Study of effect modifiers of genetically predicted CETP reduction

Marc-André Legault1,2,3 | Amina Barhdadi1,2 | Isabel Gamache1,3 | Audrey Lemaçon1,2 | Louis-Philippe Lemieux Perreault1,2 | Jean-Christophe Grenier1 | Marie-Pierre Sylvestre4,5 | Julie G. Hussin1,6 | David Rhainds1 | Jean-Claude Tardif1,6 | Marie-Pierre Dubé1,2,6

1Montreal Heart Institute, Montreal, Quebec, Canada
2Université de Montréal Beaulieu-Saucier Pharmacogenomics Centre, Montreal, Quebec, Canada
3Department of Biochemistry and Molecular Medicine, Université de Montréal, Montreal, Quebec, Canada
4Research Centre of the University of Montreal Hospital Centre, Montreal, Quebec, Canada
5Department of Social and Preventive Medicine, Université de Montréal, Montréal, Quebec, Canada
6Department of Medicine, Université de Montréal, Montreal, Quebec, Canada

Correspondence
Marie-Pierre Dubé, Montreal Heart Institute, 5000 Belanger St, Montreal, H1T 1C8, QC, Canada.
Email: marie-pierre.dube@umontreal.ca

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Abstract
Genetic variants in drug targets can be used to predict the long-term, on-target effect of drugs. Here, we extend this principle to assess how sex and body mass index may modify the effect of genetically predicted lower CETP levels on biomarkers and cardiovascular outcomes. We found sex and body mass index (BMI) to be modifiers of the association between genetically predicted lower CETP and lipid biomarkers in UK Biobank participants. Female sex and lower BMI were associated with higher high-density lipoprotein cholesterol and lower low-density lipoprotein cholesterol for the same genetically predicted reduction in CETP concentration. We found that sex also modulated the effect of genetically lower CETP on cholesterol efflux capacity in samples from the Montreal Heart Institute Biobank. However, these modifying effects did not extend to sex differences in cardiovascular outcomes in our data. Our results provide insight into the clinical effects of CETP inhibitors in the presence of effect modification based on genetic data. The approach can support precision medicine applications and help assess the external validity of clinical trials.

KEYWORDS
CETP, drug target validation, effect modification, precision medicine
1 | INTRODUCTION

Genetic variants in drug targets can be used to predict the long-term, on-target effects of drugs (Schmidt et al., 2020; Szustakowski et al., 2021). The identification of rare variants with strong effects on protein function led to the development of new drug classes, and there is a growing number of genetically supported drug targets along various phases of drug development (Cohen et al., 2006; King et al., 2019; Nelson et al., 2015).

However, few genetic studies of drug targets have focused on the identification of subgroups of individuals that could derive a greater benefit from the drug. This question is central to our quest to improve precision medicine, which can be supported by genetic techniques. Randomized controlled trials (RCTs) are powered to detect the benefit of an intervention in the full study population and analyses in subgroups of individuals are typically reported as exploratory observations. When clinical or demographic subgroups are underrepresented or excluded from trials, external validity can be put into question (Rothwell, 2006). In clinical trials of cardiovascular disease prevention, for example, women are frequently underrepresented, and only 31% of trials report sex-specific results (Melloni et al., 2010). This may be of importance as differences in body size and composition as well as hormonal and gender differences could all have an impact on drug response (Yakerson, 2019).

CETP inhibitors have a complex history of heterogeneous findings from RCTs and genetic studies. Three of the four trials of CETP inhibitors (d) did not report benefit, except for the most recent and largest trial (Randomized EValuation of the Effects of Anacetrapib through Lipid-modification, REVEAL) that showed a small reduction in risk of cardiovascular outcomes in an at-risk population, with a rate ratio of 0.91 (95% confidence interval [CI] 0.85, 0.97) for the study primary efficacy endpoint (HPS3/TIMI55–REVEAL Collaborative Group et al., 2017).

There is renewed interest in CETP inhibitors, and obicetrapib recently showed pronounced reductions of apoB and LDL-c on top of high-intensity statin therapy in a phase 2 trial (Nicholls et al., 2022). Obicetrapib is currently being investigated in PREVAIL, a phase 3 major adverse cardiovascular effect trial (NCT05202509).

In this paper, we investigate how sex and body mass index (BMI) may modify the effect of a genetically predicted CETP reduction on biomarkers and cardiovascular outcomes. We consider the effect on apolipoproteins and lipid fractions thought to be related to CETP inhibition, namely high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), and their main lipoprotein constituents: apolipoprotein A (apoA) and apolipoprotein B (apoB), respectively. We also consider C-reactive protein levels, a measure of systemic inflammation, and lipoprotein (a) an independent atherogenic lipoprotein that may be affected by CETP inhibition (Kronenberg et al., 2022).

2 | METHODS

2.1 | Study populations

Individual-level data from the UK Biobank cohort were used for the analyses relating genetically predicted CETP with biomarkers and cardiovascular outcomes. The variable definitions and genetic quality control steps are described in the Supporting Information. The UK Biobank is a population cohort including 500,000 individuals recruited in the United Kingdom with linkage to national hospitalization and death records along with dense genotyping data (Bycroft et al., 2018).

Data from the MHI Biobank cohort were used to conduct the analyses of genetically predicted CETP with cholesterol efflux (Supporting Information). The MHI Biobank is a hospital cohort and patients were recruited through advertisements within the hospital, its affiliated prevention center, and local newspapers. Cholesterol efflux measurements were done in a subset of the biobank as previously published and briefly summarized in Supporting Information (Low-Kam et al., 2018).

2.2 | Cardiovascular outcome definitions

In our cardiovascular outcome definition, we distinguish between a “soft” and a “hard” definition of CAD. The “soft” definition includes nonspecific codes indicative of some form of ischemic heart disease such as “I24 Other acute ischemic heart diseases.” In contrast, the “hard” definition is a composite of acute outcomes including MI, revascularization procedures, or unstable angina as the primary reason for hospitalization or death. Details of these definitions are provided in Supporting Information: Table 1.
2.3 | Genetic predictors of CETP activity

We evaluated various genetic scores of CETP activity based on a GWAS of plasma CETP concentration and the MAGNETIC GWAS, which includes a diverse set of human metabolites including detailed lipid fractions measured using a high throughput nuclear magnetic resonance metabolomics platform, (Blauw et al., 2018; Kettunen et al., 2016) constructed using the p-value thresholding and LD clumping method (Supporting Information). All the genetic scores were highly correlated with Pearson's r between 0.75 and 1.00 (in absolute value, Supporting Information: Table 2), and for subsequent analyses, we selected the score based on the plasma CETP concentration as it directly relates to CETP activity. The selected variants and the weights used to compute the score are presented in Supporting Information: Table 3.

Given that genetic scores and variants have complementary advantages, we also conducted analyses using the rs1800775 variant. The CETP variant -629C>A (rs1800775) is known to disrupt transcription factor binding and reduce CETP activity (Dachet et al., 2000; Thompson et al., 2004). Using such a variant as a proxy for CETP levels has the advantage of providing interpretable results in allelic units and does not rely on weights corresponding to effect sizes which may be biased with respect to the population (both in terms of sex, clinical profile, and ethnicity) in which they were estimated. For example, if genetic variants have different effects in men and women, scores based on these effects will be better predictors of the phenotype in individuals whose sex was most prevalent in the study from which the estimates are derived.

Because this study investigates the effect of genetically predicted CETP levels, it is important to validate the statistical strength of our predictors. We estimated association strength using HDL-c and LDL-c levels as proxy variables because they are known to be impacted by CETP modulation. We used univariable linear regression, and we report F statistics and $R^2$ as is usual in Mendelian randomization studies (Davies et al., 2018). When regressing on measured HDL-c in the UK Biobank, the $F$ statistic was 10,400 ($F_{1;362,466}$) for the genetic score and 7239 ($F_{1;362,466}$) for rs1800775, with corresponding $R^2$ of 0.028 and 0.020, respectively. Similarly, when regressing on LDL-c, the $F$ statistics and $R^2$ were 201 ($F_{1;394,283}$) and $R^2 = 0.00051$ for the genetic score and 160 ($F_{1;394,283}$) and $R^2 = 0.00041$ for rs1800775. The genetic score has a stronger effect than rs1800775 on CETP and consequently on HDL-c and LDL-c. The rs1800775 variant remains a strong predictor of CETP and is not prone to bias due to weighting.

2.4 | Statistical analyses

We assessed the effect of the genetic predictors of CETP on observed biomarkers and cardiovascular outcomes using linear and logistic regression models as appropriate. To estimate the effect modification by sex and BMI, we fit the models containing a product interaction term between the genetic predictor of CETP and the effect modifier of interest and fixed covariates including the component variables of the interaction, age, sex, and ancestry principal components. We adjusted for these covariates to improve the precision of our estimates. We used hypothesis testing of a null product interaction coefficient as a test of effect modification, and the p-value for this test is denoted as $p_{int}$. In linear models, the hypothesis test is for an additive interaction, and it can be interpreted as an additive deviation from the contribution of the interacting variables. In logistic regression models, the test of the product interaction term assesses a multiplicative effect modification of the odds ratio (Supporting Information). In other words, in the latter case, the test is of $OR_{11}/(OR_{01} \times OR_{10}) = 1$ where $OR_{ij}$ denotes the odds ratio when setting the first interacting variable to $i$ and the 2nd variable to $j$ compared to the reference value for both covariables (Supporting Information). Using the logistic regression model, we also computed interaction statistics on the additive scale namely the Relative Excess Risk due to Interaction (RERI) and the interaction contrast on the probability scale (Supporting Information). The additive effect statistics were developed for risk factors (and not preventive exposures) which prompted us to report interaction effects for the “male” sex, for a 1 s.d. increase in BMI and for a 1 s.d. increase in the CETP score. To facilitate interpretation, we also used interaction models to compute the marginal effects of the genetic CETP predictors on the outcomes of interest at representative values of the tested modifiers. In models with more than a single interaction term, we used the R package “margins” to estimate the marginal effect at representative cases and the corresponding 95% CI, otherwise, we computed the marginal effects directly by summing the relevant regression coefficients.

To test for possible nonlinear effects of BMI and the CETP genetic score (and their interaction), we fitted an interaction model with interacting restricted cubic splines with four knots for BMI and the CETP genetic score. We used a joint F or $\chi^2$ test for interactions which simultaneously considers all interaction coefficients. For significant interactions in the nonlinear models, we then plotted the predicted effects at varying levels of BMI and of the CETP genetic score to visualize the nonlinear
effects. We used the R “rms” package to conduct these analyses.

For analyses based on the CETP genetic score, all effects for biomarkers are reported in units of standard deviation (s.d.) of the biomarker per s.d. decrease of the score (representing a decrease in CETP concentration as for pharmacological CETP inhibition). For binary outcomes, the reported effects are odds ratios per s.d. decrease of the genetic score. For analyses based on the individual CETP variant, the results are expressed per copy of the "A" allele at rs1800775 (CETP-629C>A) which decreases CETP levels. For causal interpretation of these analyses, see Supporting Information. No adjustment was made for multiple testing of phenotypes and effect modifiers. Estimates are reported with 95% CI.

Conditioning on the observed BMI could introduce a collider bias in a situation where the CETP genetic score (or variant) would be associated with BMI (Coscia et al., 2022). See details on the possibility of inducing bias and supporting sensitivity analyses in the Supporting Information: Methods and Supporting Information: Appendix, respectively. Briefly, the association between the CETP genetic score and BMI is small, and its adjusted effect on (log-transformed) BMI is 0.00062 (95% CI 0.0001, 0.0011, \( p = 0.016 \)) (Supporting Information: Table 4, Supporting Information: Appendix), suggesting that the magnitude of bias would be small. Because the association is nominally significant at the \( \alpha = 0.05 \) level, we conducted a sensitivity analysis for the effect modification analyses by using a genetically-determined BMI. The variants and weights used to calculate the BMI genetic score are presented in Supporting Information: Table 5, and methodological details are provided in Supporting Information. Because genetically-predicted BMI is independent of the CETP genetic score, it is protected from collider stratification bias. The results from this sensitivity analysis are largely concordant with the observation from the model based on observed BMI (Supporting Information: Appendix). We also note that the rs1800775 variant was not associated with BMI (\( p = 0.101 \)) providing a second line of evidence that is not at risk of collider stratification bias.

### 2.5 | Power analyses

We estimated the power of the different association models using simulations. In the simplest case, we simulated a normally distributed genetic score with a fixed effect on a standard normal outcome and computed the proportion of rejected null hypotheses across simulation replicates at \( \alpha = 0.05 \). We extended this model to account for interaction effects, and we used a latent variable logistic regression model when estimating the power for association with binary traits. The simulation model is described in Supporting Information.

## 3 | RESULTS

### 3.1 | Study population

There were 413,138 unrelated participants of European origin from the UK Biobank included in the analyses (Supporting Information). The number of events under consideration for the cardiovascular outcomes as well as the descriptive statistics for continuous measurements are presented in Table 1.

### 3.2 | Effect of genetically predicted reduction of CETP on biomarkers and cardiovascular outcomes

We first assessed the effect of the genetic CETP predictors on biomarkers and cardiovascular outcomes without any modifiers to contextualize future results (Table 2). As expected, the strongest association was with HDL-c, with an increase of 0.167 s.d. in HDL-c (corresponding to 0.064 mmol/l) per 1 s.d. decrease of the CETP genetic score, with concordant results for the rs1800775 (CETP-629C>A) SNP alone (Supporting Information: Table 6). To offer a comparison, pharmacological CETP inhibition with anacetrapib increased HDL-c levels by 1.11 mmol/l on average at the trial midpoint, evacetrapib increased HDL-c levels by 1.52 mmol/l at 3 months whereas dalcetrapib increased HDL-c by about 0.34 mmol/l on average at 1 year (HPS3/TIMI55–REVEAL Collaborative Group et al., 2017; Lincoff et al., 2017; Schwartz et al., 2012). In these examples, the pharmacological effect of CETP inhibition is about 17x stronger for anacetrapib, 24x for evacetrapib, and 5x for dalcetrapib when compared to a 1 s.d. reduction of the CETP genetic score. This comparison is based only on the effect on HDL-c levels which may not represent the full effect spectrum of CETP inhibitors.

The CETP genetic score was strongly associated with both basal and cAMP-stimulated cholesterol efflux capacity as measured in plasma from 5215 participants of the MHI Biobank (Table 2). A 1 s.d. decrease in the score increased basal cholesterol efflux by 0.105 s.d. (95% CI 0.078, 0.130) and increased cAMP-stimulated cholesterol efflux by 0.085 s.d. (95% CI 0.059, 0.011).

The CETP genetic score was associated with LDL-c levels with a 0.023 s.d. decrease in LDL-c (corresponding
to 0.020 mmol/l) per 1 s.d. decrease of the CETP genetic score \((p = 1.4 \times 10^{-45})\). In RCTs, most CETP inhibitors led to a decrease in LDL-c cholesterol, but not in the dal-OUTCOMES trial of dalcetrapib. Recently, anacetrapib was shown to decrease the production of lp(a) which could partly explain the benefit of this CETP inhibitor (Arai et al., 2016; Thomas et al., 2017). A decrease in lp(a) levels was also observed with torcetrapib suggesting a possible class effect of CETP inhibitors (Arsenault et al., 2018). We tested the association between the CETP genetic score and lp(a) levels measured in UK Biobank participants. A reduction of 1 s.d. in the CETP genetic score was associated with a decrease in lp(a) levels by 0.011 s.d. \((95\%\ CI\ 0.008,\ 0.013)\); \(p = 1.0 \times 10^{-14}\). In laboratory units of lp(a) levels, this corresponds to 0.524 nmol/l of lp(a) per s.d. of the CETP genetic score.

The association of the CETP genetic score with cardiovascular outcomes was concordant with the observed associations with the lipid profile. One s.d. reduction in the CETP genetic score was associated with CAD (“soft” definition, Supporting Information: Table 1) with an OR of 0.97 \((95\%\ CI\ 0.96,\ 0.98)\) \(p = 8.4 \times 10^{-7}\). Previous studies of genetic CETP reduction have also reported effects scaled by a 10 mg/dl reduction in apoB levels with an OR of 0.78 \((95\%\ CI\ 0.71,\ 0.86)\) (Ference et al., 2017). After scaling for an effect of this magnitude, our estimate corresponded to an OR of 0.72 \((95\%\ CI\ 0.64,\ 0.82)\) which is in line with these previous results. We also repeated these analyses for the rs1800775 CETP promoter variant and obtained similar results (Supporting Information: Table 6). We used scaling to enable comparison between studies and to report effects on a meaningful scale. However, this result does not imply that apoB is necessarily the only mediator relating CETP to CAD.

### Table 1

Descriptive statistics of the effect modifiers, biomarkers, and cardiovascular outcomes in the UK Biobank study population.

| General characteristics | Women | Men | All |
|-------------------------|-------|-----|-----|
| \(n\)\%(\%)           | 222,684 (54%) | 190,454 (46%) | 413,138 |
| Age, mean ± s.d.       | 56.6 ± 7.88 | 57.0 ± 8.06 | 56.8 ± 7.96 |

| Effect modifiers | Women | Men | All |
|------------------|-------|-----|-----|
| Sex \(\%\)\%(\%) | 222,684 (100%) | 190,454 (100%) | 413,138 (100%) |
| Body mass index (original scale) (BMI, kg/m\(^2\)), mean ± s.d. (median ± IQR) | 27.0 ± 5.15 | 27.9 ± 4.24 | 27.4 ± 4.77 |
| Body mass index (BMI, ln [kg/m\(^2\)]), mean ± s.d. | 3.28 ± 0.18 | 3.32 ± 0.15 | 3.30 ± 0.17 |

| Biomarkers as outcomes | Women | Men | All |
|------------------------|-------|-----|-----|
| Lipoprotein(a) (lp[a], nmol/L), mean ± s.d. | 44.6 ± 49.4 | 43.4 ± 49.3 | 44.0 ± 49.4 |
| Apolipoprotein B (apoB, g/L), mean ± s.d. | 1.04 ± 0.24 | 1.03 ± 0.24 | 1.03 ± 0.24 |
| Low-density lipoprotein cholesterol (LDL-c, mmol/L), mean ± s.d. | 3.64 ± 0.87 | 3.48 ± 0.86 | 3.57 ± 0.87 |
| Apolipoprotein A (apoA, g/L), mean ± s.d. | 1.64 ± 0.27 | 1.43 ± 0.23 | 1.54 ± 0.27 |
| High-density lipoprotein cholesterol (HDL-c, mmol/L), mean ± s.d. | 1.60 ± 0.38 | 1.29 ± 0.31 | 1.45 ± 0.38 |
| C-reactive protein (original scale) (CRP, mg/L), mean ± s.d. (median ± IQR) | 1.43 ± 2.97 | 1.36 ± 2.77 | 1.39 ± 2.89 |
| C-reactive protein—(CRP, ln [mg/L]), mean ± s.d. | 0.36 ± 1.09 | 0.30 ± 1.02 | 0.33 ± 1.06 |

| Cardiovascular outcomes | Women | Men | All |
|-------------------------|-------|-----|-----|
| Myocardial infarction (MI), \(n\)\%(\%) | 4747 (2%) | 13,812 (7%) | 18,559 (4%) |
| Percutaneous coronary intervention or coronary artery bypass graft (PCI/CABG), \(n\)\%(\%) | 3395 (2%) | 13,546 (7%) | 16,941 (4%) |
| Coronary artery disease, soft (CAD), \(n\)\%(\%) | 14,803 (7%) | 29,910 (16%) | 44,713 (11%) |
| Coronary artery disease, hard (CAD), \(n\)\%(\%) | 6825 (3%) | 19,517 (11%) | 26,342 (7%) |

**Note:** If a transformation was needed to normalize the data, the statistics are given in both the original and transformed scale. The units represent the applied transformation.
3.3 | Female sex is associated with a larger benefit of genetically lower CETP on the lipid profile

The large phase III RCTs of CETP inhibitors suffered from large sex imbalances, ranging between 16% of female participants (REVEAL) and 23% (ACCELERATE) and it is unlikely that these trials could have identified effect differences between men and women. In Figure 1, we show the reported drug effects from the major RCTs of CETP inhibitors stratified by sex. We conducted an inverse variance-weighted meta-analysis of the effect of the CETP inhibitor in the dal-OUTCOMES, REVEAL and ACCELERATE studies (Supporting Information). We did not include the ILLUMINATE trial with torcetrapib, as the drug had off-target deleterious effects. The calculated meta-analysis risk ratio is 0.96 (95% CI 0.91, 1.02) in men and 0.92 (95% CI 0.82, 1.04) in women. The test for heterogeneity between the male and female effects was not significant (p = 0.50). The Cochran Q statistics for heterogeneity between studies were 5.5 (p = 0.063) for the overall effect, 0.025 (p = 0.99) for the female-specific effect and 8.0 (p = 0.018) for the male-specific effect.

We used regression models to assess the interaction effect of sex with the CETP genetic score on biomarkers and cardiovascular outcomes in the UK Biobank (Figure 2). We observed statistically significant interactions for apoA and apoB as well as LDL-c and HDL-c levels. The strongest effect modification was with HDL-c and apoA. For instance, a one s.d. unit reduction in the CETP score increased HDL-c by 0.15 s.d. (95% CI 0.14, 0.15) in men (p < 10^{-300}) and by 0.18 s.d. (95% CI 0.18, 0.19) in women (p < 10^{-300}) and the interaction p value was 5 × 10^{-32}. In general, genetically predicted lower CETP had a more beneficial effect on the lipid profile in women than men. Similar results were obtained with the rs1800775 variant alone (Supporting Information: Figure 1).

We tested for the interaction of sex with the CETP genetic score on cholesterol efflux measured in a subgroup of participants of the MHI Biobank. For cAMP-stimulated cholesterol efflux, a unit decrease in the score was associated with a 0.064 s.d. (95% CI 0.032, 0.095) increase in efflux for men (p = 7 × 10^{-5}) and 0.13 (95% CI 0.086, 0.18) for women (p = 5 × 10^{-8}) and the interaction p-value was 0.02. A similar effect was also observed for basal efflux (Supporting Information: Figure 2). Again, women had a more favorable cholesterol efflux profile than men, with lower genetically-predicted CETP levels, as their cholesterol efflux capacity was higher on average.

### Table 2  Association of the CETP genetic score with biomarkers and cardiovascular events.

| Biomarkers—in s.d. units | N   | Standardized coefficient* | p Value      |
|--------------------------|-----|---------------------------|--------------|
| Lipoprotein (a)          | 315,214 | -0.011 (-0.013, -0.008) | 1.0 × 10^{-14}|
| C-reactive protein (CRP) | 394,165 | 0.0026 (-0.0005, 0.0057) | 0.098        |
| HDL cholesterol          | 362,468 | 0.167 (0.164, 0.170)     | <10^{-300}   |
| Apolipoprotein A          | 360,451 | 0.131 (0.129, 0.134)     | <10^{-300}   |
| LDL cholesterol          | 394,287 | -0.023 (-0.026, -0.019) | 1.4 × 10^{-45}|
| Apolipoprotein B          | 393,089 | -0.033 (-0.036, -0.030) | 5.1 × 10^{-97}|
| Basal cholesterol efflux (MHI Biobank) | 5,215 | 0.105 (0.079, 0.130) | 1.9 × 10^{-15}|
| cAMP-stimulated cholesterol efflux (MHI Biobank) | 5,214 | 0.085 (0.059, 0.111) | 2.7 × 10^{-10}|

| Cardiovascular outcomes | N cases/N total | Odds ratio (95% CI)* | p Value  |
|-------------------------|-----------------|----------------------|----------|
| Coronary artery disease (“soft”) | 44,713/413,138 | 0.975 (0.965, 0.985) | 8.4 × 10^{-7}|
| Coronary artery disease (“hard”) | 26,342/394,767 | 0.971 (0.958, 0.983) | 6.0 × 10^{-6}|
| Myocardial infarction    | 18,559/413,138 | 0.980 (0.966, 0.995) | 0.0096   |
| Percutaneous coronary intervention or coronary artery bypass graft | 16,941/413,138 | 0.967 (0.952, 0.982) | 2.6 × 10^{-5}|

*Coefficients for continuous variables (biomarkers) are from a linear regression model adjusted for age, sex, and the first 10 principal components and are expressed in standard deviation units of the biomarkers per standard deviation reduction in the CETP genetic score. Odds ratios for cardiovascular outcomes are estimated using a logistic regression model adjusted for the same covariates.
**FIGURE 1** Effect of treatment from phase 3 trials of CETP inhibitors in the whole population and stratified by sex. Points are scaled with respect to the relative weight in the overall and sex-specific meta-analyses.

**FIGURE 2** Effect modification of a 1 standard deviation decrease in the CETP concentration genetic score by sex on biomarkers and cardiovascular outcomes in the UK Biobank. Displayed p values (p_{int}) are for the two-sided test of the product interaction term between the CETP score and a binary sex indicator variable.
We considered whether the differences in the effect of CETP on biomarkers according to sex also led to differences in cardiovascular outcomes. On the multiplicative scale, the difference in the effect of a genetic CETP reduction between men and women was not statistically significant (interaction p value of 0.56 for CAD). However, the RERI (0.082 95% CI [0.020, 0.146]) and interaction contrast (0.0017 95% CI [0.00024, 0.0032]) suggested a difference in the effect of the CETP score on CAD (“hard”) in men compared to women (Supporting Information: Table 7). Power analyses rule out a strong effect difference of genetically lower CETP concentration on cardiovascular outcomes between men and women (Supporting Information: Appendix, Supporting Information: Figure 3). In sensitivity analyses, we show that results are robust to further adjustment for statin use (Supporting Information: Figure 4, Table 8).

3.4 Higher BMI reduces the benefit of genetically lower CETP on the lipid profile

Previous studies have reported that the effect of CETP on HDL-c is different across BMI classes (Cole et al., 2014; Sull et al., 2019). To assess how the effect of genetic CETP is modulated by BMI, we used interaction models from which we draw inferences and report marginal effects at fixed BMI values (Figure 3). We found BMI to be a significant modulator of the association between the CETP genetic score and HDL-c (interaction \( p = 5.4 \times 10^{-73} \)) and apoA levels (interaction \( p = 5.2 \times 10^{-24} \)) in the UK Biobank. Individuals with lower BMI had higher HDL-c and apoA levels per 1 s.d. decrease in the genetic CETP score. BMI was also a modifier of the association between the CETP genetic score and LDL-c (interaction \( p = 0.00013 \)) and apoB levels (interaction \( p = 0.0012 \)) with a lower BMI being associated with lower levels of LDL-c and apoB per s.d. decrease of the CETP genetic score (Figure 3). The interaction term was also significant for lp(a) supporting that BMI is also a modulator of the association between the CETP genetic score and lp(a) (\( p = 0.0027 \), Figure 3). In individuals of normal BMI (between 18.5 and <25), 1 s.d. reduction in the genetic CETP score was associated with 0.018 s.d. lower lp(a) (95% CI 0.014, 0.023) with \( p = 8 \times 10^{-15} \) and individuals in the obese BMI category (≥30) had 0.0081 s.d. lower lp(a) (95% CI 0.0025, 0.014) with \( p = 0.004 \) (Supporting Information: Figure 5). The interaction between the genetic CETP score and BMI was not significant for C-reactive protein (\( p = 0.24 \)). In the MHI Biobank, there was no interaction between BMI and the genetic CETP score on basal and cAMP-stimulated cholesterol efflux (\( p = 0.31 \) and \( p = 0.84 \), respectively). Results based on the rs1800775 variant were concordant.

![Figure 3](image_url)

**Figure 3** Effect modification by body mass index of a 1 standard deviation decrease in the CETP concentration genetic score on biomarkers and cardiovascular outcomes in the UK Biobank. Displayed p values (\( P_{\text{pdx}} \)) are for the two-sided test of the product term between the CETP score and standardized body mass index.
with those based on the genetic CETP score (Supporting Information: Figure 6).

To allow for nonlinear effects of BMI and the CETP genetic score, we used linear and logistic regression with interacting restricted cubic splines to model these two variables. There was evidence of nonlinear effects for BMI on all considered cardiovascular outcomes and biomarkers except for cholesterol efflux (Supporting Information: Table 9). The CETP genetic score exhibited possible nonlinear effects on LDL-c ($p = 0.0013$) and HDL-c ($p < 0.0001$) and their associated apolipoproteins. When considering all linear and nonlinear interaction terms (9 degrees of freedom test), there was evidence for interaction between the CETP score and BMI for lipoprotein(a) levels ($p = 0.0233$), HDL-c ($p < 0.0001$), apolipoprotein A ($p < 0.0001$), LDL-c ($p = 0.0001$), and apolipoprotein B ($p = 0.0147$). There was no statistically significant nonlinear interaction with any of the cardiovascular outcomes. To facilitate the interpretation of the nonlinear interactions for biomarkers, we plotted the predicted value of the standardized outcome while varying the levels of the CETP genetic score and BMI (Supporting Information: Figure 7).

We tested the modulatory effect of BMI on the relationship between the CETP genetic score and cardiovascular outcomes. None of the tested outcomes had statistically significant interactions between BMI and the CETP genetic score, but the effects were directionally consistent with the effects on the lipid profile in the multiplicative scale (Figure 3, Supporting Information: Table 10). For instance, the interaction coefficient $p$ value for CAD was 0.060 and the marginal OR of the CETP score on CAD was 0.960 (95% CI 0.941, 0.980) when fixing BMI at 21.75 (normal) versus 0.986 (95% CI 0.971, 1.00) when fixing BMI at 33.75 (obese). We determined the minimum detectable interaction using power analyses (Supporting Information: Appendix, Supporting Information: Figure 8). Similar results are observed in subgroups of individuals based on their BMI class (Supporting Information: Figure 5).

In sensitivity analyses, we show that the modulatory effects of BMI are robust to further adjustment for type II diabetes, ruling out the possibility of mediation of the BMI modulatory effect through diabetes (Supporting Information: Figure 9). We also assessed the association by using predicted BMI based on a BMI genetic score (PGS000034), age, sex, and ancestry principal components (Supporting Information: Figure 10). Results are concordant. This sensitivity analysis avoids the possibility of collider stratification bias, but at reduced statistical power because the predicted BMI values do not span the whole range of observed values. The analyses and their interpretation are further described in the Supporting Information: Appendix.

Because both BMI and sex were important modifiers of the effect of CETP on biomarkers, we evaluated the possibility of a three-way interaction between sex, BMI, and the CETP genetic score. There were sex differences in the interaction between BMI and genetic CETP levels on cholesterol efflux (three-way interaction $p_{\text{fix}} = 0.0037$ and $p_{\text{fix}} = 0.007$ for basal and cAMP-stimulated efflux, respectively), LDL-c ($p_{\text{fix}} = 0.00041$) and apoB levels ($p = 0.001$) (Supporting Information: Figures 11–13). These results are further described in the Supporting Information: Appendix.

4 | DISCUSSION

Using the large UK Biobank resource, supported by cholesterol efflux measurements in the MHI Biobank, we report the effect of genetically lower CETP on lipid biomarkers, cholesterol efflux, CRP, and cardiovascular outcomes. We assessed how sex and BMI changed the effect of a genetically predicted decrease of CETP on those measurements and outcomes. We report a significant modulatory effect of both sex and BMI on the association of CETP with biomarkers, but we were unable to show that these differences resulted in an effect on cardiovascular outcomes.

In our analyses, we observed that a genetically predicted lower CETP concentration was strongly associated with higher HDL-c and apoA levels and, to a lesser extent, lower LDL-c and apoB levels. These results are concordant with previous reports of the effect of CETP on lipids and lipoproteins (Blauw et al., 2019; Kettunen et al., 2019). We also observed lp(a) levels to be slightly, but significantly, lower in individuals with a genetically predicted reduction in CETP. This observation is interesting as lp(a) is an important risk factor for CAD that is largely independent of other lipoproteins. Previous studies have reported that both torcetrapib and anacetrapib could reduce lp(a) levels (Arsenault et al., 2018; Bloomfield et al., 2009; Thomas et al., 2017). The added genetic support could be indicative of a class effect of CETP inhibitors. In a Mendelian randomization study of lp(a) levels, a 10 mg/dl genetic reduction in lp(a) was associated with an OR of 0.942 for coronary heart disease supporting the causal role of lp(a) in coronary heart disease (Burgess et al., 2018). In our study, we show that a 1 s.d. decrease in the genetic CETP score was associated with a reduction in lp(a) of approximately 2 mg/dl which corresponds to an OR for coronary artery disease of 0.988 based on this previous MR study.
Genetically lower CETP was not associated with C-reactive protein. In the dal-OUTCOMES trial of dalcetrapib and the ACCELERATE trial of evacetrapib, CETP inhibition was associated with an increase in C-reactive protein, but there was no significant difference in the DEFINE trial of anacetrapib (Cannon et al., 2010; Lincoff et al., 2017; Schwartz et al., 2012). Given our high power to detect an association with biomarker measurements in the UK Biobank, it is unlikely that a lifelong, genetically lower CETP level has an effect on C-reactive protein levels.

Cholesterol efflux capacity is the capacity of HDL particles to absorb cholesterol from peripheral tissue, such as macrophages forming atherosclerotic plaque, for transport to the liver for excretion. Cholesterol efflux capacity was associated with a regression of atherosclerosis and the odds of coronary disease (Khera et al., 2011). In our study, genetically lower CETP was associated with higher cholesterol efflux capacity. This observation is concordant with previous reports of increased cholesterol efflux in patients treated with dalcetrapib and anacetrapib (Metzinger et al., 2020; Tardif et al., 2016). Genetically lower CETP was also associated with lower rates of cardiovascular outcomes, with a 2.5% fewer CAD events per s.d. decrease in the CETP genetic score. The observed protective effect was robust to adjustment for observed apoB levels at baseline in the UK Biobank, supporting that the protective effect of CETP may not be exclusively mediated by apoB levels. However, adjusting for observed apoB levels at a single time point may not completely control for a lifetime reduction in apoB levels by CETP genetic variants. Nonetheless, we presented a unified portrait of the effect of genetically lower CETP which may help better understand the on-target effects of CETP inhibitors and the diversity of pathways through which genetic variants in CETP may exert a protective effect on CAD.

The value of using human genetic variants to predict the effect of pharmacological modulation of drug targets is gaining recognition as more examples of drug target discoveries and predictions for ongoing randomized trials are reported (Minikel et al., 2020; Schmidt et al., 2020). Human genetics can also inform on subgroup effects in the context of precision medicine, for clinical trial design, or to assess the external validity of drug effects on other patient populations. Genetic studies of CETP variants have highlighted possible effect modification by sex on HDL-c levels, carotid intima-media thickness, the HDL-c/apoAI ratio, and on the dynamics of postprandial triglyceride levels (Anagnostopoulou et al., 2009; Christen et al., 2018; Gamache et al., 2021; Kark et al., 2000; Klingel et al., 2017). Sex differences were also observed in many traits thought to be involved in the atheroprotective effect of CETP such as the apoAI and apoA-II composition of HDL and CETP-mediated cholesterol efflux (Schaefer et al., 1982; Villard et al., 2013). Whether this translates to cardiovascular outcomes remains unknown (Cai et al., 2018). Considering that the female sex is underrepresented in the majority of cardiovascular clinical trials, sex differences may have important clinical implications as inferences drawn from the unbalanced trial populations are used to inform treatment.

In our analyses, we found sex to be a strong modulator of the effect of genetically lower CETP on lipid biomarkers and cholesterol efflux. Women with CETP-lowering genetic variants had lower LDL-c and apoB levels and higher HDL-c, apoA, and cholesterol efflux. In a substudy of the DEFINE trial, anacetrapib increased cholesterol efflux in men, but not women (Metzinger et al., 2020). In that study, cholesterol efflux capacity was measured using fluorescently labeled cholesterol which mostly captures efflux through the ABCA1 pathway. Here, we used radiolabeled cholesterol, and our measurements in cAMP-stimulated conditions also include the contributions of ABCG1 and SR-BI. In healthy subjects, serum from women had more SR-BI-mediated efflux capacity whereas serum from men had more ABCA1-mediated efflux capacity (Catalano et al., 2008). We suggest that, on average, with genetically lower CETP, women have more overall cholesterol efflux capacity than men, but that specific pathways may show the inverse relationship. The modulatory effect of sex did not translate to strong differences in cardiovascular outcomes in our analysis even though the additive interaction model suggests that men had a larger relative risk of “hard” CAD than women for the same increase in the CETP score. Because the UK Biobank contains relatively few cardiovascular events, especially in women, and because the genetic variants in CETP have a modest effect size, replication from a large, well-powered study is warranted to confirm these findings. A previous study also reported sex differences in the association between CETP genetic variants and cardiovascular disease (Papp et al., 2012), but sex interaction was not formally assessed, and the sample size and power may have been limited in that study (n = 866).

We conducted a meta-analysis of the sex-stratified results of three RCTs of CETP inhibitors, and although we did observe a nominally greater protective effect in women (RR = 0.92) than in men (RR = 0.96), the difference in effect was not statistically significant (p = 0.50). However, we also note that there was evidence of heterogeneity in the meta-analysis effect in men (Cochran Q = 8.0, p = 0.018) possibly hampering our ability to detect between-sex heterogeneity. A total of
10,769 women pooled across all three studies were included in the meta-analysis for a total of 58,412 participants, which is still lower than the number of individuals included in the smallest study \((n = 12,092)\) for ACCELERATE, suggesting limited power to identify a subgroup effect in women. We conclude that there is some indication of a stronger beneficial effect of CETP inhibition in women, but that confirmation using genetic datasets enriched for cardiovascular events or clinical trials with a greater representation of women would be needed.

Plasma CETP is mainly secreted by macrophages in the liver (Kupffer cells), and adipose tissue does not appear to be a clinically relevant contributor to circulating CETP levels (Blauw et al., 2016; Wang et al., 2015). However, higher BMI may affect hepatic and systemic inflammation and result in changes in lipid homeostasis that could alter the function of CETP without affecting plasma CETP concentration. There is also previous evidence of an interaction between obesity status and a CETP variant on acute coronary syndrome from a smaller study \((n = 474)\) (Dedoussis et al., 2007).

In our analyses, the atheroprotective profile of lipoproteins attributable to genetically lower CETP levels was stronger in individuals with lower BMI, when compared to individuals with higher BMI, showing lower levels of LDL-c, apoB, and LP(a) and higher levels of HDL-c and apoA with genetically lower CETP. Similar results were observed in models allowing for nonlinear effects on the biomarkers. The modulatory effect of BMI on the relationship between CETP and biomarkers did not translate to cardiovascular outcomes, however, a larger data set may be needed to assess the possible impact on outcomes with sufficient power.

We also found evidence of three-way interactions of sex, BMI, and genetically predicted CETP on LDL-c, apoB levels, and cholesterol efflux. The attenuated effect of lower CETP on LDL-c reduction with increasing BMI was specific to men. In women, the increase in cholesterol efflux by a genetic reduction in CETP was attenuated with increasing BMI, but this effect was sex-specific.

Our study had some limitations. We relied on common genetic variants to model pharmacological CETP inhibition, but these variants do not include rare mutations which can have much stronger effects on CETP function. CETP activity can also be modulated in more subtle ways than complete inhibition, with molecules such as dalcetrapib preserving pre-β-HDL formation, a function that is inhibited by anacetrapib (Niesor et al., 2010). This effect is due to differences in the CETP-mediated HDL remodeling through the homotypic transfer of cholesteryl esters and may play an important role in atherosclerosis as pre-β-HDL are important acceptors for ABCA1-mediated cholesterol efflux. Our genetic study could not distinguish between CETP modulation or inhibition, as measurements of ABCA1-mediated efflux or HDL subtypes were not available. CETP may also have an important intracellular role in storing triglycerides and cholesteryl esters in lipid droplets. (Izem & Morton, 2007; Izem et al., 2020).

Whether this activity was altered in our genetic models or played a role in the effect modification by BMI remains to be determined. Also, the estimated effects derived from the genetic variants relate to lifelong exposure to lower CETP concentrations, which may differ from the effects of short-term exposure to pharmacological inhibition of CETP. In addition, although the UK Biobank offers large numbers of study participants, the cohort has a limited number of cardiovascular events. A case-control cohort with larger numbers of CAD events may help increase the power to assess the translation of the detected modulatory effects of sex and BMI on lipid biomarkers and cholesterol efflux to cardiovascular outcomes. We did not adjust for multiple testing of phenotypes and effect modifiers in this study. We reported confidence intervals and provided power analyses to support the interpretation of results. The genetic variants at the CETP gene have concurrent power analyses to support the interpretation of results. The genetic variants at the CETP gene have concurrent power analyses to support the interpretation of results.

In this study, we have evaluated the effect of a genetically predicted reduction in CETP concentration on lipoproteins, lipid fractions, cholesterol efflux, and CRP. We have found results to be largely concordant with those obtained from clinical trials. Using statistical interaction models, we found that sex and BMI are modifiers of the effect of CETP on lipid biomarkers and cholesterol efflux. We also discussed the conditions and assumptions under which observations based on genetic variants in drug targets can convey information on the causal relationship between the drug target and the effect of its pharmacological modulation (Supporting Information). Our analyses are particularly relevant as obeticholic acid, a new CETP inhibitor that aims to reduce LDL-c in statin-treated individuals is under development (Nicholls et al., 2022). According to our study, women are likely to benefit from a greater reduction in LDL-c than men, on average, and assessing sex-specific results from this clinical trial will be of interest.
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**SUPPORTING INFORMATION**

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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