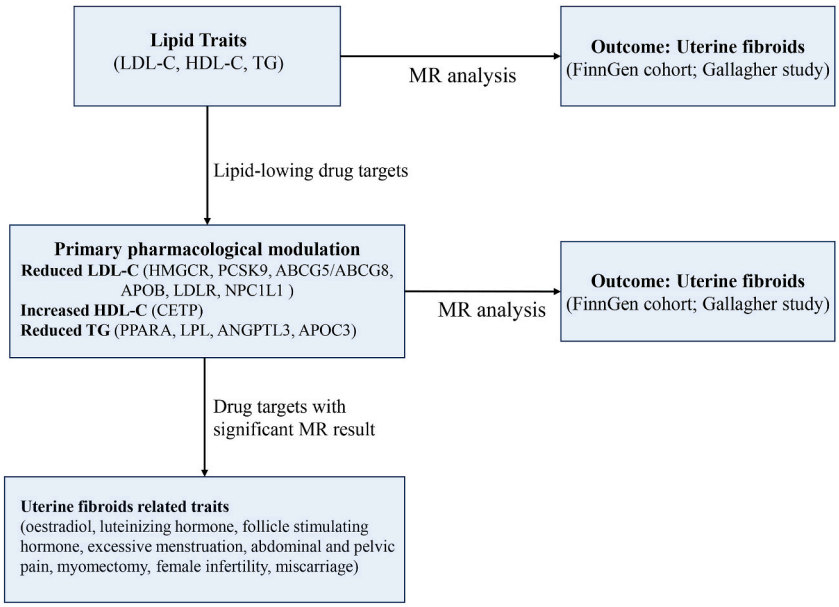

Fig. 1. Flow chart of the MR analysis for this study.
UF, uterine fibroid; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; MR, Mendelian randomization.

2. Methods

2.1. Study design

In this study, we aimed to estimate the association between genetically predicted lipid-lowering drugs and risk of UF using a drug-targeted MR approach. We first assessed the causal association between lipid traits (LDL-C, high density lipoprotein cholesterol [HDL-C], and TG) and UF. Subsequently, we examined lipid-lowering drugs (which reduce LDL-C, increase HDL-C, and lower TG) targeting these lipid traits, generating genetic IVs to proxy drug-target perturbation and assess their effect on UF. Two large-scale UF GWAS were employed as outcomes, and a pooled analysis was performed. Coronary heart disease (CHD) served as a positive control. Finally, we assessed the association of this significantly proxied drug-target gene perturbation with the clinically relevant features of UF. Publicly available GWAS datasets were used for this study, and all participants provided the required ethical informed consent and ethical approval to the relevant authorities; therefore, no additional ethical approval was required for this study. This study followed the guidelines of the Study to Enhance the Use of Mendelian Randomization for Observational Epidemiology (STROBE-MR) [20]. Flow chart of the MR analysis for this study was shown in Fig. 1.

2.2. Data source

Summary level statistics of GWAS associated with lipid traits were derived from a GWAS of circulating non-fasting lipoprotein lipid traits LDL-C, HDL-C, and TG in the UK Biobank, which included 440,546, 403,943, and 440,546 participants, respectively [21]. The UF GWAS data for the two outcomes were derived from FinnGen and a meta-analysis. In the FinnGen R9 release, patients with UF were diagnosed based on hospital records according to the International Classification of Diseases (ICD-10: D25, ICD-9:218, ICD-8:21899), including 31,661 cases and 179,209 normal control individuals [22]. The meta-analysis of Gallagher's GWAS included five FibroGENE consortium datasets—the Women's Genome Health Study, Northern Finnish Birth Cohort, QIMR Berghofer Medical Research Institute, UK Biobank, and one direct-to-consumer cohort (23andMe)—resulting in 35,474 UF cases and 267,505 female controls of White European ancestry [23]. The GWAS dataset of the clinical traits of UF, including estradiol (E2), luteinizing hormone, follicle-stimulating hormone, excessive menstruation, pelvic pain, myomectomy, female infertility, miscarriage, and CHD (positive control), was obtained from the IEU Open GWAS (https://gwas.mrcieu.ac.uk/). All of the above data sources are listed in Table S1.

2.3. Selection of instrumental variables

For lipid traits, linkage disequilibrium (LD) clumping was performed ($P < 5 \times 10^{-8}$, $r^2 < 0.001$ within a genetic distance of 10 Mb) to identify independent candidate SNPs using the 1000 Genomes Phase 3 European reference panel. The drug-target database (https://go.drugbank.com/) was searched to identify target genes of each lipid-lowering drug class, including LDL-C-lowering drugs (HMGCR inhibition, PCSK9 inhibition, ABCG5/ABCG8 enhancement, APOB inhibition, LDLR inhibition, and NPC1L1 inhibition), HDL-C-increasing drugs (cholesteryl ester transfer protein [CETP] inhibition), and TG lowing drugs (PPARA enhancement, LPL activation, ANGPTL3 inhibition, and APOC3 inhibition). As previously reported [24], to generate genetic instruments for proxying drug target perturbation, SNPs with genome-wide significance ($P < 5 \times 10^{-8}$) and LD ($r^2 < 0.3$ within a genetic distance of 250 kb) were selected within a ±100 kb window of drug class target genes. Detailed information on these lipid-lowering drugs and their target genes are provided in Table S2. When harmonizing the exposure and outcome data, palindromic and incompatible SNPs for which the direction could not be determined were excluded. Additionally, if a specific SNP was absent from the outcome data, it was also removed. MR pleiotropy residual sum and outlier (MR PRESSO) was utilized to detect outliers in IVs to reduce potential horizontal pleiotropy [25]. In addition, for lipid trait-related SNPs, we searched for SNPs associated with confounding factors ($P < 5 \times 10^{-8}$) online using Phenoscanner (www.phenoscanner.medschl.cam.ac.uk) and removed them. Confounding factors of UF include obesity, family history, early menarche, and chronic inflammation [26]. Weak IV bias was avoided by calculating the F-statistic ($Beta^2/SE^2$); $F > 10$ indicated the absence of weak IV effects [27].

2.4. MR and sensitivity analysis

We used the fixed-effects model inverse variance weighted (IVW) method as the primary approach for the analysis. If heterogeneity in the IVs was detected, the results were assessed using the random-effects model IVW method, while MR Egger and weighted median methods served as auxiliary approaches. The IVW method assumes that all IVs satisfy the required assumptions and provides the most accurate estimates when all IVs are valid [28]. MR Egger regression can detect violations of the IV assumptions, even when all genetic variants are null IVs. The Egger test provides a valid test of the null causal hypothesis and offers a consistent estimate of the causal effect [29]. The weighted median combines data from multiple IVs into a single causal estimate, even when up to 50 % of the information comes from invalid IVs, and can complement MR Egger regression [30].

Heterogeneity of IVs was detected using the Cochran's Q test in both the IVW and MR Egger methods. A $P > 0.05$ represents no heterogeneity in the IVs. Potential horizontal pleiotropy was assessed employing the MR Egger intercept analysis. A regression intercept closer to 0 suggests less likelihood of horizontal pleiotropy, with an MR Egger intercept $P > 0.05$, indicating no potential pleiotropy in the IVs [29]. Leave-one-out analysis was applied to examine the robustness of the MR results, which was used to assess whether the removal of an SNP would strongly affect the MR results.

2.5. Statistical analysis

All MR analyses were performed using the TwoSampleMR (0.5.7) and MRPRESSO (1.0) packages in R software (4.2.3). The MR results were presented as odds ratio (OR) or β and 95 % confidence interval (95 % CI) for risk of UF and its related traits. In the multiple tests of genetically proxied lipid lowing drugs for UF, statistical significance was defined as $P < 0.005$ (0.05/10) after Bonferroni correction, while P values between 0.05 and 0.005 were considered suggestively significant. A meta-analysis of the pool estimate was employed for the combined assessment of drug target gene perturbation proxies using the two final UF datasets.

3. Results

3.1. Causal association of lipid traits with UF

The IVs associated with the lipid traits are shown in Table S3. The confounder factor-associated SNPs removed utilizing Phenoscanner are listed in Table S4. IVW method results suggested (Fig. 2, Table S5) that high levels of HDL-C were significantly associated with a lower risk of UF in the FinnGen data (OR = 0.88, 95 % CI: 0.82–0.95, $P = 8.77\ E^{-4}$), whereas high levels of TG were significantly associated with a higher risk of UF (OR = 1.12, 95 % CI. 1.02–1.22, $P = 0.016$). In the Gallagher dataset, high levels of HDL-C were significantly associated with a lower risk of UF (OR = 0.88, 95 % CI: 0.81–0.95, $P = 0.002$), and high levels of TG were significantly associated with a higher risk of UF (OR = 1.15, 95 % CI: 1.05–1.25, $P = 0.003$); the results from both the Gallagher and FinnGen datasets were highly consistent. Similarly, in the pooled estimate analysis of both datasets, MR results suggested that low levels of HDL-C were a risk factor for UF (OR = 0.88, 95 % CI: 0.83–0.93, $P = 3.58\ E^{-6}$), and high levels of TG were a risk factor for UF (OR = 1.14, 95 % CI: 1.07–1.21, $P = 6.83\ E^{-5}$). Additionally, both in the FinnGen dataset alone (OR = 0.99, 95 % CI: 0.92–1.07, $P = 0.812$) and in the Gallagher dataset (OR = 1.05, 95 % CI: 0.97–1.14, $P = 0.235$), as well as in the pool estimate (OR = 1.02, 95 % CI: 0.96–1.08, $P = 0.536$), LDL-C did not show a significant causal association with UF. Sensitivity analysis (Table S6) revealed heterogeneity in all lipid-characterized IVs. However, the MR Egger intercept did not provide evidence of pleiotropy. Moreover, the leave-one-out results indicated that the MR findings were not strongly perturbed by individual SNPs (Table S7).

3.2. Effects of genetic variation in lipid lowing drug targets on UF risk

We validated that genetically predicted drug target perturbations were associated with CHD risk (positive control) (Table S8). Although ANGPTL3 and PPARA inhibition were linked to reduced CHD risk, they did not reach the corrected significance threshold, and therefore, these two targets were excluded from subsequent analyses. Other genetic proxies for drug target perturbations demonstrated significant associations with a lower CHD risk, suggesting the validity of IVs. The IVs associated with the genetic proxies for the effects of all lipid-lowering drug targets are shown in Table S9, while drug-targeted MR results are depicted in Fig. 3 and Table S10. In the FinnGen data, the IVW method results suggested that genetic proxies for ABCG5/ABCG8 enhancement (OR = 0.79, 95 % CI: 0.57–1.00, $P = 0.029$) and NPC1L1 inhibition (OR = 0.60, 95 % CI: 0.24–0.97, $P = 0.006$)—both of which represent 1-SD LDL downregulation—were suggestively associated with a lower UF risk. In the Gallagher data, genetically proxied APOB inhibition (OR = 0.74, 95 % CI: 0.64–0.85, $P = 1.47\ E^{-8}$) and CETP inhibition (OR = 0.94, 95 % CI: 0.90–0.97, $P = 8.86\ E^{-4}$), representing a 1-SD reduction in LDL-C and a 1-SD increase in HDL-C, respectively, were significantly associated with a lower risk of UF. Genetically proxied APOC3 inhibition (OR = 1.11, 95 % CI: 1.05–1.18, $P = 0.001$) was significantly associated with a higher UF risk, while genetically predicted LPL activation (OR = 1.10, 95 % CI: 1.03–1.18, $P = 0.010$) was suggestively associated with increased UF risk. In

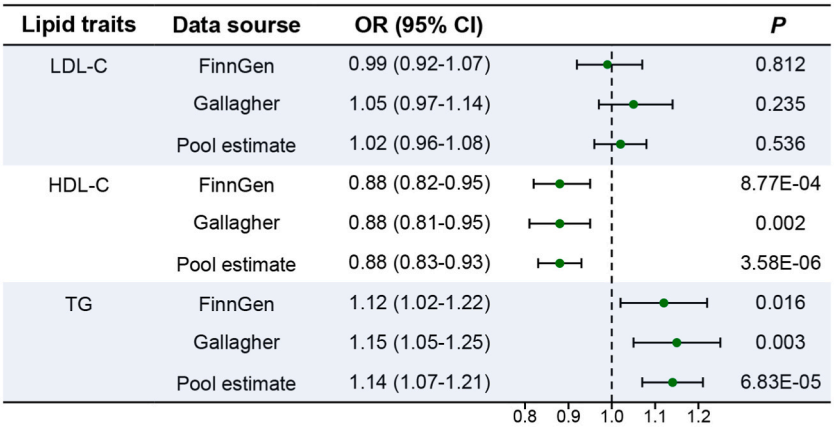

Fig. 2. Associations between lipid traits and the risk of UF.
UF, uterine fibroid; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; OR, odds ratio; CI, confidence interval.

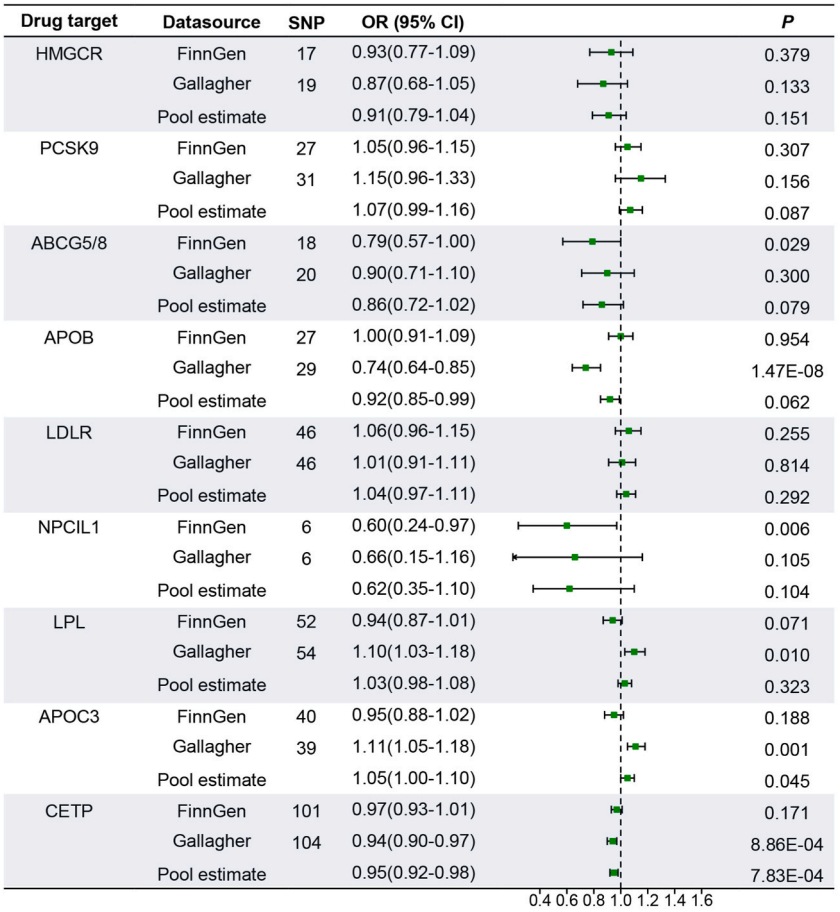

Fig. 3. Associations between genetic proxies for lipid lowing drugs and the risk of UF.
UF, uterine fibroid; SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval.

the combined analysis of the two UF datasets, we found that genetically predicted CETP inhibition was significantly associated with reduced UF risk (OR = 0.95, 95 % CI: 0.92–0.98, $P = 7.83\ E^{-4}$), whereas APOC3 inhibition was associated with a higher risk of UF (OR = 1.05, 95 % CI: 1.00–1.10, $P = 0.045$). The two supplementary methods also demonstrated trends that were generally consistent with the IVW results (Table S10). In the sensitivity analysis, for all the estimates, no heterogeneity within IVs or substantial pleiotropy was detected (Table S11).

3.3. Association of genetic proxies for CETP inhibition with UF risk

Considering the association between genetically proxied CETP perturbation and reduced UF risk, we subsequently explored its association with clinically relevant traits and indicators of UF (Table 1). We found that genetically predicted CETP inhibition was significantly correlated with lower E2 levels ($\beta = -0.05$, 95 % CI: -0.07, -0.02, $P = 7.57\ E^{-5}$). While it showed a protective effect on

Table 1
Causal estimates of genetically predicted inhibition of CETP with the risk of UF related traits accessed using inverse variance weighted.

Drug target perturbation	Uterine fibroid related traits	OR/β	OR/Effect size (95 % LCI)	OR/Effect size (95 % UCI)	*P*
CETP inhibition	Oestradiol	−0.05	−0.07	−0.02	7.57E-05
	Luteinizing hormone	−0.11	−0.39	0.17	0.436
	Follicle stimulating hormone	0.03	−0.07	0.13	0.544
	Excessive menstruation	-2E-03	-4E-03	-1E-03	7.83E-04
	Abdominal and pelvic pain	-3E-03	-5E-03	-1E-03	0.014
	Myomectomy	9.98E-01	9.97E-01	9.99E-01	1.66E-04
	Female infertility	0.97	0.89	1.06	0.510
	Miscarriage	0.99	0.98	0.99	1.78E-05

UF, uterine fibroid; SNP, single nucleotide polymorphism; OR, odds ratio; LCI, lower confidence interval; UCI, upper confidence interval.

luteinizing hormone levels, the results were not significant, and there was no significant correlation with follicle-stimulating hormone levels. In addition, we found that genetically predicted CETP inhibition exhibited protective effects on UL-related symptoms such as excessive menstruation ($\beta = -2\ E^{-3}$, 95 % CI: $-4\ E^{-3}$, $-1\ E^{-3}$, $P = 7.83\ E^{-4}$) and pelvic pain ($\beta = -3\ E^{-3}$, 95 % CI: $-5\ E^{-3}$, $-1\ E^{-3}$, $P = 0.014$). More importantly, the genetic proxy for CETP inhibition was significantly associated with a lower likelihood of myomectomy (OR = $9.98\ E^{-1}$, 95 % CI: $9.97\ E^{-1}$, $9.99\ E^{-1}$, $P = 1.66\ E^{-4}$). Moreover, while the association between CETP inhibition and lower female infertility (OR = 0.97, 95 % CI: 0.89–1.06) was not statistically significant ($P = 0.510$), it showed a significant protective effect against miscarriage (OR = 0.99, 95 % CI: 0.98–0.99, $P = 1.78\ E^{-5}$).

4. Discussion

In this study, we conducted comprehensive drug-target MR to examine the potential causal effects of lipid-lowering drugs on UF. This study utilized an MR analysis approach to minimize residual confounders and showed that HDL-C and TG levels were protective and risk factors for UF, respectively. Further drug-targeted MR analyses revealed that genetically predicted CETP inhibition was beneficial for UF and its clinical traits, such as E2 levels, menorrhagia, and pelvic pain. Additionally, genetically proxied CETP perturbation was significantly associated with a lower likelihood of undergoing myomectomy and experiencing miscarriage. In this study, this is the first assessment of the association between lipid-lowering drugs and UF risk using drug targets proxied by genetic IVs, which addresses the confounding factors of traditional observational studies and reduces time and economic costs. The two largest GWAS datasets for UF were used and meta-analyzed to ensure the reliability of the analysis.

UFs are common and serious health problems in women. The exact pathogenesis is unknown and may involve genetic factors, endocrine disorders (estrogen-progestin imbalance), neoangiogenesis, and growth factors [10]. Observational studies have shown that dyslipidemia and metabolic syndrome are associated with an increased risk of UF, with higher LDL-C and TG levels significantly raising the likelihood of developing UF [8,9,31]. However, the findings were inconsistent with those of other studies that reported either increased or unchanged HDL-C levels in relation to UF [32]. Changes in cholesterol fractions can cause visceral fat deposition, and the resulting chronic inflammation plays a decisive role in cell differentiation and proliferation, which are necessary for UF pathogenesis [9]. A retrospective study found that atorvastatin significantly inhibits UF growth in patients with hyperlipidemia. Additionally, in vitro, atorvastatin suppresses proliferation and promotes apoptosis of both immortalized and primary uterine fibroblast cells in a dose- and time-dependent manner [33]. A previous nested case-control study in a hyperlipidemic population confirmed an improvement in UF risk and associated clinical symptoms with statins [12]. These studies indicated that improving lipid profiles may be an effective strategy for the treatment of UF.

However, the present study found no evidence of a direct causal association between LDL-C or the genetic proxy of HMGCR inhibition, the main target gene of statins, and UF risk. Instead, we found that genetically proxied CETP inhibition was significantly associated with a reduced risk of UF and the associated clinical traits. Owing to the ability of CETP to increase HDL cholesterol levels, there has been considerable interest in the development of its pharmacological inhibitors [34]. In addition, CETP regulates the concentration of cholesteryl esters in very low density lipoproteins and LDL [35]. Previous human studies have found that torcetrapib, a CETP inhibitor, induces a dose-dependent increase in HDL-C by up to 106 % and a reduction in LDL-C by up to 42 % [36]. There are no clinical studies on CETP inhibitors in relation to UF, and the relevant associations and efficacy require in-depth follow-up studies.

Given that estrogen and progesterone are the primary drivers of UF, improving the levels of these hormones, especially estrogen, is fundamental to pharmacotherapy in asymptomatic UF [37]. Estrogen plays a crucial role in UF; fibroid stem cells have estrogen and progesterone receptors that promote tumor development in the presence of these hormones [38]. A previous study evaluated the relationship between serum CETP concentrations and changes in endogenous estrogens and found that postmenopausal CETP concentrations were significantly lower than premenopausal levels and were positively correlated with E2 levels [39]. A recent study found that increased protein expression of estrogen receptor-alpha (ERα) is associated with increased sensitivity to E2-ERα signaling in CETP transgenic female mice [40]. In the present study, we found that genetic perturbation of CETP was associated with lower E2 levels, indicating that targeting CETP could be an effective strategy for the pharmacologic treatment of UF.

Although UF is asymptomatic in most cases, some patients experience significant symptoms including abnormal bleeding, pelvic pain, infertility, and obstetric complications [41]. Approximately one-third of patients with UF require clinical treatment, with hysterectomy being the only definitive option, resulting in the loss of fertility and potential complications [41]. Our results suggested that gene-mediated CETP inhibition significantly ameliorated excessive and irregular menstruation, along with abdominal and pelvic pain. Interestingly, gene-agent CETP inhibition was significantly associated with lower myomectomies. Traditionally, almost half of patients with symptomatic UFs undergo surgical treatment; however, for patients who wish to be treated conservatively or who have contraindications to surgery, pharmacological therapies may be an effective option [42]. Therefore, an ideal medication is necessary for women with reproductive needs, and the effects of CETP inhibition on these symptoms require in-depth clinical and mechanistic studies.

Although there is no clear correlation between UF and infertility, an observational study conducted in the United States found that the prevalence of UFs may be slightly higher in women with infertility [43]. In the present study, the gene-agent CETP suppression was associated with female infertility; however, the difference was not significant. Subplasma leiomyomas have minimal effect on fertility, whereas submucosal UFs can negatively impact fertility [44]. This mechanism involves local anatomical location, changes in myometrial and endometrial function, and altered endocrine levels [44]. In addition, the presence of multiple submucosal lesions may increase the risk of miscarriage [45]. The present study found that gene-agent CETP inhibition was associated with a lower incidence of miscarriage, suggesting a potential role for CETP inhibition in the improvement of reproduction.

This study had certain limitations. First, the genetic IVs used were modeling lifetime effects and did not reflect the different

windows of action of the drug or the corresponding dose effects. Second, although we performed sensitivity analyses, potential pleiotropic effects could not be completely excluded. Third, the datasets included in this study were of European ancestry, and the conclusions should be validated in other populations. Fourth, when selecting IVs for proxy drug target perturbation, we adopted the more relaxed LD criteria currently used in most studies, which may have reduced the power of the IVs. In addition, owing to known data limitations, the drug targets we used may not fully reflect the effects of these relevant drugs and only represent the known target information with off-target effects. Therefore, the relevant findings should be interpreted with caution and confirmed through subsequent rigorous clinical and basic research trials.

5. Conclusions

Using large-scale GWAS data, we found evidence to support the genetic associations of HDL-C and TG with UF and that CETP inhibitors may be an effective strategy for the treatment of UF. Thus, our findings support the use of lipid-lowering drug therapies in patients with UF.

CRediT authorship contribution statement

Mei Wu: Software, Methodology, Investigation. **Qiannan Lin:** Software, Methodology, Investigation. **Siyu Li:** Software, Methodology, Data curation. **Huiyan Wang:** Writing – review & editing, Writing – original draft, Methodology, Data curation. **Wenbo Zhou:** Writing – review & editing, Writing – original draft, Validation, Software, Resources, Methodology, Funding acquisition.

Ethics approval and consent to participate

The data used for the analysis were derived from published genomic studies and were approved by the original review committees. No additional ethical approvals were required.

Consent for publication

Not applicable.

Data availability statement

The summary statistics of lipid and uterine fibroid related traits GWAS were obtained from IEU open GWAS (https://gwas.mrcieu.ac.uk/); The summary statistics of uterine fibroid GWAS data was obtained from FinnGen consortium's R9 version (https://www.finngen.fi/en/access_results) and a meta-analysis reported by Gallagher et al. (PMID: 31649266). Additional data are included in the article/supplementary material. Further queries can be directed to the corresponding author.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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List of abbreviations

UF	uterine fibroid
MR	Mendelian randomization
GWAS	genome-wide association studies
HDL-C:	high density lipoprotein cholesterol
LDL-C:	low density lipoprotein cholesterol
TG	triglyceride
UKB	United Kingdom Biobank
ICD	International Classification of Diseases
IV	instrumental variable

LD	linkage disequilibrium
CHD	coronary heart disease
IVW	Inverse variance weighted
SNP	single nucleotide polymorphism
MR-PRESSO	Mendelian randomization pleiotropy RESidual sum and outlier
OR	Odds ratio
E2	oestradiol
CETP	cholesteryl ester transfer protein

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e41539.

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