Circulating Cholesteryl Ester Transfer Protein and Coronary Heart Disease
Mendelian Randomization Meta-Analysis

Wenquan Niu, PhD; Yue Qi, MD, PhD

Background—The cholesteryl ester transfer protein (CETP) plays a central role in reverse cholesterol transport. Currently, it remains unresolved whether circulating CETP is causally associated with coronary heart disease (CHD). We aimed to investigate this causal association using CETP gene rs708272 polymorphism as an instrument in a Mendelian randomization meta-analysis.

Methods and Results—We searched PubMed and EMBASE before May 2014. Data and study quality were assessed in duplicate. Thirty-four articles (17,813 CHD patients and 22,203 controls) were qualified. Overall analyses revealed a significant association of rs708272-B1 allele with a reduced CHD risk compared with B2 allele under allelic (odds ratio and 95% confidence interval: 0.87 and 0.82–0.92; P<0.001), homozygous genotypic (0.74 and 0.66–0.83; P<0.001), and dominant (0.87 and 0.80–0.94; P<0.001) models. Carriers of rs708272-B1B1 genotype (weighted mean difference and 95% confidence interval: −0.21 and −0.41 to 0.00; P<0.001) had a marginally lower circulating CETP level compared with B2B2 genotype carriers. In Mendelian randomization analysis, there was a 25% (odds ratio and 95% confidence interval: 0.75 and 0.19–0.91) and a 17% (0.83 and 0.41–0.96) significantly reduced risk of CHD by a reduction of 0.2 μg/mL in circulating CETP for the comparison of B1B1 genotype and B1 allele with B2B2 genotype, respectively. There were low probabilities of publication bias.

Conclusions—Our findings demonstrate that the long-term genetically reduced circulating CETP might be causally associated with the low risk of CHD. (Circ Cardiovasc Genet. 2015;8:114-121. DOI: 10.1161/CIRCGENETICS.114.000748.)

Key Words: cholesterol, HDL ■ coronary disease ■ Mendelian randomization analysis ■ meta-analysis

The cholesteryl ester transfer protein (CETP) is a plasma glycoprotein that facilitates the transfer of cholesteryl ester from high-density lipoprotein (HDL) to apolipoprotein B (ApoB)-containing lipoproteins.1 Considering its central role in reverse cholesterol transport, CETP inhibition has been proposed as an attractive strategy to raise HDL cholesterol (HDL-C), an established coronary risk factor.2 However, 2 large randomized controlled trials of CETP inhibitors have failed to show any benefit for cardiovascular disease events and the progression of atherosclerosis.3,4 Currently, whether circulating CETP is causally associated with coronary heart disease (CHD) or merely a biomarker of underlying atherosclerosis remains unresolved.

Clinical Perspective on p 121

The genomic sequence of CETP gene (gene ID: 1071) is polymorphic, and several polymorphisms have been identified as a cause of CETP deficiency. An intronic polymorphism rs708272 (also called Taq1B) in CETP gene has been widely evaluated in association with CHD risk5–7 and circulating CETP changes8–10 in many observational studies. A previous large-scale meta-analysis by Thompson et al11 indicated that CETP genotypes were associated with moderate inhibition of CETP activity and inversely associated with CHD. To yield more information, we, in this meta-analysis, used Mendelian randomization technique to investigate whether the association between circulating CETP and CHD is causal by using CETP gene rs708272 polymorphism as an instrument.

Analogous to a randomized controlled trial, Mendelian randomization is developed as a viable strategy to obtain unconfounded and unbiased estimates of causal relevance from observational data and has been successfully applied to evaluating a variety of environmentally modifiable exposures for cardiovascular diseases.12,13

Methods

This meta-analysis was undertaken complying with the guidelines put forward by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.14

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**Publication Search**

We searched PubMed and EMBASE from the earliest possible year to May 1, 2014, using the subject terms CETP or cholesteryl ester transfer protein or CETP and CHD or ischemic heart disease or myocardial infarction or atherosclerosis or arteriosclerosis or coronary stenosis or coronary artery disease or coronary disease, along with polymorphism or variant or variation or mutation or single-nucleotide polymorphism. We additionally extended our search to the perusal of the bibliographies of retrieved original articles and reviews for other relevant publications.

The titles and abstracts of all retrieved articles were independently reviewed by 2 investigators (W.N. and Y.Q.) to assess their eligibility. We extracted data from the most recent or complete publication where >1 publication of a study population existed.

**Inclusion/Exclusion Criteria**

For inclusion, qualified studies had to examine the hypothesis that CETP gene rs708272 polymorphism was associated with CHD or circulating levels of CETP or relevant lipid biomarkers, be a retrospective or nested-case–control study for association with CHD and be free of design restrictions for association with circulating levels and CETP or relevant lipids, and provide genotype counts between CHD patients and controls or circulating levels of CETP or relevant lipid biomarkers across rs708272 genotypes. Articles were excluded if they assessed the progression, severity, genotype modification, and response to treatment or survival of CHD, or if they lacked control groups, or if they were case reports or series, editorials, narrative reviews, and non-English articles.

**Data Extraction**

The following data were independently extracted by 2 investigators (W.N. and Y.Q.) from each qualified article according to a fixed protocol: the first author, publication year, ethnicity, diagnostic criteria, CHD subtypes (coronary stenosis or myocardial infarction), study design, genotyping platform, source of controls, matching situation, sample size, rs708272 genotype counts in patients with CHD and controls, mean circulating levels of CETP or HDL-C or triglycerides or low-density lipoprotein cholesterol (LDL-C) or apolipoprotein AI (ApoAI) or ApoB expressed as mean (SD) across rs708272 genotypes, as well as some baseline characteristics if available, including age, sex, body mass index (BMI), smoking, the percentages of dyslipidemia, hypertension, and diabetes mellitus, and mean circulating levels of CETP, triglycerides, total cholesterol, HDL-C, LDL-C, ApoAI, and ApoB expressed as mean (SD) across rs708272 genotypes, as well as some baseline characteristics if available, including age, sex, body mass index (BMI), smoking, the percentages of dyslipidemia, hypertension, and diabetes mellitus, and mean circulating levels of CETP, triglycerides, total cholesterol, HDL-C, LDL-C, ApoAI, and ApoB expressed as mean (SD) across rs708272 genotypes, as well as some baseline characteristics if available, including age, sex, body mass index (BMI), smoking, the percentages of dyslipidemia, hypertension, and diabetes mellitus.

**Statistics**

Data management and statistical analyses described below were completed with the STATA software (version 11.2 for Windows; StataCorp, College Station, TX).

Irrespective of between-study heterogeneity, a random-effects model using the DerSimonian and Laird method was used to bring individual effect-size estimates together. Unadjusted odds ratio (OR) and weighted mean difference (WMD), as well as 95% confidence interval (CI), were calculated to compare the distributional differences of genotypes or alleles of rs708272 polymorphism between patients with CHD and controls, as well as to compare the changes of circulating levels of CETP, LDL-C, triglycerides, LDL-C, ApoAI, and ApoB across genotype carriers.

Between-study heterogeneity was quantified using the inconsistency index ($I^2$) statistic (ranging from 0%–100%), which is defined as the percentage of observed between-study variability that is because of heterogeneity rather than chance. In this meta-analysis, $I^2>50\%$ was set as a threshold indicating significant heterogeneity.

**Results**

### Eligible Articles

Altogether, 398 potentially relevant articles were identified after the initial search, and 43 of them were deemed as eligible according to the inclusion criteria. All articles written in English were published between 1990 and 2013.

For the association between CETP gene rs708272 polymorphism and CHD, there were 34 eligible articles involving 40 study populations (17,813 CHD patients and 22,203 controls). For the association between CETP gene rs708272 polymorphism and circulating lipids, there were 3 articles for CETP and circulating lipids.

### Study Characteristics

The baseline characteristics of study populations are summarized in Tables I (1A, 1B, and 1C) and II (2A, 2B, 2C, and 2D) in the Data Supplement. Of 40 studies involved in the genotype-disease association, 18 were of white origin, 12 of Eastern Asian origin, 3 of Middle Eastern origin, and 7 of mixed origins. Coronary stenosis was assessed in 26 studies, myocardial infarction in 11 studies, and CHD (combination of coronary stenosis and myocardial infarction) in 3 studies. Controls of 25 and 15 studies were, respectively, enrolled from hospitals and general populations. Twenty-seven study populations were collected in a retrospective case–control design and 13 in a nested case–control design. Twenty-nine studies were free of design restrictions for association with circulating levels and CETP or relevant lipids, and provide genotype counts between CHD patients and controls or circulating levels of CETP or relevant lipid biomarkers across rs708272 genotypes.
genotyped rs708272 on restriction fragment length polymorphism platform and 11 studies on non–length polymorphism platform. Seventeen of 40 studies involved patients with CHD and controls matched on age. Twenty-one studies had a total sample size of ≥500, and 19 studies had a total sample size of <500. The frequency of rs708272 minor B1 allele ranged from 29.01% to 64.77% in patients with CHD and from 34.13% to 70.27% in controls.

Of 48 study populations involved in the genotype-phenotype association, 21 were of white origin, 19 of Eastern Asian origin, 3 of Middle Eastern origin, and 5 of mixed origins (Table II in the Data Supplement).

Association of CETP Gene rs708272 With CHD
Table 1 summarizes the overall and subgroup analyses of CETP gene rs708272 polymorphism with CHD under 3 genetic models. Overall analyses of 40 study populations revealed a significant association of rs708272-B1 allele with a reduced CHD risk compared with B2 allele under allelic (OR, 0.87; 95% CI, 0.82–0.92; P<0.001), homozygous genotypic (OR, 0.74; 95% CI, 0.66–0.83; P<0.001), and dominant (OR, 0.87; 95% CI, 0.80–0.94; P<0.001) models, accompanying moderate heterogeneity (I²=57.7%, 61.3%, and 50.6%, respectively) and high probabilities of publication bias (Egger test: P=0.006, 0.01, and 0.021, respectively; Figure 1). In addition, although Egger test provided small P values, no missing studies were identified from the trim-and-fill analysis. Excluding 6 studies with rs708272 genotypes deviating from Hardy–Weinberg equilibrium in controls had no material changes in risk estimates under 3 genetic models (Table 1).

In subgroup analyses by ethnicity, the magnitude of this association was potentiated in populations of Eastern Asian (OR=0.76, 0.56, and 0.69, respectively) and Middle Eastern (OR=0.77, 0.40, and 0.81, respectively) origins but attenuated in populations of white (OR=0.91, 0.80, and 0.94, Table 1).
respectively) origin across 3 genetic models, and heterogeneity was greatly improved for most comparisons.

Grouping studies by CHD subtypes indicated that the association of rs708272-B1 allele with the risk of coronary stenosis (OR=0.82, 0.65, and 0.81, respectively) was consistently stronger than that of myocardial infarction (OR=0.92, 0.82, and 0.93, respectively) across 3 genetic models, with significant heterogeneity only for coronary stenosis. In contrast, the effect estimates were comparable between studies involving hospital- and population-based controls across 3 genetic models.

By study design, the ORs of having CHD for rs708272-B1 allele were 0.82, 0.65, and 0.80 in retrospective case–control studies (P<0.001 for all) and 0.96, 0.91, and 0.96 (P>0.1 for all) in nested case–control studies under allelic, homozygous genotypic, and dominant models, respectively, with evident heterogeneity for retrospective studies only. Stratifying studies by genotyping platform found relatively conserved estimates for studies using the non–length polymorphism platform, and there was low evidence of heterogeneity. Whether the age-matched situation was reported had no material changes in association of rs708272-B1 allele with CHD across 3 genetic models.

When the analyses were restricted to the large studies (≥500 participants), summary risk effects were slightly weakened but still significant relative to the overall effects across 3 genetic models, whereas analyses of the small studies (<500 participants) detected an overestimation of effect estimates, yielding an OR of 0.79 (P<0.001), 0.59 (P<0.001), and 0.78 (P=0.008), respectively, under allelic, homozygous genotypic, and dominant models, and heterogeneity was not improved.

**Association of CETP Gene rs708272 With CETP and Other Lipids**

Table 2 presents the overall analyses of CETP gene rs708272 polymorphism with circulating levels of CETP and relevant lipids, including HDL-C, triglycerides, LDL-C, ApoAI, and ApoB under homozygous genotypic and dominant models. Carriers of rs708272-B1B1 genotype (WMD=−0.21 μg/dL; 95% CI, −0.41 to 0.00; P=0.052) or B1 allele (B1B1 and B1B2 genotypes) (WMD, −0.15 μg/dL; 95% CI, −0.30 to 0.00; P=0.056) had a marginally lower circulating CETP level compared with B2B2 genotype carriers, with strong evidence of heterogeneity (I²=95.2% and 96.0%), possibly because of the small sample sizes involved.

As expected, higher circulating HDL-C was observed in those with rs708272-B1B1 genotype (WMD, 3.98 mg/dL; 95% CI, 3.18–4.78; P<0.001) or B1 allele (WMD, 3.33 mg/dL; 95% CI, 2.74–3.92; P<0.001) than B2B2 genotype carriers, and there was significant heterogeneity (I²=77.6% and 79.0%; Table 2). Likewise, circulating ApoAI was observed significantly higher in B1B1 genotype (WMD, 3.12; 95% CI, 2.52–3.72; P<0.001) or B1 allele (WMD, 2.60; 95% CI, 2.11–3.10; P<0.001) than the noncarriers, with significant heterogeneity (I²=99.5% and 99.6%). There were no observable differences in circulating levels of triglycerides, LDL-C, and ApoB across genotypes.

**Prediction of CETP for CHD: Mendelian Randomization**

Under the assumptions required for Mendelian randomization, overall analyses indicated a 25% (OR, 0.75; 95% CI, 0.19–0.91) and a 17% (OR, 0.83; 95% CI, 0.41–0.96) reduced risk of CHD by a reduction of 0.2 μg/mL in circulating CETP for the comparison of B1B1 genotype carriers and B1 allele carriers with B2B2 genotype carriers, respectively. Considering that the null hypothesis value of unity was not covered by derived
CETP deficiency is associated with premature atherosclerosis. In humans, CETP deficiencies result in elevated HDL-C and reduced CHD risk.

Sensitivity Analysis and Metaregression Analysis

With regard to the association of CETP gene rs708272 polymorphism with CHD risk, sensitivity analyses confirmed the overall differences in both direction and magnitude under 3 genetic models (Figure I in the Data Supplement).

To further account for potential sources of heterogeneity within a multivariable framework, metaregression analyses were undertaken by incorporating various study-level continuous characteristics, including age (*P* = 0.566), sex (*P* = 0.928), BMI (*P* = 0.102), smoking (*P* = 0.853), and the percentages of dyslipidemia (*P* = 0.730), hypertension (*P* = 0.344), and diabetes mellitus (*P* = 0.651), as independent variables, and none were observed to contribute significantly to the association of CETP gene rs708272 polymorphism with CHD risk.

Discussion

The most noteworthy finding of this study is that the long-term genetically reduced circulating CETP might be causally associated with the low risk of CHD when using CETP gene rs708272 polymorphism as an instrument in a Mendelian randomization meta-analysis. Although the potential sources of heterogeneity could not be easily eliminated, to date, this report is the first to provide evidence for putative causal nature of the association between circulating CETP and CHD.

A note of caution should be sounded when interpreting the causal relevance of circulating CETP with CHD risk in this meta-analysis because only 3 studies of limited sample sizes were available for comparing mean levels of circulating CETP across rs708272 genotypes. CETP is a 476-residue glycoprotein that facilitates the generation of atherogenic lipoproteins.

Overexpression of CETP gene in transgenic mice was reported to display a reduction in circulating HDL-C and develop premature atherosclerosis. In humans, CETP deficiencies resulted in elevated HDL-C and exhibited antiatherogenic properties. A recent Mendelian randomization meta-analysis using CETP gene rs708272 polymorphism as an instrument failed to support a causal relevance between elevated circulating HDL-C and reduced CHD risk, and this failure might be because of the fact that using a single polymorphism in CETP gene to judge the causality of HDL-C on CHD risk is not valid, given that CETP also affects LDL-C and triglycerides. Extending previous findings in observational studies, we instead, for the first time, demonstrated that the long-term genetic reduction in circulating CETP was causally related to low risk of CHD by implementing Mendelian randomization in a meta-analysis. However, our finding must be viewed with critical reservation because several clinical investigations of CETP inhibitors, such as dalceptrapib and torcetrapib, in CHD patients treated with statin have failed to reduce cardiovascular risk but instead increased cardiovascular morbidity and mortality, which may have been related in part to off-target toxicity as reasoned by Masson et al.

Fortunately, 2 ongoing phase III clinical trials using a more potent CETP inhibitor, anacetrapib, may help clarify the contributory mechanisms of CETP in the progression and severity of cardiovascular diseases.

CETP is established to play a central role in HDL metabolism. It is reasonable to expect that individuals carrying protective genotypes in CETP can be benefitted by increasing circulating HDL-C, as well as ApoAI, a rough measure of HDL particle. Currently, the association between circulating HDL-C and CHD is still subject to an ongoing debate, and the updated American Heart Association/American College of Cardiology and European Society of Cardiology guidelines do not recommend to raise HDL-C as a preventive means for atherosclerotic cardiovascular diseases. In contrast, there is growing recognition for an emerging role of HDL particle rather than HDL-C in improving HDL function, which might account for the failure of 2 recent randomized controlled trials that found little effect of CETP inhibitor or niacin on HDL particle number despite the fact that circulating HDL-C was substantially increased. Moreover, because the association of CETP gene rs708272 polymorphism with the changes of circulating triglycerides or LDL-C was valid, given that CETP also affects LDL-C and triglycerides. Extending previous findings in observational studies, we instead, for the first time, demonstrated that the long-term genetic reduction in circulating CETP was causally related to low risk of CHD by implementing Mendelian randomization in a meta-analysis. However, our finding must be viewed with critical reservation because several clinical investigations of CETP inhibitors, such as dalceptrapib and torcetrapib, in CHD patients treated with statin have failed to reduce cardiovascular risk but instead increased cardiovascular morbidity and mortality, which may have been related in part to off-target toxicity as reasoned by Masson et al. Fortunately, 2 ongoing phase III clinical trials using a more potent CETP inhibitor, anacetrapib, may help clarify the contributory mechanisms of CETP in the progression and severity of cardiovascular diseases.

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nonsignificant, we cannot, with certainty, rule out the regulatory effect of circulating CETP on triglycerides and LDL-C because their relationships with reduced CETP activity were in the expected directions of effect, likely because of lack of statistical power in quantifying effect estimates. However, there is additional evidence suggesting that CETP activity may be a 2-edged sword that affects atherosclerosis.52,64 As exemplified in animal models, either high or low level of CETP was observed to increase atherosclerosis susceptibility. As exemplified in animal models, either high or low level of CETP was observed to increase atherosclerosis susceptibility.52,64 Furthermore, based on our preliminary findings, it is tempting to speculate that the potential causal relevance of circulating CETP with CHD risk might be mediated by its improving effects on HDL-C and ApoAI.

Despite the clear strengths of this meta-analysis, including the large sample size and the implementation of Mendelian randomization technique, several possible limitations merit consideration. Because only published studies were retrieved and the grey literature (articles in languages other than English) was not covered, publication bias might be possible. In fact, asymmetry in the funnel plot, being either visually interpreted or statistically tested, may result from an essential difference between small and large studies that arises from inherent between-study heterogeneity. Moreover, with respect to the early onset of CHD in youth, because most of the eligible studies in this meta-analysis recruited participants aged >50 years for whom environmental factors are likely to contribute more prominently than a genetic component to the development of CHD, more large studies in a younger population of CHD will be of great interest. In addition, this single-locus-based meta-analysis precluded the possibility of gene-to-gene and gene-to-environment interactions, as well as haplotype-based and genetic score effects. To overcome this limitation, one usually needs to undertake a meta-analysis of individual participant data, which is not always feasible. Furthermore, we only focused on CETP gene rs708272 polymorphism and did not cover other candidate genes or polymorphisms. It is challengeable to test whether this polymorphism integrated with other risk determinants will enhance CHD risk prediction. Therefore, we cannot jump to a firm conclusion until large well-performed studies confirm or refuse our findings.

In conclusion, our findings in a Mendelian randomization meta-analysis demonstrate that the long-term genetically reduced circulating CETP might be causally associated with the low risk of CHD. Further investigations within the clinical and epidemiological framework are warranted.

Sources of Funding
This study was supported by Shanghai Rising Star Program (11QA1405500).

Disclosures
None.

References


### CLINICAL PERSPECTIVE

The cholesteryl ester transfer protein (CETP) plays a central role in reverse cholesterol transport, and CETP inhibition has been proposed as an attractive strategy to raise high-density lipoprotein cholesterol. However, several large randomized controlled trials of CETP inhibitors have failed to show any benefit for cardiovascular disease events and the progression of atherosclerosis. Currently, whether circulating CETP is causally associated with coronary heart disease (CHD) or merely a biomarker of underlying atherosclerosis remains unresolved. To address this issue, we, in this meta-analysis, used Mendelian randomization technique to investigate whether the association between circulating CETP and CHD is causal by using CETP gene rs708272 polymorphism as an instrument. Overall analyses of 40 study populations revealed a significant association of rs708272-B1 allele with a reduced CHD risk compared with B2 allele under allelic, homozygous genotypic, and dominant models. In addition, carriers of rs708272-B1B1 genotype or B1 allele (B1B1 and B1B2 genotypes) had a marginally lower circulating CETP level compared with B2B2 genotype carriers. Furthermore, under the assumptions required for Mendelian randomization, overall analyses indicated a 25% and a 17% reduced risk of CHD by a reduction of 0.2 μg/mL in circulating CETP for the comparison of B1B1 genotype carriers and B1 allele carriers with B2B2 genotype carriers, respectively. Taken together, our findings in a Mendelian randomization meta-analysis demonstrate that the long-term genetically reduced circulating CETP might be causally associated with the low risk of CHD.
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### Supplementary Table 1A. The baseline characteristics of eligible studies for the association of CETP gene rs708272 polymorphism with CHD risk

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<th>Study ID</th>
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<th>Ethnicity</th>
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<th>Match</th>
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Supplementary Table 1B. The baseline characteristics of study populations for the association of CETP gene rs708272 polymorphism with CHD risk

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### Supplementary Table 1C. The baseline characteristics of study populations for the association of CETP gene rs708272 polymorphism with CHD risk

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**Abbreviations:** RFLP, restriction fragment length polymorphism; NA, not available; BMI, body mass index; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CETP, cholesteryl ester transfer protein; CHD, coronary heart disease; Apo AI, apolipoprotein AI; Apo B, apolipoprotein B. \( P_{\text{HWE}} \), \( P \) for Hardy-Weinberg equilibrium in control groups.
### Supplementary Table 2A. The distributions of circulating CETP and other lipids across rs708272 genotypes in all eligible studies

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Supplementary Table 2D. The distributions of circulating CETP and other lipids across rs708272 genotypes in all eligible studies

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*Abbreviations*: N, number; SD, standard deviation; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CETP, cholesteryl ester transfer protein; Apo AI, apolipoprotein AI; Apo B, apolipoprotein B; CHD, coronary heart disease; NA, not available.
Supplementary Figure S1. Sensitivity analysis of CETP gene rs708272 polymorphism with CHD risk under the allelic (the upper panel), Homozygous genotypic (the middle panel) and dominant (the lower panel) models