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TNF inhibitors associated with cardiovascular diseases and cardiometabolic risk factors: a Mendelian randomization study

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Abstract. – OBJECTIVE: There is still disagreement about whether anti-tumor necrosis factor (TNF) therapy is beneficial or detrimental to cardiovascular conditions. This two-sample Mendelian randomization (MR) study aimed to evaluate the effects of long-term tumor necrosis factor (TNF) inhibition on cardiovascular diseases (CVDs) and cardiometabolic risk factors *via* genetically proxied inhibition of tumor necrosis factor receptor 1 (TNFR1) and TNF.

MATERIALS AND METHODS: Two genetic instruments were examined to mimic the long-term effect of TNF inhibitors. The first were single-nucleotide polymorphisms (SNPs) within or nearby drug-target genes TNFRSF1A and TNF (encoding *TNFR1* and *TNF*) associated with circulating CRP levels. The other instruments were the expression quantitative trait loci (eQTLs) near the genes. Inverse variance-weighted MR (IVW-MR) and summary-based MR (SMR) methods were employed to estimate causal effects.

RESULTS: In IVW-MR analysis, *TNF*-mediated circulating CRP levels were significantly associated with 4 out of 12 CVDs, including hypertension [odds ratio (OR) = 1.13; 95% CI, 1.09-1.18], coronary artery disease (OR = 3.18; 95% CI, 1.77-5.71), coronary atherosclerosis (OR = 1.05; 95% CI, 1.02-1.08) and type 2 diabetes (OR = 3.48; 95% CI, 1.98-6.10). These findings were also validated in the FinnGen study. Moreover, *TNF* inhibition was also associated with total cholesterol, triglycerides, apolipoprotein B, systolic blood pressure, serum cystatin C, height, weight, and body mass index.

CONCLUSIONS: In this study, the decrease in several CVDs and cardiometabolic risk factors has been found to be causally associated with genetically proxied TNF inhibitors.

Key Words:
Tumor necrosis factor inhibitors, Cardiovascular conditions, Cardiometabolic risk factors, Mendelian randomization.

Introduction

Tumor necrosis factor (TNF) is a pro-inflammatory cytokine that plays indispensable roles in many immunopathogenic processes. It exists in transmembrane (mTNF) and circulating soluble forms perceived by two kinds of TNF receptors, TNFR1 and TNFR2. Both receptors are transmembrane proteins that can bind to and neutralize the activity of circulating TNF when shed and released in soluble form. Moreover, mTNF can function as a receptor that sends signals from external to internal (opposite) into the TNF-producing cells[1]. TNF plays a key role in the development of many inflammatory diseases (e.g., rheumatoid arthritis, Crohn's disease, etc.), and its stimulation of TNF receptors and activation of the TNF pathway can cause a variety of pro-inflammatory or anti-inflammatory effects[2]. Because of its numerous pathophysiological activities, TNF was chosen as the first target of cytokine-targeted therapy[3,4]. A variety of TNF inhibitors block TNF-mediated inflammatory responses by binding specifically to TNF and preventing binding to its receptor[5]. In clinical experience, infliximab, golimumab, etanercept, adalimumab, and certolizumab pegol have been widely used in the treatment of systemic inflammatory diseases[6-8]. However, their beneficial or adverse effects on cardiovascular conditions are still debated. Although anti-TNF therapy generally reduces the risk of cardiovascular events in people with autoimmune diseases, the use of high-dose TNF inhibitors in patients with heart failure and myocardial infarction may not work or may become less effective[9-11]. Moreover, it is linked to cardiometabolic risk factors such as lipids, lipoproteins, and adipokines, which may act as potential mediators of cardiovascular events[12-15]. However, most of the evidence to date

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comes from studies[6-11,13] on anti-TNF treatment with possible unavoidable biases, such as confounding bias and inverse causation.

Mendelian randomization (MR) is a statistical genetics method that utilizes genetic variants from the whole genome to draw causal inferences between exposure and outcome[16]. Because genetic variants are assigned in a random manner at meiosis, and before disease onset, observational studies are conducted using the same design as randomized clinical trials, in order to minimize confounding biases and reverse causation. Drug-target MR is the latest approach that uses genetic instruments (variants) near or in the genes encoding the drug-target proteins to proxy its inhibition effects. Thus, it can be used to mimic the effect of long-term pharmacological modulation of a drug target in clinical trials[17]. Available evidence[18,19] suggests that the toxic effects of TNF are largely mediated by the activation of TNFR1, while the cardioprotective ones are mediated by TNFR2 activation, implying that blocking TNFR1 receptor, not TNFR2, should be the strategy of novel TNF inhibitors[20,21]. The current research hypothesized that inhibiting the TNRF1-encoding TNF receptor superfamily member 1A (*TNFRSF1A*) gene with genetic variants proxies the inhibitory effect of TNF inhibitors on TNFR1 protein. Therefore, *TNFRSF1A* was selected as the first target gene for a drug-target MR analysis performed in this study. The study also considered the outside-to-inside (reverse) signaling *via* mTNF triggered by anti-TNF agents during pharmacological action. When infliximab and adalimumab bind to TNF-expressing cells, they lead to cell cycle stagnation in the G0/G1 phase[22,23], reducing the circulating TNF levels and further anti-inflammatory reaction. Thus, the *TNF* gene that encodes the TNF protein was selected as the second drug-target gene. Our drug-target MR analysis explored the association of genetic instruments in the selected drug-target genes, *TNF* and *TNFRSF1A*, with CVDs and cardiometabolic risk factors.

Materials and Methods

Study Design

The present research had a two-sample MR design, and its steps are illustrated in Figure 1.

Step 1: selection and validation of genetic instruments that were proxies of the TNF inhibitor effect;

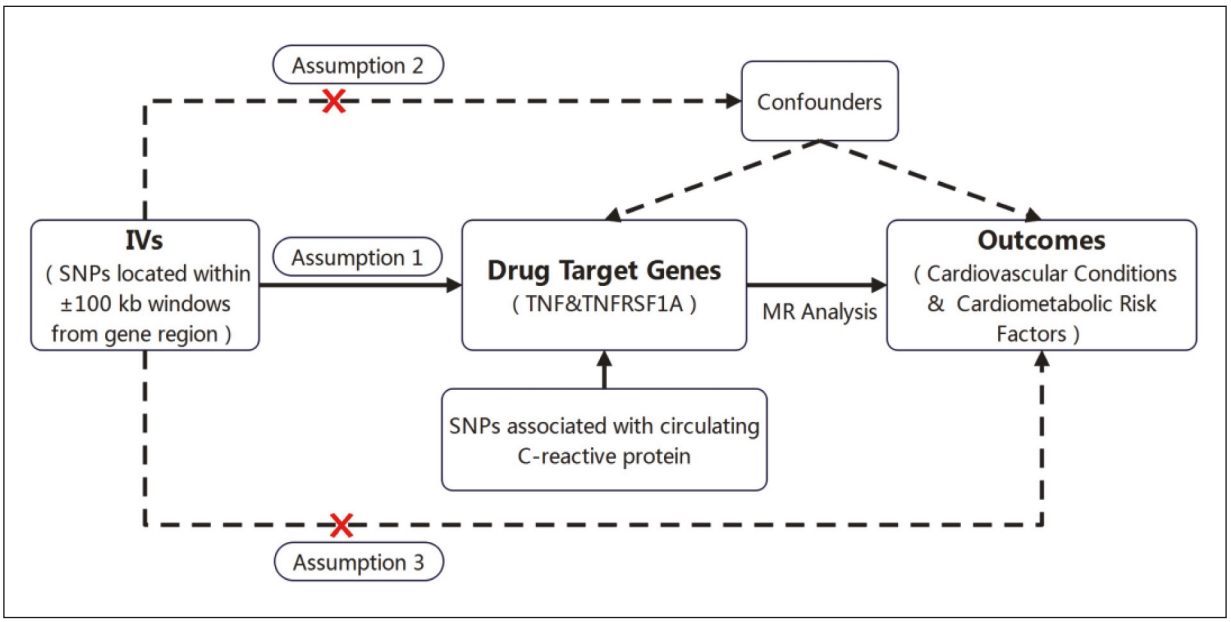

Figure 1. Design of the drug-target Mendelian randomization (MR) analysis performed in this study. Two genetic instruments were chosen to proxy the inhibition of tumor necrosis factor receptor 1 (TNFR1) and tumor necrosis factor (TNF) proteins. The first instruments were single nucleotide polymorphisms (SNPs) linked to circulating CRP levels and located within ± 100 kb windows from the *TNF* gene. The second instruments were cis-eQTL SNPs within 1 Mb on either side of the TNFR1-encoding *TNFRSF1A* gene. TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein B; Lp(A), Lipoprotein A; HOMA-B, homeostasis model assessment of beta-cell function; HOMA-IR, homeostasis model assessment of insulin resistance; BMI, body mass index; WHR, waist-to-hip ratio.

Step 2: inverse variance-weighted MR (IVW-MR) and summary-based MR (SMR) methods were used to estimate the causal impacts of TNF inhibition on 12 cardiovascular conditions and 20 cardiometabolic risk factors;

Step 3: validation of cardiovascular conditions in the FinnGen study[24].

Several assumptions are essential for MR design to sustain the validity of causal assessment: 1, a robust association of instrumental variables (IVs) with the drug target (relevance); 2, Independence of IVs from confounders (interchangeability); 3, No direct effect of IVs on the results except by drug target (exclusionary restriction) (Figure 2). All analyses used genome-wide association study (GWAS) as well as expression quantitative trait locus (eQTL) data, while individual-level data was unavailable.

Selection of Genetic Instruments

The study involved generating instruments that proxy TNF and TNFRSF1A inhibition by selecting single-nucleotide polymorphisms (SNPs) in the range of ± 100 kb windows from both genes [genomic coordinates per Telomere-to-Telomere, T2T, complete hydatidiform mole 13, CHM13 (T2T-CHM13) v2.0 assembly, TNF (chr6:31428617-31431388), TNFRSF1A (chr12:6338163-6351461)]. Only those SNPs linked to circulating C-reactive protein (CRP) levels at the whole genome level of significance ($p < 5.0 \times 10^{-8}$) were recognized as proxies for target gene inhibition. Circulating CRP levels from a large genome-wide association study (GWAS) meta-analysis[25] (n = 204,402) were used to identify these SNPs (**Supplementary File**). C-reactive protein is a sensitive inflammatory biomarker induced by TNF signaling and is often used as an indicator for clinical evaluation of the efficacy of TNF inhibitors[26-28]. Thus, if the target gene is inhibited, it will reduce CRP levels. Selected SNPs were in low-weak linkage disequilibrium ($r^2 < 0.30$) to maximize their strength as genetic instruments.

Moreover, the current study also utilized another type of genetic instrument to avoid the scenario with no identified SNPs (associated with decreased circulating CRP levels and located within ± 100 kb windows from the target gene region). Publicly available data from eQTLGen have been analyzed[29] (n=31,684; meta-analysis of 37 studies; https://www.eqtlgen.org/) with an SMR method to detect common single-nucleotide polymorphisms (SNPs) with minor allele frequency (MAF) > 1% substantially ($p < 5.0 \times 10^{-8}$) associated with the drug target gene expression in the blood. This approach uses overall-level GWAS and eQTL data to analyze the relationship between gene expression

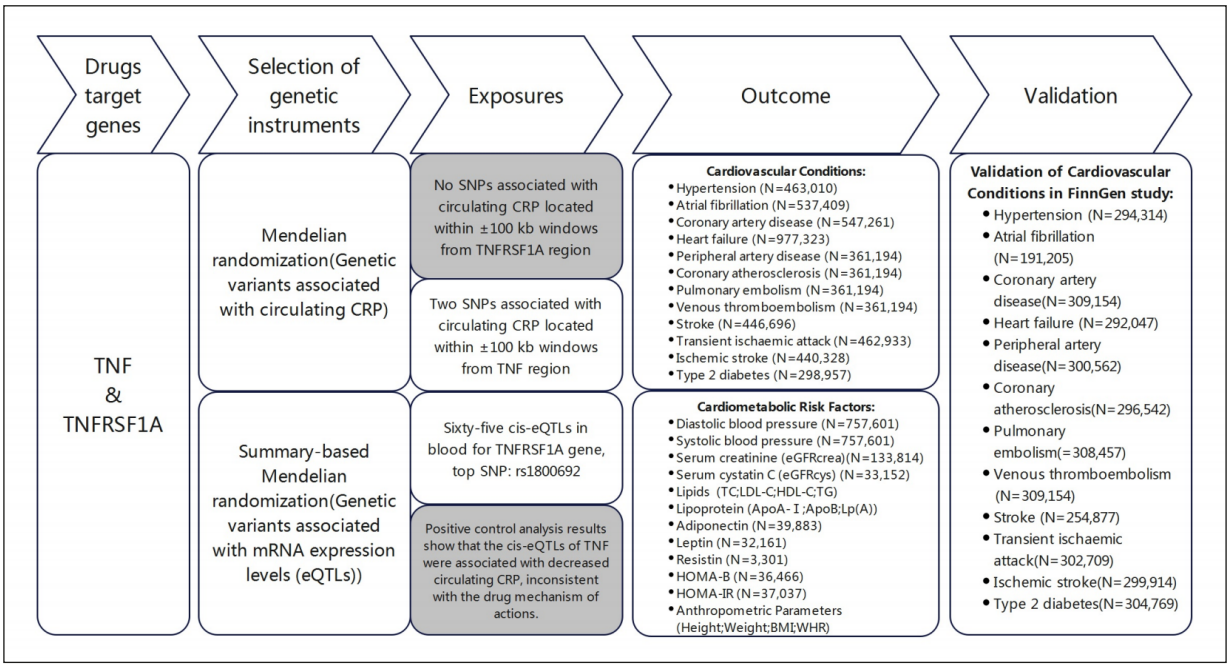

Figure 2. Direct acyclic graph of two-sample Mendelian randomization (MR) analysis. Genetic variants assigned at birth and randomly assorted in the population can be used as instrumental variables (IVs) to estimate the causal association of exposure with the outcome of interest. The arrows depict a causal association between two variables, pointing from the cause to the effect. The red cross denotes an association that should be avoided in an MR analysis.

patterns and the outcome of interest[30]. Only eQTLs within 1 Mb on either side of the gene were used to create genetic tools. The scale of the eQTL data was a 1-SD change in the gene's expression pattern for each additional effect allele.

Outcome Sources

The sources of genetic association data for CVDs were as follows: atrial fibrillation, AFGen consortium (537,409 cases)[31]; coronary artery disease, a meta-GWAS from CARDIoGRAMplusC4D and UK Biobank (547,261 cases)[32]; heart failure, Heart Failure Molecular Epidemiology for Therapeutic Targets (HERMES) consortium (977,323 cases)[33]; type 2 diabetes, the Diabetes Genetics Replication, and Meta-analysis (DIAGRAM) consortium (298,957 cases)[34]; stroke (446,696 cases) and ischemic stroke (440,328 cases), MEGASTROKE consortium[35]; and hypertension (n = 463,010), peripheral artery disease (n = 361,194), coronary atherosclerosis (n = 361,194), pulmonary embolism (n = 361,194), venous thromboembolism (n = 361,194), and transient ischemic attack (n = 462,933), a GWAS from the UK Biobank.

In addition, the FinnGen study[24] data served as validation data sets (**Supplementary File**): hypertension, (n = 294,314); atrial fibrillation, (n = 191,205); coronary artery disease, (n = 309,154); heart failure, (n = 292,047); peripheral artery disease, (n = 300,562); coronary atherosclerosis, (n = 296,542); pulmonary embolism, (n = 308,457); venous thromboembolism, (n = 309,154); stroke, (n = 254,877); transient ischemic attack, (n = 302,709); ischemic stroke, (n = 299,914); and type 2 diabetes (n = 304,769).

Summary-level GWAS statistics data for 20 cardiometabolic risk factors were used: lipids [total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL), and triglycerides (TG)], lipoprotein (apolipoprotein A-I, apolipoprotein B, and lipoprotein), anthropometric parameters (height, weight, body condition index, and waist-to-hip ratio), diastolic blood pressure, systolic blood pressure, serum creatinine, serum cystatin C, homeostasis model assessment of beta-cell function (HOMA-B) and homeostasis model assessment of insulin resistance (HOMA-IR), adiponectin, leptin, and resistin. Most data were retrieved from the following consortia web pages: Global Lipids Genetics Consortium (GLGC)[36], UK Biobank[37], Genetic Investigation of Anthropometric Traits (GIANT) consortium[38-41], International Consortium of Blood Pressure[42], CKDGen Consortium[43], Malignant Germ Cell International Consortium (MAGIC)[44], and ADIPOGen[45]. Published GWAS studies[46,47] were also used to gather data. European pedigree population data (**Supplementary File**) were restricted to reduce the bias caused by the population level.

Validation of Genetic Instruments

Positive control analyses were conducted to validate both genetic instrument types. The association between selected SNPs and biomarkers or disease risks from published sources were examined: 1) white blood cell count (n = 563,946)[48]; 2) risk of Crohn's disease (n = 51,874)[49]; 3) risk of rheumatoid arthritis (n = 309,154); and 4) risk of ankylosing spondylitis (n = 22,964). An SMR analysis was also conducted to determine the association of a 1-SD change correlation with drug-target gene expression levels in the blood (using data from eQTLGen) with the aforementioned outcomes (including CRP levels). Protective effects of variants proxying gene inhibition were expected on the inflammatory biomarkers or disease risks because TNF inhibitors are approved for treating them[6] (**Supplementary File**).

Statistical Analysis

Mendelian randomization primary analysis involved an IVW-MR method to calculate the causal association when SNPs associated with circulating CRP levels were the genetic tools. The TwoSampleMR package in R (Auckland CBD, Auckland, New Zealand), version 4.2.2 was used for conducting allele harmonization and analysis. The primary analysis also contained an SMR method to estimate causal effects when eQTLs were the tools. SMR software, version 1.03 (available at: https://yanglab.westlake.edu.cn/software/smr/), was employed to perform allele harmonization and analysis. The results are represented as the odds ratio (OR) per 1-SD gene expression change or β, in which the direction of gene expression change is unified as representing the association of CRP reduction. Therefore, in the results of the study, the estimation of effect size showed a possible correlation between the use of anti-TNF therapy and the risk of diseases. The F-statistic was employed to assess the strength of the instrument. An F-statistic of at least 10 indicates weak instrument bias[50].

Several sensitivity analyses were done in the IVW-MR method. Cochran's Q test was performed to determine heterogeneity ($p < 0.05$)[51], while MR-Egger regression and MR-PRESSO were also used to investigate the possible horizontal polymorphisms ($p < 0.05$)[52,53]. R software, ver-

sion 4.2.2 (Auckland, New Zealand) was utilized for all analyses. In the SMR method, the heterogeneity in dependent instruments (HEIDI) test, implemented within the SMR tool, was utilized to determine whether the correlation between gene expression and the result was caused by linkage disequilibrium ($p < 0.01$)[54].

Results

Genetic Instrument Selection and Validation

Based on a GWAS study[25] that determined SNPs related to circulating CRP levels, 2 SNPs within ± 100 kb of the *TNF* gene have been identified, but none for the *TNFRSF1A* gene. Positive control analyses showed these *TNF*-related SNP candidates were associated with a low white blood cell count and low risk of Crohn's disease, ankylosing spondylitis, and rheumatoid arthritis, which is consistent with the mechanism of operation of *TNF* inhibitors. In addition, 1973 cis-eQTL SNPs from the eQTLGen Consortium were identified for the *TNF* gene. However, the most important cis-eQTL SNP (rs1121800) was not chosen as a tool for genetically proxied *TNF* inhibition because it was absent from the GWAS summary data of CRP. Positive control analyses also showed that this cis-eQTL SNP was associated with raised circulating CRP levels, inconsistent with the *TNF* inhibitor action. Moreover, the HEIDI test results also suggested that linkage disequilibrium ($p < 0.01$) was responsible for the correlation between *TNF* expression and the result of the positive control, implying a correlation between SNPs. Therefore, to ensure the accuracy and stability of the analysis, we did not use cis-eQTL SNPs as an instrumental variable in the analysis.

For the second target gene *TNFRSF1A*, 65 cis-eQTL SNPs in total were discovered by the eQTLGen Consortium. Positive control analyses revealed that genetically proxied *TNFRSF1A* inhibition *via* these genetic variants was associated with reduced inflammatory biomarker levels or all 3 disease risks, consistent with the *TNF* inhibitor action. Furthermore, all instrument variants in this investigation had F-statistics of more than 25, indicating that our instruments were not weak (**Supplementary File**).

A Causal Association Between Genetically Proxied Gene Inhibition and Cardiovascular Diseases

As shown in Figure 3 and **Supplementary File**, an IVW-MR analysis demonstrated that *TNF*-mediated circulating CRP levels (equivalent to a 1-SD unit increase) were considerably linked to the risk of the following CVDs: hypertension (OR = 1.13; 95% CI, 1.09-1.18; $p = 4.04 \times 10^{-09}$); coronary artery disease (OR = 3.18; 95% CI, 1.77-5.71; $p = 1.05 \times 10^{-04}$), coronary atherosclerosis (OR = 1.05; 95% CI, 1.02-1.08; $p = 1.41 \times 10^{-03}$), pulmonary embolism (OR = 0.98; 95% CI, 0.97-0.99; $p = 3.29 \times 10^{-04}$), venous thromboembolism (OR = 0.97; 95% CI, 0.95-0.99; $p = 1.88 \times 10^{-04}$), and type 2 diabetes (OR = 3.48; 95% CI, 1.98-6.10; $p = 1.35 \times 10^{-05}$). Positive associations were inferred between *TNF*-mediated circulating CRP level increase and the stroke risk (OR = 3.81; 95% CI, 1.04-13.91; $p = 0.04$) or transient ischemic attack (OR = 1.01; 95% CI, 1.00-1.02; $p = 0.03$) but did not conclude an association between *TNF*-mediated circulating CRP level increase and the risk of atrial fibrillation, heart failure, peripheral artery disease, or ischemic stroke. In the FinnGen study[24], we also found that TNF-mediated increases in circulating CRP levels were positively associated with the risk of developing hypertension, coronary artery disease, coronary atherosclerosis, and type 2 diabetes (Figure 2 and **Supplementary File**). Although all findings were not heterogeneous according to our Cochran's Q test ($p > 0.05$), a similar one from the FinnGen study24, yielded $p < 0.05$ for atrial fibrillation, peripheral artery disease, venous thromboembolism, and diabetes mellitus, suggesting potential heterogeneity for some results.

A subsequent SMR analysis found an association between elevated *TNFRSF1A* expression levels in the blood (equivalent to a 1-SD unit rise) and hypertension risk (OR = 0.99; 95% CI, 0.9891-0.9996; $p = 0.0339$) (Figure 4 and **Supplementary File**). However, in the FinnGen study data sets (Figure 3 and **Supplementary File**), this association was not validated. In addition, the study did not find a causal relationship between the expression of *TNFRSF1A* and the risk of other CVDs. As for the SMR, HEIDI testing revealed that most of the correlations found were not due to connection imbalance ($p > 0.01$), with only *TNFRSF1A* performance in the FinnGen test correlating with cardiac insufficiency ($p = 0.0173$) or peripheral vascular disease ($p = 0.0214$).

A Causal Association Between Genetically Proxied Gene Inhibition and Cardiometabolic Risk Factors

As can be seen in Figure 5 and **Supplementary File**, an IVW-MR analysis uncovered that

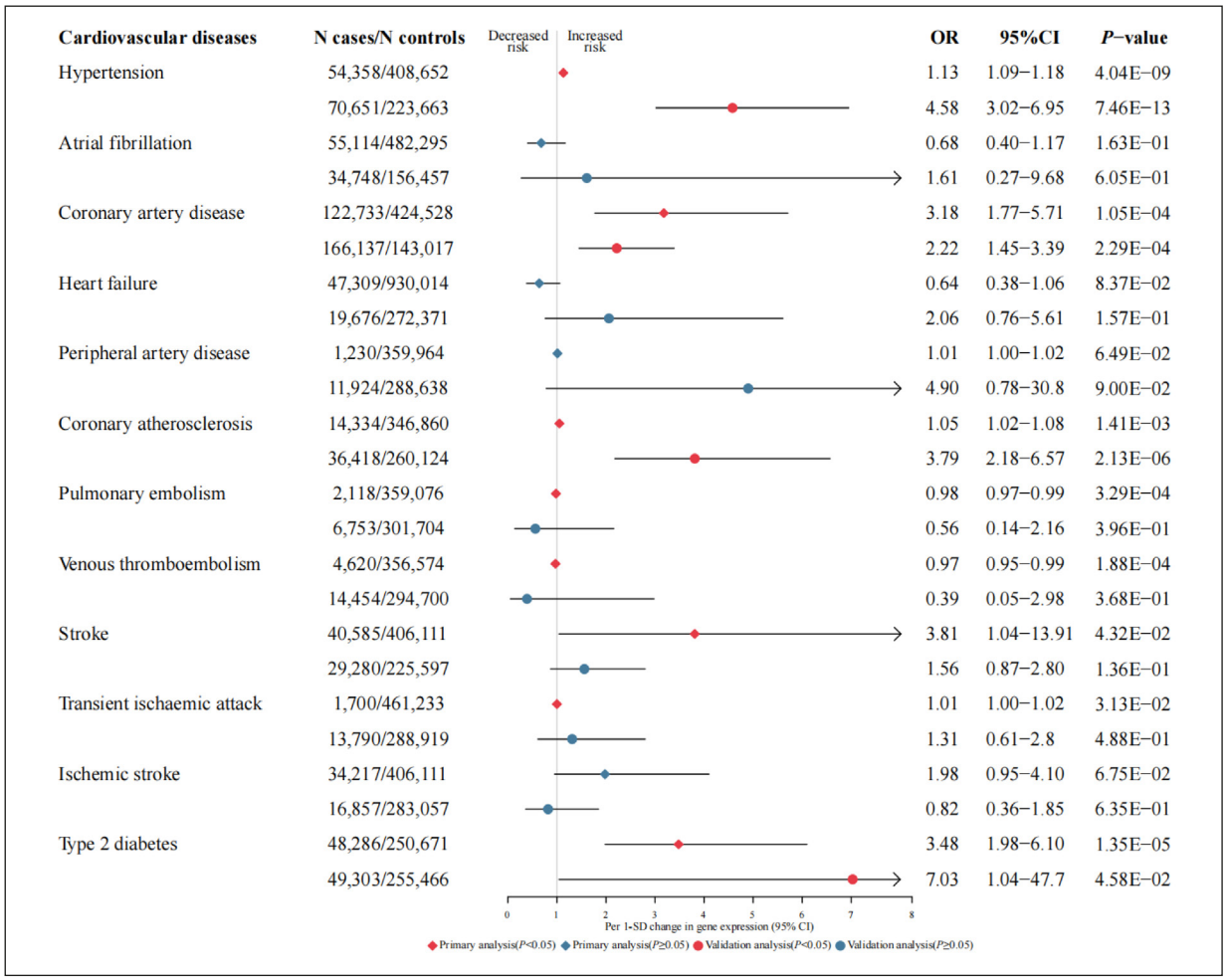

Figure 3. The causal effect of genetically proxied tumor necrosis factor (*TNF*) inhibition on cardiovascular diseases. Causal associations were determined with an inverse variance-weighted Mendelian randomization (IVW-MR) method. Data were presented as odds ratios (ORs) with 95% confidence intervals (CIs) (error bars). If OR > 1.00, *TNF* inhibition-mediated circulating CRP levels (equivalent to a 1-SD unit increase) was associated with increased disease risk.

TNF-mediated circulating CRP levels (equivalent to a 1-SD unit increase) were associated with elevated cardiometabolic risk factors: systolic blood pressure (β = 7.54; 95% CI, 5.42-9.67; $p = 3.53 \times 10^{-12}$), serum cystatin C (β = 0.13; 95% CI, 0.01-0.25; $p = 0.03$), total cholesterol (β = 0.48; 95% CI, 0.03-0.91; $p = 0.038$), triglycerides (β = 0.29; 95% CI, 0.17-0.42; $p = 3.27 \times 10\text{-}6$), and apolipoprotein B (β = 0.17; 95% CI, 0.029-0.31; $p = 0.018$). They also had a link with reduced anthropometric parameters: height (β = −1.12; 95% CI, −1.33-−0.91; $p = 1.03 \times 10^{-25}$), weight (β = −1.03; 95% CI, −1.42-−0.64; $p = 2.09 \times 10^{-07}$), and body mass index (β = −0.30; 95% CI, −0.53-−0.07; $p = 0.012$). The current analysis did not reveal any relationship between *TNF*-mediated circulating CRP levels and other cardiometabolic risk factors. For most results, *TNF*-mediated circulating CRP was only associated with diastolic blood pressure ($p = 7.7 \times 10^{-04}$), HDL ($p = 0.004$), and apolipoprotein A-I ($p = 0.007$), while in other results associations were not revealed.

As shown in Figure 6 and **Supplementary File**, genetically proxied *TNFRSF1A* inhibition (equivalent to a 1-SD unit increase) was associated with several decreased cardiometabolic factors: diastolic blood pressure (β = −0.25; 95% CI, −0.39-−0.11; $p = 5.05 \times 10^{-04}$), systolic blood pressure (β = −0.28; 95% CI, −0.52-−0.04; $p = 0.022$), and height (β = −0.028; 95% CI, −0.05-−0.0033; $p = 0.026$). The study did not indicate a cause-effect relationship between the expression of *TNFRSF1A* and other cardiometabolic risk factors. Furthermore, HEIDI test findings revealed that most observed associations were not attributable to linkage disequilibrium ($p > 0.01$), with the exception of

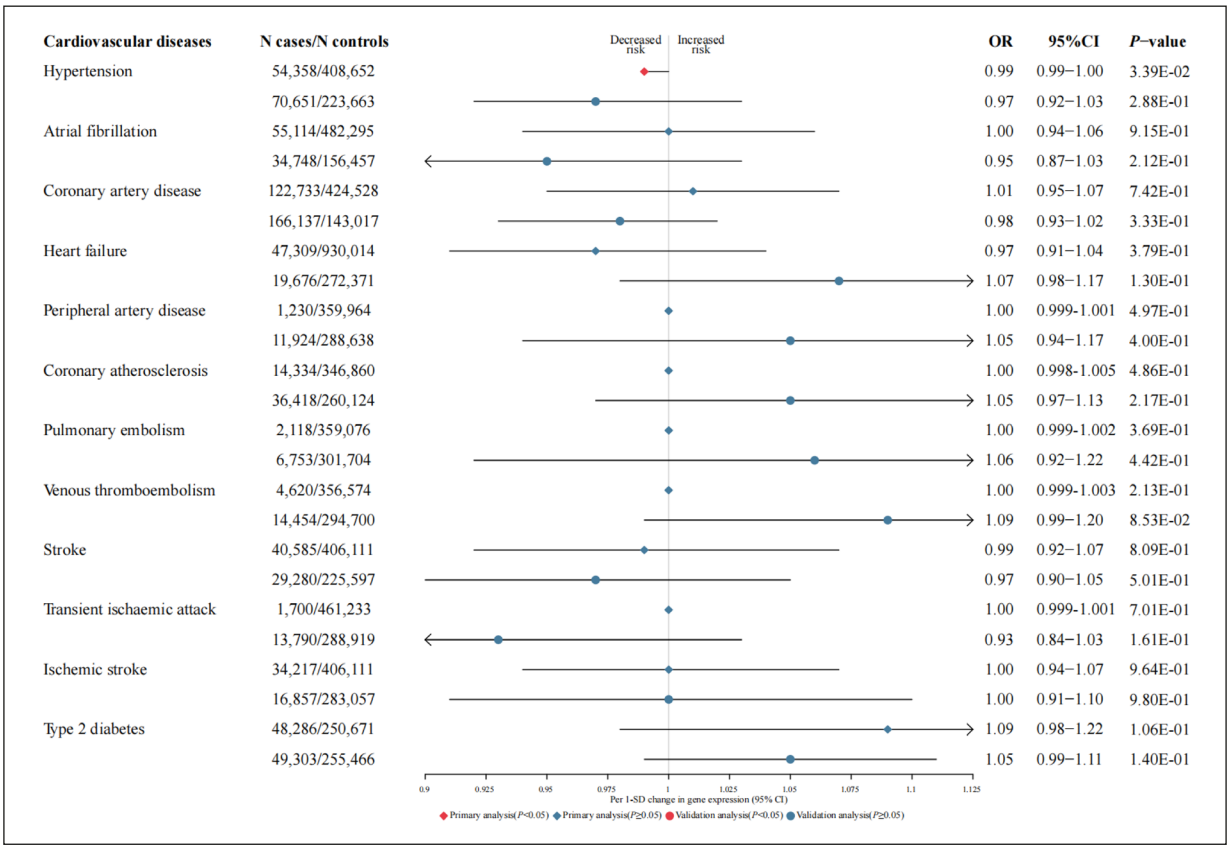

Figure 4. The causal effect of genetically proxied *TNFRSF1A* inhibition on cardiovascular diseases. Causal associations were concluded using a summary-based Mendelian randomization (SMR) method. Data were presented as odds ratios (ORs) with 95% confidence intervals (CIs) (error bars). When OR > 1.00, increased *TNFRSF1A* expression in the blood (equivalent to a 1-SD unit increase) was associated with increased disease risk.

those between *TNFRSF1A* expression and diastolic blood pressure ($p = 3.88 \times 10^{-03}$), HDL cholesterol ($p = 4.69 \times 10^{-02}$), apolipoprotein A-I ($p = 4.70 \times 10^{-02}$), and HOMA-B ($p = 4.83 \times 10^{-02}$).

Discussion

In this study, eQTL and GWAS summary-level data were utilized to infer the possible effects of anti-TNF therapy on CVDs and cardiometabolic risk factors. The research offered a positive causal association between the *TNF*-mediated circulating CRP levels and the raised risk of hypertension, coronary artery disease, coronary atherosclerosis, and diabetes mellitus. Moreover, the study provided evidence of the positive association of the *TNF*-mediated circulating CRP levels with increased systolic blood pressure, serum cystatin C, total cholesterol, triglycerides, and apolipoprotein B, but decreased height, weight, and body mass index (BMI). Similarly, we demonstrated the correlation between *TNFRSF1A* expression and decreased diastolic blood pressure, systolic blood pressure, and height.

A Mendelian randomization study[55] suggested that circulating *TNF* is causally related to coronary heart disease and stroke risk in the general population. However, another research[56] has demonstrated that *TNFRSF1A* inhibition had no causal effect on them, yielding contradictory evidence. Hence, the summary-based MR (SMR) method was employed to clarify this association while exploring correlations between *TNFRSF1A* expression and other cardiovascular conditions. In addition to TNFR1 signaling, outside-to-inside (reverse) signaling has a vital role in anti-TNF treatment[5,23]. In reverse signaling mediated by transmembrane TNF (mTNF), mTNF acts as a receptor during the interaction with anti-TNF antibodies, activating intracellular signaling pathways1. This signaling is crucial for macrophage apoptosis and immune cell activation[57,58]. After binding with mTNF-expressing cells[23,59], infliximab and adalimumab, but not

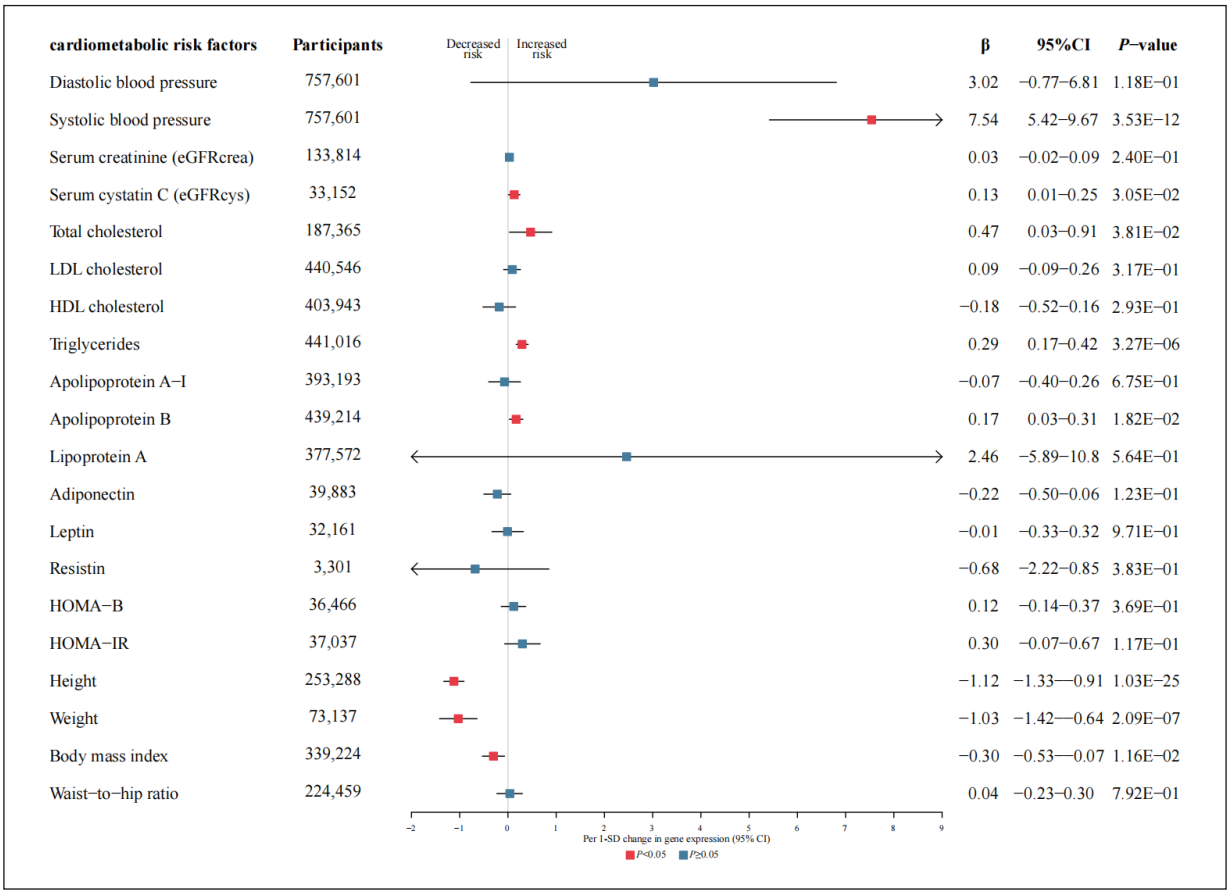

Figure 5. The causal effect of genetically proxied *TNF* inhibition on cardiometabolic risk factors. An inverse variance-weighted Mendelian randomization (IVW-MR) method was employed to assess the causal effect. Data were presented as β with 95% confidence intervals (CIs) (error bars). β > 0 suggests *TNF*-mediated circulating CRP levels (equivalent to a 1-SD unit increase) were associated with increased cardiometabolic risk factors.

etanercept, cause apoptosis and stop the cell cycle at G0/G1, thereby reducing circulating TNF levels to support the anti-inflammatory effects of TNF inhibitors. Thus, the TNF-mediated circulating CRP levels were utilized to proxy for the partial effects of reverse signaling and clarify the potential association between reverse signaling and CVDs in anti-TNF treatment.

Our analyses for associations between genetically proxied *TNF* inhibition and CVDs are consistent with many previous studies[60-66]. Vascular diseases can be successfully prevented by anti-TNF therapy, especially atherosclerosis[60]. When utilized in treating rheumatoid arthritis, it decreases the levels of soluble endothelial adhesion molecules[61] and improves arterial stiffness[62] and endothelial functions[63]. It may also reduce the risk of myocardial infarction and coronary artery disease[64,65] and may even guard against increased cardiovascular complications and death[66]. We also examined associations between TNF inhibition and lipids, lipoprotein, or adipokines to clarify the potential mechanisms of a decreased risk of vascular diseases. Previous studies[67] have found that cardiometabolic risk factors are significantly associated with some CVDs. Our results suggest a causal effect of TNF inhibition with lower total cholesterol, triglycerides, and apolipoprotein B, which may potentially play a role in the association between anti-TNF treatment and coronary artery disease.

Contrary to people with autoimmune inflammatory disease, long-term anti-TNF therapy does not appear to be beneficial in people with heart failure and may even make the condition worse[9,10,68]. Consistent with these studies[9,10,68], our MR analysis also captured potential associations between the *TNF* inhibition and increased risk of heart failure (β = −0.45), although the causal effect was insignificant (p = 0.0837). In addition, it highlighted a significant impact of *TNF* inhibition on reducing the hypertension risk and lowering

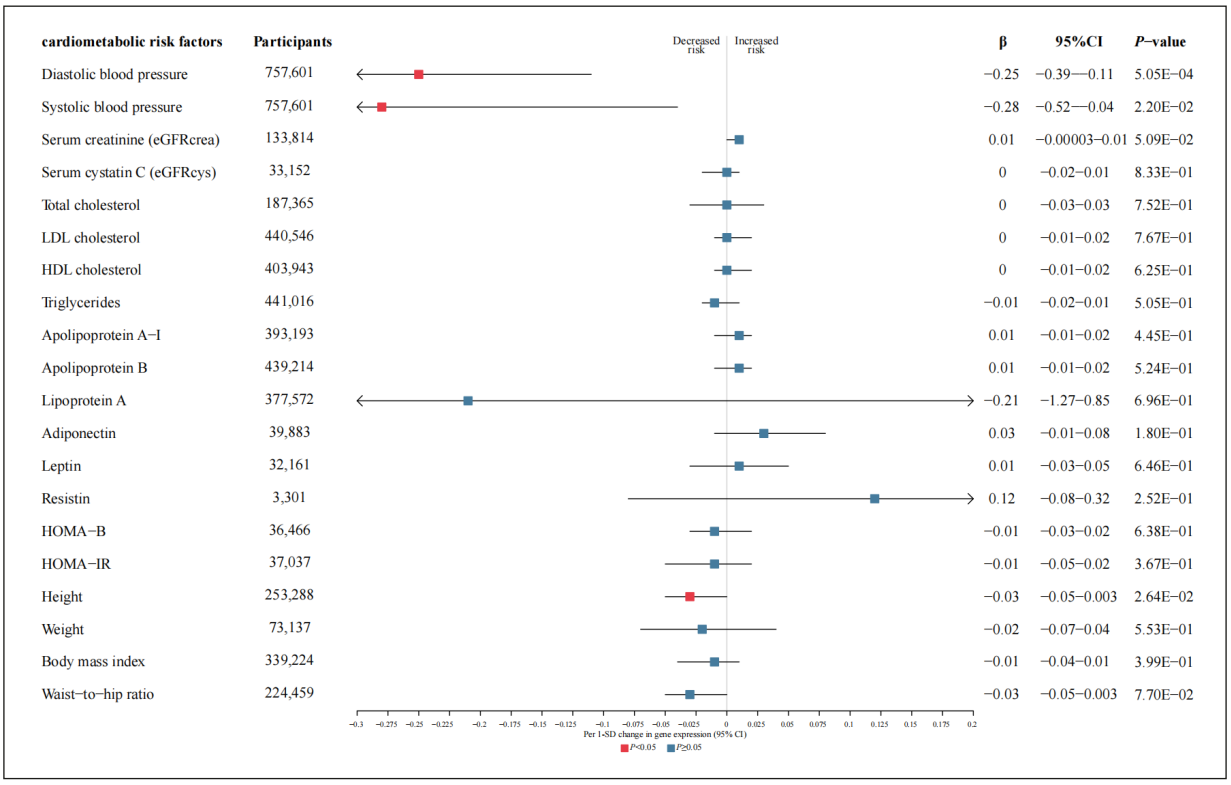

Figure 6. The causal effect of genetically proxied *TNFRSF1A* inhibition on cardiometabolic risk factors. A summary-based Mendelian randomization (SMR) method was used to assess the causal effect. Data are represented as β with 95% confidence intervals (CIs) (error bars). β > 0 suggests that increased *TNFRSF1A* expression in the blood (equivalent to a 1-SD unit increase) was associated with increased cardiometabolic risk factors.

systolic blood pressure. Indeed, a hypotensive effect of anti-TNF agents is also suggested by combined estimates from a recent meta-analysis[69]. Paradoxically, *TNF* inhibitor recipients have higher rates of hypertensive adverse events[70], consistent with our results, showing that genetically proxied *TNFRSF1A* inhibition is linked to a higher risk of hypertension and elevated diastolic/systolic blood pressure. The different effects of forward and reverse signaling on blood pressure may partially explain this contradiction. Similarly, our analysis uncovered that the *TNF*-mediated circulating CRP level decrease was linked to the elevated risk of venous thromboembolism and pulmonary embolism. However, these associations could not be verified in the FinnGen study. Several recent observational studies[71-73] also showed no statistical association between venous thromboembolism risk and TNF inhibitor use relative to other biologics or non-biologics, underscoring the need for additional relevant randomized controlled studies for clarification. According to the available evidence[74-76], TNF inhibitors can improve insulin resistance and reduce the incidence of type 2 diabetes. TNF inhibition also reduced the risk of developing diabetes, which is consistent with the above results. Moreover, a retrospective cohort study[77] showed that patients with RA and psoriasis receiving anti-TNF therapy had a lower risk of developing type 2 diabetes as compared to those receiving disease-modifying anti-rheumatic drugs (DMARDs). Regarding anthropometric parameters, previous studies[78] have found that cardiac metabolism is significantly associated with it. A recent meta-analysis[79] showed that anti-TNF treatment in inflammatory bowel disease was linked to increased body weight, body mass index, and height. The findings were consistent with our results of the analysis. These anthropometric measures were associated with a reduction in TNF-mediated CRP levels, suggesting that anti-TNF therapy may play an important role in physical changes by ameliorating disease status.

The current study demonstrated a causal association between *TNF* inhibition and reduction of risk of multiple CVDs or decreased cardiometabolic risk factors, while *TNFRSF1A* inhibition lacked significant cardiovascular benefit. Althou-

gh TNF inhibitors selectively targeting TNF receptors rather than blocking TNF activity may represent a more effective therapeutic concept in the future, this selective blockade may lose part of the original pharmacological effects that benefit the cardiovascular system, thus requiring future observational and randomized controlled studies.

Strengths and Limitations

The current MR study has some strengths. Firstly, it was able to model exposure to medicines with the help of genetics, minimizing the confounding effects and preventing the occurrence of the inverse causal relationship. Indeed, human genetics has a novel role in selecting new targets for drug discovery and evaluating drug safety assessments[80,81]. Secondly, the F-statistics for all instrument variables in this study are greater than 25, indicating that weak instrument bias has been circumvented. Various positive control analyses in this study also validated the strength of our instrumental variables. Finally, compared with short drug use periods in conventional observational studies or randomized trials, our approach relying on genetic variants as proxies of TNF inhibition facilitates evaluating its long-term effects.

There are also several limitations to this study. First, because genetic effects are lifelong, our estimates cannot account for the impacts of TNF inhibitor exposure at a specific time in life. Second, since the efficacy and toxicity of drugs vary with alterations in drug dose, exposure duration, and drug binding affinity, among others, the effect sizes of drug exposure inferred by genetic analysis may be different from those in reality. Third, the genetic summary data used in this study were predominantly obtained from populations with European ancestry, limiting our results to only these populations.

Conclusions

The current MR study indicates that genetic proxied *TNF* inhibition may be associated with reduced risk of several CVDs or reduced cardiometabolic risk factors in the general European population. By contrast, it indicates that the proxied *TNFR1A* inhibition lacks significant cardiovascular benefit.

Ethics Approval

Ethical approval was not required because all data used in this study were obtained from publicly available databases.

Informed Consent

Not applicable.

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Availability of Data and Materials

The datasets used in the study are GWAS summary-level statistics and were accessed through the IEU OpenGWAS project (https://gwas.mrcieu.ac.uk/), the eQTLGen Consortium (https://eqtlgen.org/), and the FinnGen study (https://finngen.gitbook.io/documentation/data-download) web browsers. Individual-level data were not provided.

Authors' Contributions

Sheng Zhao has provided the design and feedback of the manuscript. Zhi-yuan Liu has contributed to the acquisition and conceived of analysis data. All authors participated in drafting the manuscript, and Xiao-bi Huang and Guiming Yang revised it critically. The final version of the manuscript was read and approved by all authors.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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