JAMA Cardiology | Original Investigation

# Association of *CETP* Gene Variants With Risk for Vascular and Nonvascular Diseases Among Chinese Adults

Iona Y. Millwood, DPhil; Derrick A. Bennett, PhD; Michael V. Holmes, PhD; Ruth Boxall, MSc; Yu Guo, MSc; Zheng Bian, MSc; Ling Yang, PhD; Sam Sansome, BSc; Yiping Chen, DPhil; Huaidong Du, PhD; Canqing Yu, PhD; Alex Hacker, MA; Dermot F. Reilly, PhD; Yunlong Tan, MBBS; Michael R. Hill, PhD; Junshi Chen, MD; Richard Peto, FRS; Hongbing Shen, PhD; Rory Collins, FRS; Robert Clarke, MD; Liming Li, MPH; Robin G. Walters, PhD; Zhengming Chen, DPhil; for the China Kadoorie Biobank Collaborative Group

**IMPORTANCE** Increasing levels of high-density lipoprotein (HDL) cholesterol through pharmacologic inhibition of cholesteryl ester transfer protein (CETP) is a potentially important strategy for prevention and treatment of cardiovascular disease (CVD).

**OBJECTIVE** To use genetic variants in the *CETP* gene to assess potential risks and benefits of lifelong lower CETP activity on CVD and other outcomes.

**DESIGN, SETTING, AND PARTICIPANTS** This prospective biobank study included 151 217 individuals aged 30 to 79 years who were enrolled from 5 urban and 5 rural areas of China from June 25, 2004, through July 15, 2008. All participants had baseline genotype data, 17 854 of whom had lipid measurements and 4657 of whom had lipoprotein particle measurements. Median follow-up of 9.2 years (interquartile range, 8.2-10.1 years) was completed January 1, 2016, through linkage to health insurance records and death and disease registries.

**EXPOSURES** Five *CETP* variants, including an East Asian loss-of-function variant (rs2303790), combined in a genetic score weighted to associations with HDL cholesterol levels.

**MAIN OUTCOMES AND MEASURES** Baseline levels of lipids and lipoprotein particles, cardiovascular risk factors, incidence of carotid plaque and predefined major vascular and nonvascular diseases, and a phenome-wide range of diseases.

**RESULTS** Among the 151 217 individuals included in this study (58.4% women and 41.6% men), the mean (SD) age was 52.3 (10.9) years. Overall, the mean (SD) low-density lipoprotein (LDL) cholesterol level was 91 (27) mg/dL; HDL cholesterol level, 48 (12) mg/dL. *CETP* variants were strongly associated with higher concentrations of HDL cholesterol (eg, 6.1 [SE, 0.4] mg/dL per rs2303790-G allele; $P = 9.4 \times 10^{-47}$) but were not associated with lower LDL cholesterol levels. Within HDL particles, cholesterol esters were increased and triglycerides reduced, whereas within very low-density lipoprotein particles, cholesterol esters were reduced and triglycerides increased. When scaled to 10-mg/dL higher levels of HDL cholesterol, the *CETP* genetic score was not associated with occlusive CVD (18 550 events; odds ratio [OR], 0.98; 95% CI, 0.91-1.06), major coronary events (5767 events; OR, 1.08; 95% CI, 0.95-1.22), myocardial infarction (3118 events; OR, 1.14; 95% CI, 0.97-1.35), ischemic stroke (13 759 events; OR, 0.94; 95% CI, 0.86-1.02), intracerebral hemorrhage (6532 events; OR, 0.94; 95% CI, 0.83-1.06), or other vascular diseases or carotid plaque. Similarly, rs2303790 was not associated with any vascular diseases or plaque. No associations with nonvascular diseases were found other than an increased risk for eye diseases with rs2303790 (4090 events; OR, 1.43; 95% CI, 1.13-1.80; $P = .003$).

**CONCLUSIONS AND RELEVANCE** *CETP* variants were associated with altered HDL metabolism but did not lower LDL cholesterol levels and had no significant association with risk for CVD. These results suggest that in the absence of reduced LDL cholesterol levels, increasing HDL cholesterol levels by inhibition of CETP may not confer significant benefits for CVD.

*JAMA Cardiol*. 2018;3(1):34-43. doi:10.1001/jamacardio.2017.4177
Published online November 15, 2017. Corrected on January 17, 2018.

Supplemental content

**Author Affiliations:** Author affiliations are listed at the end of this article.

**Group Information:** Members of the China Kadoorie Biobank Collaborative Group are listed at the end of this article.

**Corresponding Author:** Iona Y. Millwood, DPhil, Medical Research Council Population Health Research Unit, Nuffield Department of Population Health, University of Oxford, Oxford OX3 7LF, England (iona.millwood@ndph.ox.ac.uk).

Observational epidemiologic studies have reported that low plasma concentrations of high-density lipoprotein (HDL) cholesterol are an independent risk factor for occlusive cardiovascular disease (CVD), including coronary heart disease (CHD) and ischemic stroke.[1,2] Given these associations, therapeutic strategies to reduce CVD risk by increasing HDL cholesterol concentrations have attracted considerable interest. One such approach is through pharmacologic inhibition of cholesterol ester transfer protein (CETP), which transfers esterified cholesterol from HDL to apolipoprotein B-containing lipoproteins, including very low-density lipoprotein (VLDL), in exchange for triglycerides.[3] The first CETP inhibitor assessed in phase 3 trials, torcetrapib, was associated with increased CVD risk, probably owing to off-target effects.[4,5] Subsequent trials of dalcetrapib (which had only modest effects on HDL cholesterol) or evacetrapib (which increased HDL cholesterol levels substantially and lowered LDL cholesterol levels) were stopped early for futility after 2 to 3 years of treatment in high-risk individuals.[6,7] A trial of the potent CETP inhibitor anacetrapib (which doubled HDL cholesterol levels and lowered non-HDL cholesterol levels by about one-fifth) that involved approximately 30 000 high-risk individuals treated for 4 years recently reported a benefit for risk of major coronary events consistent with the effects of lowering non-HDL cholesterol levels.[8]

Genetic variants can be used to assess causal associations with a mendelian randomization approach that resembles a randomized trial because genetic variants are randomly allocated at conception and should not be subject to confounding or reverse causation bias.[9] As such, genetic studies can be used to estimate the effects of alterations of the expression or activity of a drug target, such as CETP.[10] Common *CETP* gene (HGNC 1869) variants associated with lower CETP mass and activity have been associated with lower risks for CHD and ischemic stroke and a higher risk for intracerebral hemorrhage.[11-16] Previous studies were conducted mainly in populations of European origin, among whom the mean LDL cholesterol level is high compared with the Chinese population, and common *CETP* variants tend to be associated not only with higher HDL cholesterol concentrations but also with lower LDL cholesterol concentrations, as is the case for several CETP inhibitors.[17,18] A loss-of-function variant in *CETP* (rs2303790; c.1376A>G; p.D459G) that results in lower plasma CETP levels and activity has been identified in Japanese individuals with elevated HDL cholesterol concentrations.[19-21] Some studies of rs2303790 and other *CETP* loss-of-function variants suggest an association with lower CHD risk that may be mediated by lower LDL cholesterol levels, but findings are inconsistent.[22-25]

To assess the potential benefits and risks of lifelong lower CETP activity, we examined the association of *CETP* variants (rs2303790 and a genetic score consisting of this and 4 other common *CETP* variants) with lipid and lipoprotein metabolism, CVD risk factors, and a range of vascular and nonvascular diseases in as many as 151 217 adults from the China Kadoorie Biobank (CKB) study.

### Key Points

**Question** What is the association of genetic variants in the *CETP* gene that lower cholesteryl ester transfer protein activity with risk for cardiovascular and other diseases?

**Findings** In this biobank study of 151 217 Chinese adults, *CETP* gene variants were associated with higher levels of high-density lipoprotein cholesterol but not with lower levels of low-density lipoprotein cholesterol and were not associated with risk for cardiovascular disease.

**Meaning** Increasing levels of high-density lipoprotein cholesterol by cholesteryl ester transfer protein inhibition in the absence of lower levels of low-density lipoprotein cholesterol may not confer significant benefits for cardiovascular disease.

## Methods

### Study Population, Baseline Survey, and Resurvey

The design and methods of the CKB study have been reported in detail elsewhere.[26,27] Overall, 512 891 adults aged 30 to 79 years were enrolled from June 25, 2004, through July 15, 2008, from 5 rural and 5 urban areas in China. CKB participants were confirmed to be of Chinese ancestry based on findings of principal component analysis of genotyping data, where available. The baseline survey included a detailed questionnaire and physical measurements (including anthropometry and blood pressure). A nonfasting blood sample was collected for on-site testing (including plasma glucose level using the SureStep Plus meter [LifeScan]) and then separated into plasma and buffy-coat fractions for long-term storage. Study procedures and staff training were standardized across regions. Periodic resurveys were conducted for approximately 5% of surviving participants. The second resurvey from August 4, 2013, through September 18, 2014, included measurements of carotid intima media thickness and plaque using a diagnostic ultrasound system (GM-72P00A; Panasonic Healthcare Co, Ltd). Ethical approval for the study was obtained from the University of Oxford, Oxford, England, the Chinese Centre for Disease Control and Prevention, and the local Centres for Disease Control and Prevention in the 10 study areas. All participants provided written informed consent.

### Long-term Follow-up

Vital status and incidence of disease events were recorded using electronic linkage of each participant's unique national identification number with established registries for morbidity (stroke, CHD, cancer, and diabetes) and mortality in each locality and a nationwide health insurance system. Registry data included scanned copies of official death certificates and reports for hospitalization of specific diseases. Health insurance reports included detailed information (eg, disease description, *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* [*ICD-10*] code, and procedure or examination codes) about each hospital admission. Events related to major chronic diseases (stroke, CHD, diabetes, chronic obstructive pulmonary disease [COPD], and cancer) were carefully reviewed and standardized. By January

1, 2016, after a median follow-up of 9.2 years (interquartile range, 8.2-10.1 years), 37 289 deaths were recorded among the 512 891 CKB participants, and 4875 (<1%) were lost to follow-up.

### Genotyping and Lipid and Lipoprotein Measurements

Five *CETP* gene variants (rs3764261, rs1800775, rs708272, rs9939224, and rs2303790; eTable 1 in the Supplement) were selected on the basis of previously reported associations with HDL cholesterol and CETP activity.[11,19,28] Genotyping was conducted in 151 217 individuals by using a 384-single-nucleotide polymorphism (SNP) array (GoldenGate; Illumina) or a custom-designed 800K-SNP array (Axiom; Affymetrix) (call rates were >99.97% for all variants). Genotyping consisted of a population-based sample of 134 790 participants included in analyses of all disease outcomes, an additional 13 000 participants with an incident CVD event and control participants included in analyses of specified CVD outcomes, and an additional 3427 participants with an incident COPD event included in analyses of COPD. A subset of the genotyped population (17 854 selected for CVD case-control studies) had measurements of plasma concentrations of total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, lipoprotein(a), apolipoprotein B, and apolipoprotein A1 using a clinical chemistry analyzer (AU680; Beckman-Coulter). Among these individuals, 4657 also had plasma measurements of metabolomics using proton nuclear magnetic resonance spectroscopy providing data on 225 metabolic measures, including detailed lipid and lipoprotein particle profiles.[29] Further details of assays and participants included are shown in eFigure 1 and eMethods 1 in the Supplement.

### Main Outcome Measures

Prespecified vascular outcomes included major coronary events (myocardial infarction, coronary revascularization, or death from CHD), stroke, occlusive CVD (major coronary events or ischemic stroke), major vascular events (major coronary events, stroke, or vascular-associated death), and their components (see eMethods 2 in the Supplement for *ICD-10* codes). Common controls for vascular outcomes excluded individuals reporting a history of CHD, stroke, or transient ischemic attack at baseline or any major vascular event during follow-up. Other outcomes included diabetes, COPD, chronic kidney disease, liver disease, cancer, eye disease, and nonvascular death; controls for these outcomes excluded individuals reporting a history of that disease at baseline when appropriate. Incident events in the range of *ICD-10* codes A00 to N99 were grouped into 41 distinct categories for a phenome-wide analysis using a previously described approach.[30] For these 41 *ICD-10* categorized outcomes, no exclusions for prevalent diseases were made from controls. For all outcomes, no exclusions for prevalent diseases were made from cases (ie, not all cases were new onset), and hospital episodes were restricted to those identified from inpatient records.

### Statistical Analyses

Measurements of lipid and lipoprotein levels were stratified by area and standardized by rank inverse normal transformation after adjustment for sex and age. Continuous traits were assessed by linear regression, and disease outcomes were assessed by logistic regression with stratification by area and adjustment for sex and age. Individuals with missing genotype data were excluded from analyses of the relevant variant or the genetic score. An additive (per allele) model was used for individual variants. A multivariable model including 5 *CETP* variants was used to obtain independent per-allele associations with rank inverse normal-transformed HDL cholesterol levels, with mutual adjustment to account for linkage disequilibrium (ie, correlation) between variants (eTable 2 in the Supplement). Per-allele associations from the multivariable model (eTable 3 in the Supplement) were used to construct a weighted genetic score.[31] Among participants with lipid-level measurements, unbiased internal weights were derived by 100-fold cross-validation. Among participants without lipid-level measurements, weights were derived directly from the multivariable model. Given the variance in HDL cholesterol levels explained by the genetic score (eTable 3 in the Supplement), the study had more than 80% power at $P < .05$ to detect a 20% lower risk for major coronary events or a 10% lower risk for major vascular events, for a 1-SD higher HDL cholesterol level. Associations of rs2303790 and the *CETP* genetic score with outcomes were scaled to correspond to 10-mg/dL higher HDL cholesterol levels (to convert to millimoles per liter, multiply by 0.0259). Subgroup analyses were performed by urban or rural area, age group, sex, smoking, and alcohol consumption. *P* values are presented as unadjusted for multiple testing, unless otherwise indicated. For assessment of significance, $\alpha = .05$, a Bonferroni-corrected threshold was used that divided 0.05 by the number of outcomes examined (8 vascular, 7 nonvascular, or 41 phenome wide) or by the number of principal components accounting for 95% of variation in the proton nuclear magnetic resonance metabolomics data set (18). All analyses used SAS software (version 9.3; SAS Institute, Inc).

## Results

Among the 151 217 individuals included in this study, the mean (SD) age was 52.3 (10.9) years. A total of 58.4% were women and 41.6% were men; 42.0% were from urban areas (**Table**). Compared with controls, individuals reporting a major vascular event during follow-up were older, less likely to be female, and more likely to reside in urban areas (eTable 4 in the Supplement). In a subset selected for CVD case-control studies with no self-reported history of CVD or treatment to lower lipid levels at baseline, the mean (SD) baseline plasma HDL cholesterol concentration was 48 (12) mg/dL; LDL cholesterol concentration, 91 (27) mg/dL; and total cholesterol concentration, 180 (38) mg/dL. Median triglyceride concentration was 139.8 mg/dL (interquartile range, 95.6-211.5 mg/dL; to convert to millimoles per liter, multiply by 0.0113).

The *CETP* loss-of-function variant rs2303790-G (allele frequency, 2%; eTable 1 in the Supplement) was associated with 6.1-mg/dL (SE, 0.4-mg/dL) higher HDL cholesterol levels per allele (equivalent to 0.53 of the SD; $P = 9.4 \times 10^{-47}$) (eTable 5 in the Supplement). The 4 common *CETP* variants were also

associated with higher HDL cholesterol levels (1.4-3.6 mg/dL per allele; allele frequencies, 16%-88%). In a joint model, all 5 variants had independent associations with HDL cholesterol level (0.7-4.0 mg/dL per allele) (eTable 3 in the Supplement), and in the absence of measured CETP activity, a genetic score was weighted according to these HDL cholesterol associations.

Baseline characteristics of the study participants, including age, income, smoking, and alcohol drinking, did not vary significantly by rs2303790 genotype or the *CETP* genetic score after adjustment for sex, age, and area (eTable 6 in the Supplement), indicating that analyses of rs2303790 and the genetic score were not confounded by these factors. However, the prevalence of previously diagnosed hypertension varied across the tertiles of the genetic score (12.8% vs 11.9% for the lowest compared with highest tertile; $P = 3.5 \times 10^{-5}$ for trend).

The loss-of-function variant rs2303790 was not associated with LDL cholesterol or triglyceride levels but was associated with 0.19 mg/dL (95% CI, 0.04-0.35 mg/dL) lower lipoprotein(a) levels when scaled to a 10-mg/dL higher HDL cholesterol level (**Figure 1**). The *CETP* genetic score, similarly scaled to 10-mg/dL higher HDL cholesterol levels, was associated with 2.4-mg/dL (95% CI, 0.6- to 4.2-mg/dL) higher LDL cholesterol levels, 14.6-mg/dL (95% CI, 5.2- to 24.0-mg/dL) lower triglyceride levels, and 0.09-mg/dL (95% CI, 0.00- to 0.18-mg/dL) lower lipoprotein(a) levels. The 4 common *CETP* variants assessed individually were all associated with higher LDL cholesterol levels (0.6-1.2 mg/dL per allele) (eTable 5 in the Supplement), and all except rs9939224 were associated with lower triglyceride levels (3.1-4.9 mg/dL per allele). When assessed separately by area, the associations of rs2303790 or the genetic score with LDL cholesterol level were not related to the mean LDL cholesterol level in each area (eTable 7 in the Supplement).

We found similar patterns of association for rs2303790 and the *CETP* genetic score with the lipid compositions of lipoprotein particles measured by proton nuclear magnetic resonance metabolomics. Consistent with the expected associations of lower CETP activity (ie, a genetic proxy for CETP inhibition), *CETP* variants that increased HDL cholesterol levels were associated with higher levels of esterified cholesterol within large and medium HDL particles and lower levels within extra large, very large, and large VLDL particles relative to the total lipid content of these particles (**Figure 2**). Conversely, levels of triglycerides relative to total lipids were higher in VLDL particles and lower in HDL particles. Furthermore, HDL particle size was larger and LDL particle size smaller, and the concentration of mature (large and very large) HDL particles was higher (eFigure 2 in the Supplement). The overall concentration of cholesterol in HDL and LDL particles was higher and, in VLDL particles, was lower.

In analyses of continuous traits, the *CETP* genetic score was associated with lower systolic blood pressure of 0.74 (SE, 0.25) mm Hg per 10-mg/dL higher HDL cholesterol level ($P = .004$) (eTable 8 in the Supplement). Neither rs2303790 nor the *CETP* genetic score was associated with body mass index, waist circumference, or random plasma glucose levels, nor were they associated with carotid intima media thickness or carotid plaque.

**Table. Selected Baseline Characteristics of the Study Population**

| Characteristic | Data (N = 151 217) |
|---|---|
| Age, mean (SD), y | 52.3 (10.9) |
| Female, No. (%) | 88 361 (58.4) |
| Urban area, No. (%) | 63 447 (42.0) |
| Educational attainment >6 y, No. (%) | 30 018 (19.9) |
| Income >20 000 yuan/y, No. (%)[a] | 60 936 (40.3) |
| Disease history, No. (%) | |
| Hypertension | 18 731 (12.4) |
| CHD | 4534 (3.0) |
| Stroke or transient ischemic attack | 2358 (1.6) |
| Diabetes | 5145 (3.4) |
| Medication use, No. (%) | |
| Antihypertensives | 7616 (5.0) |
| Statins | 332 (0.2) |
| Regular smoking, No. (%) | 40 634 (26.9) |
| Regular alcohol consumption, No. (%) | 22 742 (15.0) |
| Physical activity, mean (SD), MET-h/d | 20.7 (13.9) |
| Systolic blood pressure (SD), mm Hg | 132.5 (22.1) |
| Standing height, mean (SD), cm | 158.6 (82.8) |
| Body mass index, mean (SD)[b] | 23.6 (3.4) |
| Waist circumference, mean (SD), cm | 80.2 (9.9) |
| Random plasma glucose level, mean (SD), mg/dL[c] | 109.9 (43.2) |
| Lipid and lipoprotein levels, mean (SD)[d] | |
| HDL cholesterol | 47.7 (11.5) |
| LDL cholesterol | 91.4 (27.4) |
| Total cholesterol | 180.0 (38.3) |
| Lipoprotein(a) | 1.04 (1.31) |
| Apolipoprotein A1 | 134.1 (22.3) |
| Apolipoprotein B | 83.8 (21.2) |
| Triglycerides, median (IQR) | 139.8 (95.6-211.5) |

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; MET, metabolic task equivalent.

SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.0259; glucose to millimoles per liter, multiply by 0.0555; lipoprotein(a) to micromoles per liter, multiply by 0.0357; lipoproteins A1 and B to grams per liter, multiply by 0.01; and triglycerides to millimoles per liter, multiply by 0.0113.

[a] One yuan equals US $0.15.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Measured in 148 693 individuals.

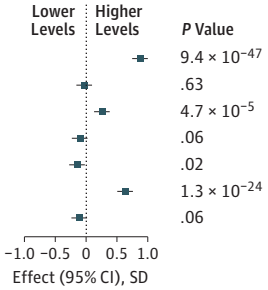
[d] Measured by clinical biochemistry in a selected subset of 17 854 individuals with incident CVD and control individuals with no history of CVD at baseline and not using statin treatment. Unless otherwise indicated, data are reported as milligrams per deciliter.

We found no associations of rs2303790 or the *CETP* genetic score with risk for major vascular diseases (**Figure 3**). For major occlusive CVD events, the adjusted odds ratios (ORs) were 1.01 (95% CI, 0.89-1.16; 18 585 events) for rs2303790 and 0.98 (95% CI, 0.91-1.06; 18 550 events) for the genetic score, both scaled to 10-mg/dL higher HDL cholesterol levels. The *CETP* genetic score was not associated with the components of occlusive CVD, including major coronary events (OR, 1.08; 95% CI, 0.95-1.22; 5767 events) and ischemic stroke (OR, 0.94;

Figure 1. Associations of rs2303790 and a *CETP* Genetic Score With Lipids and Lipoproteins Measured by Clinical Biochemical Analysis

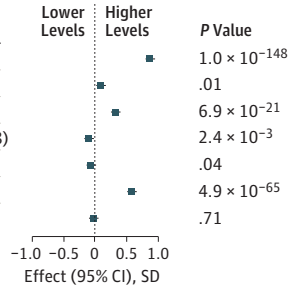
A rs2303790

| Lipid and Lipoprotein | No. of Participants | Effect (95% CI), mg/dL | *P* Value |
|---|---|---|---|
| HDL cholesterol | 17835 | 10.00 (8.63 to 11.37) | $9.4 \times 10^{-47}$ |
| LDL cholesterol | 17835 | −0.80 (−4.08 to 2.47) | .63 |
| Total cholesterol | 17835 | 9.52 (4.94 to 14.11) | $4.7 \times 10^{-5}$ |
| Triglycerides | 17835 | −15.97 (−32.79 to 0.85) | .06 |
| Lipoprotein(a) | 17833 | −0.19 (−0.35 to −0.04) | .02 |
| Apolipoprotein A1 | 17792 | 13.95 (11.28 to 16.62) | $1.3 \times 10^{-24}$ |
| Apolipoprotein B | 17835 | −2.42 (−4.96 to 0.12) | .06 |




B *CETP* genetic score

| Lipid and Lipoprotein | No. of Participants | Effect (95% CI), mg/dL | *P* Value |
|---|---|---|---|
| HDL cholesterol | 17761 | 10.00 (9.25 to 10.75) | $1.0 \times 10^{-148}$ |
| LDL cholesterol | 17761 | 2.40 (0.57 to 4.24) | .01 |
| Total cholesterol | 17761 | 12.25 (9.69 to 14.82) | $6.9 \times 10^{-21}$ |
| Triglycerides | 17761 | −14.60 (−24.01 to −5.18) | $2.4 \times 10^{-3}$ |
| Lipoprotein(a) | 17759 | −0.09 (−0.18 to −0.00) | .04 |
| Apolipoprotein A1 | 17718 | 12.91 (11.43 to 14.40) | $4.9 \times 10^{-65}$ |
| Apolipoprotein B | 17761 | −0.27 (−1.69 to 1.15) | .71 |




The association of rs2303790 and a *CETP* genetic score (consisting of rs3764261, rs1800775, rs708272, rs9939224, and rs2303790) with rank inverse normal transformation–standardized traits measured by clinical biochemical analysis in a subset of 17 854 individuals was scaled to 10-mg/dL higher levels of high-density lipoprotein (HDL) cholesterol. Findings were adjusted for sex and age and stratified by study area. Further adjustment for time since the last meal or cardiovascular disease case or control status had no appreciable effect on the associations. Squares represent the associations in standard deviations of each trait. Error bars represent the corresponding 95% CIs. *P* values are not adjusted for multiple testing. To convert cholesterol to millimoles per liter, multiply by 0.0259; lipoprotein(a) to micromoles per liter, multiply by 0.0357; lipoproteins A1 and B to grams per liter, multiply by 0.01; and triglycerides to millimoles per liter, multiply by 0.0113. LDL indicates low-density lipoprotein.

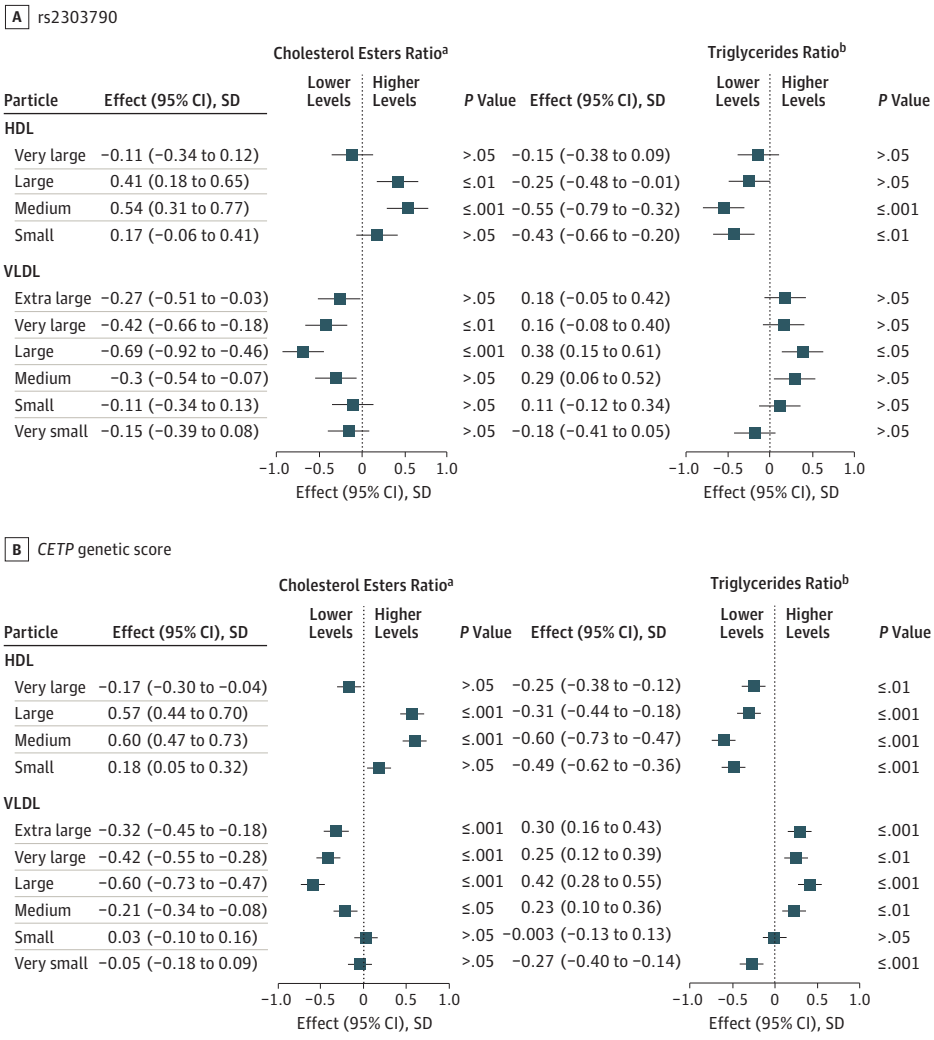
95% CI, 0.86-1.02; 13 759 events). Similarly, we found no associations of the genetic score with myocardial infarction (OR, 1.14; 95% CI, 0.97-1.35), intracerebral hemorrhage (OR, 0.94; 95% CI, 0.83-1.06), total stroke (OR, 0.94; 95% CI, 0.87-1.01), vascular death (OR, 1.01; 95% CI, 0.90-1.12), or major vascular events (OR, 0.97; 95% CI, 0.91-1.04). Estimates for rs2303790 were similar. We found no differences in the associations of the *CETP* genetic score with occlusive CVD among several subgroups (eTable 9 in the Supplement). Adjusting for systolic blood pressure had no material effect on the association of the genetic score with occlusive CVD.

No associations were observed for diabetes, COPD, chronic kidney disease, cancer, and nonvascular death (**Figure 4**). However, a higher risk for eye diseases was found with rs2303790 (OR, 1.43; 95% CI, 1.13-1.80; *P* = .003), which was significant after adjustment for multiple testing. Of 4090 eye disease events, 2980 were cataracts, and rs2303790 showed the same direction of association with cataracts (OR, 1.43; 95% CI, 1.09-1.88; *P* = .01) as with noncataract eye diseases (OR, 1.53; 95% CI, 0.99-2.35; *P* = .06). The association of the *CETP* genetic score with eye diseases was directionally consistent (OR, 1.17; 95% CI, 1.02-1.35; *P* = .03) but was not significant after correction for multiple testing. Analyses of age-related macular degeneration suggested a direction of association (OR, 1.39; 95% CI, 0.42-4.44 for the genetic score) consistent with previous reports of the association of age-related macular degeneration with *CETP* gene variants; however, rs2303790 could not be reliably assessed owing to the low allele frequency and limited number of cases (70 reported among genotyped participants).[24,32,33] In the phenome-wide screen, we found no associations of the *CETP* genetic score with any of the 41 *ICD-10* coded disease categories, including diseases of the nervous system (OR, 1.49; 95% CI, 1.16-1.92; *P* = .002), after correction for multiple testing (Bonferroni-corrected threshold *P* = .05 for 41 disease categories, *P* = .001) (eFigure 3 in the Supplement).

## Discussion

This large genetic study of 151 217 Chinese adults found no evidence to support a beneficial association with CVD of increasing HDL cholesterol concentration through CETP inhibition. Four common *CETP* variants and an East Asian loss-of-function variant were associated with higher HDL cholesterol levels but did not lower LDL cholesterol levels, as seen in previous genetic studies performed mainly in European populations and with pharmacologic CETP inhibitors.[7,8,17] These genetic variants influenced lipid and lipoprotein particle metabolism in a manner consistent with lower CETP activity, including reduced CETP-mediated movement of esterified cholesterol from mature HDL particles to VLDL in parallel with reduced movement of triglycerides from VLDL to HDL. However, we found no significant association of the loss-of-function variant rs2303790 or a *CETP* genetic score with the risk of occlusive CVD, major coronary events, stroke subtypes, or other major vascular diseases. When we assessed a range of predefined nonvascular diseases to identify other potential risks and benefits of CETP inhibition, rs2303790 was associated with an increased risk for eye diseases.

Figure 2. Associations of rs2303790 and a *CETP* Genetic Score With Lipoprotein Particle Composition Measured by Proton Nuclear Magnetic Resonance (NMR) Metabolomics




The association of rs2303790 and a *CETP* genetic score (consisting of rs3764261, rs1800775, rs708272, rs9939224, and rs2303790) with rank inverse normal transformation–standardized traits measured by NMR metabolomics was scaled to 10-mg/dL higher levels of high-density lipoprotein (HDL) cholesterol. Findings were adjusted for sex and age and stratified by study area. NMR measurements were performed for 4657 individuals, but data for these analyses were available for 4422 to 4652 participants after exclusions for missing data for individual traits and genotypes. Squares represent the associations in standard deviations of each trait. Error bars represent the corresponding 95% CIs. *P* values were calculated after Bonferroni adjustment for 18 principal components among the 225 measured NMR traits. VLDL indicates very low-density lipoprotein.

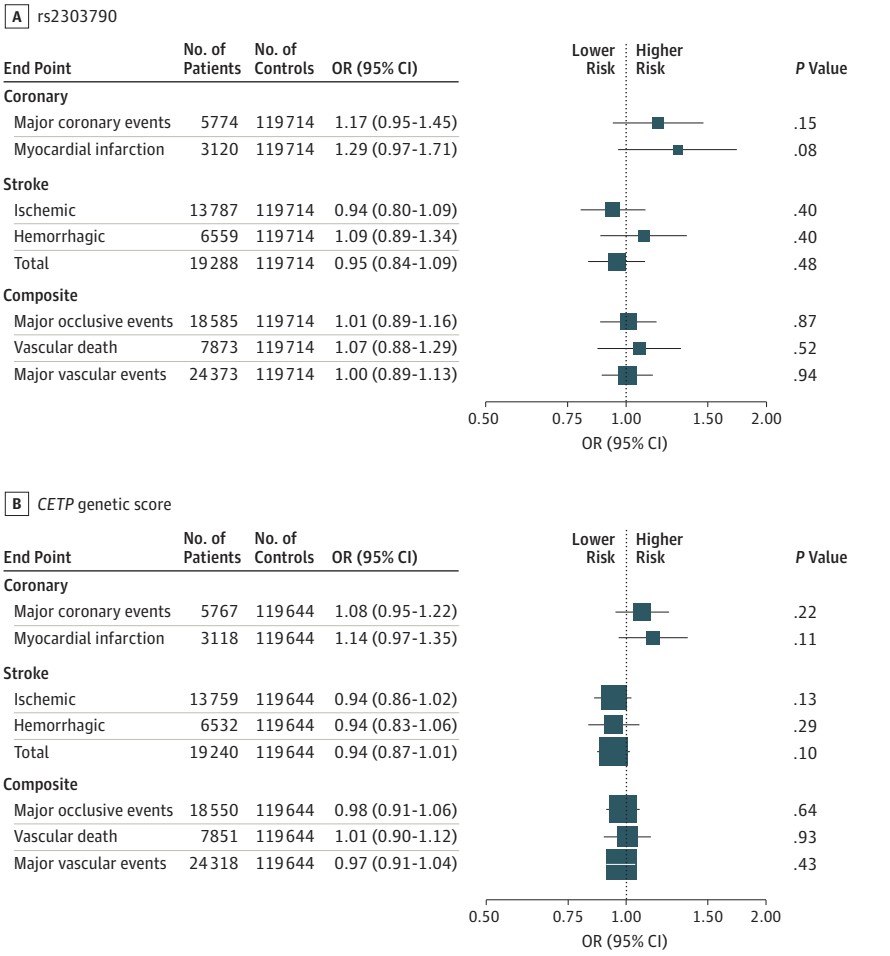
[a] Data are presented as the ratio of cholesterol esters to total lipids in lipoprotein particle subtypes.

[b] Data are presented as the ratio of triglycerides to total lipids in lipoprotein particle subtypes.

Common *CETP* variants have been associated with a modest lower risk for CHD, mainly in populations of European origin, including recent large studies that reported an approximately 5% lower risk with genetic variants that increased HDL cholesterol levels.[12,15,16] These results are in contrast to the present null findings. Common *CETP* variants were also associated with an almost 2-fold increased risk for intracerebral hemorrhage in a meta-analysis involving 2800 cases of European origin,[14] but with 6500 cases, we found no such association with intracerebral hemorrhage. Rare protein-truncating variants in populations of East Asian and European ancestry have been associated with lower CHD risk, and 2 studies in East Asians involving a total of 5082 cases reported an approximately 17% lower risk for CHD with rs2303790.[23-25] However, when published data for rs2303790 were meta-analyzed with results from the present study, no significant association was evident (for 10 856 coronary events, OR, 0.97; 95% CI, 0.88-1.07) (eTable 10 in the Supplement) nor was there any association with the intermediate CVD traits carotid thickness and plaque. Of note, coronary events in the present study population showed the expected associations with variants at 9p21 (eTable 11 in the Supplement).

The association of *CETP* variants with CVD risk in previous studies[16,25] may have been influenced, partly or wholly, by lower LDL cholesterol level or other lipid-related factors rather than higher HDL cholesterol level. The association of common *CETP* variants with LDL cholesterol levels in the present study were consistent with other studies in East Asians[28] but directionally different from previous studies in Europeans[17] (eTable 12 in the Supplement). Differences in LDL cholesterol level measurement methods may have contributed to such discrepancies because most previous studies contributing to the large European consortia[17] estimated LDL cholesterol level using the Friedewald formula in contrast to the present study, which measured LDL cholesterol level directly. A study in Japanese adults also using the Friedewald formula[23] found that rs2303790 was associated with 0.2-SD lower LDL cholesterol level, an association not seen in the

Figure 3. Associations of rs2303790 and a *CETP* Genetic Score With Vascular Diseases




The association of rs2303790 and a *CETP* genetic score (consisting of rs3764261, rs1800775, rs708272, rs9939224, and rs2303790) with vascular diseases was scaled to 10-mg/dL higher levels of high-density lipoprotein cholesterol. Findings were adjusted for sex and age and stratified by study area. Squares represent the odds ratio (OR) with area inversely proportional to the variance of the logarithm OR. Error bars represent the corresponding 95% CIs. *P* values in the plot are not adjusted for multiple testing, but Bonferroni adjustment for 8 outcomes would result in a threshold of $P < .0063$ (.05/8).

present study. If the composition of VLDL particles is altered, as with genetic or pharmacologic CETP inhibition, then this alteration may affect the comparability of LDL cholesterol levels measured directly or estimated using the Friedewald formula.[34]

Although inverse associations between HDL cholesterol concentration and occlusive CVD have been widely reported in large prospective studies,[1,2] including the CKB,[35] the causal relevance of such associations has not been established.[12,36,37] In a prospective study, HDL efflux capacity was inversely associated with atherosclerotic CVD risk in a population in which HDL cholesterol concentration had no significant association.[38] Another recent study reported that a functional variant in the scavenger receptor B1 (*SRB1*) gene, which blocks uptake of HDL-associated cholesterol into the liver, was associated with higher HDL cholesterol level and increased CHD risk.[39] Any associations of elevated HDL cholesterol level with vascular disease may vary depending on the mechanisms involved and may not be beneficial if aspects of reverse cholesterol transport, such as cholesterol efflux, or other important functions of HDL are impeded.

With linkage to electronic health records in a large prospective study, we were able to assess the associations of *CETP* genetic variants with a range of diseases, which could identify other potential beneficial or adverse associations with lifelong lower CETP activity. The risk for eye disease was elevated with rs2303790, with weaker but directionally consistent findings for the *CETP* genetic score. In a recent genome-wide study of age-related macular degeneration in East Asians,[24] the strongest association signal was observed for rs2303790 (OR, 1.70; $P = 5.6 \times 10^{-22}$). Other studies of age-related macular degeneration in East Asians and Europeans[32,33,40] have identified associations at *CETP* and other loci associated with HDL cholesterol levels, suggesting that higher HDL cholesterol level or other changes may be associated with an increased risk for age-related macular degeneration. The present study had only a limited number of reported age-related macular degeneration cases, but the direction of association with *CETP* variants was consistent with previous reports. These results suggest that CETP inhibition may have a potential adverse association with eye diseases.

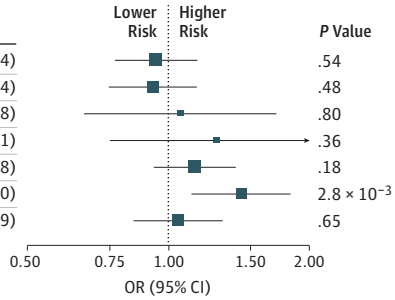
## Strengths and Limitations

Genetic studies are a useful tool in drug development, specifically by prioritizing targets, assessing safety, and identifying opportunities for alternative indications.[10] Although the

Figure 4. Associations of rs2303790 and a *CETP* Genetic Score With Nonvascular Diseases

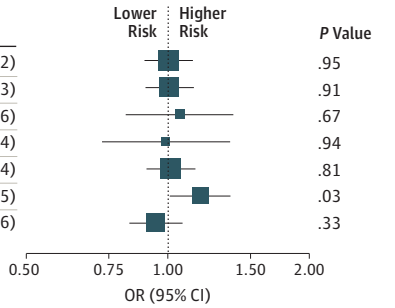
A rs2303790

| End Point | No. of Patients | No. of Controls | OR (95% CI) | *P* Value |
|---|---|---|---|---|
| Diabetes | 6974 | 125837 | 0.94 (0.78-1.14) | .54 |
| Chronic obstructive pulmonary disease | 6922 | 128557 | 0.93 (0.75-1.14) | .48 |
| Chronic kidney disease | 1187 | 124899 | 1.06 (0.67-1.68) | .80 |
| Chronic liver disease | 876 | 132398 | 1.27 (0.76-2.11) | .36 |
| Malignant neoplasms | 6458 | 127882 | 1.14 (0.94-1.38) | .18 |
| Eye diseases | 4090 | 130697 | 1.43 (1.13-1.80) | $2.8 \times 10^{-3}$ |
| Nonvascular mortality | 5991 | 128796 | 1.05 (0.85-1.29) | .65 |




B *CETP* genetic score

| End Point | No. of Patients | No. of Controls | OR (95% CI) | *P* Value |
|---|---|---|---|---|
| Diabetes | 6972 | 125790 | 1.00 (0.90-1.12) | .95 |
| Chronic obstructive pulmonary disease | 6900 | 128506 | 1.01 (0.90-1.13) | .91 |
| Chronic kidney disease | 1221 | 131596 | 1.06 (0.82-1.36) | .67 |
| Chronic liver disease | 876 | 132347 | 0.99 (0.73-1.34) | .94 |
| Malignant neoplasms | 6457 | 127832 | 1.01 (0.90-1.14) | .81 |
| Eye diseases | 4085 | 130651 | 1.17 (1.02-1.35) | .03 |
| Nonvascular mortality | 5990 | 128746 | 0.94 (0.83-1.06) | .33 |




The association of rs2303790 and a *CETP* genetic score (consisting of rs3764261, rs1800775, rs708272, rs9939224, and rs2303790) with nonvascular diseases was scaled to 10-mg/dL higher levels of high-density lipoprotein cholesterol. Findings were adjusted for sex and age and stratified by study area. Squares represent the odds ratio (OR) with area inversely proportional to the variance of the logarithm OR. Error bars represent the corresponding 95% CIs. *P* values in the plot are not adjusted for multiple testing, but Bonferroni adjustment for 7 outcomes would result in a threshold of $P < .0071$ (.05/7).

present study did not measure CETP levels or activity, the genetic associations with lipid and lipoprotein metabolism were consistent with lower CETP activity and suggest that increasing HDL cholesterol levels through this pathway may not be associated with reduced CVD risk. Pharmacologic CETP inhibitors, however, have more potent effects to raise HDL cholesterol levels than genetic variants, as well as other potentially favorable lipid modifications, including lowering LDL cholesterol levels.[7,8,18] In contrast, in the present study, LDL cholesterol level was modestly increased in association with the *CETP* genetic score. Genetic studies are also limited to assessing on-target drug effects and are not able to identify off-target toxic effects, such as the increased blood pressure seen with torcetrapib (blood pressure was also slightly increased with other CETP inhibitors).[4-8] Systolic blood pressure was, in contrast, modestly lower with *CETP* variants in the present study. The present study provides important new evidence about the relevance of increasing HDL cholesterol levels through lower CETP activity and complements findings from the Randomized Evaluation of the Effects of Anacetrapib Through Lipid Modification (REVEAL) trial,[8] in which the approximately 10% lower risk for major coronary events was consistent with the observed reduction in non-HDL cholesterol levels, suggesting that the benefits were not driven by increasing HDL cholesterol levels.

## Conclusions

Genetic variants in the *CETP* gene that were associated with altered HDL metabolism but not lower LDL cholesterol levels had no association with CVD risk in 151 217 Chinese adults. These results suggest that in the absence of significantly reduced LDL cholesterol, increasing HDL cholesterol levels by CETP inhibition may not be associated with reduced risk for CVD.

ARTICLE INFORMATION

**Accepted for Publication:** September 20, 2017.

**Published Online:** November 15, 2017. doi:10.1001/jamacardio.2017.4177

**Correction:** This article was changed on January 17, 2018, to fix an incorrect affiliation for Li.



**Author Affiliations:** Medical Research Council Population Health Research Unit, Nuffield Department of Population Health, University of Oxford, Oxford, England (Millwood, Holmes, Boxall, Yang, Y. Chen, Du); Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford, Oxford, England (Millwood, Bennett, Holmes, Boxall, Yang, Sansome, Y. Chen, Du, Hacker, Hill, Peto, Collins, Clarke, Walters, Z. Chen); National Institute for Health Research Oxford Biomedical Research Centre, Oxford University Hospital, Oxford, England (Holmes); Chinese Academy of Medical Sciences, Dong Cheng District, Beijing, China (Guo, Bian, Yu, Tan, J. Chen); MRL, Merck Sharp & Dohme Corp, Boston, Masschusetts (Reilly); Department of Epidemiology and Biostatistics, Nanjing Medical University School of Public Health, Nanjing, China (Shen); Department of Epidemiology and Biostatistics, Peking University Health Science Centre, Peking University, Beijing, China (Li).

**Author Contributions:** Drs Millwood, Bennett, and Holmes are joint first authors. Drs Li, Walters, and Z. Chen are joint senior authors. Drs Millwood and Z. Chen had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
*Study concept and design:* Millwood, Bennett, Holmes, Reilly, Peto, Collins, Li, Walters, Z. Chen.
*Acquisition, analysis, or interpretation of data:* Millwood, Bennett, Holmes, Boxall, Guo,

Bian, Sansome, Y. Chen, Du, Yu, Hacker, Tan, Hill, J. Chen, Peto, Shen, Clarke, Li, Walters, Z. Chen.
*Drafting of the manuscript:* Millwood, Holmes, Walters, Z. Chen.
*Critical revision of the manuscript for important intellectual content:* All authors.
*Statistical analysis:* Millwood, Bennett, Boxall, Walters.
*Obtained funding:* Millwood, Reilly, Peto, Collins, Li, Walters, Z. Chen.
*Administrative, technical, or material support:* Millwood, Guo, Bian, Yang, Sansome, Y. Chen, Du, Yu, Hacker, Tan, Hill, J. Chen, Shen, Collins, Li, Z. Chen.
*Study supervision:* Millwood, Holmes, Reilly, Peto, Shen, Collins, Clarke, Li, Walters, Z. Chen.

**Conflict of Interest Disclosures**: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Drs Millwood, Holmes, Yang, Y. Chen, Du, and Peto report working in a unit funded by the UK Medical Research Council. Drs Collins, Y. Chen, and Z. Chen report serving as members of the Randomized Evaluation of the Effects of Anacetrapib Through Lipid Modification (REVEAL) Steering Committee. Dr Reilly reports being an employee of MSD. Genotyping of *CETP* variants was partially funded by a research grant to the University of Oxford from MSD, who manufactures the CETP inhibitor anacetrapib. University of Oxford is a sponsor of the REVEAL trial of anacetrapib, which is funded by MSD. No other disclosures were reported.

**Funding/Support:** This study was supported by the Kadoorie Charitable Foundation in Hong Kong; grants 202922/Z/16/Z, 088158/Z/09/Z, and 104085/Z/14/Z from the UK Wellcome Trust; grant 2011BAI09B01 from the Chinese Ministry of Science and Technology; grants 81390540, 81390541, and 81390544 from the National Natural Science Foundation of China; grants MC_PC_13049 and MC PC 14135 from the UK Medical Research Council; GlaxoSmithKline; MSD; grant RE/13/1/30181 from the BHF Centre of Research Excellence, Oxford (Dr Millwood); the British Heart Foundation; and Cancer Research UK.

**Role of the Funder/Sponsor:** MSD was involved in selection of *CETP* variants for genotyping, initial planning of the study, and review of the study manuscript. Otherwise, the sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

**Group Information:** The following are members of the China Kadoorie Biobank (CKB) Collaborative Group. International Steering Committee: Junshi Chen, Zhengming Chen (principal investigator [PI]), Robert Clarke, Rory Collins, Yu Guo, Liming Li (PI), Jun Lv, Richard Peto, and Robin G. Walters. International Coordinating Centre, Oxford, England: Daniel Avery, Ruth Boxall, Derrick A. Bennett, Fiona Bragg, Yumei Chang, Yiping Chen, Zhengming Chen, Robert Clarke, Huaidong Du, Simon Gilbert, Alex Hacker, Michael R. Hill, Michael V. Holmes, Christiana Kartsonaki, Rene Kerosi, Om Kurmi, Garry Lancaster, Kuang Lin, John McDonnell, Iona Y. Millwood, Qunhua Nie, Jayakrishnan Radhakrishnan, Paul Ryder, Sam Sansome, Dan Schmidt, Rajani Sohoni, Becky Stevens, Iain Turnbull, Robin G. Walters, Jenny Wang, Lin Wang, Neil Wright, Ling Yang, and Xiaoming Yang. National Coordinating Centre, Beijing, China: Zheng Bian, Ge Chen, Yu Guo, Xiao Han, Can Hou, Jun Lv, Pei Pei, Shuzhen Qu, Yunlong Tan, and Canqing Yu. Regional Coordinating Centre Qingdao Centre for Disease Control and Prevention (CDC): Zengchang Pang, Ruqin Gao, Shaojie Wang, Yongmei Liu, Ranran Du, Yajing Zang, Liang Cheng, Xiaocao Tian, and Hua Zhang. Licang CDC: Silu Lv, Junzheng Wang, and Wei Hou. Regional Coordinating Centre Heilongjiang Provincial CDC: Jiyuan Yin, Ge Jiang, and Xue Zhou. Nangang CDC: Liqiu Yang, Hui He, Bo Yu, Yanjie Li, Huaiyi Mu, Qinai Xu, Meiling Dou, and Jiaojiao Ren. Regional Coordinating Centre Hainan Provincial CDC: Shanqing Wang, Ximin Hu, Hongmei Wang, Jinyan Chen, Yan Fu, Zhenwang Fu, and Xiaohuan Wang. Meilan CDC: Min Weng, Xiangyang Zheng, Yilei Li, Huimei Li, and Yanjun Wang. Regional Coordinating Centre Jiangsu Provincial CDC: Ming Wu, Jinyi Zhou, Ran Tao, and Jie Yang. Regional Coordinating Centre Suzhou CDC: Chuanming Ni, Jun Zhang, Yihe Hu, Yan Lu, Liangcai Ma, Aiyu Tang, Shuo Zhang, Jianrong Jin, and Jingchao Liu. Regional Coordinating Centre Guangxi Provincial CDC: Zhenzhu Tang, Naying Chen, and Ying Huang. Liuzhou CDC: Mingqiang Li, Jinhuai Meng, Rong Pan, Qilian Jiang, Weiyuan Zhang, Yun Liu, Liuping Wei, Liyuan Zhou, Ningyu Chen, and Hairong Guan. Regional Coordinating Centre Sichuan Provincial CDC: Xianping Wu, Ningmei Zhang, Xiaofang Chen, and Xuefeng Tang. Pengzhou CDC: Guojin Luo, Jianguo Li, Xiaofang Chen, Xunfu Zhong, Jiaqiu Liu, and Qiang Sun. Regional Coordinating Centre Gansu Provincial CDC: Pengfei Ge, Xiaolan Ren, and Caixia Dong. Maiji CDC: Hui Zhang, Enke Mao, Xiaoping Wang, Tao Wang, and Xi Zhang. Regional Coordinating Centre Henan Provincial CDC: Ding Zhang, Gang Zhou, Shixian Feng, Liang Chang, and Lei Fan. Huixian CDC: Yulian Gao, Tianyou He, Huarong Sun, Pan He, Chen Hu, Qiannan Lv, and Xukui Zhang. Regional Coordinating Centre Zhejiang Provincial CDC: Min Yu, Ruying Hu, and Hao Wang. Tongxiang CDC: Yijian Qian, Chunmei Wang, Kaixue Xie, Lingli Chen, Yidan Zhang, and Dongxia Pan. Regional Coordinating Centre Hunan Provincial CDC: Yuelong Huang, Biyun Chen, Li Yin, Donghui Jin, Huilin Liu, Zhongxi Fu, and Qiaohua Xu. Liuyang CDC: Xin Xu, Hao Zhang, Youping Xiong, Huajun Long, Xianzhi Li, Libo Zhang, and Zhe Qiu. BGI, Shenzhen, China: Jieqin Liang, Haoxiang Lin, Zhen Zhong, and Hongcheng Zhou. University of Oulu, Oulu, Finland: Mika Ala-Korpela and Peter Wurtz. MRL, Merck Sharp & Dohme Corp (MSD), Boston, Massachusetts: Karen Akinsanya, Cliona Molony, Dermot F. Reilly, and Win Yu.

**Additional Contributions:** We thank the CKB participants and the project staff based at Beijing, Oxford, the 10 regional centres, the China National CDC, and its regional offices for assisting with the fieldwork. BGI assisted in conducting DNA extraction and genotyping, and Brainshake assisted in conducting proton nuclear magnetic resonance metabolomics assays.

## REFERENCES

1. Lewington S, Whitlock G, Clarke R, et al; Prospective Studies Collaboration. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. *Lancet*. 2007;370(9602):1829-1839.

2. Di Angelantonio E, Sarwar N, Perry P, et al; Emerging Risk Factors Collaboration. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA*. 2009;302(18):1993-2000.

3. Tall AR. Plasma cholesteryl ester transfer protein. *J Lipid Res*. 1993;34(8):1255-1274.

4. Barter PJ, Caulfield M, Eriksson M, et al; ILLUMINATE Investigators. Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med*. 2007;357(21):2109-2122.

5. Johns DG, Duffy J, Fisher T, Hubbard BK, Forrest MJ. On- and off-target pharmacology of torcetrapib: current understanding and implications for the structure activity relationships (SAR), discovery and development of cholesteryl ester-transfer protein (CETP) inhibitors. *Drugs*. 2012;72(4):491-507.

6. Schwartz GG, Olsson AG, Abt M, et al; dal-OUTCOMES Investigators. Effects of dalcetrapib in patients with a recent acute coronary syndrome. *N Engl J Med*. 2012;367(22):2089-2099.

7. Lincoff AM, Nicholls SJ, Riesmeyer JS, et al; ACCELERATE Investigators. Evacetrapib and cardiovascular outcomes in high-risk vascular disease. *N Engl J Med*. 2017;376(20):1933-1942.

8. HPS3/TIMI55-REVEAL Collaborative Group. Effects of anacetrapib in patients with atherosclerotic vascular disease. *N Engl J Med*. 2017;377(13):1217-1227.

9. Evans DM, Davey Smith G. Mendelian randomization: new applications in the coming age of hypothesis-free causality. *Annu Rev Genomics Hum Genet*. 2015;16:327-350.

10. Plenge RM, Scolnick EM, Altshuler D. Validating therapeutic targets through human genetics. *Nat Rev Drug Discov*. 2013;12(8):581-594.

11. Thompson A, Di Angelantonio E, Sarwar N, et al. Association of cholesteryl ester transfer protein genotypes with CETP mass and activity, lipid levels, and coronary risk. *JAMA*. 2008;299(23):2777-2788.

12. Voight BF, Peloso GM, Orho-Melander M, et al. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. *Lancet*. 2012;380(9841):572-580.

13. Johannsen TH, Frikke-Schmidt R, Schou J, Nordestgaard BG, Tybjærg-Hansen A. Genetic inhibition of *CETP*, ischemic vascular disease and mortality, and possible adverse effects. *J Am Coll Cardiol*. 2012;60(20):2041-2048.

14. Anderson CD, Falcone GJ, Phuah CL, et al; Global Lipids Genetics Consortium and International Stroke Genetics Consortium. Genetic variants in *CETP* increase risk of intracerebral hemorrhage. *Ann Neurol*. 2016;80(5):730-740.

15. Webb TR, Erdmann J, Stirrups KE, et al; Wellcome Trust Case Control Consortium; MORGAM Investigators; Myocardial Infarction Genetics and CARDIoGRAM Exome Consortia Investigators. Systematic evaluation of pleiotropy identifies 6 further loci associated with coronary artery disease. *J Am Coll Cardiol*. 2017;69(7):823-836.

16. Ference BA, Kastelein JJP, Ginsberg HN, et al. Association of genetic variants related to CETP inhibitors and statins with lipoprotein levels and cardiovascular risk. *JAMA*. 2017;318(10):947-956.

17. Willer CJ, Schmidt EM, Sengupta S, et al; Global Lipids Genetics Consortium. Discovery and

refinement of loci associated with lipid levels. *Nat Genet*. 2013;45(11):1274-1283.

**18**. Rader DJ, deGoma EM. Future of cholesteryl ester transfer protein inhibitors. *Annu Rev Med*. 2014;65:385-403.

**19**. Takahashi K, Jiang XC, Sakai N, et al. A missense mutation in the cholesteryl ester transfer protein gene with possible dominant effects on plasma high density lipoproteins. *J Clin Invest*. 1993;92(4):2060-2064.

**20**. Inazu A, Jiang XC, Haraki T, et al. Genetic cholesteryl ester transfer protein deficiency caused by two prevalent mutations as a major determinant of increased levels of high density lipoprotein cholesterol. *J Clin Invest*. 1994;94(5):1872-1882.

**21**. Nagano M, Yamashita S, Hirano K, et al. Molecular mechanisms of cholesteryl ester transfer protein deficiency in Japanese. *J Atheroscler Thromb*. 2004;11(3):110-121.

**22**. Zhong S, Sharp DS, Grove JS, et al. Increased coronary heart disease in Japanese-American men with mutation in the cholesteryl ester transfer protein gene despite increased HDL levels. *J Clin Invest*. 1996;97(12):2917-2923.

**23**. Takeuchi F, Isono M, Katsuya T, et al. Association of genetic variants influencing lipid levels with coronary artery disease in Japanese individuals. *PLoS One*. 2012;7(9):e46385.

**24**. Cheng CY, Yamashiro K, Chen LJ, et al. New loci and coding variants confer risk for age-related macular degeneration in East Asians. *Nat Commun*. 2015;6:6063.

**25**. Nomura A, Won HH, Khera AV, et al. Protein-truncating variants at the cholesteryl ester transfer protein gene and risk for coronary heart disease. *Circ Res*. 2017;121(1):81-88.

**26**. Chen Z, Lee L, Chen J, et al. Cohort profile: the Kadoorie Study of Chronic Disease in China (KSCDC). *Int J Epidemiol*. 2005;34(6):1243-1249.

**27**. Chen Z, Chen J, Collins R, et al; China Kadoorie Biobank (CKB) Collaborative Group. China Kadoorie Biobank of 0.5 million people: survey methods, baseline characteristics and long-term follow-up. *Int J Epidemiol*. 2011;40(6):1652-1666.

**28**. Teslovich TM, Musunuru K, Smith AV, et al. Biological, clinical and population relevance of 95 loci for blood lipids. *Nature*. 2010;466(7307):707-713.

**29**. Soininen P, Kangas AJ, Würtz P, et al. High-throughput serum NMR metabonomics for cost-effective holistic studies on systemic metabolism. *Analyst*. 2009;134(9):1781-1785.

**30**. Millwood IY, Bennett DA, Walters RG, et al; China Kadoorie Biobank Collaborative Group. A phenome-wide association study of a lipoprotein-associated phospholipase A2 loss-of-function variant in 90 000 Chinese adults. *Int J Epidemiol*. 2016;45(5):1588-1599.

**31**. Burgess S, Thompson SG. Use of allele scores as instrumental variables for Mendelian randomization. *Int J Epidemiol*. 2013;42(4):1134-1144.

**32**. Momozawa Y, Akiyama M, Kamatani Y, et al. Low-frequency coding variants in CETP and CFB are associated with susceptibility of exudative age-related macular degeneration in the Japanese population. *Hum Mol Genet*. 2016;25(22):5027-5034.

**33**. Burgess S, Davey Smith G. Mendelian randomization implicates high-density lipoprotein cholesterol–associated mechanisms in etiology of age-related macular degeneration. *Ophthalmology*. 2017;124(8):1165-1174.

**34**. Davidson M, Liu SX, Barter P, et al. Measurement of LDL-C after treatment with the CETP inhibitor anacetrapib. *J Lipid Res*. 2013;54(2):467-472.

**35**. Holmes MV, Millwood IY, Kartsonaki C, et al. Serum NMR metabolomics identifies similar associations of lipoproteins and lipids with risk of myocardial infarction and ischemic stroke but not with hemorrhagic stroke. *Circulation*. 2016;134:A14009.

**36**. Holmes MV, Asselbergs FW, Palmer TM, et al; UCLEB Consortium. Mendelian randomization of blood lipids for coronary heart disease. *Eur Heart J*. 2015;36(9):539-550.

**37**. White J, Swerdlow DI, Preiss D, et al. Association of lipid fractions with risks for coronary artery disease and diabetes. *JAMA Cardiol*. 2016;1(6):692-699.

**38**. Rohatgi A, Khera A, Berry JD, et al. HDL cholesterol efflux capacity and incident cardiovascular events. *N Engl J Med*. 2014;371(25):2383-2393.

**39**. Zanoni P, Khetarpal SA, Larach DB, et al; CHD Exome+ Consortium; CARDIoGRAM Exome Consortium; Global Lipids Genetics Consortium. Rare variant in scavenger receptor BI raises HDL cholesterol and increases risk of coronary heart disease. *Science*. 2016;351(6278):1166-1171.

**40**. Chen W, Stambolian D, Edwards AO, et al; Complications of Age-Related Macular Degeneration Prevention Trial Research Group. Genetic variants near *TIMP3* and high-density lipoprotein–associated loci influence susceptibility to age-related macular degeneration. *Proc Natl Acad Sci U S A*. 2010;107(16):7401-7406.