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Genome-Wide Pleiotropic Analyses Characterize the Genetic Etiology Shared between Cardiovascular and Gastrointestinal Tract Diseases

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Genome-Wide Pleiotropic Analyses Characterize the Genetic Etiology Shared between Cardiovascular and Gastrointestinal Tract Diseases

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Abstract

Background: This study aimed to investigate the shared genetic etiology between gastrointestinal tract and cardiovascular diseases, and to identify shared genomic loci, genes, and pathways.

Methods: Using aggregated genome-wide association statistics from public data sources, a genome-wide pleiotropic association study was conducted. Multiple

statistical genetic approaches were applied to sequentially explore pleiotropic associations across genome-wide single-nucleotide variations, genes, biological pathways, and gut microbiota. The potential shared genetic causes among 7 gastrointestinal tract diseases and 11 cardiovascular diseases were analyzed.

Results: A total of 350 pleiotropic loci were identified. Co-localization analysis detected 95 shared causal loci across disease pairs. Multiple gene pathways were found to be closely associated with these diseases, and key biological processes—including cell signal transduction and T-cell activation—exhibited significant correlations across the studied diseases. A robust pleiotropic association was observed between gastrointestinal tract and cardiovascular diseases, suggesting that these diseases may cross-influence each other in the context of different immune cells and tissues, while sharing common immune response mechanisms. Several immune cell populations, such as $CD103^+$ $CD11b^+$ dendritic cells, $CD8^+$ splenic lymph node DCs, and γδ T cells, showed cross-disease correlations, highlighting the critical role of the immune system in the pathogenesis of both gastrointestinal tract and cardiovascular diseases. Multitrait colocalization analysis via HyPrColoc identified 6 pleiotropic loci harboring shared microbiota, underscoring the significant involvement of gut microbiota in disease pleiotropy.

Conclusions: This study establishes a genetic and mechanistic framework for the shared etiology of gastrointestinal tract and cardiovascular diseases, with pleiotropic variants, inflammatory pathways, and gut microbiota interactions as key drivers. These insights not only deepen our understanding of cardiovascular-gastrointestinal comorbidities but also lay the groundwork for precision medicine strategies targeting shared biological mechanisms.

Keywords

Genome-Wide Pleiotropic Analyses; Gastrointestinal Tract Disease; Cardiovascular Disease; Inflammation and Immunity; Microbiota

Background

Cardiovascular diseases (CVDs) and gastrointestinal tract diseases (GTDs) frequently cooccur, imposing greater health burdens than either condition does in isolation. Clinically, patients with GTDs such as inflammatory bowel disease (IBD) exhibit a significantly elevated risk of developing CVDs[1]. Individuals with CVDs face an increased risk of developing GTDs, including gastrointestinal ulcers, gastroesophageal reflux disease (GORD), and irritable bowel syndrome (IBS)[2]. These observations suggest a potential bidirectional relationship between CVDs and GTDs. Elucidating the high prevalence of CVDs in GTDs represents a critical research priority. Emerging evidence highlights inflammation and gut microbiota dysregulation as shared pathophysiological drivers of both cardiac and gastrointestinal disorders[3]. For example, intestinal inflammation in IBD patients, characterized by elevated levels of cytokines, C-reactive protein (CRP), and homocysteine, induces endothelial dysfunction, an early hallmark of atherosclerosis[4]. Moreover, lipid profile alterations in IBD closely mirror those observed in atherosclerotic patients[3,5]. Hypertension, atherosclerosis, and other CVDs, alongside GTDs such as IBD and IBS, are associated with alterations in the gut microbial composition[6]. Deciphering the shared mechanisms between these diseases could facilitate early diagnosis of co-occurring health events in patients and identify convergent therapeutic targets for novel interventions.

Genome-wide association study (GWAS) involve diverse genetic variants, including single nucleotide variants (SNVs)[7,8]. Methods such as linkage disequilibrium (LD) score regression (LDSC) have been applied to investigate genetic correlations between psychiatric disorders, lung diseases, CVDs, liver diseases and many disease[9] [10] [11]. These studies, conducted by consortia such as the Inflammation Working Group of the CHARGE Consortium and the METASTROKE Consortium of the International Stroke Genetics Consortium, highlight the utility of genetic correlation analyses in uncovering shared biological pathways across diverse phenotypes. Increasing evidence supports a potential association between CVDs and GTDs clinically. However, systematic exploration of their common genetic etiology—specifically, identifying genome-wide significant genetic variants or loci underlying their shared genetic

correlation—remains under explored. A shared genetic basis may reflect pleiotropy, a critical confounding factor in trait–pair associations that can obscure causal inference[12]. Cross-trait analyses have been developed to identify pleiotropic genetic variants or loci across multiple traits by leveraging correlations in GWAS signals[13,14,15]. These analyses enable the identification of pleiotropic loci as intervention targets, potentially contributing to the prevention or treatment of these diseases.

In this genome-wide pleiotropic analyses study, large-scale GWAS summary data were leveraged, and multiple statistical genetics approaches were employed to perform a comprehensive genome-wide pairwise pleiotropic analysis across CVDs and GTDs. CVDs included abdominal aortic aneurysm (ABAORTANEUR), atrial fibrillation and flutter (AF), aortic aneurysm (AORTANEUR), aortic dissection (AORTDIS), calcific aortic valvular stenosis (CAVS_OPERATED), major coronary heart disease (CHD), heart failure (HEARTFAIL), essential hypertension (HYPTENSESS), other peripheral vascular diseases (OTHPER), stroke (STR), and thoracic aortic aneurysm (THAORTANEUR). GTDs included common gastrointestinal tract diseases, such as inflammatory bowel disease (IBD), Crohn's disease (CD), ulcerative colitis (UC), peptic ulcer disease (PUD), gastroesophageal reflux disease (GORD), and irritable bowel syndrome (IBS), and a combined phenotype of PUD, GORD, and related medications (PGM). This study aimed to systematically investigate the pleiotropic associations between CVDs and GTDs at the whole-genome, single-nucleotide variants (SNVs), gene, and biological pathway levels, with the goal of disentangling their shared genetic etiology. Specifically, LD score regression (LDSC) and hierarchical decomposition of linkage disequilibrium (HDL) were used to quantify genetic correlations, applied the PLACO method to identify pleiotropic loci and genes, conducted multitissue transcriptome-wide association studies (TWAS) and expression quantitative trait locus (eQTL) analyses to pinpoint common pathogenic genes and signaling pathways, utilized stratified LD score regression (SLDSC) and HyPrColoc to explore shared immune and gut microbiota mechanisms, and employed two-sample bidirectional Mendelian randomization (MR) to evaluate causal relationships between the disease classes.

Methods

1. GWAS datasets

A total of 11 CVDs and 7 GTDs were selected from publicly available GWAS summary statistics in European-ancestry populations. This selection was motivated by the limited availability of adequately powered GWAS datasets for other ancestries. To ensure sufficient statistical power, only GWASs with sample sizes exceeding 20,000 were included. Data were collected until August 25, 2021. The analysis included 286,935 CVD cases with 3,931,419 controls and 239,815 GTD cases with 1,730,685 controls. Detailed information on the total number of participants, cases, and controls is provided in Supplement Table S1. This genome-wide pleiotropic association study adhered to the Strengthening the Reporting of Genetic Association Studies (STREGA) guidelines.

2. Data quality control

To ensure data reliability and consistency, rigorous quality control measures were implemented as follows: 1) Exclusion of nonbiallelic and ambiguous SNPs: Nonstandard SNPs, including multiallelic variants and those with indistinguishable alleles, were systematically excluded from the analysis. 2) Removal of SNPs without rs tags: SNPs lacking standard rsID tags were excluded to ensure that each variant had a definitive identifier. 3) Filtering of duplicate and mismatched SNPs: Duplicate SNPs, as well as those absent from the 1000 Genomes Project reference panel or with allele information inconsistent with reference data, were removed. 4) Exclusion of major histocompatibility complex(MHC) region SNPs: Due to the complex LD structure, SNPs within the MHC region on chromosome 6 (chr6: 28.5-33.5Mb) were excluded.5) Retention of SNPs with an minor allele frequency(MAF) > 0.01: SNPs with a MAF greater than 0.01 were retained to minimize statistical bias from low-frequency variants.

Given that the GTDs and CVDs data originated from distinct research consortia, sample overlap was negligible, thereby reducing confounding effects from sample crossover. For each remaining SNPs, key statistics—including effect size, standard

error, effect allele, and *P* value—were retained for subsequent analyses.

3. Genetic correlation analysis

Genetic correlation analyses across traits were performed via two distinct methodologies: LDSC[16] (PMID: 25642630) and hierarchical decomposition of linkage disequilibrium (HDL)[17] (PMID: 32601477). These approaches aim to quantify genetic associations between trait pairs and characterize their shared polygenic architecture. For LDSC, European ancestry samples from the 1000 Genomes Project were used as a reference panel to calculate LD scores for each variant locus. LD scores quantify the extent to which genetic variation in one genomic region can be explained by neighboring regions, serving as a key metric for assessing polygenic trait structure. Genetic correlations were estimated while accounting for confounding factors such as population stratification and shared genetic variation between unrelated traits. To further mitigate biases, an unconstrained LDSC analysis was performed, allowing free estimation of the intercept to identify and adjust for residual confounding from a limited sample size, environmental factors, or population structure. This approach also facilitates the detection of potential sample overlap between GWAS datasets, as a significantly elevated intercept (>1) may indicate overlapping samples and bias in genetic correlation estimates. For HDL, high-resolution likelihood estimation was employed to refine genetic correlation estimates, enhancing the precision of shared polygenic pattern detection across traits.

4. SNPs-level pleiotropic analysis under the composite null hypothesis (PLACO)

SNPs-level PLACO is an innovative analytical framework for identifying pleiotropic loci associated with complex traits, relying solely on summary-level genotype–phenotype association statistics[18]. This method utilizes the squared Z scores (Z^2) of individual genetic variants to assess pleiotropic effects across multiple traits. First, Z^2 values were calculated for each variant, and SNPs with extreme Z^2 values (>80) were excluded to mitigate analytical bias from strong association signals or data anomalies. Given the potential genetic correlation between gastrointestinal and cardiovascular diseases, a Z^2 correlation matrix was estimated for each variant. This matrix captures the correlation in effect directions and magnitudes across traits at each

genomic locus, enabling the identification of shared genetic bases between the two disease categories. The intersection-union test (IUT) was subsequently applied to perform pleiotropy tests for each variant within a multiple hypothesis testing framework. The null hypothesis (H_0) assumes that the variant has no effect on either trait or influences only one trait, whereas the alternative hypothesis (H_1) posits simultaneous influence on both traits. The final IUT *P* value is defined as the maximum *P* value from all tests of H_0 and H_1, controlling for false positive rates due to multiple testing. This approach balances power and specificity in detecting pleiotropic effects under stringent multiple-testing conditions.

5. Multi-marker Analysis of Genomic Annotation (MAGMA)

Building upon the PLACO results, the identified loci were mapped to nearby genes to elucidate the shared biological mechanisms underlying pleiotropic sites. MAGMA was applied to genes at or overlapping with pleiotropic sites derived from the PLACO output and single-trait GWAS, aiming to identify candidate pleiotropic genes. The significance threshold for MAGMA was set at $P < 0.05/N_genes = 3\times10^{-6}$. Functional mapping and annotation of genetic associations were used to characterize the biological functions of these loci[19]. Additionally, pathway enrichment analyses were performed via the Molecular Signatures Database (MSigDB) to functionally annotate the mapped genes. SNPs and risk loci within the MHC region were excluded from both the PLACO and MAGMA gene and gene-set analyses.

6. Colocalization analysis

For pleiotropic loci annotated by FUMA, Bayesian colocalization analysis was performed via the R package Coloc[20] (PMID: 27866706) to evaluate the probability of shared causal variants between trait pairs. This approach assumes a single causal variant (SCV) within each gene region, suggesting that both traits are influenced by the same genetic variant. Colocalization analysis computes posterior probabilities (PPs) for five hypotheses: H0: Neither trait has a genetic association in the region; H1: Only trait 1 is associated; H2: Only trait 2 is associated; H3: Both traits are associated but via distinct causal variants; H4: Both traits are associated and share a common causal variant. The coloc.abf function was used with explicitly specified prior probabilities for (i) each

trait having a causal variant and (ii) the two traits sharing a causal variant. This systematic assessment of pleiotropic loci across traits provides evidence for potential shared biological mechanisms.

7. Hypothesis prioritization for multitrait colocalization analysis (Hyprcoloc)

HyPrColoc[21] (PMID:33536417), combined with multitrait colocalization analysis of immune GWAS data, has revealed the potential pivotal role of immune cells in the pathogenesis of CVDs and GTDs. This approach prioritizes gene loci with shared genetic variants across multiple traits, thereby uncovering genetic associations among diverse phenotypes. By applying HyPrColoc, GWAS data from various immune traits and target diseases (CVDs and GTDs) can be efficiently integrated to identify gene loci with significant colocalization signals.

GWAS summary statistics for gut microbiota traits (as exposure data) were downloaded from the MiBioGen consortium (http://www.mibiogen.org/)[22]. The gut microbiota was categorized into 211 taxonomic units, including 131 genera, 35 families, 20 orders, 16 classes, and 9 phyla. Microbiota data from 18,340 individuals across 24 cohorts were analyzed, comprising 5,717,754 SNPs derived from 16S fecal genotyping. Genotype imputation was performed via the HRC 1.0 or 1.1 reference panel. Subsequent association analyses employed Spearman correlation, adjusting for covariates, including age, sex, technical factors, and genetic principal components.

8. MR study

All significant genetic loci independently associated with exposure were selected as instrumental variables ($P < 5\times10^{-8}$) via the clumping function in PLINK software (version 1.9)[23]. The r^2 threshold for defining linkage disequilibrium between instrumental variables was set at 0.001, and the genomic window size was defined as 10,000kb. To ensure the robustness and strength of the selected instrumental variables, we further calculated the r^2 values and F statistics[24] for each variable. The formula for calculating the F value is as follows:

$$F = (\frac{n-1-k}{k})(\frac{r^2}{1-r^2})$$

In MR analyses, R^2 denotes the proportion of variance explained by instrumental

variables (IVs), n represents the sample size, and k indicates the number of SNPs. The inverse variance weighted (IVW) method is the primary approach in MR, requiring IVs to satisfy three core assumptions: (1) the IV must be associated with the exposure; (2) the IV should not be correlated with confounding factors related to both the exposure and the outcome; and (3) the effect of the IV on the outcome must be entirely mediated through the exposure. The sensitivity analyses included the following. First, the Q test for IVW and MR–Egger can detect potential violations of assumption[25] by assessing the heterogeneity of associations among individual instrumental variables (IVs). Second, MR–Egger is employed to estimate horizontal pleiotropy through its intercept term, ensuring that genetic variants are independently associated with exposure and outcome as per assumption[26]. Additionally, supplementary analyses using alternative MR methods, such as the weighted median and weighted mode, which incorporate distinct modeling assumptions and advantages, further enhance the stability and robustness of the findings. Statistical analyses were conducted in R v3.5.3 via the Mendelian randomization package[27]

9. Ethics

This study was designed and conducted in accordance with ethical guidelines for human subject research and adheres to the principles of the Declaration of Helsinki. Data were obtained through an approved UK Biobank (UKB) project application.

Results

1. Genetic correlations between CVDs and GTDs

LDSC genetic correlation analysis revealed significant genetic correlations between CVDs and GTDs. Sensitivity analyses using HDL traits further validated the robustness of most findings. To account for multiple testing, the Bonferroni correction was applied ($P < 0.05/77 = 6.5\times10^{-4}$), and numerous disease pairs retained statistically significant associations (Figure 1 and Supplement Table S2).

2. Shared loci and genes between CVDs and GTDs

Pleiotropy analysis by PLACO was conducted on disease pairs with significant correlations, resulting in the identification of a total of 350 pleiotropic loci. The identified pleiotropic loci and their corresponding basic information for each genomic

risk locus are summarized in Supplement Table S3. The functional impacts of pleiotropic SNPs on genes are detailed in Supplement Table S4. Additionally, Manhattan and quantile–quantile plots illustrating the relationships between diseases are provided in Supplement Figures S1-S12.

Colocalization analysis revealed 95 shared causal loci (PP.H4 > 0.8) across the investigated diseases, as shown in Figure 2A and summarized in Table 1. MAGMA gene set analysis for CVDs and GTDs revealed multiple associated gene pathways (Supplement Figure S13 and Table S5). Key findings include the following: 1) Biological processes linked to diseases, such as muscle contraction, cell signaling, and macro-molecule synthesis, are significantly associated. 2) Disease-specific pathways: GORD: Strong associations with muscle structure development, positive regulation of cholesterol storage, and transcriptional regulation (*P* values: 10^{-9}-10^{-5}). AF: Enriched pathways related to cardiac conduction, circulatory system processes, and vascular processes. IBD and HYPTENSESS: Close links to immune/inflammatory pathways (e.g., T-cell activation, response to oxidized compounds), implicating immune mechanisms in disease pathogenesis.

Tissue-specific enrichment patterns across diseases and biomarkers are depicted in Figure 2B and Supplement Table S6, highlighting significant associations between multiple diseases and corresponding tissues. Notably, the small intestine terminal ileum and whole blood showed robust enrichment of numerous markers, suggesting that these tissues may play pivotal roles in the pathogenesis of related diseases, including IBD, AF, and HYPTENSESS. For example, IBD and HYPTENSESS exhibited substantial enrichment in these tissues, indicating their involvement in immune responses and metabolic dysregulation. Additionally, the spleen and whole blood were strongly enriched for markers associated with atrial fibrillation and diabetes, underscoring their critical roles in immune and cardiovascular health. Conversely, tissues such as Uterus, Esophagus muscularis, and others were enriched in digestive system diseases (e.g., peptic ulcers), highlighting their potential influence on gastrointestinal pathologies.

3. Prioritization of candidate pleiotropic genes and characterization of phenotype and tissue specificity

MAGMA gene-based analysis of the PLACO results revealed 337 pleiotropic genes (P <0.05/18,645=2.682×10^{-6}; Supplement Table S7). By integrating eQTL data from gastrointestinal, cardiovascular, and whole blood tissues to map pleiotropic genes, a total of 1,427 genes were identified. Figure 3A illustrates the overlap of genes across methods, with details in Supplement Table S8. Figure 3B shows genes identified by neighboring gene mapping, MAGMA, and eQTL analysis, along with their expression profiles across 54 tissues. Tissue-specific enrichment analysis revealed significant enrichment in heart, pancreas, and brain tissues (Figure 3C).

4. Protein–protein interaction (PPI) network analysis

Pathway enrichment analysis of pleiotropic genes is depicted in Figure 4 and Supplement Table S9, while protein–protein interaction (PPI) network analysis is shown in Supplement Figure S14. Positive regulation of interleukin-17(IL-17) production is the most important pathway in both CVDs and GTDs.

5. Synaptic and immune-related mechanisms shared between CVDs and GTDs

Immunological abnormalities are a common pathogenic cause of various diseases. Meanwhile, PPI network analysis demonstrated the key role of immunological factor-IL17. This study explored the common role of immunity in CVDs and GTDs. Significant pleiotropic associations were identified between GTDs (e.g., GERD and IBD) and CVDs (e.g., HYPTENSESS and AF). These findings suggest bidirectional interactions between these diseases, potentially mediated by shared immune cell populations and tissues, with common immune response mechanisms likely playing a role. Specifically, immune cell subsets such as $CD8^+$ T cells, T follicular helper (Tfh) cells, regulatory B cells, and $MTS15^+$ Th17 cells were significantly enriched in both disease categories, highlighting their critical roles in the pathogenesis of gastrointestinal and cardiovascular conditions. Additionally, cross-disease correlations were observed for multiple cell populations, including $CD103^+$ $CD11b^+$ dendritic cells (DCs), $CD8^+$ splenic lymph node DCs ($DC.8^+SLNs$), and γδ T cells ($Tgd.vgd^+24ah^+17$. Th), underscoring the pleiotropic nature of immune system involvement. The results are visualized in Figure 5.

6. Multitrait colocalization analysis to pinpoint critical gut microbiota

Multitrait colocalization analysis via HyPrColoc identified 6 pleiotropic loci harboring shared pathogenic microbiota, highlighting the significant role of the gut microbiota in disease pleiotropy (Supplement Table S10). For example, the Ruminococcus gauvreauii group was critically associated with CD/IBD and AF, whereas Firmicutes phylum members were significantly linked to PGM/PUD and HYPTENSESS.

7. MR and Associations between CVDs and GTDs

Two-sample MR analysis revealed that significant causal associations were identified from CVDs to GTDs and vice versa (Supplement Figure S15).

Discussion

This study systematically identified extensive genome-wide genetic associations and significant genetic overlap between CVDs and GTDs. Comprehensive analyses revealed pleiotropic genetic variants, shared causal loci, and converging biological pathways, alongside gut microbiota signatures, that underpin the shared pathogenesis of these disease categories. These findings provide robust evidence for a common genetic etiology linking CVDs and GTDs, with implications for their comorbidity and joint therapeutic targeting.

Using PLACO, 350 pleiotropic loci were identified, 95 of which were demonstrated to have shared causal variants (PP.H4 > 0.8) via colocalization analysis. These loci include genes such as ZHX3 (20q12), ATXN2 (12q24.12), and THADA (2p21), which are independently linked to both CVDs (e.g., AF) and GTDs (e.g., IBD). Two-sample Mendelian randomization (MR) analysis further revealed bidirectional causal associations between CVDs and GTDs, which is consistent with vertical pleiotropy, where shared variants influence both traits through common biological pathways. LDSC-based sample overlap detection and LHC-MR adjustments confirmed the robustness of these findings, ruling out major confounding factors from overlapping datasets.

Central to the shared pathogenesis are inflammatory and immune pathways, particularly those involving IL-17 and Th17 cells[28]. MAGMA analysis identified IL-17

signaling as a key shared pathway, with Th17 cells serving as a critical immune cell subset. In GTDs, IL-17 exacerbates intestinal mucosal barrier dysfunction in ulcerative colitis and Crohn's disease by increasing the levels of proinflammatory cytokines (e.g., IL-6 and CXCL1) and chemokines[29 31]. In CVDs, IL-17 promotes atherosclerotic plaque instability, endothelial dysfunction, and thrombosis, linking it to hypertension, myocardial infarction, and ischemic stroke[32 33 34–37]. Clinical studies have shown elevated plasma IL-17 levels and Th17 cell counts in patients with acute coronary syndrome compared with stable angina patients or healthy controls[48,49], underscoring their role in disease progression. The plasticity of TH17 cells in diverse inflammatory micro-environments—regulated by transcription factors such as RORγt and cytokines such as IL-23—further bridges CVDs and GTDs[39 40–44]. For example, IL-17-induced secretion of granulocyte–macrophage colony–stimulating factor promotes both atherosclerotic lesion development and ulcerative colitis progression[45,46], highlighting mechanistic convergence.

The gut microbiota has emerged as a critical mediator of shared pathogenesis. HyPrColoc identified 6 pleiotropic loci involving taxa such as the Ruminococcus gauvreauii group, Collinsella, and Firmicutes phylum members, which were enriched in both CVDs and GTDs. Mechanistically, the microbiota influences cardiovascular health through pathways such as epithelial sodium/hydrogen exchanger activation and myocyte enhancer factor signaling[52], whereas in the gut, taxa such as AKK modulate inflammation via FXR receptor activation[50]. The observed cross-disease correlations for the Ruminococcus gauvreauii and Lachnospiraceae FCS020 groups highlight their dual roles in gastrointestinal homeostasis and vascular dysfunction.

The identification of shared genetic biomarkers (e.g., NMT1 and CDC27) and immune cell targets (e.g., TH17 and γδ T cells) offers opportunities for the early prediction of GTD-CVD comorbidities. For example, IL-17-targeted biologics, which are already used to treat inflammatory bowel disease, may have broader utility in preventing cardiovascular complications. Additionally, microbiota modulation—such as probiotic interventions targeting Ruminococcus or Collinsella—could represent a novel strategy to disrupt shared pathogenic pathways. While this study leveraged large-

scale GWAS data, it is limited by the European-ancestry focus, which may restrict its generalizability to other populations. Future studies incorporating diverse ancestries and longitudinal data will be critical to validate these findings and dissect temporal relationships. Single-cell RNA sequencing and functional genomics experiments (e.g., CRISPR-Cas9) could further mechanistically validate the roles of pleiotropic genes such as THADA and ZHX3 in both tissue contexts.

This study has several advantages. It is a large-scale sample focuses on the shared genetic characteristics between CVDs and GTDs. Through a systematic design, it comprehensively evaluates the genetic associations among various diseases, providing extensive data support for understanding the comorbidity mechanism of these two types of diseases. This study is the first to report a number of previously unrecognized pleiotropic variants or genes. These findings help elucidate the biological mechanisms of genetic factors in cardiovascular and gastrointestinal comorbidities, help promote an in-depth understanding of the genetic basis of disease co-occurrence in related fields, and provide a basis for further development of clinical therapies.

This study also has several limitations that should be acknowledged. First, there was insufficient population representativeness. The study is limited to the European population. In the future, it is necessary to expand the sample size of the abovementioned population to enhance the ethnic/racial universality of the research conclusions. The existing analysis still has room for improvement. More refined statistical methods (such as local-level analysis) should be adopted to explore more potential genetic associations between CVDs and GTDs. At present, the identified pleiotropic genetic biomarkers have not been verified by in vivo or in vitro experiments, and their specific biological functions are still unclear. In the future, it will be necessary to analyze the mechanism of action of these biomarkers through cell models, animal experiments, etc. Although the discovered biomarkers are expected to become therapeutic targets and promote personalized medicine, their practical application value has not been verified in clinical settings. Subsequent studies should focus on their potential for clinical transformation, such as their diagnostic efficacy and ability to predict treatment response. In addition, there are various potential risks of bias,

including insufficient statistical power in the analysis of genetic evidence for low-incidence diseases and weak instrument bias in Mendelian randomization analysis. Although multiple statistical methods have been used to correct for confounding factors, more rigorous study designs are still needed to further verify the robustness of the research results.

Conclusion

This study establishes a genetic and mechanistic framework for the shared etiology of CVDs and GTDs, highlighting pleiotropic variants, inflammatory pathways, and gut microbiota interactions as key drivers. These insights not only deepen our understanding of cardiovascular–gastrointestinal comorbidities but also pave the way for precision medicine approaches targeting shared biological mechanisms.

Abbreviations

gastrointestinal tract diseases (GTDs), cardiovascular diseases (CVDs), inflammatory bowel disease (IBD), Crohn's disease (CD), ulcerative colitis (UC), peptic ulcer disease (PUD), gastroesophageal reflux disease (GORD), irritable bowel syndrome (IBS), a combined phenotype of PUD, GORD, and related medications (PGM), abdominal aortic aneurysm (ABAORTANEUR), atrial fibrillation and flutter (AF), aortic aneurysm (AORTANEUR), aortic dissection (AORTDIS), calcific aortic valvular stenosis (CAVS_OPERATED), major coronary heart disease (CHD), heart failure (HEARTFAIL), essential hypertension (HYPTENSESS), other peripheral vascular diseases (OTHPER), stroke (STR), and thoracic aortic aneurysm (THAORTANEUR).

Ethics approval and consent to participate

This study was designed and conducted in accordance with ethical guidelines for human subject research and adheres to the principles of the Declaration of Helsinki. Data were obtained through an approved UK Biobank (UKB) project application.

Consent for publication

All authors have agreed to the publication of this article.

Availability of data and materials

The Program in Complex Trait Genomics (https://cnsgenomics.com/content/data), GWAS Catalog (https://www.ebi.ac.uk/gwas/), Regensburg GEM Platform (https://www.uni-regensburg.de/medizin/epidemiologie-praeventivmedizin/genetische-epidemiologie/software/index.html), and GWAS Atlas (https://atlas.ctglab.nl/traitDB) provided access to genome-wide association study data. We thank all research participants who provided DNA samples for these studies.

Competing interests

The authors declare that they have no conflicts of interest. All authors contributed to data analysis, drafting, or revision of the article; agreed on the journal to which the article is being submitted; provided final approval of the version to be published; and agreed to be accountable for all aspects of the work.

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Authors' contributions

Yang Li, Zhengxi Qiu, and Zhiyuan Li drafted the manuscript and created all the tables. Yirong Wu, Jinchen Chong, and Jiaze Ma collected the data. Chen Chen, Jiepin Li, Yirong Yang, Zhihua Lu, Xiaomin Yuan, Yijia Zhu, and Tuo Chen analyzed the data and generated all the figures. Yang Li provided research funding and designed the study. All the authors reviewed the manuscript.

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Clinical trial number

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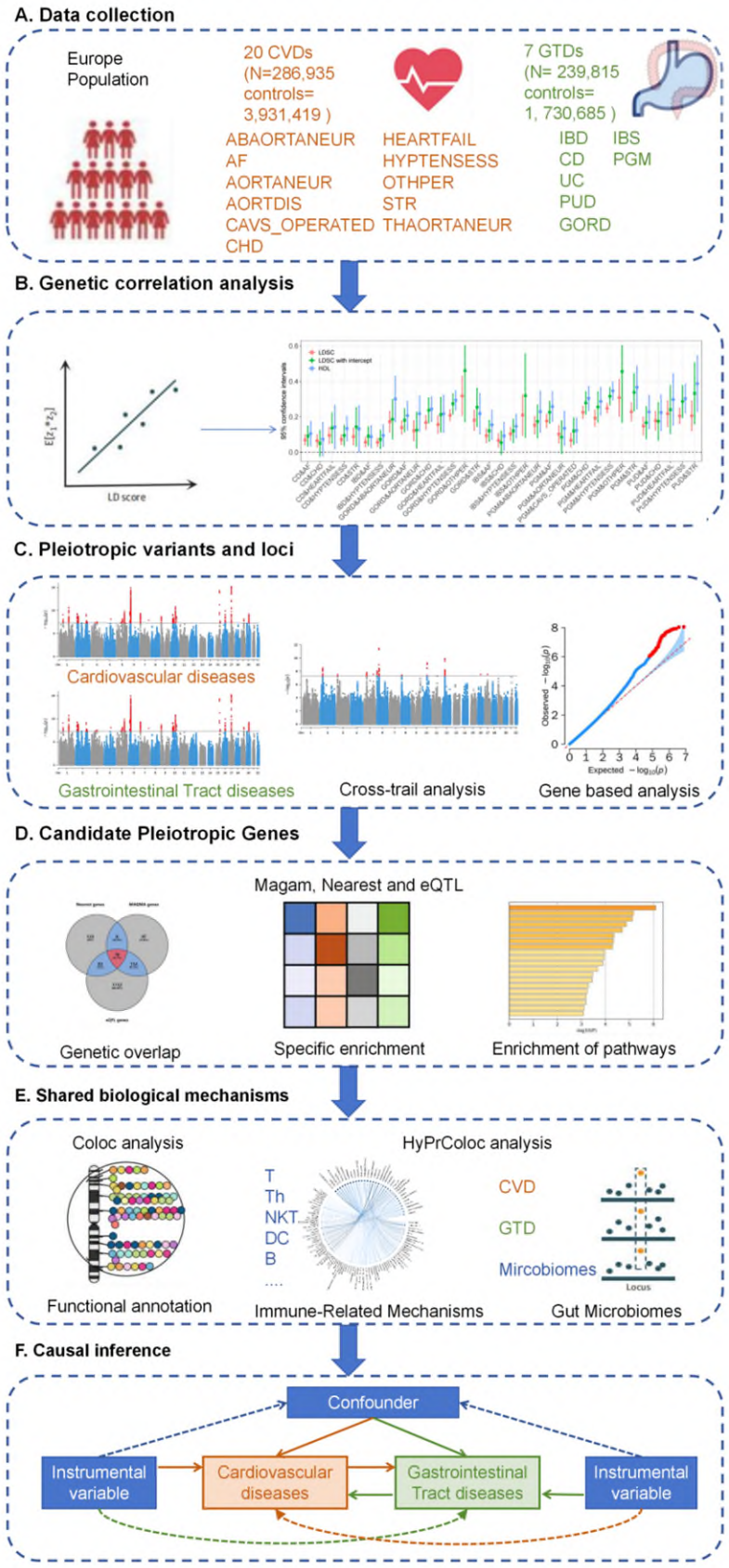


Figure Flowchart

Figure legend

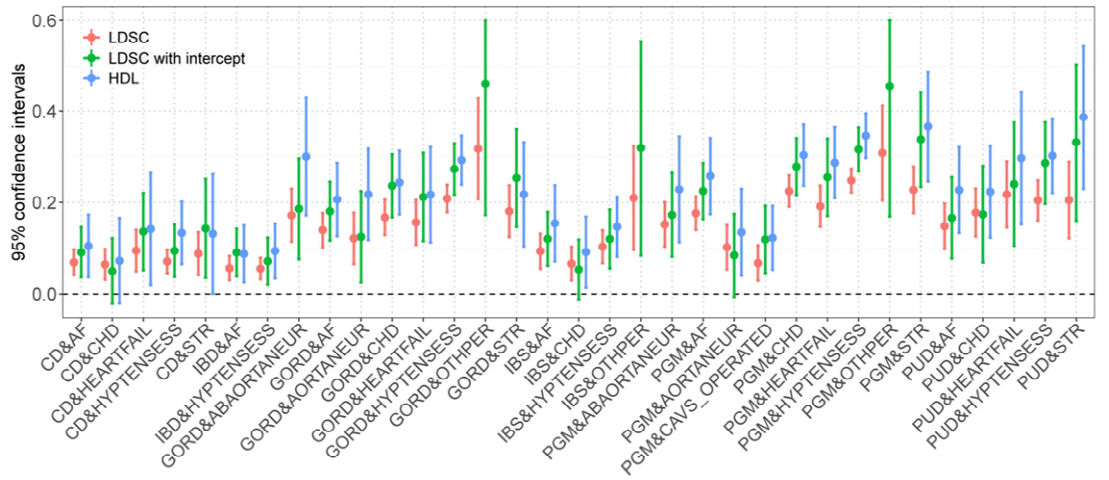


Figure1. LDSC genetic correlation analysis revealed significant genetic correlations between gastrointestinal tract diseases and cardiovascular diseases, and HDL analysis verified the stability of most results. Further multiple test correction using Bonferroni ($P < 0.05/77 = 6.5E\text{-}4$) showed that there were still significant associations between many disease pairs. The specific data are shown in Table S2.

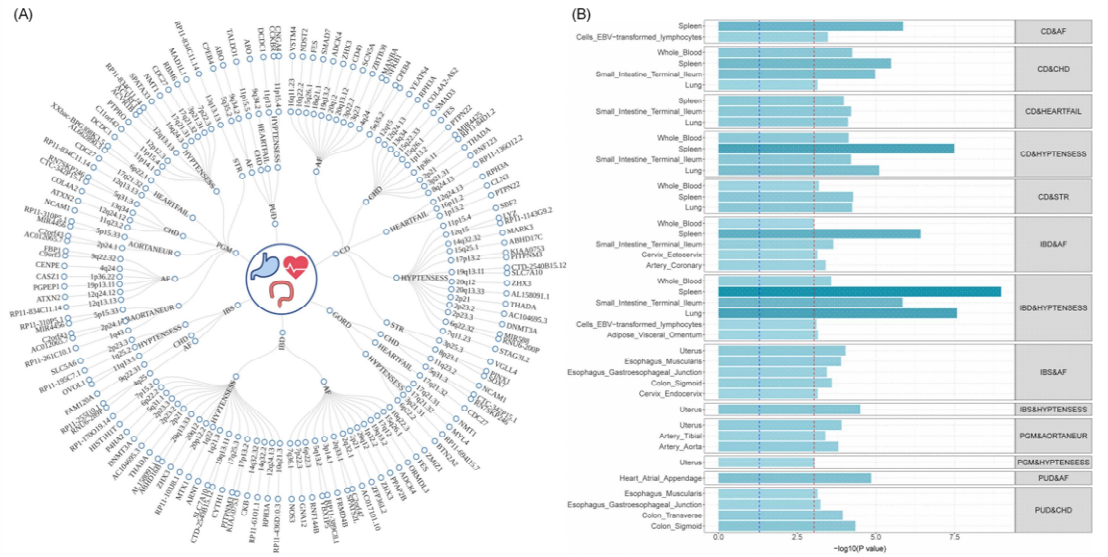


Figure2. A. Co-localization analysis identified 95 shared causal loci (PP.H4 > 0.8) among disease pairs. B. The enrichment of different tissues in specific diseases or biomarkers reveals significant associations between multiple diseases and tissues, with detailed information provided in Supplementary Table S6.

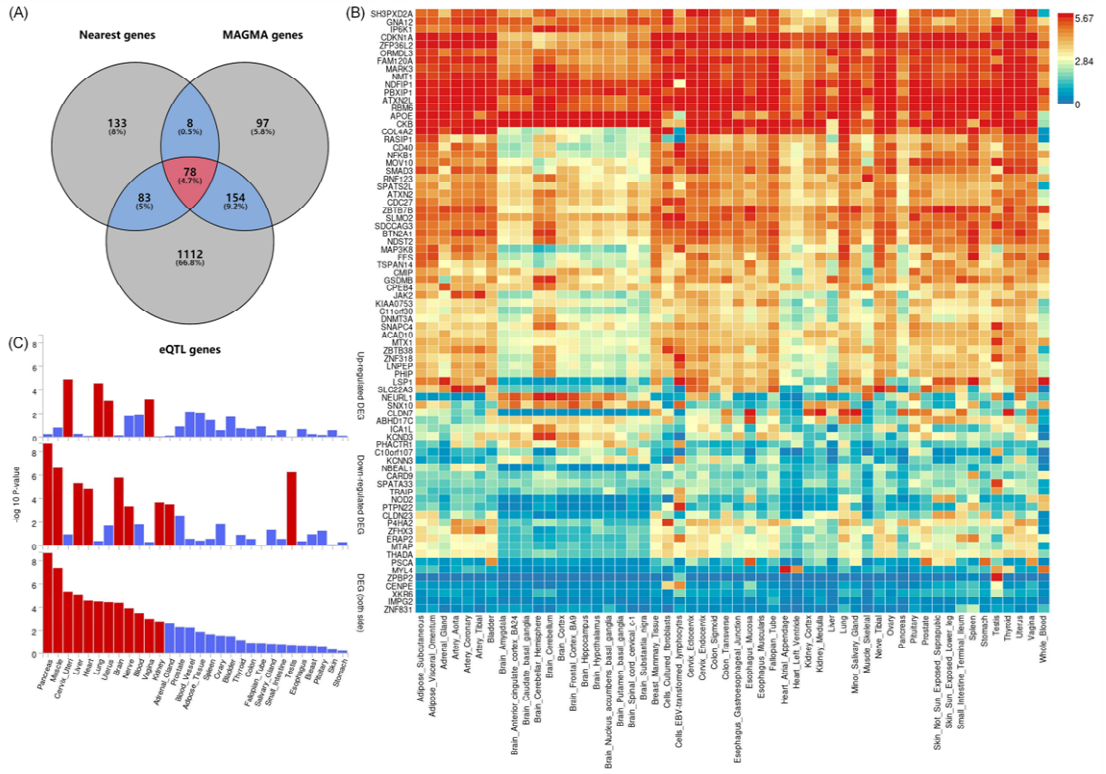


Figure 3. A. Gene overlap across different methods, with detailed information on these genes available in Supplementary Table S8; B. Expression profiles of pleiotropy-associated genes—identified via overlapping nearby genes, Magma-derived genes, and eQTL-related genes—in 54 distinct tissues; C. Tissue-specific enrichment analysis reveals that genes mapped to these loci are enriched in tissues including the heart, pancreas, and brain.

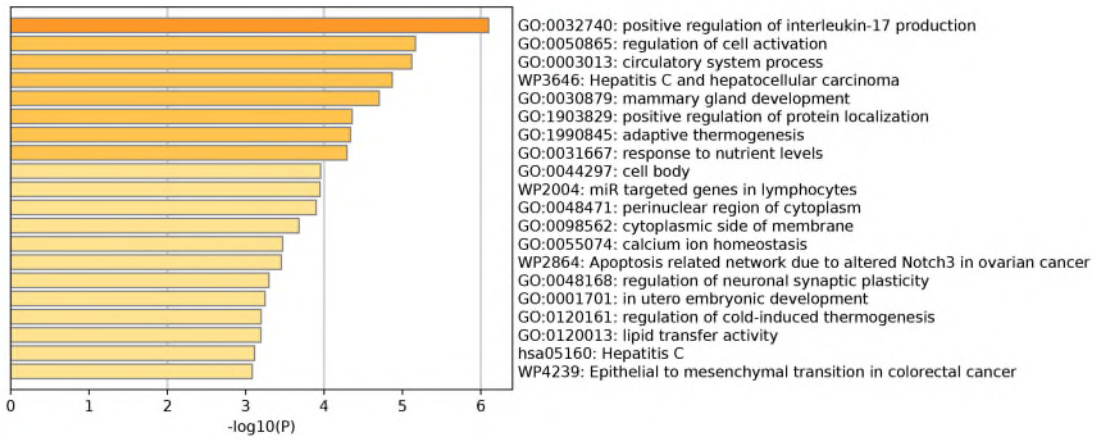


Figure 4. Pathway enrichment analysis of pleiotropic genes, with detailed information provided in Supplementary Table S9; the protein-protein interaction (PPI) network analysis of pleiotropic genes is shown in Supplementary Figure S14.

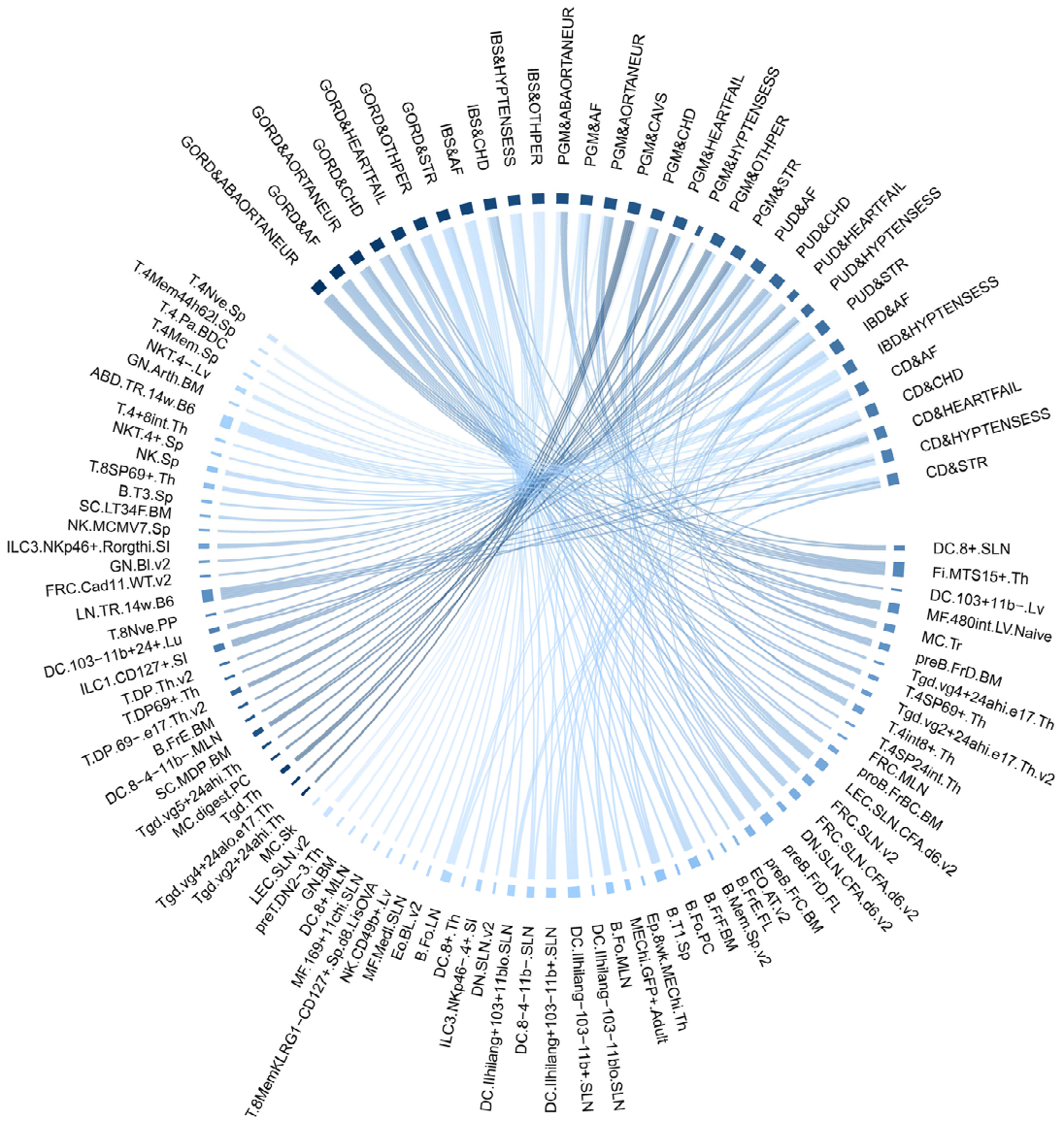


Figure 5. Immune cell atlas displaying co-localization signals across different phenotype pairs. Significant pleiotropic associations exist between gastrointestinal diseases (e.g., GORD, IBD) and cardiovascular diseases (e.g., PUD, $CD8^{+}AF$), indicating that these diseases may interact reciprocally under the influence of distinct immune cells and tissues, sharing common immune response mechanisms.

Table1. Overlapping pleiotropic loci and colocalization analysis of gastrointestinal diseases and different cardiovascular diseases

Trait pairs	Genomic Locus	LeadSNPs	P	Nearby genes	PP H4
CD & AF	10q11.23	rs4240499	9.74E-11	VSTM4	0.838
IBD & HYPTENSESS	10q21.3	rs7922082	2.01E-09	RP11-436D10.3	0.958
CD & AF	10q22.2	rs4691	3.46E-09	NDST2	0.834
PUD & HYPTENSESS	11p13	rs11604176	1.98E-08	DCDC1	0.966
PGM & HYPTENSESS	11p14.1	rs921880	2.55E-08	DCDC1	0.956
PGM & HYPTENSESS	11p15.4	rs11040804	6.59E-11	C11orf42	0.884
PUD & HYPTENSESS	11p15.4	rs10500661	9.04E-12	CNGA4, CCKBR	0.874
PUD & CHD	11p15.5	rs75613328	1.41E-08	TALDO1	0.874
PGM & HYPTENSESS	12p12.3	rs12297543	6.97E-10	PTPRO	0.860
PGM & AF	12q13.13	rs736825	1.13E-08	RP11-834C11.14	0.901
PGM & HEARTFAIL	12q13.13	rs12426399	5.58E-09	RP11-834C11.14	0.955
PGM & HYPTENSESS	12q13.13	rs11450619	3.03E-08	ACVRL1, ACVR1B	0.899
PGM & HYPTENSESS	12q13.13	rs2077177	6.44E-14	RP11-834C11.14	0.860
PGM & STR	12q13.13	rs4759318	8.88E-09	RP11-834C11.14	0.906
CD & CHD	12q15	rs10878972	3.82E-08	YEATS4	0.847
CD & HYPTENSESS	12q15	rs12366463	2.77E-08	RP11-1143G9.2, LYZ	0.946
PGM & AF	12q24.12	rs653178	2.59E-11	ATXN2	0.989
PGM & CHD	12q24.12	rs653178	1.72E-16	ATXN2	0.989
IBD & HYPTENSESS	12q24.13	rs233724	2.20E-12	RPH3A	0.938
CD & CHD	12q24.13	rs233724	6.80E-11	RPH3A	0.997
PGM & CHD	13q34	rs7333991	1.31E-09	COL4A2	0.809
CD & CHD	13q34	rs9521787	1.36E-08	COL4A2-AS2	0.918
IBD & HYPTENSESS	14q32.2	rs1461584	4.39E-08	RP11-61O1.1	0.931
IBD & HYPTENSESS	14q32.32	rs1136165	2.52E-12	CKB	0.930
CD & HYPTENSESS	14q32.32	rs7157631	6.12E-13	MARK3	0.912
CD & CHD	15q22.33	rs56062135	4.28E-19	SMAD3	0.997

CD & AF	15q26.1	rs4932373	1.35E-08	FES	0.837
CD & HEARTFAIL	16p11.2	rs34838	1.21E-13	CLN3, CLN3	0.912
PGM & HYPTENSESS	16q24.3	rs258319	4.82E-08	SPATA33	0.853
IBD & AF	17q12	rs12603332	6.52E-16	ORMDL3	0.855
GORD & HYPTENSESS	17q21.31	rs1053739	2.04E-08	NMT1	0.967
PGM & HYPTENSESS	17q21.31	rs1053739	2.78E-08	NMT1	0.953
GORD & HEARTFAIL	17q21.32	rs221606	1.24E-09	CDC27	0.901
GORD & HYPTENSESS	17q21.32	rs4968309	9.63E-09	MYL4	0.896
PGM & HYPTENSESS	17q21.32	rs6504743	4.54E-08	CDC27	0.852
IBD & HYPTENSESS	17q25.3	rs11658134	4.15E-08	CYTH1	0.888
CD & AF	18q21.1	rs79544247	6.41E-09	SMAD7	0.971
PGM & AF	19p13.11	rs34068189	2.40E-08	PGPEP1	0.839
IBD & HYPTENSESS	19q13.11	rs62126611	1.60E-12	SLC7A10, CTD-2540B15.12	0.845
IBD & AF	19q13.2	rs2115239	8.08E-09	ADCK4	0.930
CD & AF	19q13.2	rs2115239	1.55E-08	ADCK4	0.941
CD & CHD	1p13.2	rs2476601	3.79E-13	PTPN22	0.909
IBD & AF	1p32.2	rs72664358	8.23E-10	PPAP2B	0.980
PGM & AF	1p36.22	rs6660242	8.07E-09	CASZ1	0.922
IBD & HYPTENSESS	1q21.3	rs10305667	4.28E-08	ARNT	0.849
IBD & HYPTENSESS	1q22	rs760077	3.24E-09	MTX1	0.898
IBS & HYPTENSESS	1q25.2	rs2175177	3.98E-08	RP11-195C7.1	0.945
IBD & HYPTENSESS	20p12.2	rs6040076	2.58E-08	RP11-103J8.1	0.947
IBD & AF	20q12	rs17181845	6.41E-10	ZHX3	0.898
IBD & HYPTENSESS	20q12	rs17181845	1.42E-09	ZHX3	0.897
CD & AF	20q12	rs6065325	1.40E-08	ZHX3	0.958
CD & HYPTENSESS	20q12	rs6065325	2.62E-08	ZHX3	0.947
CD & AF	20q13.12	rs4810485	2.70E-08	CD40	0.807
IBD & HYPTENSESS	20q13.33	rs2427541	8.98E-10	AL158091.1, ABHD16B	0.985

CD & HYPTENSESS	20q13.33	rs2427539	4.93E-10	AL158091.1	0.989
IBD & HYPTENSESS	2p21	rs6747202	8.53E-10	THADA	0.973
CD & CHD	2p21	rs7589033	7.76E-10	THADA	0.936
CD & HYPTENSESS	2p21	rs12477432	1.96E-09	THADA	0.972
IBD & HYPTENSESS	2p23.2	rs1260326;rs11677002	4.12E-13	AC104695.3	0.948
CD & HYPTENSESS	2p23.2	rs1260326;rs4666067	9.65E-13	AC104695.3	0.958
IBS & HYPTENSESS	2p23.3	rs11608	6.79E-10	SLC5A6	0.931
IBD & HYPTENSESS	2p23.3	rs7578575	2.96E-13	DNMT3A	0.996
CD & HYPTENSESS	2p23.3	rs7578575	1.27E-11	DNMT3A	0.994
PGM & ABAORTANEUR	2p24.1	rs10193919	4.72E-12	AC012065.7, C2orf43	0.992
PGM & AORTANEUR	2p24.1	rs10193919	9.60E-12	AC012065.7, C2orf43	0.968
IBD & AF	2q32.1	rs2595391	1.74E-08	AC017101.10	0.816
IBD & AF	2q33.1	rs1217429	3.36E-08	C2orf47, SPATS2L	0.885
IBD & AF	3p14.1	rs6786528	4.46E-08	FRMD4B	0.824
GORD & HYPTENSESS	3p21.31	rs143171929	6.36E-09	RP11-694I15.7	0.967
PGM & HYPTENSESS	3p21.31	rs76367790	9.19E-09	RBM6	0.965
CD & AF	3p22.2	rs71323670	1.93E-08	SCN5A	0.893
CD & STR	3p25.3	rs62248311	3.32E-08	VGLL4	0.850
CD & AF	3q23	rs2871960	1.17E-09	ZBTB38	0.917
PGM & AF	4q24	rs2711894	6.86E-09	CENPE	0.908
CD & AF	4q24	rs4698861	1.09E-08	NFKB1, MANBA	0.947
IBS & AF	4q25	rs149054443	5.49E-10	RNU6-289P, RP11-255I10.1	0.933
PGM & ABAORTANEUR	5p15.33	rs61580655	9.39E-09	MIR4456, RP11-310P5.1	0.847
PGM & AORTANEUR	5p15.33	rs61384641	6.55E-09	MIR4456, RP11-310P5.1	0.852
IBD & AF	5q13.2	rs4703855	3.33E-08	RP11-389C8.1, YBX1P5	0.842
IBD & HYPTENSESS	5q31.1	rs3792894	4.14E-14	P4HA2	0.918

GORD & CHD	5q31.3	rs7356639	6.56E-09	RN7SKP246, CTC-342P15.1	0.953
PGM & CHD	5q31.3	rs7356639	7.23E-10	RN7SKP246, CTC-342P15.1	0.979
PUD & AF	5q35.2	rs75049939	7.64E-09	CPEB4	0.801
IBD & HYPTENSESS	6p22.2	rs198846	1.47E-10	HIST1H1T	0.825
CD & HYPTENSESS	6q22.32	rs10457481	4.75E-08	MIR588, RNU6-200P	0.911
IBD & HYPTENSESS	7p15.2	rs4722672	4.54E-10	RP1-170O19.14	0.994
PGM & HYPTENSESS	7p22.3	rs4721096	1.27E-12	MAD1L1	0.931
IBD & AF	7p22.3	rs798508	4.66E-10	GNA12	0.910
CD & HYPTENSESS	7q11.23	rs2529275;rs236660	4.02E-10	STAG3L2	0.810
IBD & AF	7q36.1	rs3918226	1.24E-08	NOS3	0.941
CD & STR	8p23.1	rs6601535	3.80E-08	SOX7, PINX1	0.814
CD & CHD	8q24.13	rs2980862	5.85E-09	RP11-136O12.2	0.910
PUD & AF	9q34.2	rs115478735	2.63E-11	ABO	0.925
PUD & HEARTFAIL	9q34.2	rs115478735	2.76E-10	ABO	0.955

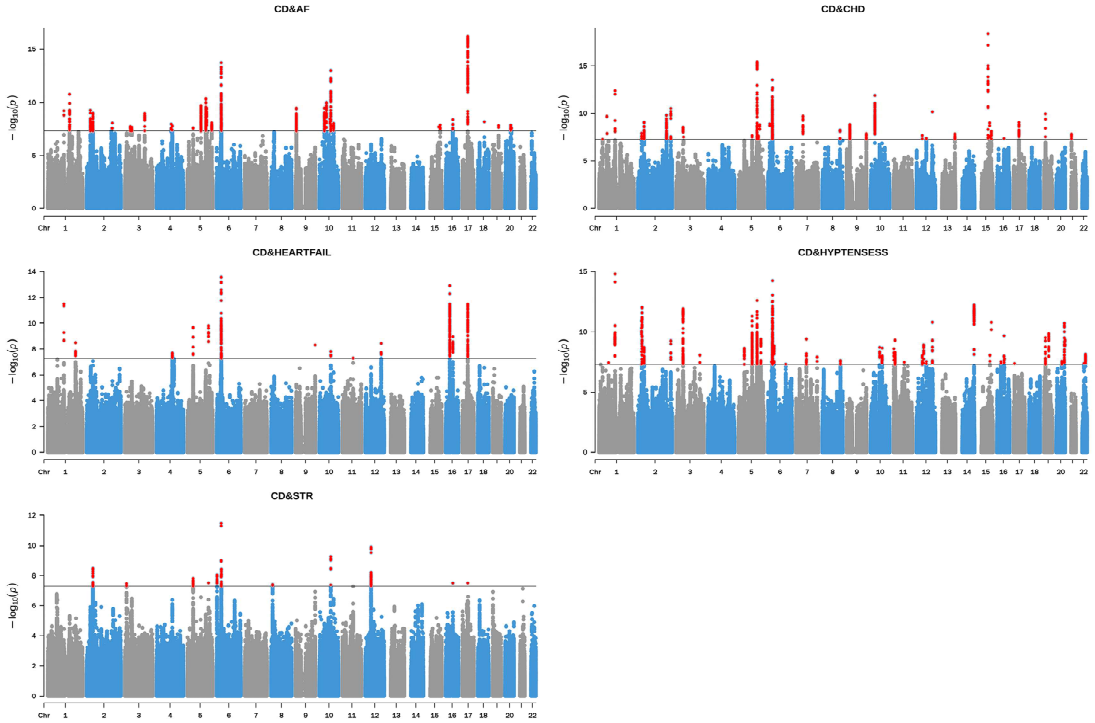


Figure S1. Manhattan plot of pleiotropic signals between CD and cardiovascular diseases

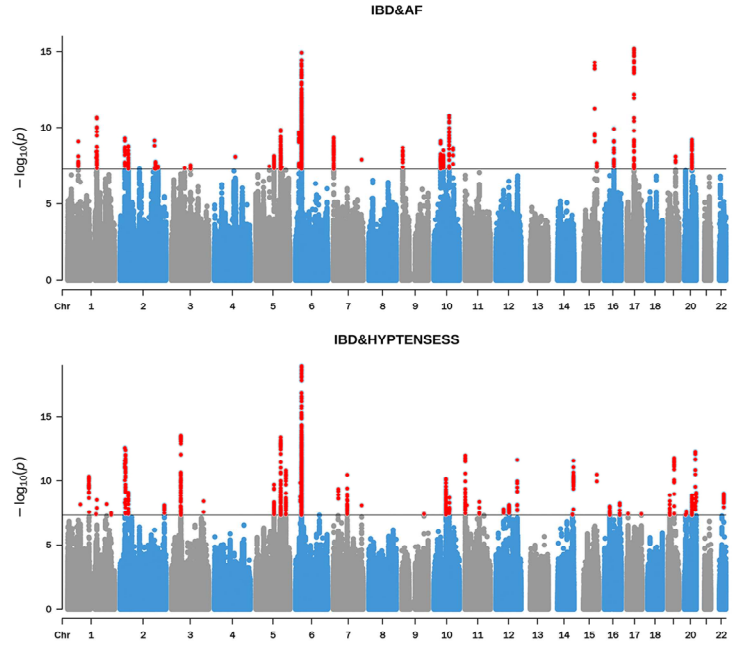


Figure S2. Manhattan plot of pleiotropic signals between IBD and cardiovascular diseases

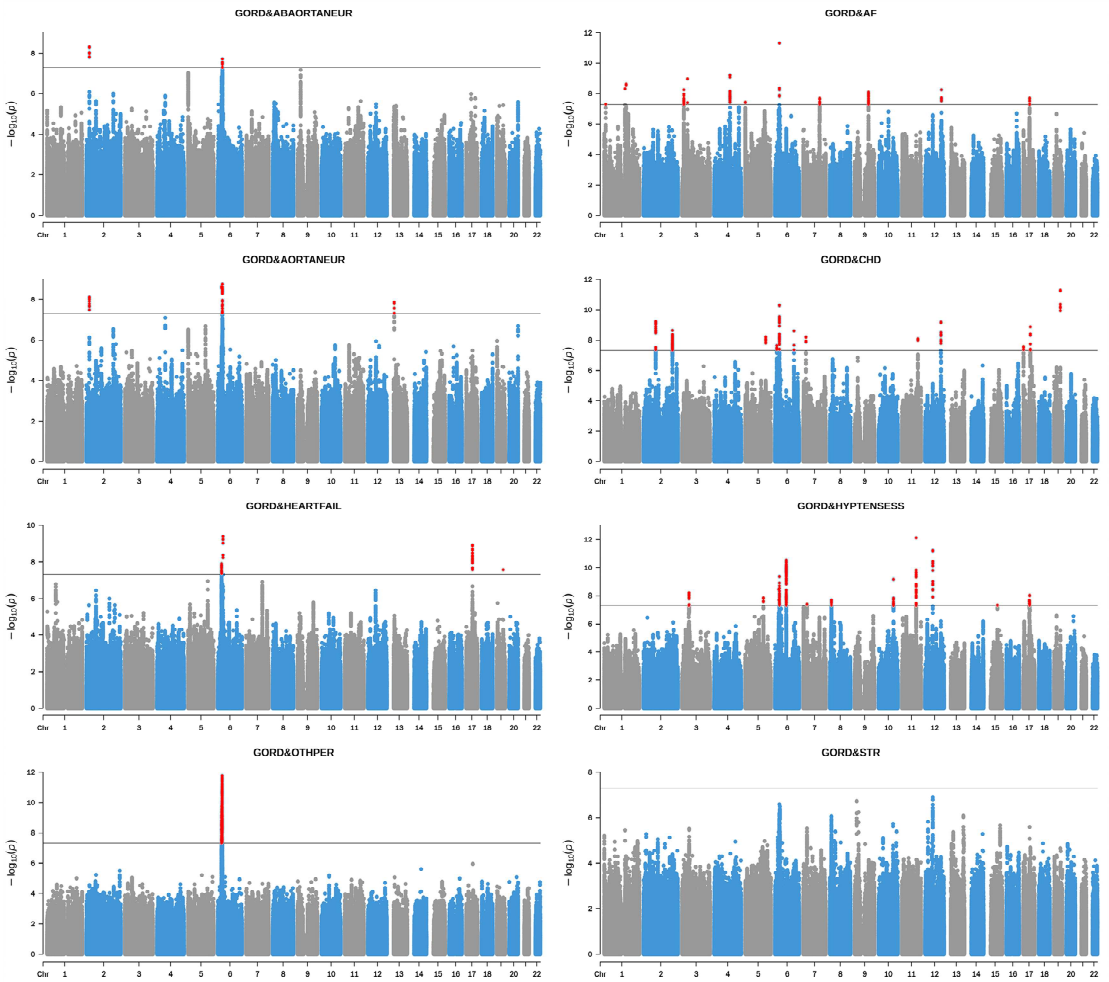


Figure S3. Manhattan plot of pleiotropic signals between GORD and cardiovascular diseases

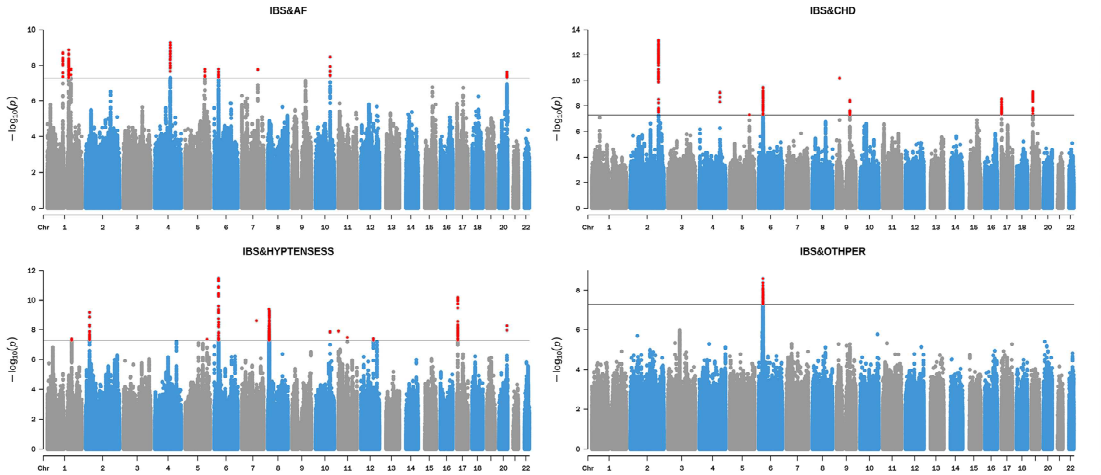


Figure S4. Manhattan plot of pleiotropic signals between IBS and cardiovascular diseases

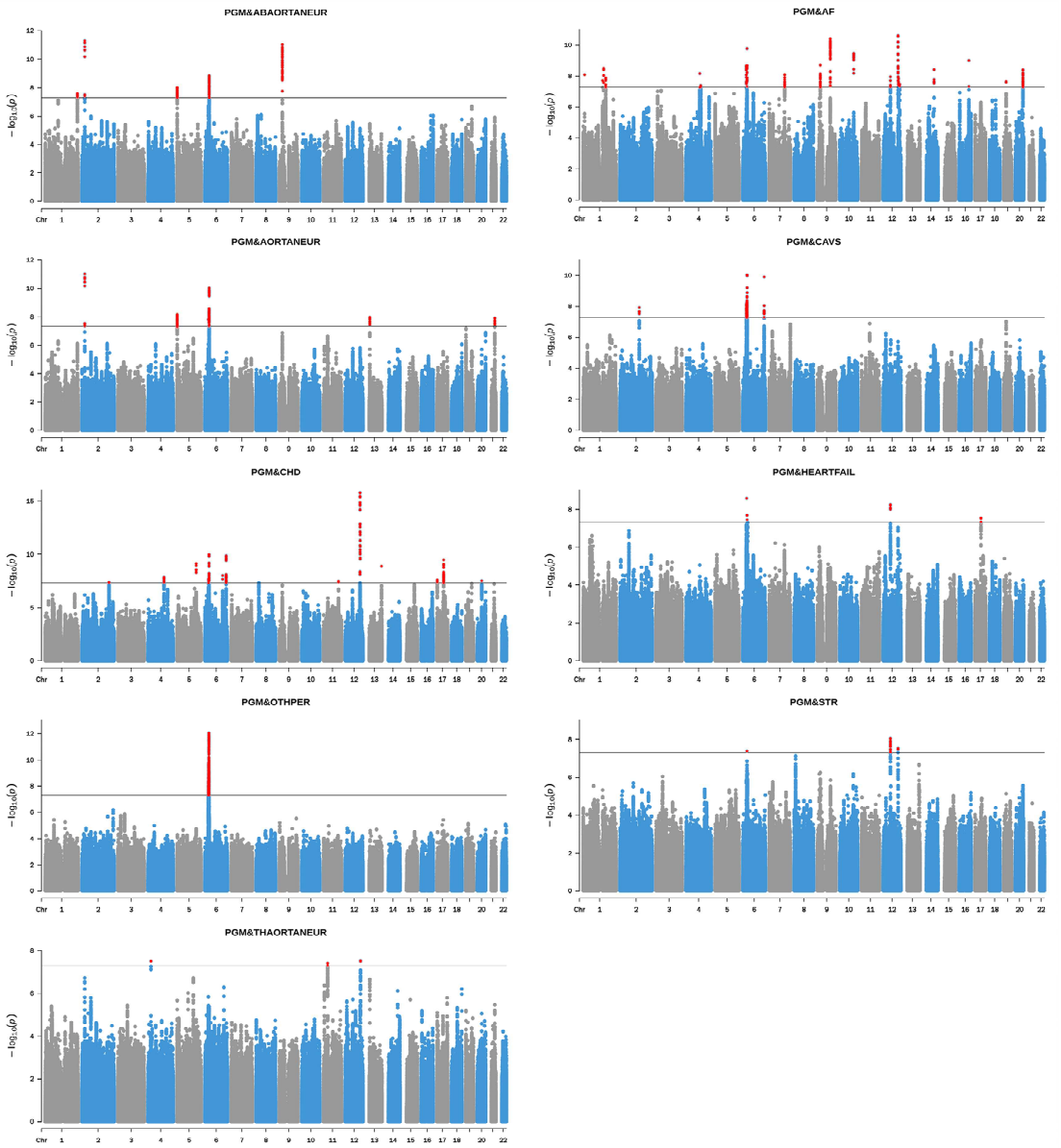


Figure S5. Manhattan plot of pleiotropic signals between PGM and cardiovascular diseases

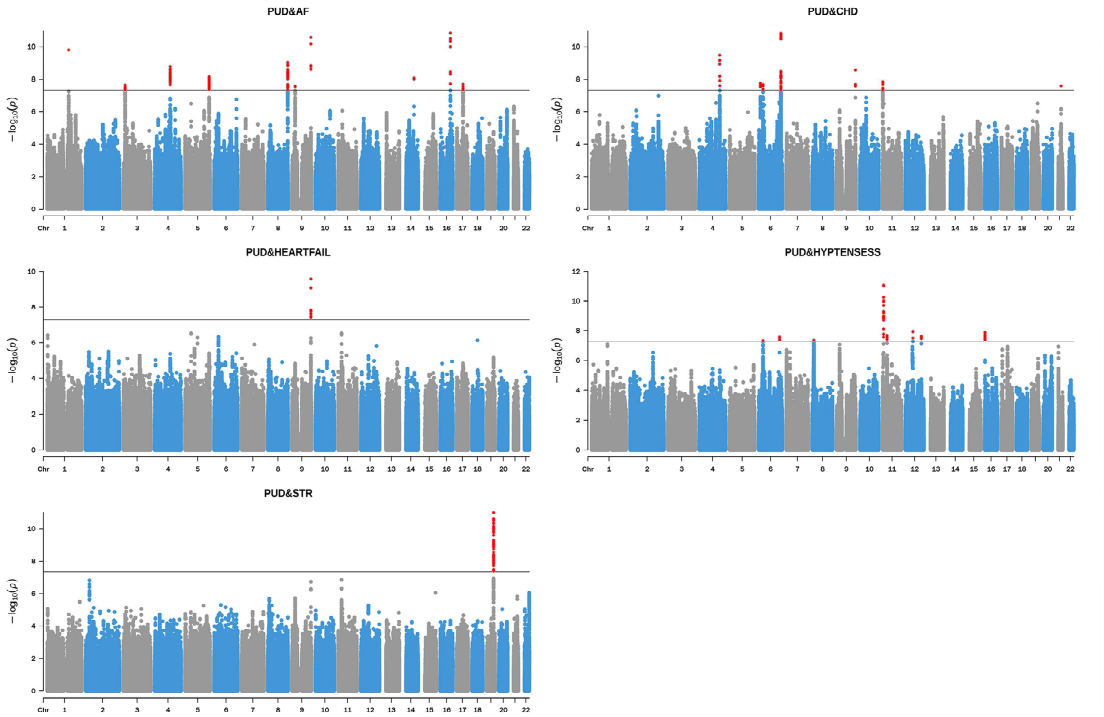


Figure S6. Manhattan plot of pleiotropic signals between PUD and cardiovascular diseases

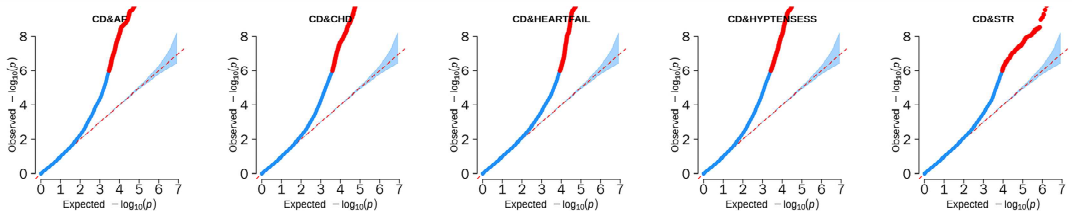


Figure S7. Quantile-Quantile plot of pleiotropic signals between CD and cardiovascular diseases

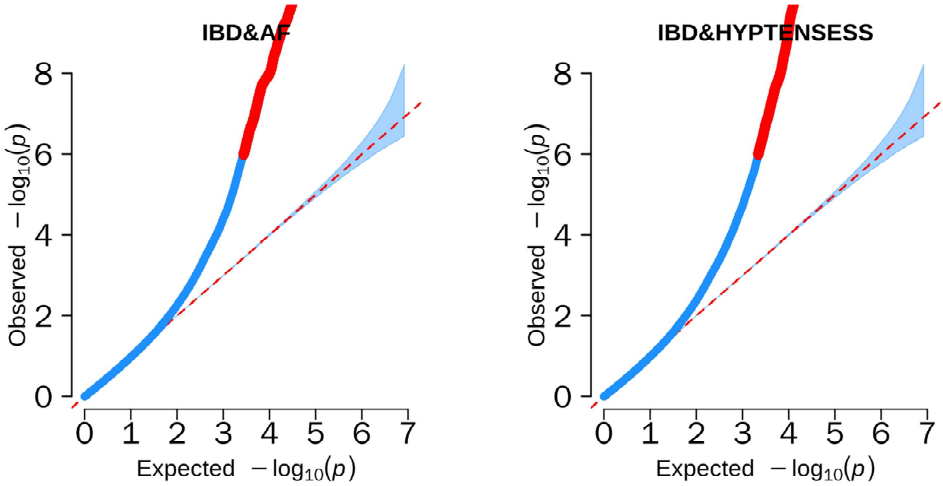


Figure S8. Quantile-Quantile plot of pleiotropic signals between IBD and

cardiovascular diseases

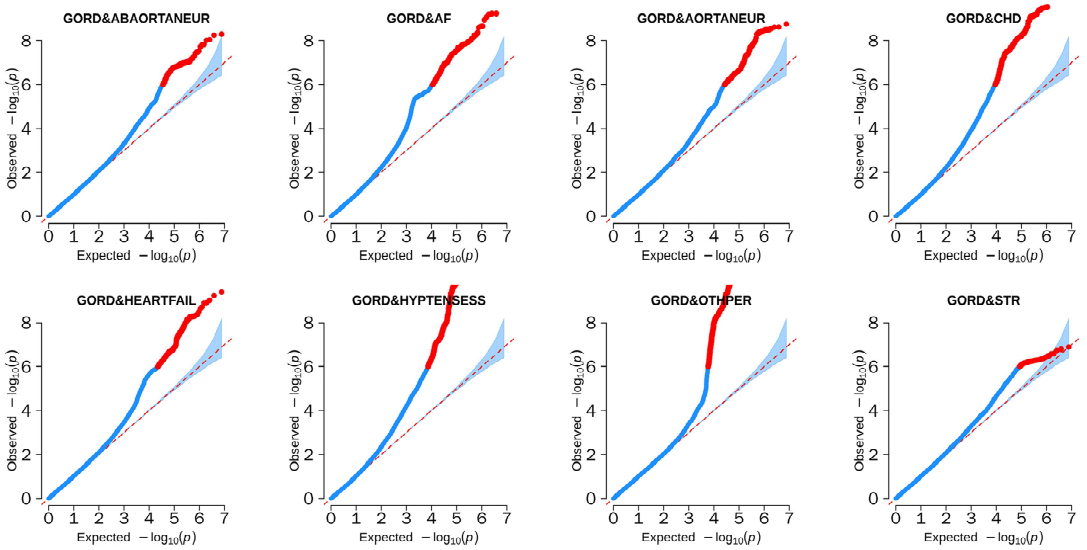


Figure S9. Quantile-Quantile plot of pleiotropic signals between GORD and cardiovascular diseases

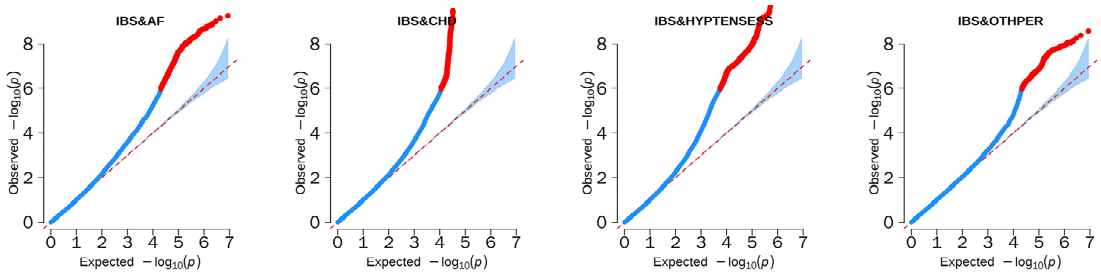


Figure S10. Quantile-Quantile plot of pleiotropic signals between IBS and cardiovascular diseases

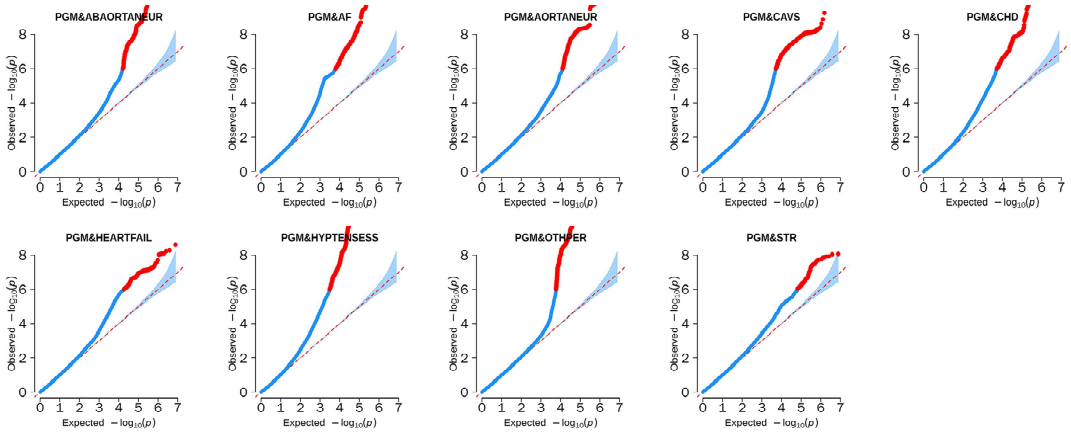


Figure S11. Quantile-Quantile plot of pleiotropic signals between PGM and cardiovascular diseases

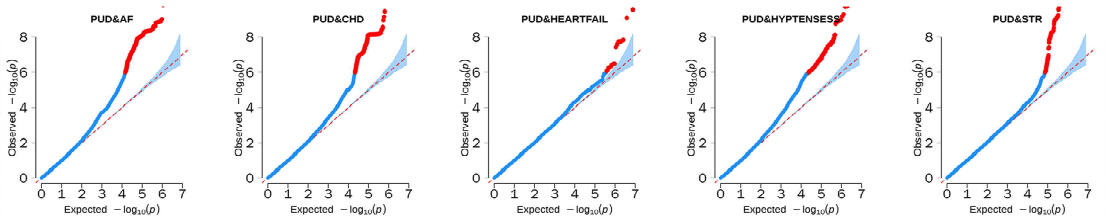


Figure S12. Quantile-Quantile plot of pleiotropic signals between PUD and cardiovascular diseases

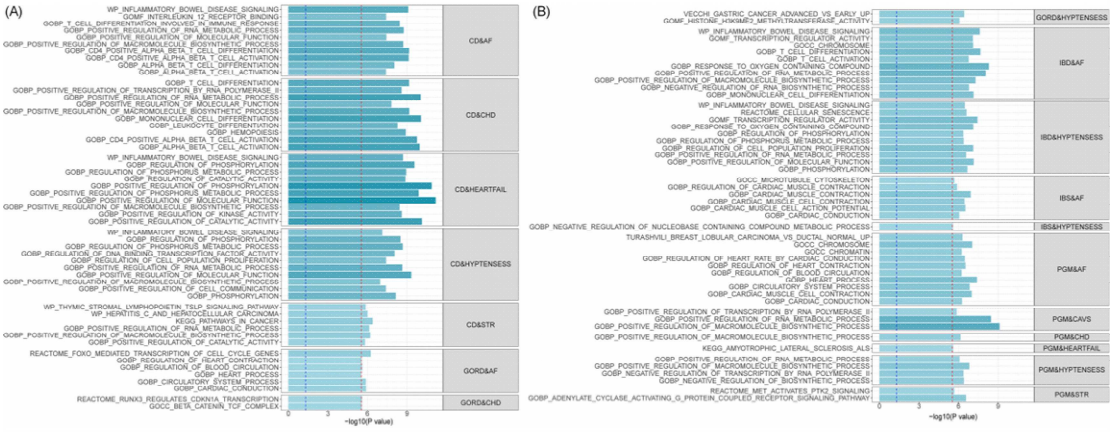


Figure S13. Multiple gene pathways closely associated with these diseases based on the results of MAGMA-derived genes (Table S5)

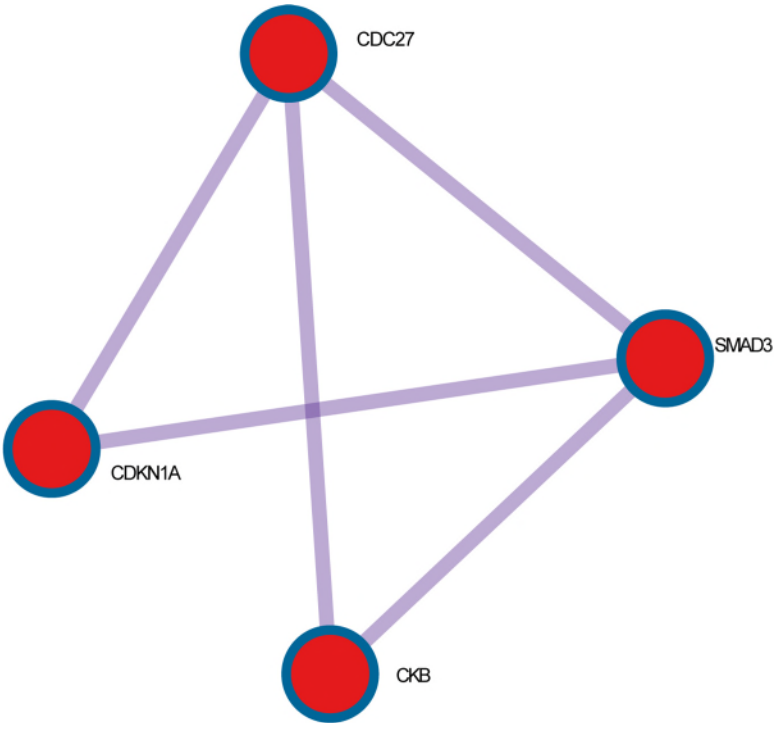


Figure S14. Protein-protein interaction (PPI) network analysis of pleiotropic genes is shown in Figure S14.

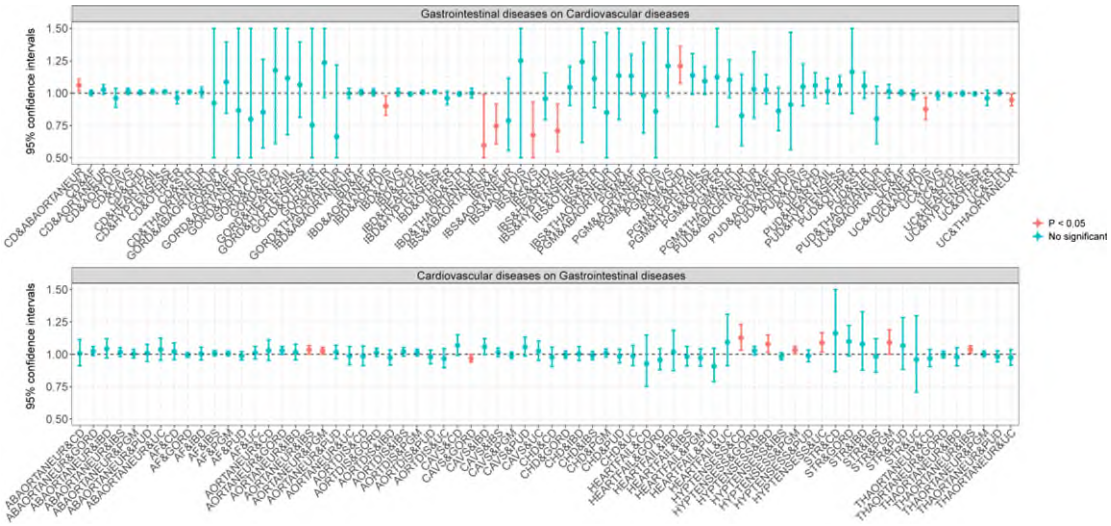


Figure S15. Forest plot of Mendelian randomization analysis, with green indicating positive phenotype pairs and red indicating negative phenotype pairs

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- FigureSupp.pdf