Genetic associations with carotid intima-media thickness in the Chinese population and shared genetic architecture with cardiometabolic diseases and traits

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Abstract

Background: Carotid artery intima-media thickness (cIMT) is a highly heritable measure of subclinical atherosclerosis and a predictor of cardiovascular diseases. However, knowledge about their shared genetic basis remains limited. The majority of genome-wide association studies (GWASs) have been conducted in individuals of European ancestry, leaving the genetic determinants of cIMT in non-European ancestry populations largely understudied.

Methods: A single-trait GWAS was performed in 22,370 participants from the China Kadoorie Biobank (CKB) to identify new genetic variants associated with cIMT. We then leveraged cIMT and cardiometabolic diseases and traits data from populations of European and East Asian ancestries, to conduct linkage disequilibrium score regression and genome-wide cross-trait analysis, followed by gene-based analysis and Mendelian randomization (MR).

Results: We identified two genome-wide significant loci for cIMT in the overall CKB analysis, including the known *APOE* locus and a novel locus at *GGT5*. In addition, a female-specific analysis identified a further novel locus at *LINC02732*. cIMT showed significant positive genetic correlation with coronary artery disease (CAD), type 2 diabetes (T2D), body mass index (BMI), and systolic blood pressure (SBP) in both European and East Asian populations. Pleiotropic analysis found 110 and 699 significant pleiotropic variants in four trait pairs for East Asian and European populations, respectively, with 27 and 186 colocalized loci detected. Gene-based analysis highlighted important biological pathways involving lipid metabolism and carbohydrate metabolism. MR estimates indicated that higher SBP and BMI levels, and CAD and T2D were causal for cIMT, and a reverse effect was observed between cIMT and SBP.

Conclusion: Our large-scale GWAS of cIMT identified novel loci in Chinese population and shared genetic underpinnings and causal relationships with cardiometabolic diseases and traits. These findings potentially provide targets of intervention that may allow the development of new strategies targeting this aspect of atherosclerosis.

Keywords: Carotid artery intima-media thickness; Shared genetic architecture; Cardiometabolic diseases; Genetic correlation; Mendelian randomization.

Non-standard Abbreviations and Acronyms

BMI: body mass index

CAD: coronary artery disease

CKB: China Kadoorie Biobank

cIMT: carotid artery intima-media thickness

CVD: cardiovascular disease

DBP: diastolic blood pressure

GGT: gamma-glutamyl transpeptidase

GWAS: genome-wide association study

HDL-C: high-density lipoprotein cholesterol

LD: linkage disequilibrium

LDL-C: low-density lipoprotein cholesterol

LDSC: linkage disequilibrium score regression

MAF: minor allele frequency

MR: Mendelian randomization

MTAG: multi-trait analysis of genome-wide association study

SBP: systolic blood pressure

SNP: single nucleotide polymorphism

TC: total cholesterol

TG: triglyceride

T2D: type 2 diabetes

TWAS: transcriptome-wide association study

UKB: UK Biobank

WHR: waist-hip ratio

Introduction

Carotid artery intima-media thickness (cIMT) is a widely accepted indicator of subclinical atherosclerosis, and can be detected non-invasively using carotid ultrasonography[1]. It is estimated that the global prevalence of increased cIMT reached 27.6% in 2020, equivalent to approximately 1.07 billion affected individuals[2]. Increased cIMT is closely related to increased cardiovascular and cerebrovascular risks[3, 4]. A meta-analysis of 119 clinical trials reported that each 10 μm/y reduction of cIMT progression resulted in a 9% reduced risk for cardiovascular disease (CVD)[5]. Moreover, previous studies have shown significant associations between cIMT and multiple cardiometabolic risk factors, including hypertension, diabetes, and obesity[6, 7]. The combined effect of these factors substantially elevated the population-level risk of increased cIMT[6]. The evidence supports the hypothesis that cIMT and cardiometabolic diseases and risk factors may share a common genetic etiology, that is, they may share genetic variants affecting metabolic process or response to environmental risk factors[8, 9]. Thus, it is important to understand the genetic mechanism of increased cIMT and its clustering with CVD and risk factors.

Twin and family studies demonstrated that genetic factors have an important role in explaining cIMT with a high heritability (38-65%)[10, 11]. To date, genome-wide association studies (GWASs) have identified dozens of single nucleotide polymorphisms (SNPs) associated with cIMT[9, 12-14]. However, the majority of individuals in GWAS are of European ancestry; only few studies included a limited number of non-European ancestry participants[9, 14]. Therefore, large-scale genome-wide studies based on non-European populations are crucial for in-depth exploration of the genetic heterogeneity of cIMT among different ethnic groups. In addition, genetic correlation analysis can be applied to delineate the shared genetic architecture of cIMT with other related phenotypes. Several studies have reported the significant genetic correlations between cIMT and coronary artery disease (CAD), type 2 diabetes (T2D), and obesity in European ancestry populations[12, 13]. However, it remains unclear whether cIMT shares genetic loci with cardiometabolic diseases and traits, or through which common regulatory pathways they exert their effects.

In the present study, we performed a large-scale GWAS in the China Kadoorie Biobank (CKB) and conducted genetic correlation and Mendelian randomization (MR) analysis in East Asian and European population to address following objectives: 1) to identify novel genetic variants for cIMT in the Chinese population; 2) to estimate genetic correlation between cIMT and cardiometabolic diseases and traits in both East Asian and European population; 3) to investigate the bidirectional causal associations between cIMT and cardiometabolic diseases/traits across both populations. The overall study design is shown in **Figure 1**.

Methods

Individual-level data from the CKB are available through application at www.ckbiobank.org/site/Data+Access. The CKB has approval from the Ethical Review Committee of the Chinese Center for Disease Control and Prevention (Beijing, China), the Peking University Institutional Review Board (Beijing, China), and the Oxford Tropical Research Ethics Committee, University of Oxford (UK). Written informed consent was received from all participants. GWAS summary statistics used in the present study were obtained from publicly available studies and consortia, with details provided in the **Table S1**. GWAS summary statistics generated in the present study from CKB have been deposited in the Genome Variation Map[15] in National Genomics Data Center, Beijing Institute of Genomics, Chinese Academy of Sciences and China National Center for Bioinformation[16], under accession number GVP000089. The GWAS summary statistics are publicly available in https://bigd.big.ac.cn/gvm/getProjectDetail?Project=GVP000089. A detailed description of the Methods is provided in the Supplemental Material.

Results

GWAS results of cIMT

The baseline characteristics of the CKB are summarized in **Table S2**. We included 22,370 CKB participants in the study (mean [SD] age, 59.6 [10.2] years; 8,493 males [38.0%]; mean [SD] cIMT, 0.8 [0.2] mm). The GWAS found two genome-wide significant susceptibility loci

($P < 5 \times 10^{-8}$), one of them are novel (**Table 1**). A Manhattan plot and QQ plot are shown in **Figure 2A**. The QQ plot showed some evidence of inflation (λ = 1.10), which is mainly due to polygenicity rather than population stratification (linkage disequilibrium [LD] score regression [LDSC] intercept [SE] = 1.03 [0.01])[17]. Minor allele frequency (MAF)-stratified QQ plots also indicated greater inflation among common variants (λ = 1.097) than rare variants (λ = 1.047) (**Figure S1**). Our most significant locus is near the Apolipoprotein E (*APOE*) region (rs1065853, $P = 9.5 \times 10^{-39}$, info score = 0.99) that has been previously reported in European populations[9, 12]. The novel gene had lead variants located in the intronic region of gamma-glutamyltransferase 5 (*GGT5*) (rs72617245, $P = 5.5 \times 10^{-9}$, info score = 0.96). These findings remained unchanged after adjusting for smoking status. We further examined the interaction between rs72617245 and smoking status on cIMT and found no significant interaction (*P* for interaction = 0.96). Regional association plot demonstrating regional LD for these two SNPs with other variants (**Figure 2D and Figure 2E**). Single-variant MR showed that rs72617245 was significantly associated with random blood glucose in CKB, whereas no corresponding association was observed in UK Biobank (UKB), indicating a potential Chinese-specific pathway (**Table S3**). Although rs72617245 showed similar MAF in Asian and European populations in the 1000 Genomes reference data (0.250 vs. 0.252), the lack of replication in UKB may reflect population-specific differences in linkage disequilibrium structure. In contrast, rs1065853 was genome-wide significant for cIMT in both CKB and European populations. Wald ratio MR demonstrated that rs1065853 was significantly associated with total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and diastolic blood pressure (DBP) in CKB, and showed consistent associations in UKB, with additional significant effects on CAD, systolic blood pressure (SBP), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and body mass index (BMI). These findings support a cross-ancestry causal role of this shared cIMT locus in cardiometabolic pathways. We also investigated the replication of 71 previous cIMT genetic associations in our GWAS study. Among them, we found 16 were significant ($P < 0.05/71 = 7.0 \times 10^{-4}$) with consistent effect size direction (**Table S4**).

Sex-specific analyses revealed three genome-wide significant SNPs, including one variant identified in the all population analysis (**Figure 2B and Figure 2C**). Male-specific analysis identified an additional variant, rs72654473, is 1.1 kb from the reported rs1065853 but in high LD ($r^2 = 0.87$). A novel variant rs2852998 was identified in the female-specific analysis, which is mapped to a long intergenic non-protein coding RNA (lncRNA), *LINC02732* (**Figure 2F**). No significant interaction between rs2852998 and sex was observed for cIMT (*P* for interaction = 0.25). In stratified analyses, rs2852998 was associated with cIMT in both females and males, with a stronger effect estimate in females (β = -0.0105, $P < 0.001$) than in males (β = -0.0065, $P = 0.03$). Among women, no significant interaction between rs2852998 and menopausal status was observed (*P* for interaction = 0.26).

Genetic correlations between cIMT and cardiometabolic diseases and traits

LDSC estimates of SNP-based heritability were (mean ± SE) 14.66 ± 2.49% and 20.24 ± 2.48% for cIMT in the CKB and UKB, respectively (**Table S5**). The heritability of cardiometabolic diseases and traits ranged from 3.7% (fasting glucose) to 34.3% (T2D) in East Asian population, and ranged from 8.2% (LDL-C) to 35.6% (CAD) in European population. Subsequently, we investigated the genetic correlation between cIMT and 15 cardiometabolic diseases and traits. In the East Asian population, four genetic correlations were significant following Bonferroni correction: CAD ($r_g = 0.32$, $P = 3.7 \times 10^{-7}$), T2D ($r_g = 0.25$, $P = 4.2 \times 10^{-6}$), BMI ($r_g = 0.18$, $P = 1.4 \times 10^{-3}$), and SBP ($r_g = 0.38$, $P = 4.3 \times 10^{-7}$) (**Figure 3A** and **Table S6**). These findings have also been replicated in the European population, with additional significant genetic correlations further identified (heart failure, ischemic stroke, WHR [waist-hip ratio], and HDL-C). Sex-specific analyses revealed stronger genetic correlation between cIMT and CAD in males than in females in East Asian population, whereas the strength of genetic correlation for other traits is similar between genders (**Table S7**). The trans-ancestry genetic correlation analysis of cIMT between East Asian and European ancestries showed that the genetic correlation was 1.13 for genetic effects and 1.02 for genetic impact, which were not statistically significantly different from no difference (*P* = 0.60 and 0.93, respectively).

Given that significant genetic correlations between cIMT and cardiometabolic diseases/traits were only found for CAD, T2D, BMI, and SBP across East Asian and European populations, we further performed local-level genetic correlation analysis for these traits. In the functional partitioned genetic correlation analysis, significant genetic correlations were observed in 11 out of 12 functional categories, with repressed regions being the exception (**Figure 3B** and **Figure 3C**, and **Table S8**). Overall, the partitioned genetic correlations across functional categories were broadly similar to the overall genetic correlation. For the local-level genetic correlation, we identified five significant shared regions (*P* value ≤ 0.05/1703) in the pair trait of cIMT and SBP in European population, including 8p22-8p23.1, 11q22.1, and 16q23.1 (**Table S9**).

Cross-trait associations between cIMT and cardiometabolic diseases and traits

For the trait pairs that showed significant genetic correlation after Bonferroni correction in both East Asian and European populations, we conducted a cross-trait meta-analysis to identify pleiotropic genetic variants. In the East Asian population, after clumping, we found 13 loci significantly associated with cIMT and CAD, five loci with T2D, four loci with SBP, and two loci with BMI (**Table S10**). Among these pleiotropic variants, we identified two shared loci in cIMT and cardiometabolic traits pairs, including *FIGN* on 2q24.3 (CAD and SBP) and *CDKAL1* on 6p22.3 (T2D and BMI). Interestingly, *FIGN* on 2q24.3 was also identified in the same trait pairs in the European population (**Table S11**).

Fine-mapping and colocalization analysis

For each significantly shared locus identified by the cross-trait meta-analysis, we captured a 99% credible set of causal variants. Lists of credible set SNPs in each shared locus from fine-mapping are provided in **Tables S12-S13**. In total, 110 and 699 potential causal variants were identified for East Asian and European populations, respectively. Results of colocalization indicated that 110 and 644 SNPs (27 and 186 loci) were colocalized at the risk of four trait pairs in East Asian and European populations, and these variants were considered causal

pleiotropic genetic variants (**Tables S14-S15**). Notably, six loci were shared by cIMT and CAD across both East Asian and European populations, including *EDNRA*, *FIGN*, *PECAM1*, *APOE*, *FGD5*, and *APOB* (**Figure 3D**). Among these loci, *EDNRA*, *PECAM1*, *APOE*, and *FGD5* showed overlapping colocalized variants between East Asian and European populations. Additionally, four loci were shared between cIMT and SBP in both populations, specifically *FGF5*, *KCNK3*, *ARHGAP42*, and *FIGN*, among which *FGF5* showed overlapping colocalized variants in the two populations.

Gene-based and enrichment analysis

Gene-based analysis was conducted to evaluate the gene-level shared associations of four cIMT and cardiometabolic trait pairs. A total of 622 and 1890 risk genes were identified for East Asian and European populations (**Tables S16-S17**), respectively. Gene set enrichment analysis indicated that risk genes were mainly related to the biological processes of lipid metabolism and carbohydrate metabolism for CAD and T2D in both East Asian and European populations (**Figure 3E, Tables S18-S19**). Tissue-specific enrichment analysis indicated that most genes were enriched in several tissues, including coronary and aorta artery, subcutaneous adipose, pancreas, and muscle (**Tables S20-S21**). Cell-type specific enrichment analysis showed that these risk genes were mainly related to several endothelial cell types (**Tables S22-S23**).

Transcriptome-wide association study (TWAS)

We conducted a TWAS analysis to explore the association between the gene expression levels of pleiotropic causal genes in each tissue. A total of 23 pleiotropic genes were found to have significant associations both in cIMT and cardiometabolic diseases and traits, and the effects of most of these genes were detected in the aorta artery, pancreas, and esophagogastric junction (**Figure 3F, Table S24**). Notably, *CFDP1* was associated with cIMT, CAD, and SBP in most tissues.

MR results

The MR analyses indicated unidirectional associations for CAD and T2D on cIMT in East

Asian (CAD: $\beta = 1.90$, $P = 8.0 \times 10^{-6}$; T2D: $\beta = 0.44$, $P = 2.1 \times 10^{-3}$) and European population (CAD: $\beta = 0.85$, $P = 1.6 \times 10^{-4}$; T2D: $\beta = 0.50$, $P = 8.7 \times 10^{-9}$), while cIMT was marginally but not significantly related to CAD in East Asian population ($\beta = 0.28$, $P = 2.6 \times 10^{-2}$). A positive bidirectional association between cIMT and SBP was detected (cIMT-to-SBP: $\beta_{eas} = 0.97$, $P_{eas} = 6.5 \times 10^{-3}$, $\beta_{eur} = 1.89$, $P_{eur} = 5.0 \times 10^{-3}$; SBP-to-cIMT: $\beta_{eas} = 0.25$, $P_{eas} = 2.7 \times 10^{-7}$, $\beta_{eur} = 0.18$, $P_{eur} = 9.8 \times 10^{-38}$) (**Figure 4, Table S25**). By contrast, genetically predicted BMI was positively associated with cIMT in European population ($\beta = 1.60$, $P = 1.8 \times 10^{-21}$), but the association was not significant in East Asians. The inverse-variance weighted estimates were confirmed by at least one alternative MR method (Table S25). The F-statistics for all selected genetic instruments were all greater than 10, indicating a relatively low risk of weak instrument bias in MR analyses. Results of single variant association analyses are presented in **Tables S26-S29**.

Discussion

In this study, we have conducted the largest GWAS on cIMT in the Chinese population to date. We also found broadly consistent genome-wide genetic correlations between cIMT and cardiometabolic diseases and traits across East Asian and European populations. Further comprehensive analysis highlighted the pleiotropic causal variants, biological pathways, and bidirectional causal associations. These findings collectively supported that cIMT not only shares a common genetic etiology with cardiometabolic diseases and traits, but also serves as an important indicator for cardiometabolic health.

Our study revealed two loci associated with cIMT in the Chinese population, including *APOE* and one novel locus *GGT5* on 22q11.23. *GGT5* is a member of the gamma-glutamyl transpeptidase (GGT) gene family. The protein it encodes plays a crucial role in the catalysis of anti-oxidant glutathione, converting leukotriene C4 to LTD4[18]. GGT was once considered as a specific marker of hepatic dysfunction, but it is now known to have extra-hepatic implications related to metabolism and CVD[19]. Previous observational studies have also addressed associations of GGT with carotid atherosclerosis, which further confirmed a link

between it and the early development of atherosclerosis[20]. We also found a novel independent locus at 11q22.3 in the female-stratified analysis, where the sentinel SNP is mapped to an lncRNA *LINC02732*. The mutation of *LINC02732* was previously reported to be associated with coronary heart disease in the East Asian and European populations[21, 22]. Besides, *LINC02732* was responsible for oestrone levels in the previous study[23], which may partly account for the stronger association observed in women in our study, although the formal interaction analyses by sex were not statistically significant. Because oestrone in postmenopausal women is predominantly produced in adipose tissue, the tissue expression pattern of *LINC02732* may provide clues to its potential biological pathway. However, publicly available expression data suggest that *LINC02732* is detectable across tissues, without clear vascular- or adipose-specific enrichment[24]. Therefore, although an oestrone-related mechanism is biologically plausible, the tissue context through which *LINC02732* may influence cIMT remains uncertain and requires further investigation. The modest replication of previously reported European-ancestry cIMT loci in the Chinese population reflects both genetic and method differences. Genetic architecture differs substantially between European and East Asian populations, including allele frequencies and effect sizes. Differences in cIMT ultrasound protocols across studies may also contribute to heterogeneity. In addition, limited statistical power due to the relatively modest sample size of the CKB cohort may have reduced our ability to detect some previously reported variants. This further underscores the necessity of large-scale GWAS in non-European populations to uncover ancestry-specific loci.

By leveraging the large-scale and trans-ancestry GWAS datasets, our LDSC analysis found four trait pairs with significant genetic correlations, which have been reported in previous genetic studies in European population. For example, we have demonstrated a positive genetic correlation for cIMT and T2D in East Asian (r_g = 0.25) and European populations (r_g = 0.20), which was similar to the results of the studies by Strawbridge et al. (r_g = 0.25)[12]. Using the comprehensive approach of cross-trait meta-analysis, fine-mapping, and colocalization, we have found 27 and 186 pleiotropic loci of trait pairs in East Asian and European populations.

Six causal loci including *EDNRA*, *FIGN*, *PECAM1*, *APOE*, *FGD5*, and *APOB* were identified as contributing loci associated with cIMT and CAD across East Asian and European populations. Four loci were shared between cIMT and SBP, namely *FGF5*, *KCNK3*, *ARHGAP42*, and *FIGN*. These genes shared may exhibit cross-ethnic pleiotropic effects that contribute to systemic homeostasis of cardiometabolic function. Notably, *FIGN* showed consistent genetically predicted associations in cIMT, CAD, and hypertension. *FIGN* encodes an ATPase associated with diverse cellular activities, which is highly expressed in multiple organs including the heart[25]. Results from large population-based genetic studies have shown that *FIGN* plays a critical role in the regulation of blood pressure and progression of coronary heart disease[26, 27]. This indicates the potential therapeutic benefit of *FIGN* in cardiometabolic comorbidity, and supports the value of prioritized application in dual-benefit treatment strategies.

Gene set enrichment analysis indicated that genes associated with the risk of cIMT-cardiometabolic comorbidity were mainly related to the biological process of lipid and carbohydrate metabolism, which was consistent with previous findings. For example, a previous study reported that metabolites associated with coronary and carotid atherosclerosis revealed disturbances in lipid and carbohydrate metabolism[28]. These metabolites were also related to incident cardiovascular events, highlighting the importance of these pathways in the development from subclinical atherosclerosis to clinical CVD[28]. We further investigate the biological mechanisms of pleiotropic causal loci from a transcriptomic perspective, wherein *CFDP1* was expressed in almost all tissues. *CFDP1* gene maps to chromosome 16q22.2-q22.3 and encodes the CFDP1 protein, which was essential for the structural stability of centromeric heterochromatin[29]. Some genetic studies have observed significant associations between *CFDP1* and carotid atherosclerosis and CAD[9, 22, 30], indicating *CFDP1* is a therapeutic gene target for clinically actionable drugs treating atherosclerosis.

Building on the genetic correlations identified between cIMT and cardiometabolic diseases and traits, we further investigated the bidirectional causal relationships between them. The

MR estimates in the present study suggested a positive causal effect of CAD and T2D on cIMT. The results of causal association from T2D to carotid atherosclerosis were supported by the previous genetic studies in both East Asian and European populations[8, 31]. We also detected a marginally significant association for cIMT on CAD in East Asian population, which was consistent with previous studies that carotid and coronary artery atherosclerosis shared similar pathophysiology and contributing risk factors[32]. These estimates provided evidence that patients with clinical cardiometabolic diseases not only have an inherent shared genetic risk of cIMT, but also could causally lead to an increase in cIMT. Notably, in line with the previous MR study[33], a positive causal relationship was observed from BMI to cIMT in European population. However, no significant association between them was found in East Asians, potentially related to the obesity paradox observed in some Asian populations. Several environmental factors such as differences in sociodemographic variables and lifestyle factors may lead to variations in the measured heritability and the magnitude of genetic effects. In addition, we found a mutually causal relationship between SBP and cIMT. Elevated SBP may increase the risk of atherosclerosis through vascular damage caused by local shearing forces[34]. The reverse association, although modest, may be explained by vascular remodeling reflected by increased cIMT, which could lead to reduced arterial compliance and increased peripheral resistance[35]. However, genetic instruments for cIMT may also capture broader processes such as arterial stiffness or vascular aging, and thus this reverse effect should be interpreted with caution. The underlying mechanism of carotid-induced hypertension may be that increased peripheral vascular resistance leads to arterial hypertension, whereas oxidative stress and endothelial dysfunction due to hypertension were a possible mechanism on the reverse[36]. These cross-ancestry causal associations we have found between carotid atherosclerosis and atherosclerotic risk factors may help in formulating prevention strategies for both conditions individually and when they occur together.

The present study has several strengths, including similar findings across East Asian and European ancestries, which suggest generalizability despite the variations in sociodemographic characteristics. Moreover, by adopting the largest representative GWAS

summary statistics, multi-level genetic methods, and rigorous analytical standards, the reliability of the results of this study could be enhanced. However, the study also had several limitations that deserve further discussion. First, the sample size of CKB GWAS is only half that of UKB. Despite being the largest reported so far for the East Asian population, this discrepancy may lead to some findings not being directly comparable. Future work with larger sample sizes in East Asian populations may help to address this issue. In addition, future studies in other Chinese populations are needed to replicate the novel loci. Second, fine-mapping relied on ancestry-matched external reference panels from the 1000 Genomes Project. Although this approach is consistent with the imputation framework, residual differences in local LD structure between the reference panels and the study populations may have affected the precision of the credible sets. Third, our analyses involve assumptions whose violations can produce biased results. For example, multi-trait analysis of genome-wide association study (MTAG) might be biased by potential violations of the assumption of perfect genetic correlation and equal heritability. Moreover, given the smaller sample size of the East Asian cIMT GWAS, the MTAG results in this population may be more susceptible to Winner's Curse, and the effect sizes of some pleiotropic loci may therefore be overestimated. These findings should thus be interpreted cautiously and validated in larger populations. Finally, the present study was limited to investigate shared genetic factors between cIMT and cardiometabolic-related diseases and traits, which could only account for a small portion of these traits. Gene-environment interactions may partly explain the unexplained heritability. Future research should be to perform large-scale, longitudinal studies to explore to what extent genetic variations and environmental factors contribute to the longitudinal co-occurrence of these disorders.

In conclusion, our large-scale genome analyses have expanded existing knowledge of the genetic basis of cIMT in the Chinese population. We systematically explored the shared genetic architecture between cIMT and cardiometabolic diseases and related traits across different ancestries, which may provide novel insight into the intervention and treatment targets of these comorbidities.

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Contributors

TH conceived and designed the study, contributed to the interpretation of the results and critical revision of the manuscript for valuable intellectual content. LL, JL, ZC, and JC: as the members of the CKB steering committee, designed and supervised the conduct of the whole study, obtained funding, and together with CY, DS, PP, LY, IM, RW, YC, HD, MB, and XL acquired the CKB data. WW analyzed the data. NH verified the data. WW drafted the manuscript. All authors have read and approved the final manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. All authors read and approved the final manuscript.

Declaration of Interests

None declared.

Supplemental Materials

Supplemental Methods

Tables S1-S29

Figure S1

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Table 1. Genome-wide significantly associated SNPs ($P < 5 \times 10^{-8}$) with mean-max cIMT in CKB

SNP	CHR	POS	Effect allele	Other allele	Beta	SE	*P*	Nearest gene	Genic position
All participants									
rs1065853	19	45413233	G	T	0.228	0.017	9.50E-39	*APOE*	downstream
rs72617245*	22	24638596	G	A	-0.069	0.012	5.50E-09	*GGT5*	intronic
Male-specific									
rs72654473	19	45414399	C	A	0.241	0.028	1.00E-17	*APOE*	intergenic
Female-specific									
rs1065853	19	45413233	G	T	0.224	0.022	2.60E-24	*APOE*	downstream
rs2852998*	11	110256762	T	A	0.078	0.014	1.10E-08	*LINC02732*	ncRNA_intronic
Additionally adjusted for smoking status									
rs1065853	19	45413233	G	T	0.228	0.017	8.50E-39	*APOE*	downstream
rs72617245*	22	24638596	G	A	-0.068	0.011	6.80E-09	*GGT5*	intronic

*novel locus. Adjustment was made for age, age^2, sex, region, array, and the first 10 principal components in CKB. CHR, chromosome; cIMT, carotid intima-media thickness; CKB, China Kadoorie Biobank; POS, position; SNP, single-nucleotide polymorphism; SE, standard error.

Figure legends

Figure 1. Schematic overview of study design

Abbreviations: AF, atrial fibrillation; AIS, all ischemic stroke; BMI, body mass index; CAD, coronary artery disease; cIMT, carotid intima-media thickness; DBP, diastolic blood pressure; FG, fasting glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; IV, instrumental variable; LD, linkage disequilibrium; LDL-C, low-density lipoprotein cholesterol; MR, Mendelian randomization; r_g, genetic correlation; SBP, systolic blood pressure; T2D, type 2 diabetes; TC, total cholesterol; TG, triglyceride; TWAS, transcriptome-wide association study; WHR, waist-hip ratio.

Figure 2. GWAS result for cIMT in CKB

A-C. Manhattan plot and QQ plot for cIMT in all population (A), males (B), and females (C). The lambda value is 1.10, 1.05, and 1.05, respectively. The red line indicates the genome-wide significance threshold ($P = 5 \times 10^{-8}$), and the blue line indicates the suggestive significance threshold ($P = 5 \times 10^{-6}$). **D**. Regional plots for novel loci of cIMT on chromosome 22 (rs72617245). The lead SNP is labeled in purple, with other SNPs colored by degree of linkage disequilibrium. **E**. Regional plot for known loci of cIMT on chromosome 19 (rs1065853). **F**. Regional plot for novel loci of cIMT on chromosome 11 (rs2852998) in females. Abbreviations: cIMT, carotid intima-media thickness; CKB, China Kadoorie Biobank; GWAS, genome-wide association study; SNP, single-nucleotide polymorphism.

Figure 3. Genetic correlation result for cIMT and cardiometabolic diseases and traits in

East Asian and European populations

A. Genetic correlations between cIMT and cardiometabolic diseases and traits in East Asian and European populations. The intensity of the color is proportional to the magnitude of the genetic correlation. Values marked with 1 star were considered significant after correcting for multiple testing ($P < 0.05/15$). r_g represents the coefficient of genetic correlation. **B, C**. Partitioned genetic correlation between cIMT and cardiometabolic diseases and traits in East Asian (B) and European (C) populations. The asterisk represents significance ($P < 0.05/12$). **D**. Circus genome-wide plot of pleiotropic causal genetic variants between cIMT and cardiometabolic diseases and traits in both East Asian and European populations. Green lines indicate cIMT-CAD shared loci, and blue lines indicate cIMT-SBP shared loci. No overlapping loci were observed for BMI or T2D. **E**. The lollipop chart of significant gene set enrichment results in both East Asian and European populations. Only cIMT-CAD and cIMT-T2D show overlapping enriched pathways across the two populations, whereas SBP and BMI do not. **F**. Significant expression-trait associations in linkage pairs of cIMT and cardiometabolic diseases and traits in TWAS (FDR $P < 0.05$) among East Asian and European populations. Single-trait TWAS was performed to assess pleiotropic causal loci identified by colocalization analysis, and results were intersected to identify loci shared between cIMT and cardiometabolic traits. Blue color in the heatmap represents Europeans, red represents East Asians, and black represents significance in both populations. Abbreviations: AF, atrial fibrillation; AIS, all ischemic stroke; BMI, body mass index; CAD, coronary artery disease; cIMT, carotid intima-media thickness; DBP, diastolic blood pressure; EAS, East Asian; EUR, European; FG, fasting glucose; HbA1c, glycated hemoglobin; HDL-C, high-density

lipoprotein cholesterol; HF, heart failure; LDL-C, low-density lipoprotein cholesterol; r_g, genetic correlation; SBP, systolic blood pressure; SE, standard error; T2D, type 2 diabetes; TC, total cholesterol; TG, triglyceride; TWAS, transcriptome-wide association study; WHR, waist-hip ratio.

Figure 4. Bidirectional MR result of cIMT and cardiometabolic diseases and traits in East Asian and European populations

A. Bidirectional MR results between cIMT and four cardiometabolic diseases and traits using five complementary MR methods. Results are shown separately for East Asian (red) and European (blue) populations. Effect estimates are presented as beta coefficients (or odds ratios for binary outcomes) with 95% confidence intervals. Beta coefficients for cardiometabolic diseases and traits on cIMT are scaled per 0.1-mm increase in cIMT. **B**. Summary of statistically significant bidirectional causal associations identified in panel A. Only associations reaching Bonferroni-corrected significance are shown ($P < 0.05/4$ for East Asian and European ancestry). Effect directions and magnitudes are indicated for each population. Abbreviations: BMI, body mass index; CAD, coronary artery disease; cIMT, carotid intima-media thickness; IVW, inverse-variance weighted method; MR, Mendelian randomization; PRESSO, pleiotropy residual sum and outlier; SBP, systolic blood pressure; SE, standard error; T2D, type 2 diabetes.