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Triglyceride-Glucose Index and the Risk of Calcific Aortic Valve Stenosis: A Bidirectional Mendelian Randomization Study

ABSTRACT

Background: Calcific aortic valve stenosis (CAVS), the predominant valvular heart disease in developed countries, arises primarily from metabolic and inflammatory dysregulation. The triglyceride-glucose (TyG) index, a composite biomarker of insulin resistance and systemic inflammation, has been associated with cardiovascular diseases. However, its causal association with CAVS remains unclear. This study employs bidirectional Mendelian randomization (MR) to elucidate the potential causal relationship between the TyG index and CAVS.

Methods: Genome-wide association study) summary statistics of TyG index and CAVS were obtained from UK-biobank cohort (n = 273 368) and FinnGen database (cases = 12 418 and controls = 487 930). Two-sample MR and multiple MR analyses were conducted to evaluate the association of TyG index with CAVS. The primary method was inverse variance weighted (IVW), complemented by MR-Egger, weighted median, and sensitivity analyses to ensure robustness.

Results: The MR analysis demonstrated a significant causal effect of the higher TyG index (per 1-unit increment of TyG index) on CAVS risk (odds ratio [OR] = 1.50, P = .007, 95% CI: 1.12-2.02). Similar causal relationships were observed for triglyceride and glucose levels with CAVS. Sensitivity analyses confirmed robustness with no evidence of horizontal pleiotropy (P > .05). This association remained statistically significant in multiple MR analyses after adjusting for potential confounders (OR = 1.64, P = .003, 95% CI: 1.18-2.28). No reverse causality from CAVS to the TyG index was detected.

Conclusion: This MR study provides evidence supporting the causal effect of higher TyG index on CAVS.

Keywords: Calcific aortic valve stenosis, inflammation, insulin resistance, Mendelian randomization, triglyceride-glucose index

ORIGINAL INVESTIGATION

INTRODUCTION

Calcific aortic valve stenosis (CAVS) is the most prevalent valvular heart disease in developed countries, with an incidence of 2%-3% in individuals aged >65 years.[1-4] Surgical or transcatheter valve replacement remains the primary effective therapeutic option.[5,6] Pathologically, CAVS is increasingly recognized as an active process involving inflammation, oxidative stress, and metabolic dysregulation, akin to atherosclerosis.[7,8] Among these mechanisms, metabolic disturbances, particularly insulin resistance, have emerged as a critical contributor to CAVS pathogenesis.[9,10] Insulin resistance exacerbates systemic inflammation, oxidative stress, and endothelial dysfunction, all of which are implicated in aortic valve calcification.[11-14]

The triglyceride-glucose (TyG) index, a novel and cost-effective marker of insulin resistance derived from fasting triglyceride and glucose levels, has gained attention for its clinical utility.[15-20] Unlike traditional measures such as the Homeostasis Model Assessment of Insulin Resistance, the TyG index offers greater accessibility and reflects both lipid and glucose dysregulation, key drivers of systemic inflammation and vascular calcification.[21-27] Recent studies have underscored its relevance in CAVS, with a case-control study demonstrating a significant association between the TyG index and the presence of aortic valve calcification

Xuecheng Song[1,2]
Xinghong Lin[1]
Xin Xu[1]
Yongming He[1]

[1]*Department of Cardiology, The First Affiliated Hospital of Soochow University, Suzhou City, China*
[2]*Department of Cardiology, The Third People's Hospital of Bengbu, Bengbu City, China*

Corresponding author:
Yongming He
✉ heyongming@suda.edu.cn

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(OR = 1.743, $P < .05$, 95% CI: 1.04-2.93).[28] Furthermore, retrospective cohort studies have demonstrated that a higher TyG index is linked to poor prognosis in patients with CAVS undergoing transcatheter aortic valve replacement [Hazard ratio (HR) = 5.41, $P < .001$, 95% CI: 4.01-7.32],[29] and increases all-cause mortality in severe aortic stenosis (HR = 1.622, $P = .018$, 95% CI: 1.09-2.42).[30] These findings collectively suggest a potential role of the TyG index in CAVS progression.

However, the causal relationship between the TyG index and CAVS remains unclear, necessitating robust analytical approaches such as Mendelian randomization (MR) to address potential confounding and reverse causality.[31,32] While previous MR studies have separately established robust causal associations between triglycerides, diabetes, and CAVS,[33-35] the potential causal association between the TyG index, a composite metabolic biomarker, and CAVS remains unexplored. To address this knowledge gap, bidirectional 2-sample MR and multiple MR were employed to elucidate the independent causal effect of the TyG index on CAVS.

METHODS

Study Design

This study utilized a bidirectional MR framework to assess causal relationships in both directions: (1) the effect of the TyG index on the risk of CAVS and (2) the effect of CAVS on the TyG index. The MR analysis is grounded in 3 fundamental assumptions: (1) the selected instrumental variables (IVs) must exhibit strong associations with the TyG index, triglyceride levels, and glucose levels; (2) the IVs must be independent of potential confounders; and (3) the IVs should influence CAVS exclusively through the TyG index, triglycerides, and glucose levels, but not other pathways. A schematic overview of the study design is presented in Figure 1.

Two Sample Mendelian Randomization Analysis

The 2-sample MR was adopted to investigate the causal association between TyG index and CAVS. Summary statistics were obtained from publicly available genome-wide association study (GWAS) databases, including the Integrative Epidemiology Unit Open GWAS Project (IEU-GWAS), the United Kingdom Biobank (UK Biobank), and the Finnish Genetics (FinnGen) database. In this study, single nucleotide polymorphisms (SNPs) strongly associated with the TyG index, triglyceride, and glucose levels were selected as IVs. These SNPs are randomly allocated at the time of conception, ensuring the minimal influence of environmental factors.[36] Initially, the random-effects inverse variance weighted (IVW) method was applied to estimate the causal effect of TyG index on CAVS. To enhance the robustness of the outcomes, complementary approaches such as the MR Egger, weighted median, simple mode, and weighted mode methods were applied. Furthermore, heterogeneity and pleiotropy were assessed using the IVW method and MR-Egger intercept, while leave-one-out analysis was performed to evaluate the influence of individual variants. All study procedures adhered to the STROBE-MR guidelines.[37,38]

Multiple Mendelian Randomization Analysis

To further address potential pleiotropy arising from confounding factors, multiple MR analyses were conducted, adjusting for body mass index (BMI), low-density lipoprotein cholesterol (LDL-C), diabetes mellitus (DM), and hypertension (HTN). First, the causal effects of TyG index, triglyceride, and glucose levels on CAVS were evaluated through multiple MR analyses. Subsequently, the IVW method and the MR-Egger intercept were utilized to evaluate heterogeneity and pleiotropy. All results were visualized in forest plots for clarity and comparison.

Date Sources and Single Nucleotide Polymorphisms Selection

Genetic variants associated with the TyG index were derived from a prior GWAS based on the UK Biobank cohort,[39] which included 273368 individuals aged 40-69 years without diabetes or lipid metabolism disorders. The SNPs associated with the TyG index at genome-wide significance ($P < 5 \times 10^{-8}$) were identified using linear regression, adjusted for age, sex, and the top 5 genetic principal components to control population stratification. These SNPs were further pruned by linkage disequilibrium with $r^2 < .01$, and those that were significantly associated with triglyceride or glucose were also excluded. In total, 192 initial SNPs were selected for TyG index (Supplementary Table 1).

To ensure effectiveness of the SNPs and avoid bias, linkage disequilibrium was defined with $r^2 < 0.001$ for triglyceride and glucose levels. The Data Harmonization key steps were as follows: (1) SNPs matching and strand alignment: genetic instruments for the exposure and outcome were initially matched by their ID. The effect alleles for all SNPs were aligned to the forward strand to ensure a consistent reference framework across datasets; (2) harmonization of effect alleles: for each SNP, it was ensured that the effect allele reported in the outcome dataset corresponded to the same physical allele as the effect allele in the exposure dataset. This was achieved by flipping the sign of the beta coefficient for the outcome association when the effect alleles were complementary or mismatched, thereby aligning the direction of effect; (3) quality control and exclusion criteria: ① palindromic SNPs: all ambiguous palindromic SNPs were excluded to prevent errors caused by indeterminate strand orientation, ② allele frequency check: for non-palindromic SNPs, the effect allele frequencies were compared between the exposure and outcome samples. The SNPs with an absolute allele frequency difference > 0.08 were removed to

HIGHLIGHTS

- This study reveals a unidirectional causal relationship between elevated triglyceride-glucose (TyG) index and higher calcific aortic valve stenosis (CAVS) risk, employing bidirectional Mendelian randomization analysis.
- This study supports the involvement of insulin resistance and systemic inflammation in CAVS development.
- This study proposes the TyG index as a metabolic biomarker to stratify CAVS risk and guide prevention.

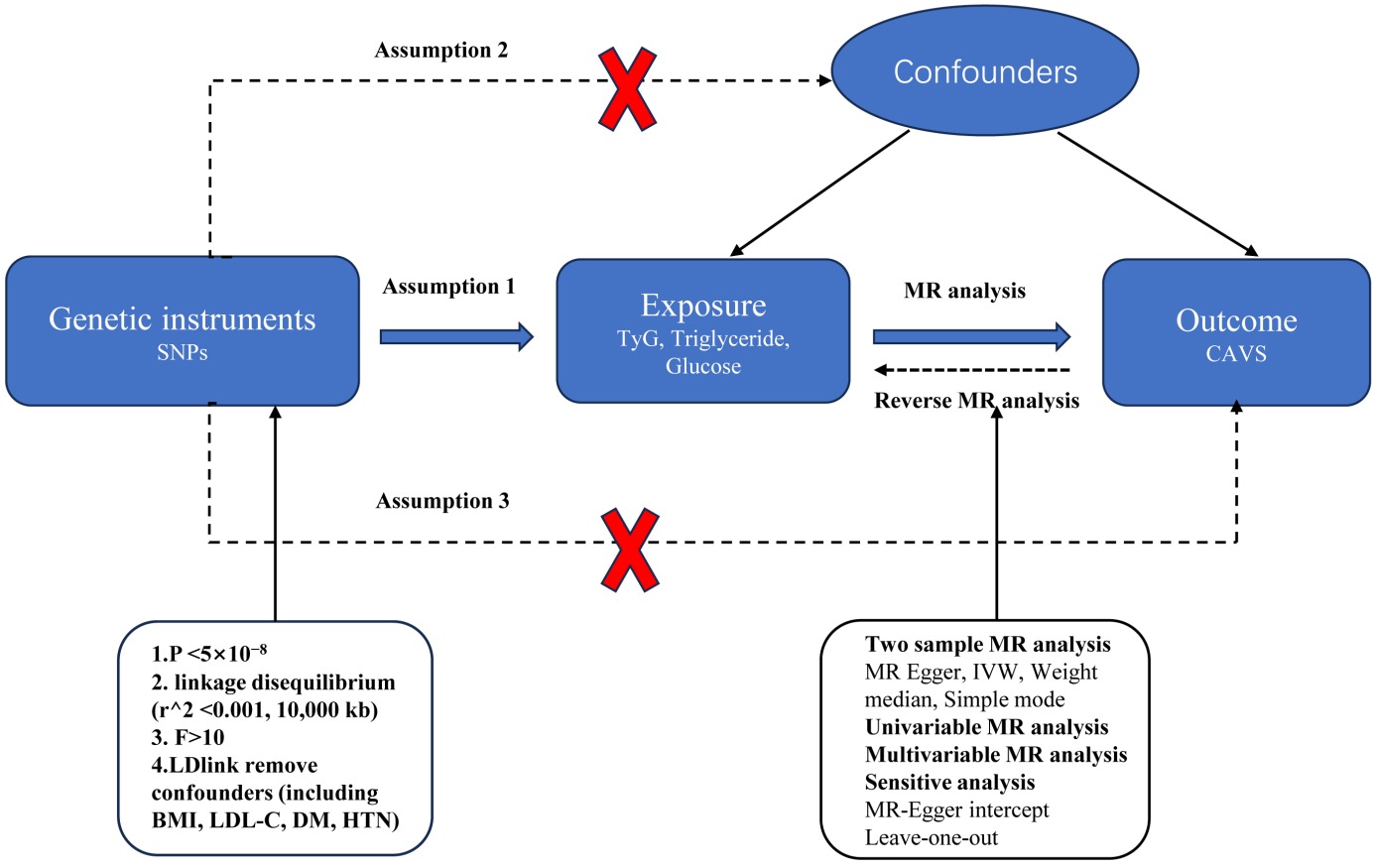

Figure 1. Study designed. BMI, body mass index; AVS, calcific aortic valvular stenosis; DM, diabetes mellitus; GWAS, genome-wide association studies; HTN, hypertension; IVW, inverse variance weighted; LDL-C, low density lipoprotein cholesterol; MR, Mendelian randomization; SNPs, single nucleotide polymorphisms.

minimize bias from potential population stratification or poor imputation quality, ③ incompatible SNPs: any SNPs with non-matching alleles (e.g., A/C in the exposure vs. G/T in the outcome) that could not be resolved through strand flipping were deemed incompatible and excluded from the analysis.

Genetic variants for triglycerides and glucose were sourced from IEU-GWAS (https://gwas.mrcieu.ac.uk/), comprising 389 562 and 314 916 participants, respectively. The CAVS outcome data were obtained from the FinnGen database (https://www.finngen.fi/en), which included 12 418 cases and 487 930 controls. Further details are provided in Table 1. All studies were reviewed and approved by local institutional review boards. Genetic variants associated with exposure were rigorously selected based on their strength of association and independence. To assess the strength of the IVs, the F-statistics was calculated. All IVs were selected for the MR analyses only if they exceeded the empirical threshold of $F > 10$.[40] Additionally, the LDlink database (https://ldlink.nih.gov/) was utilized to exclude SNPs that were significantly associated with potential confounders or other traits related to CAVS and eliminated all SNPs associated ($P < 5 \times 10^{-8}$) with the following traits. This step ensured that the selected IVs were specific to the exposures of interest (TyG index, triglycerides, and glucose) and not influenced by other metabolic factors such as BMI, LDL-C, DM, or HTN. These confounders were selected a priori based on their established associations in the existing epidemiological literature.[34,41-44]

Details on all datasets downloaded and screened are displayed in Table 1. Finally, 312 and 109 SNPs for triglyceride and glucose, respectively, were selectively obtained. In addition, 34 SNPs for CAVS were sourced from the FinnGen database for further reverse causality analysis (Supplementary Tables 2-4).

Statistical Analysis

All statistics were calculated using R software version 4.4.2 (The R Foundation for Statistical Computing, Vienna, Austria). The causal effect was deemed significant if the IVW *P* value was below the Bonferroni-corrected threshold ($P < .05/3 \approx .017$), while *P* values in the range of .017 to .05 were considered suggestive.

RESULTS

Two-Sample Mendelian Randomization Analysis

The 2-sample MR analysis based on the IVW method demonstrated a significant causal association between genetically predicted TyG index (n = 273 368 individuals) and CAVS (OR = 1.50, *P* = .007, 95% CI: 1.12-2.02) (Figure 2). Consistent findings were observed using the MR-Egger method (n = 500 348 individuals) (Figure 2). Furthermore, MR analysis

Table 1. Information on Data Included in the Study

Phenotypes/ID	Data Source	Population/PMID	Sample Size/Cases	Author/Year
TyG				
UK Biobank cohort[39]	UK Biobank database	European/NA	273 368	Si S/2020
Triglyceride levels				
ebi-a-GCST90014014	IEU-GWAS database	European/34017140	389 562	Mbatch J/2021
Glucose levels				
ebi-a-GCST90018955	IEU-GWAS database	European/34594039	314 916	Sakaue S/2021
CAVS				
finn_I9_CAVS_OPERATED	FinnGen database	European/NA	500 348/12 418	NA/2024
Confounders				
BMI				
ebi-a-GCST006368	IEU-GWAS database	European/30108127	315 347	Hoffmann TJ/2018
LDL-C				
ebi-a-GCST90092883	IEU-GWAS database	European/35213538	115 082	Richardson TG/2022
DM				
finn-b-E4_DIABETES	FinnGen database	European/30108127	218 792/35 607	NA/2021
Hypertension				
ebi-a-GCST90038604	IEU-GWAS database	European/33959723	484 598/129 909	Dönertas HM/2021

BMI, body mass index; CAVS, calcific aortic valvular stenosis; DM, diabetes mellitus; FinnGen, Finnish Genetics IEU-GWAS; Integrative Epidemiology Unit Open Genome-Wide Association Studies Project; LDL-C, low density lipoprotein cholesterol; TyG, triglyceride-glucose; UK Biobank: United Kingdom Biobank.

supported a causal role of triglycerides in CAVS development (OR = 1.29, $P < .001$, 95% CI: 1.15-1.45). A similar significant causal relationship was identified between glucose and CAVS (OR = 1.21, $P = .01$, 95% CI: 1.05-1.40) (Figure 2).

The IVW method was used to test for heterogeneity, and the MR-Egger intercept to test pleiotropy. Although significant heterogeneity was observed ($P < .001$), no directional pleiotropy was detected in the associations between the TyG index

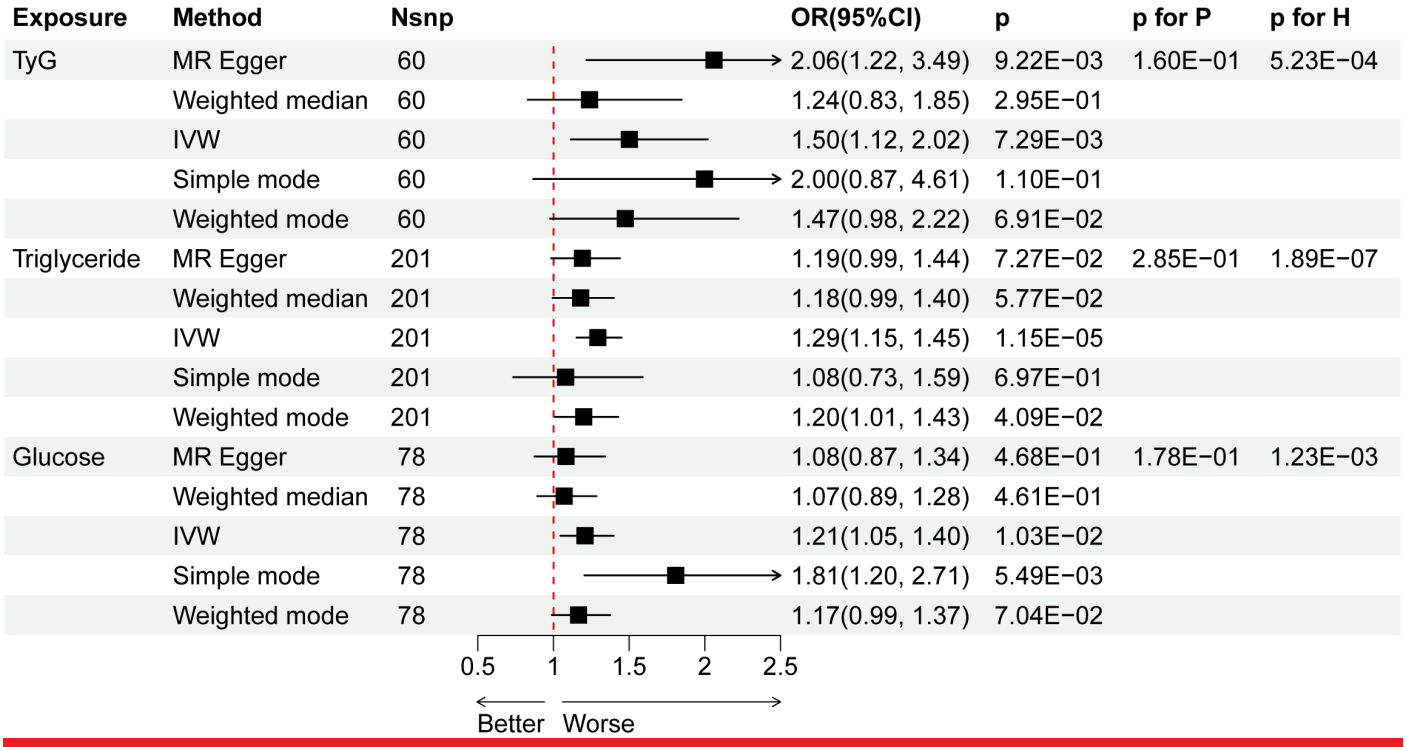

Figure 2. Two-sample MR analysis about exposures to CAVS. CAVS, calcific aortic valve stenosis; H, heterogeneity; IVW, inverse variance weighted; MR, Mendelian randomization; OR, odds ratio; P, pleiotropy; TyG, triglyceride-glucose.

and CAVS ($P = .16$) (Figure 2, Supplementary Table 5). This suggested that the IVs exert their effects through the intended pathway, supporting the validity of the causal inference. Similarly, no significant evidence of directional pleiotropy was detected for the associations of triglycerides ($P = .285$) or glucose ($P = .178$) with CAVS. The effects of TyG index on CAVS were illustrated in scatter plots (Figure 3), where each point represents a genetic variant, demonstrating the association between its effect on exposure and outcome. Sensitivity analysis employing a leave-one-out approach demonstrated that no individual SNP exerted a disproportionate influence on the causal association between the TyG index and CAVS (Supplementary Figure 2). Additional visual representations, including scatter plots for triglycerides and glucose, as well as funnel and forest plots, are shown in Supplementary Figures 1-3.

Multiple Mendelian Randomization Analysis

Univariable MR analysis supported a causal role of the TyG index in CAVS development (OR = 1.77, $P < .001$, 95% CI: 1.47-2.12). Similar causal relationships were observed for triglycerides (OR = 1.28, $P < .001$, 95% CI: 1.16-1.41) and glucose (OR = 1.20, $P = .011$, 95% CI: 1.04-1.38) (Figure 4). To further rule out the influence of confounding factors, multiple MR analysis was performed, adjusting for BMI, LDL-C, DM, and HTN. The multiple MR analysis confirmed a significant association between the TyG index and CAVS (OR = 1.64, $P = .003$, 95% CI: 1.18-2.28) (Figure 4).

Reverse 2-Sample Mendelian Randomization Analysis

The reverse 2 sample MR analysis based on the IVW method revealed no significant association between genetically predicted CAVS (n = 500 348 individuals) and triglycerides (OR = 1.01, $P = .129$, 95% CI: 1.00-1.03) (Figure 5). Similarly, MR-Egger analysis showed no association between CAVS and triglycerides (n = 389 562 individuals) (Supplementary Table 7). No significant relationship was observed between CAVS and glucose (OR=1.01, $P = .188$, 95% CI: 1.00-1.02) (Figure 5), indicating the absence of reverse causality.

No significant evidence of directional pleiotropy was detected in the association between CAVS and triglycerides ($P = .431$) (Figure 5). For glucose, there is no evidence of heterogeneity ($P = .112$) and pleiotropy ($P = .922$). The effects of CAVS on TyG index were illustrated in scatter plots (Figure 6). Sensitivity analyses, including leave-one-out, funnel, and forest plots, were presented in Supplementary Figures 4-6.

DISCUSSION

To the best of knowledge, this is the first bidirectional MR study to comprehensively assess the causal relationship between the TyG index and CAVS. Conversely, no substantial causal effect of CAVS on the TyG index was observed. These results highlight that insulin resistance, as reflected by the TyG index, contributes to CAVS pathophysiology independently of established clinical and metabolic confounders.

Previous observational studies have suggested that the TyG index, a surrogate marker of insulin resistance, may contribute to CAVS through its pro-oxidant and pro-inflammatory properties. However, the evidence remains inconsistent and limited. For instance, a case-control study involving 361 patients with aortic valve calcification and 89 controls reported a significant predictive value of the TyG index for aortic valve calcification (OR = 1.743, $P < .05$, 95% CI: 1.04-2.93).[28] Similarly, Milad et al[34] identified a significant association between triglycerides and aortic stenosis risk in an MR study (OR = 1.52, $P = .006$, 95% CI: 1.12-2.03). The Copenhagen General Population Study, encompassing 108 559 individuals, further corroborated these findings, showing that higher triglyceride levels (>5 mmol/L) were both observationally and genetically linked to an increased risk of aortic valve stenosis (OR = 1.52, $P < .001$, 95% CI: 1.02-2.27).[45] Additionally, another MR study revealed that genetically predicted type 2 diabetes was associated with increased CAVS risk (OR = 1.15, $P < .001$, 95% CI: 1.10-1.21).[43] Conversely, a cross-sectional study of 183 elderly patients with CAVS reported a negative association between the TyG index and CAVS (OR = 0.43, $P < .001$, 95% CI:

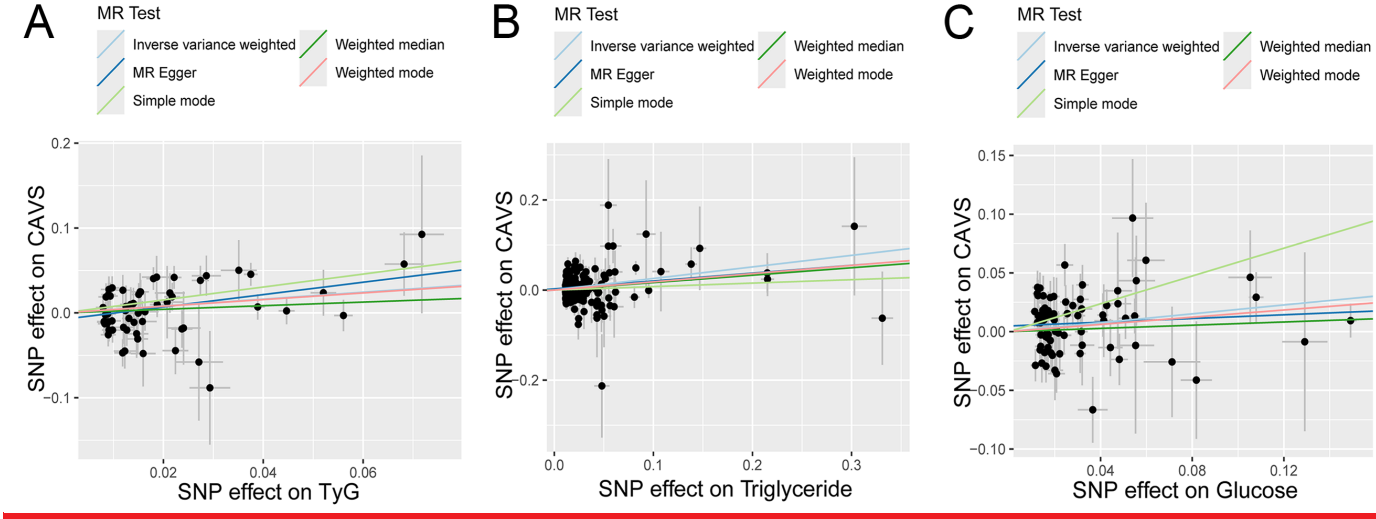

Figure 3. Scatter plots of MR analysis about exposures to CAVS. CAVS, calcific aortic valve stenosis; MR, Mendelian randomization; SNP, single nucleotide polymorphism; TyG, triglyceride-glucose.

Exposure	Method	Nsnp	OR(95%CI)	p	p for P	p for H
TyG(crude analysis)	MR Egger	150	2.18(1.60, 2.96)	1.74E−06	9.61E−02	<0.01
	Weighted median	150	1.68(1.28, 2.22)	2.06E−04		
	IVW	150	1.77(1.47, 2.12)	1.13E−09		
	Simple mode	150	1.76(0.99, 3.12)	5.48E−02		
	Weighted mode	150	1.72(1.29, 2.28)	2.79E−04		
TyG(r^2<0.001)	IVW	85	1.70(1.33, 2.17)	2.20E−05	2.23E−01	<0.01
Adjusted for BMI, LDL−C, DM, HTN	IVW	86	1.64(1.18, 2.28)	3.01E−03	9.60E−02	<0.01
Triglyceride(crude analysis)	MR Egger	245	1.28(1.09, 1.50)	3.18E−03	9.46E−01	<0.01
	Weighted median	245	1.25(1.10, 1.43)	8.54E−04		
	IVW	245	1.28(1.16, 1.41)	5.14E−07		
	Simple mode	245	1.19(0.89, 1.60)	2.35E−01		
	Weighted mode	245	1.27(1.10, 1.47)	1.56E−03		
Adjusted for BMI, LDL−C, DM, HTN	IVW	148	1.20(1.07, 1.35)	2.45E−03	5.10E−02	<0.01
Glucose(crude analysis)	MR Egger	92	1.03(0.83, 1.28)	7.71E−01	7.98E−02	<0.01
	Weighted median	92	1.07(0.89, 1.28)	4.70E−01		
	IVW	92	1.20(1.04, 1.38)	1.11E−02		
	Simple mode	92	1.65(1.08, 2.53)	2.27E−02		
	Weighted mode	92	1.12(0.96, 1.30)	1.51E−01		
Adjusted for BMI, LDL−C, DM, HTN	IVW	54	1.25(1.05, 1.49)	1.35E−02	9.37E−01	<0.01

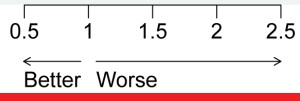

Figure 4. Multiple MR analyses about exposures to CAVS. BMI, body mass index; CAVS, calcific aortic valvular stenosis; DM, diabetes mellitus; H, heterogeneity; HTN, hypertension; IVW, inverse variance weighted; LDL-C, low density lipoprotein cholesterol; OR, odds ratio; P, pleiotropy; TyG, triglyceride-glucose index.

0.28-0.68).[46] These discrepancies likely stem from confounding factors and reverse causality, which the MR approach effectively mitigates.

In this 2-sample MR study, genetic variants were utilized as IVs to establish a robust causal association between elevated TyG index (n=273368 individuals) and increased CAVS risk (OR=1.50, *P* = .007, 95% CI: 1.12-2.02). Consistent results were observed for triglycerides and glucose levels, with complementary MR methods and sensitivity analyses confirming the robustness and reliability of these associations (*P* > .05). It was stated that while the primary sensitivity

Outcome	Method	Nsnp	OR(95%CI)	p	p for P	p for H
Triglyceride	MR Egger	25	0.99(0.93, 1.05)	6.84E−01	4.31E−01	7.20E−05
	Weighted median	25	1.00(0.99, 1.02)	7.34E−01		
	IVW	25	1.01(1.00, 1.03)	1.29E−01		
	Simple mode	25	1.00(0.97, 1.03)	8.25E−01		
	Weighted mode	25	1.00(0.98, 1.02)	8.83E−01		
Glucose	MR Egger	30	1.01(0.99, 1.03)	5.16E−01	9.22E−01	1.12E−01
	Weighted median	30	1.00(0.99, 1.01)	7.01E−01		
	IVW	30	1.01(1.00, 1.02)	1.88E−01		
	Simple mode	30	1.00(0.98, 1.02)	7.84E−01		
	Weighted mode	30	1.00(0.99, 1.02)	6.85E−01		

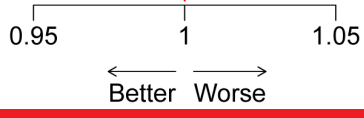

Figure 5. Reverse 2-sample MR analysis about CAVS to outcomes. CAVS, calcific aortic valve stenosis; H, heterogeneity; IVW, inverse variance weighted; MR, Mendelian randomization; OR, odds ratio; P, pleiotropy.

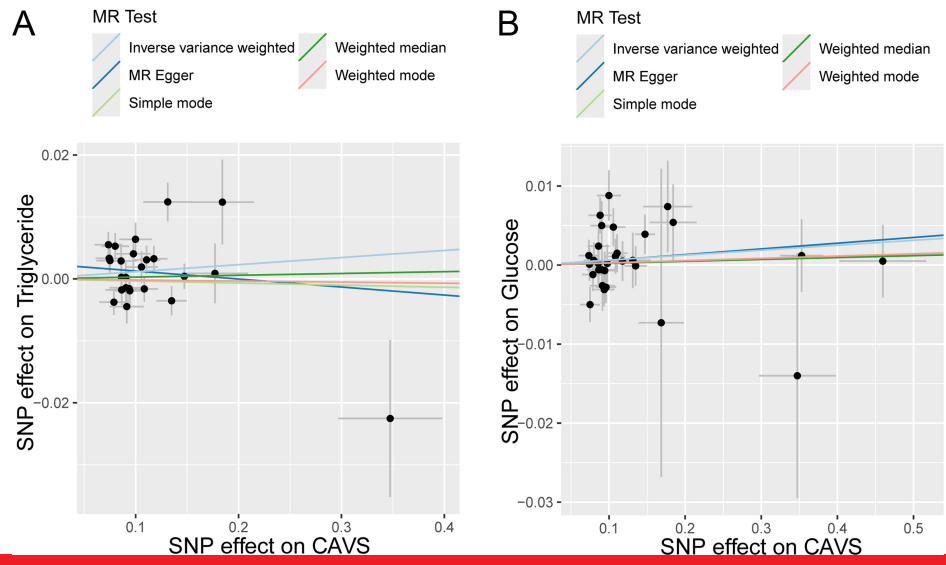

Figure 6. Scatter plots of MR analysis about CAVS to outcomes. CAVS, calcific aortic valve stenosis; MR, Mendelian randomization; SNP, single nucleotide polymorphism.

analyses did not detect directional pleiotropy, heterogeneity might still reflect pleiotropic effects. Reverse MR analyses further excluded the possibility of reverse causality (triglycerides: OR = 1.01, *P* = .129, 95% CI: 1.00-1.03; glucose: OR = 1.01, *P* = .188, 95% CI: 1.00-1.02). Multiple MR analysis, adjusted for potential confounders, reinforced the positive association between the TyG index and CAVS (OR = 1.64, *P* = .003, 95% CI: 1.18-2.28). These findings collectively highlight a consistent causal relationship and address critical limitations inherent in observational studies, thereby advancing the understanding of the potential pathogenesis of CAVS.

Several plausible mechanisms may explain the observed positive correlation between elevated TyG index and CAVS. First, systemic inflammation plays a pivotal role. Insulin resistance, as indicated by a higher TyG index, promotes systemic inflammation through the activation of pro-inflammatory pathways, such as nuclear factor-kappaB and the NLRP3 inflammasome.[47,48] These pathways are critical in driving aortic valve calcification by inducing osteogenic differentiation of valvular interstitial cells.[49,50] Second, oxidative stress is another key contributor. Insulin resistance is associated with increased oxidative stress, which exacerbates endothelial dysfunction and lipid deposition in the aortic valve.[51,52] Oxidative stress enhances the uptake of oxidized LDL by macrophages, leading to foam cell formation and subsequent calcification.[53] Third, the TyG index, as a composite marker of triglyceride and glucose dysregulation, is closely associated with lipid metabolism abnormalities. Elevated triglyceride levels promote lipoprotein deposition within the valve leaflets, a process that can initiate calcific remodeling and contribute to the pathogenesis of CAVS.[12,35,54]

The TyG index may serve as an accessible and cost-effective biomarker for identifying individuals at high risk for CAVS. Early identification of at-risk populations could facilitate targeted preventive strategies. Further research is necessary to demonstrate the precise mechanistic pathways through which insulin resistance promotes valvular calcification, particularly the roles of inflammation, oxidative stress, and lipid metabolism.

Strengths and Limitations

This study is the first to investigate the causal relationship between the TyG index and CAVS, filling a significant gap in the literature. The bidirectional MR design provides a robust framework for assessing causality in both directions, effectively mitigating potential reverse causation. The use of genetic variants as IVs minimizes confounding and enhances causal inference. Nevertheless, several limitations should be acknowledged. First, the study population was exclusively of European ancestry, which may limit the generalizability of the findings to other ethnic groups. Genetic determinants of the TyG index and their impact on CAVS risk may vary across populations, underscoring the need for replication in more diverse cohorts. Second, while the MR approach reduces confounding, it relies on the assumption that the genetic instruments are valid, which may not hold in all cases. Although sensitivity analyses, including MR-Egger and IVW methods, were employed to address pleiotropy, residual pleiotropic effects cannot be entirely ruled out. Third, the limited GWAS data for the TyG index restricted its direct application in reverse MR analysis. Future studies with larger, more diverse populations are warranted to validate these findings.

CONCLUSION

In conclusion, the MR study demonstrates a causal association between higher TyG index and increased risk of CAVS, highlighting the important role of metabolic regulation in CAVS pathogenesis and prevention.

Data availability statement: The complete dataset produced or examined in this research is available within the manuscript and its supplementary materials. For further inquiries, please contact the corresponding author.

Ethics Committee Approval: All data used in this study were obtained from publicly available sources and are in the public domain. Thus, no ethical approval or clinical trial registration was required.

Peer-review: Externally peer-reviewed.

Author Contributions: Conception – Y.H., X.S.; Design – X.S.; Supervision – Y.H.; Resource – Y.H., X.S.; Materials – X.S., Y.H.; Date Collection – X.S., X.X.; Analysis and interpretation – X.S., X.L.; Literature Search – X.S., X.L., X.X.; Writing – X.S., Y.H.; Critical Reviews – Y.H.

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Declaration of Interests: The authors declare no competing interests.

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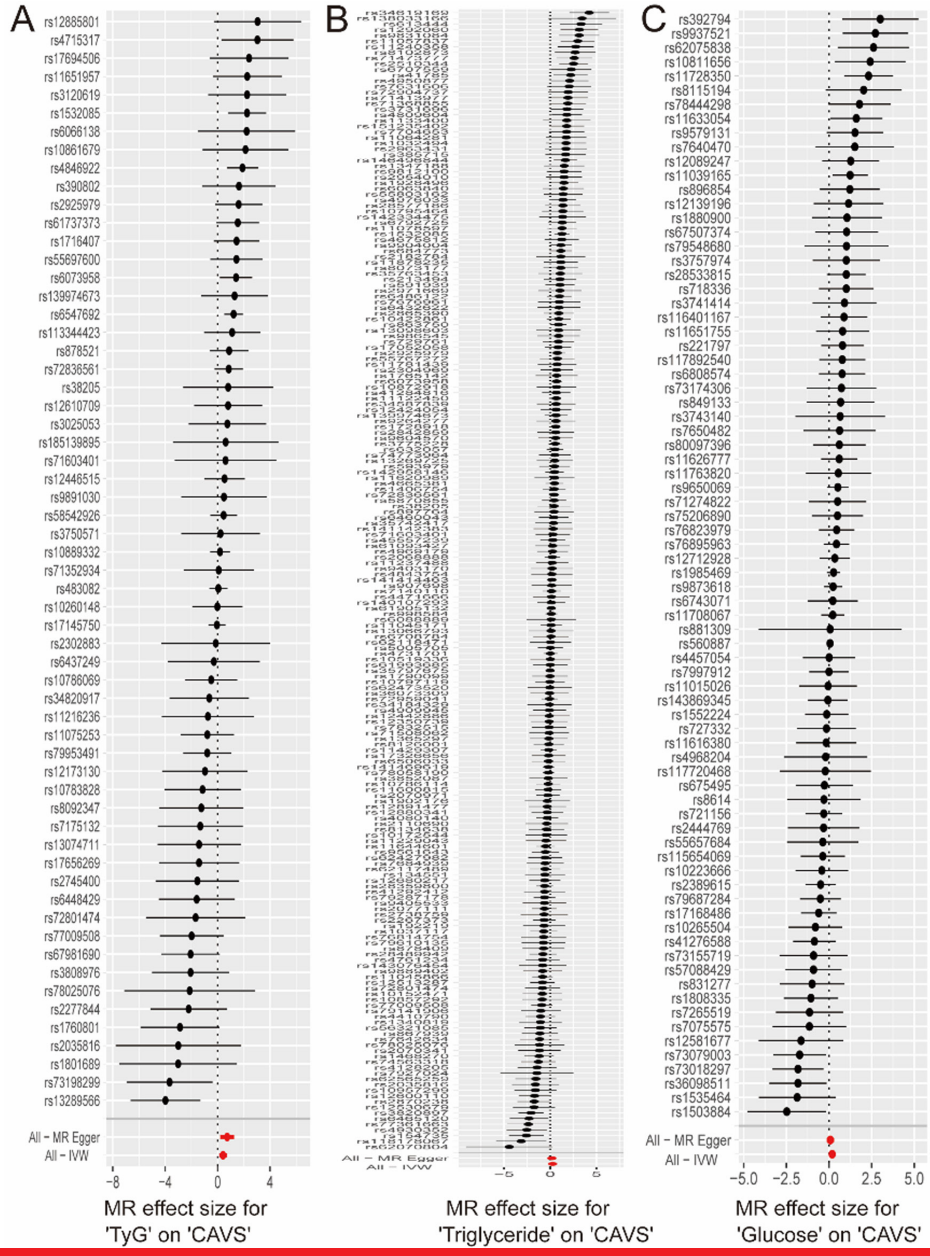
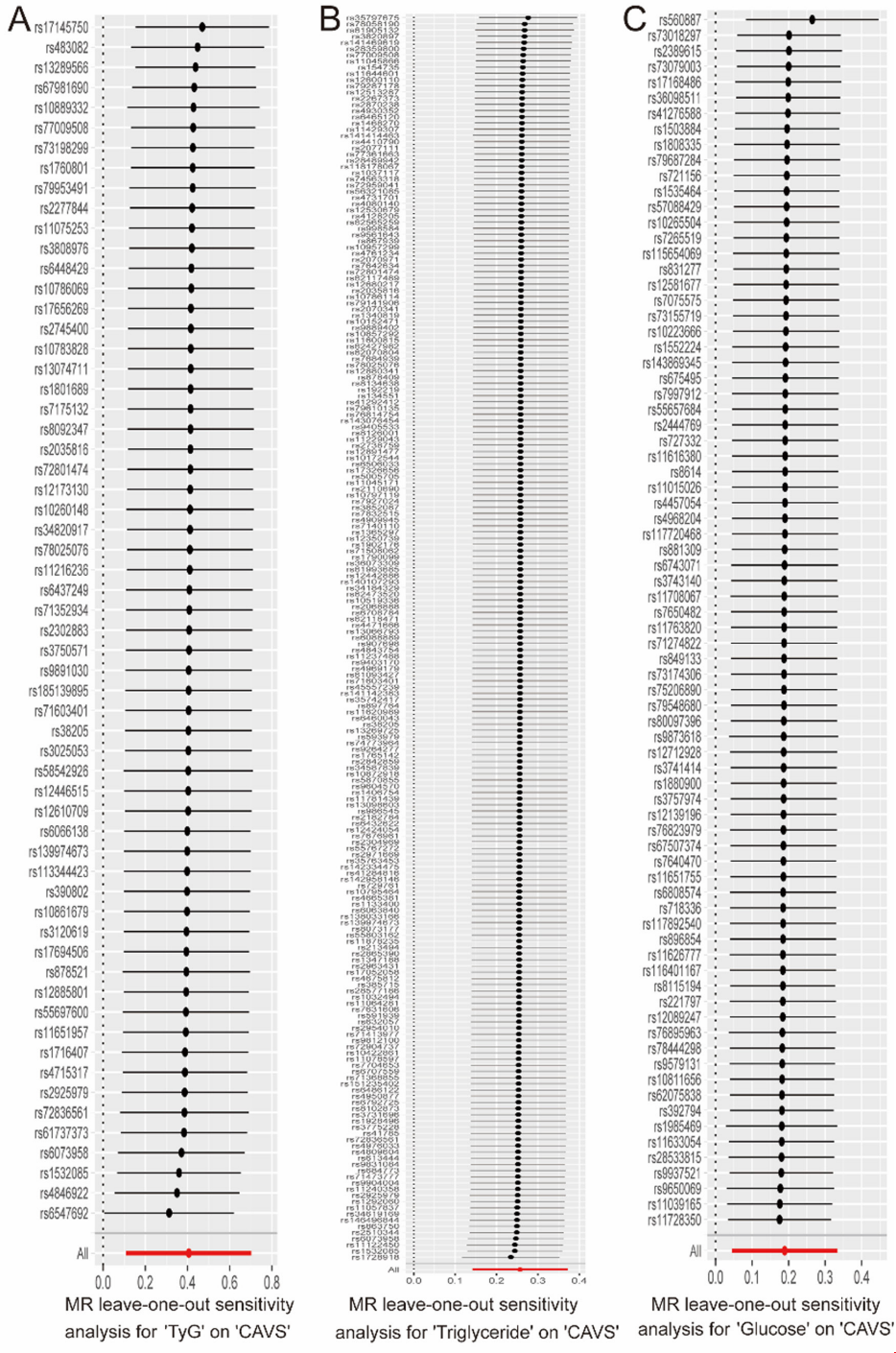
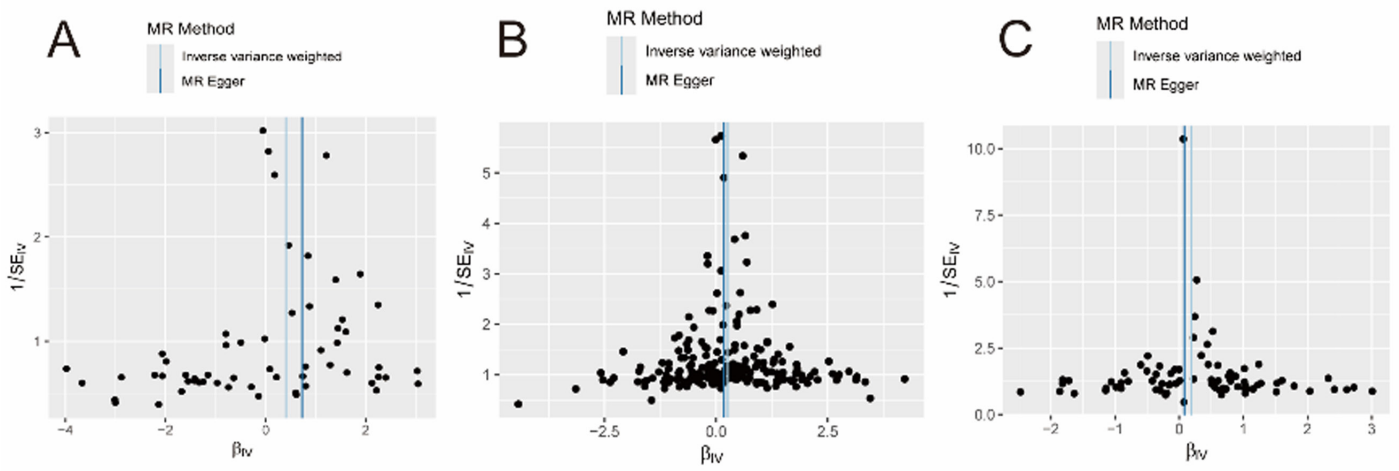


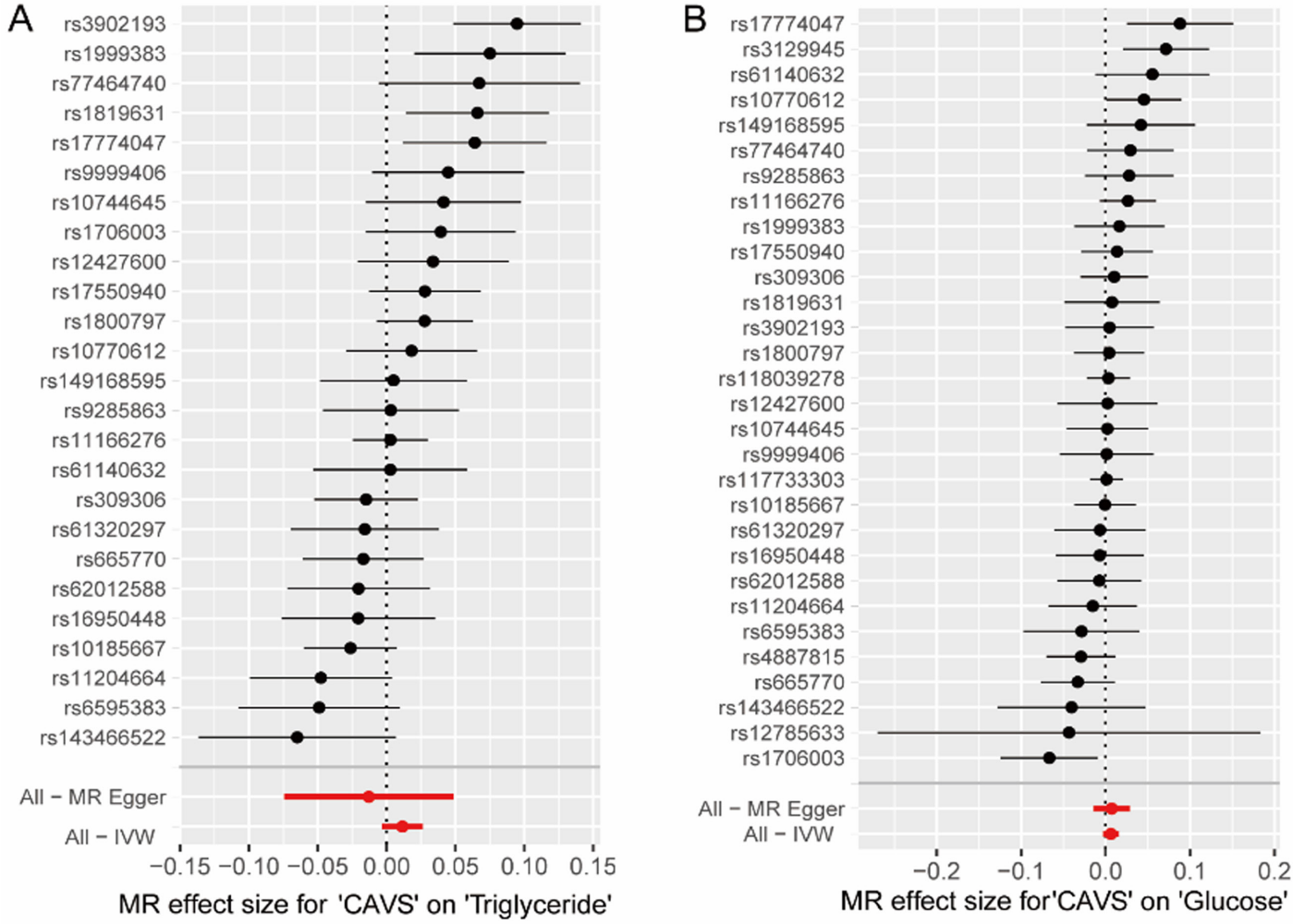
Supplementary Figure 1. Forest plots of the causal effect of SNPs of exposures on CAVS. (A)TyG index, (B)Triglyceride and (C) Glucose. MR: Mendelian randomization; TyG index: triglyceride-glucose index; CAVS: calcific aortic valve stenosis; IVW: inverse variance weighted; SNPs: Single nucleotide polymorphisms.



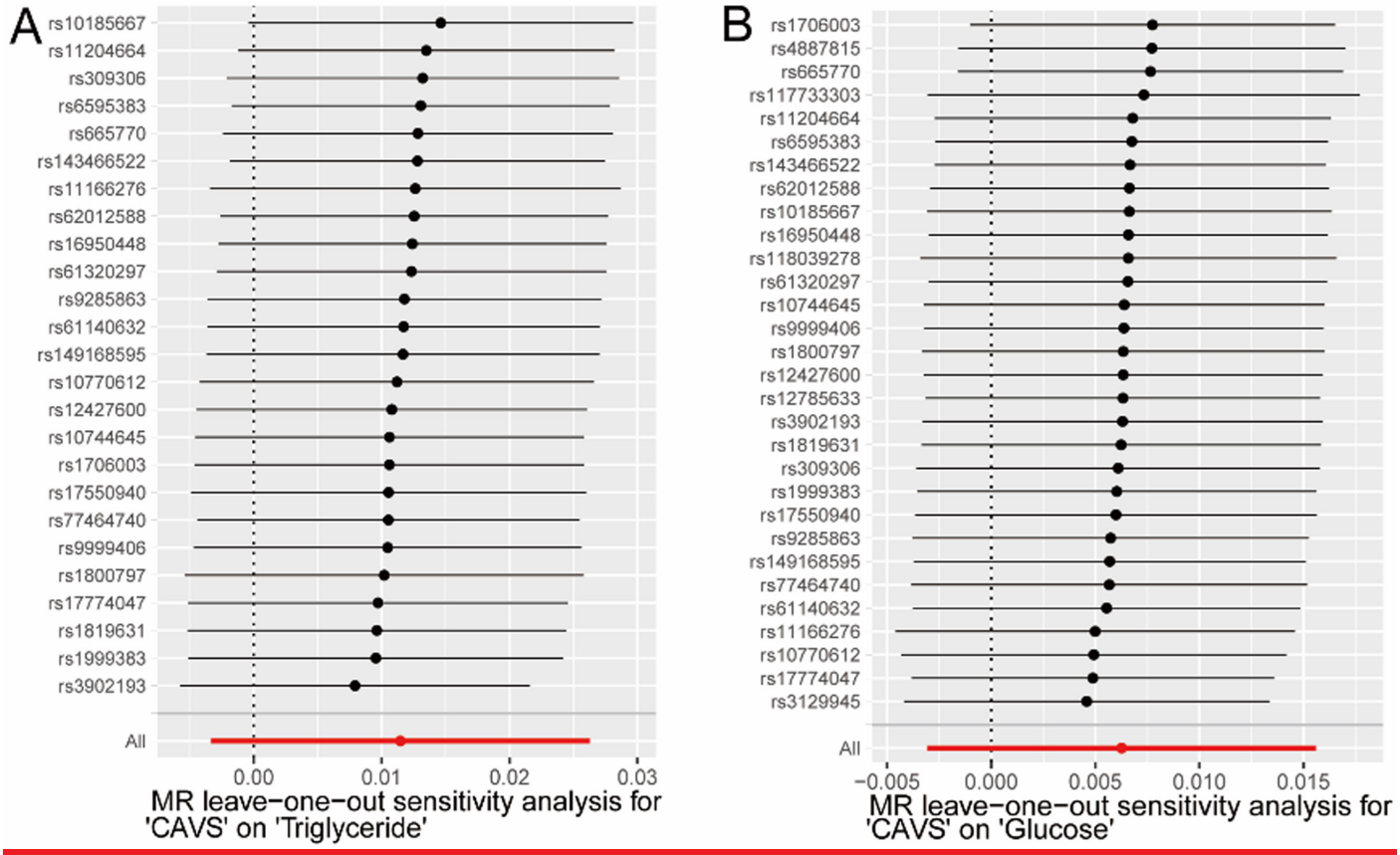
Supplementary Figure 2. Leave-one-out analysis for the effect of exposures on CAVS. (A)TyG index, (B)Triglyceride and (C) Glucose. MR: Mendelian randomization; TyG index: triglyceride-glucose index; CAVS: calcific aortic valve stenosis.



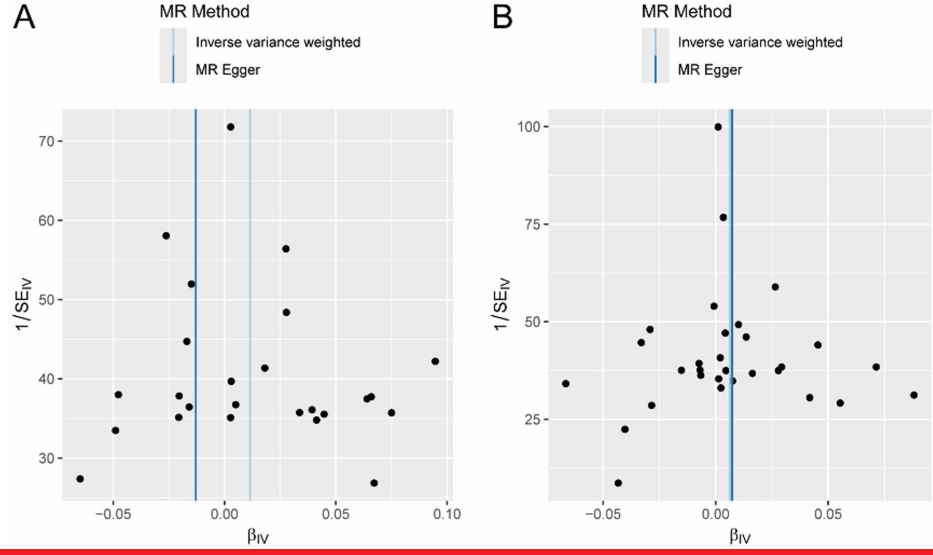
Supplementary Figure 3. Funnel plots of exposures to CAVS. (A)TyG index, (B)Triglyceride and (C)Glucose. TyG index: triglyceride-glucose index; CAVS: calcific aortic valve stenosis; MR: Mendelian randomization; SE: standard Error; IV: instrument variable.



Supplementary Figure 4. Forest plots of the causal effect of SNPs of CAVS on outcomes. (A) Triglyceride and (B)Glucose. MR: Mendelian randomization; CAVS: calcific aortic valve stenosis; IVW: inverse variance weighted; SNPs: Single nucleotide polymorphisms.



Supplementary Figure 5. Leave-one-out analysis for the effect of CAVS on outcomes. (A) Triglyceride and (B)Glucose. MR: Mendelian randomization; CAVS: calcific aortic valve stenosis.



Supplementary Figure 6. Funnel plots of CAVS to outcomes. (A) Triglyceride and (B)Glucose. CAVS: calcific aortic valve stenosis; MR: Mendelian randomization; TyG index: triglyceride-glucose index; SE: standard Error; IV: instrument variable.

Supplementary Table 1. SNPs of TyG index

Exposure	SNP	Other Allele	Effect Allele	Beta	SE	*P*
TyG	rs114165349	G	C	0.04453	0.004653	1.07E-21
TyG	rs72904790	T	C	-0.01371	0.002406	1.20E-08
TyG	rs213498	T	A	-0.00803	0.001464	4.17E-08
TyG	rs10889332	C	T	-0.0389	0.00143	1.34E-162
TyG	rs72669514	C	T	0.018609	0.003207	6.53E-09
TyG	rs17656269	C	T	0.008749	0.00147	2.65E-09
TyG	rs16836630	G	C	-0.01734	0.002521	6.14E-12
TyG	rs1760801	G	A	-0.00896	0.001513	3.19E-09
TyG	rs340836	T	C	-0.0087	0.001396	4.71E-10
TyG	rs76172548	A	C	0.022814	0.003832	2.64E-09
TyG	rs3120619	G	A	0.011881	0.001803	4.45E-11
TyG	rs11118610	A	C	-0.00903	0.001389	8.09E-11
TyG	rs4846922	C	T	0.022155	0.001463	8.63E-52
TyG	rs907866	G	A	-0.00928	0.001388	2.31E-11
TyG	rs111585158	C	T	0.012113	0.002114	1.00E-08
TyG	rs144470864	A	C	0.017261	0.003078	2.05E-08
TyG	rs76384951	A	C	-0.02955	0.002524	1.16E-31
TyG	rs533617	T	C	-0.04645	0.003467	6.48E-41
TyG	rs35750610	T	C	0.018513	0.002347	3.09E-15
TyG	rs34921778	A	G	0.008426	0.00145	6.21E-09
TyG	rs12617848	C	T	0.014279	0.002006	1.09E-12
TyG	rs80216311	C	T	-0.01417	0.00239	3.05E-09
TyG	rs61737373	G	A	-0.02861	0.002929	1.57E-22
TyG	rs6547692	A	G	0.037507	0.001384	2.05E-161
TyG	rs10206462	T	C	-0.00894	0.001428	3.85E-10
TyG	rs6760053	C	G	-0.00779	0.001377	1.55E-08
TyG	rs6710938	A	C	-0.00899	0.001618	2.76E-08
TyG	rs79953491	A	G	-0.0237	0.002108	2.49E-29
TyG	rs115128825	C	A	0.026901	0.004876	3.46E-08
TyG	rs484066	T	A	-0.01592	0.001419	3.31E-29
TyG	rs17694506	T	C	0.009005	0.001419	2.19E-10
TyG	rs2943645	T	C	-0.02092	0.001432	2.40E-48
TyG	rs6437249	C	T	0.008385	0.001493	1.95E-08
TyG	rs147764624	G	C	-0.03019	0.005506	4.18E-08
TyG	rs390802	G	A	-0.01534	0.001765	3.63E-18
TyG	rs62271373	T	A	0.025359	0.003039	7.16E-17
TyG	rs13074711	T	C	0.012011	0.002185	3.86E-08
TyG	rs13108218	G	A	0.01564	0.001438	1.54E-27
TyG	rs71603401	A	G	0.012509	0.002055	1.15E-09
TyG	rs6448429	C	T	0.012675	0.001878	1.49E-11
TyG	rs1471251	A	T	0.016447	0.001408	1.56E-31
TyG	rs4134363	G	A	-0.0095	0.001702	2.37E-08
TyG	rs3822076	T	A	0.008671	0.001382	3.50E-10
TyG	rs2035816	A	G	-0.01594	0.002491	1.54E-10
TyG	rs78025076	C	T	0.027112	0.004828	1.96E-08
TyG	rs390556	T	C	-0.01327	0.002204	1.73E-09
TyG	rs72754154	G	A	-0.0214	0.003141	9.58E-12
TyG	rs3936511	A	G	0.021613	0.001747	3.69E-35
TyG	rs151913	G	A	0.00787	0.001414	2.60E-08

(*Continued*)

Supplementary Table 1. SNPs of TyG index (*Continued*)

Exposure	SNP	Other Allele	Effect Allele	Beta	SE	*P*
TyG	rs7703744	C	G	-0.01093	0.001552	1.84E-12
TyG	rs72801474	G	A	-0.01464	0.002353	4.88E-10
TyG	rs12173130	T	C	0.009711	0.001769	4.07E-08
TyG	rs11134475	G	A	-0.01694	0.001423	1.15E-32
TyG	rs2963476	A	G	0.013369	0.001699	3.58E-15
TyG	rs6923241	C	T	-0.01092	0.001547	1.67E-12
TyG	rs2745400	G	A	0.00826	0.001372	1.76E-09
TyG	rs2894211	C	A	0.017465	0.002189	1.46E-15
TyG	rs7758790	T	C	0.01428	0.001648	4.52E-18
TyG	rs55697600	A	G	0.035107	0.003604	2.05E-22
TyG	rs185139895	G	A	0.020756	0.003384	8.63E-10
TyG	rs3025053	G	A	-0.01346	0.002125	2.40E-10
TyG	rs4715317	G	T	0.009743	0.001439	1.30E-11
TyG	rs1967685	G	C	-0.01428	0.001371	2.25E-25
TyG	rs632057	G	T	0.015367	0.001421	2.94E-27
TyG	rs12208357	C	T	0.021956	0.002725	7.75E-16
TyG	rs77009508	A	G	0.022418	0.002596	5.86E-18
TyG	rs55730499	C	T	-0.01825	0.002552	8.74E-13
TyG	rs186696265	C	T	-0.04726	0.005925	1.51E-15
TyG	rs4709746	C	T	-0.01125	0.002032	3.11E-08
TyG	rs852424	C	T	0.008528	0.001463	5.55E-09
TyG	rs38205	C	A	0.007915	0.00144	3.87E-08
TyG	rs2106727	G	A	-0.01082	0.001428	3.59E-14
TyG	rs4722551	T	C	-0.01858	0.001881	5.21E-23
TyG	rs1534696	A	C	0.010737	0.001376	6.18E-15
TyG	rs2971676	G	A	0.013349	0.002398	2.61E-08
TyG	rs878521	G	A	0.021762	0.001587	8.43E-43
TyG	rs62459110	G	C	-0.02139	0.003643	4.32E-09
TyG	rs799157	C	T	0.040791	0.003402	4.05E-33
TyG	rs17145750	C	T	-0.05606	0.001856	5.28E-200
TyG	rs10260148	C	T	0.014959	0.001542	2.96E-22
TyG	rs73198299	T	C	0.012271	0.002229	3.68E-08
TyG	rs7821812	G	C	0.016336	0.001697	6.39E-22
TyG	rs904009	A	C	0.015931	0.001626	1.16E-22
TyG	rs4921914	T	C	0.019439	0.001659	1.07E-31
TyG	rs2975424	T	C	0.010605	0.001755	1.53E-09
TyG	rs1388941	G	A	0.014354	0.001459	8.01E-23
TyG	rs268	A	G	0.10865	0.005152	1.25E-98
TyG	rs117026536	G	T	-0.09518	0.002263	1.00E-200
TyG	rs57295072	G	C	-0.03049	0.004697	8.60E-11
TyG	rs17091881	T	C	0.078595	0.004274	1.82E-75
TyG	rs74444445	T	C	0.034928	0.004886	8.82E-13
TyG	rs117805502	C	T	-0.03217	0.004394	2.48E-13
TyG	rs28550053	A	G	-0.01771	0.001821	2.42E-22
TyG	rs75662196	G	C	-0.02793	0.004345	1.30E-10
TyG	rs17092008	C	T	0.020825	0.002853	2.91E-13
TyG	rs11781356	T	A	0.009932	0.001766	1.85E-08
TyG	rs2081687	C	T	0.011677	0.001454	9.63E-16
TyG	rs71525127	C	G	0.019603	0.002547	1.42E-14

(*Continued*)

Supplementary Table 1. SNPs of TyG index (*Continued*)

Exposure	SNP	Other Allele	Effect Allele	Beta	SE	*P*
TyG	rs11558471	A	G	-0.01148	0.001471	6.29E-15
TyG	rs17321515	A	G	-0.0439	0.001371	1.00E-200
TyG	rs62521590	T	G	0.014654	0.001558	5.11E-21
TyG	rs10811661	T	C	-0.00987	0.001805	4.53E-08
TyG	rs13289566	C	T	-0.01183	0.001669	1.37E-12
TyG	rs2244278	C	A	-0.01339	0.002119	2.62E-10
TyG	rs3750571	C	A	-0.01241	0.001898	6.27E-11
TyG	rs11006681	G	A	-0.01101	0.001844	2.38E-09
TyG	rs142164605	T	A	-0.01776	0.002781	1.71E-10
TyG	rs10786069	T	C	0.013098	0.001378	2.06E-21
TyG	rs113344423	G	A	0.021299	0.003018	1.70E-12
TyG	rs2792736	A	T	-0.01005	0.001538	6.40E-11
TyG	rs10832027	A	G	-0.01226	0.001482	1.37E-16
TyG	rs3808976	A	G	0.009819	0.001701	7.84E-09
TyG	rs99780	C	T	0.020203	0.001436	5.73E-45
TyG	rs35169799	C	T	0.024724	0.002833	2.61E-18
TyG	rs678614	C	A	0.009351	0.001532	1.04E-09
TyG	rs2302883	T	C	0.008865	0.001623	4.71E-08
TyG	rs187217942	G	A	0.031159	0.005403	8.06E-09
TyG	rs17119701	A	G	0.037068	0.00375	4.94E-23
TyG	rs61362984	A	G	-0.01395	0.001422	1.06E-22
TyG	rs61904855	C	A	0.023378	0.004096	1.15E-08
TyG	rs11216122	G	T	-0.01819	0.003103	4.59E-09
TyG	rs7930786	G	C	0.124688	0.002787	1.00E-200
TyG	rs56225305	G	A	0.108415	0.002786	1.00E-200
TyG	rs2075294	G	T	0.038812	0.005799	2.19E-11
TyG	rs75919952	C	T	-0.04681	0.00317	2.56E-49
TyG	rs11600380	T	C	-0.03673	0.002541	2.34E-47
TyG	rs5110	C	A	-0.01854	0.002485	8.59E-14
TyG	rs12721078	C	A	-0.03228	0.003938	2.46E-16
TyG	rs71480323	G	A	-0.01956	0.002114	2.24E-20
TyG	rs11216236	C	T	0.024039	0.003424	2.21E-12
TyG	rs187929675	C	T	-0.07679	0.006068	1.07E-36
TyG	rs11045171	A	G	-0.01166	0.001737	1.91E-11
TyG	rs67981690	A	G	0.014856	0.002075	8.09E-13
TyG	rs10783828	G	A	0.009035	0.001475	9.04E-10
TyG	rs7296326	T	C	-0.01186	0.002173	4.84E-08
TyG	rs1585705	A	C	0.008766	0.001496	4.64E-09
TyG	rs10861679	T	C	0.009354	0.001507	5.35E-10
TyG	rs1882491	T	C	-0.0135	0.001481	8.04E-20
TyG	rs1716407	A	G	-0.01506	0.001399	4.90E-27
TyG	rs7140110	T	C	0.01437	0.001508	1.61E-21
TyG	rs112740904	T	G	-0.0149	0.001958	2.76E-14
TyG	rs12885801	C	A	0.009085	0.001622	2.11E-08
TyG	rs34820917	G	A	-0.0158	0.00285	2.97E-08
TyG	rs35477346	T	C	0.009297	0.001497	5.32E-10
TyG	rs139974673	T	C	0.071769	0.00443	5.34E-59
TyG	rs72739147	A	T	-0.01212	0.002061	4.04E-09
TyG	rs1532085	G	A	0.018004	0.00141	2.64E-37

(*Continued*)

Supplementary Table 1. SNPs of TyG index (*Continued*)

Exposure	SNP	Other Allele	Effect Allele	Beta	SE	*P*
TyG	rs261334	C	G	0.026145	0.001678	9.88E-55
TyG	rs11636087	T	C	0.011653	0.001545	4.65E-14
TyG	rs8028620	T	C	-0.00898	0.001375	6.53E-11
TyG	rs7175132	A	G	-0.00812	0.001414	9.44E-09
TyG	rs8025505	C	T	0.009647	0.001584	1.13E-09
TyG	rs9935836	A	C	0.009882	0.001773	2.49E-08
TyG	rs11075253	C	A	-0.01411	0.001502	5.65E-21
TyG	rs12446515	C	T	-0.01876	0.001475	4.76E-37
TyG	rs5880	G	C	0.022114	0.002981	1.18E-13
TyG	rs12934528	T	C	0.013515	0.001958	5.15E-12
TyG	rs2925979	C	T	0.015438	0.001498	6.79E-25
TyG	rs11651957	G	A	0.018648	0.002936	2.14E-10
TyG	rs12937081	A	G	0.010884	0.001891	8.64E-09
TyG	rs72836561	C	T	0.068218	0.003899	1.69E-68
TyG	rs231539	C	T	0.013065	0.001881	3.76E-12
TyG	rs11657238	G	A	-0.00785	0.001384	1.41E-08
TyG	rs1801689	A	C	-0.02932	0.004081	6.78E-13
TyG	rs77244849	T	C	-0.00875	0.001488	4.09E-09
TyG	rs9891030	G	A	0.009938	0.001594	4.54E-10
TyG	rs71352934	A	C	-0.01631	0.002736	2.50E-09
TyG	rs8092347	A	G	0.008121	0.001411	8.69E-09
TyG	rs197156	A	G	-0.00925	0.001454	1.99E-10
TyG	rs1035941	G	A	0.011015	0.001533	6.75E-13
TyG	rs4804413	C	T	0.009485	0.001385	7.53E-12
TyG	rs116843064	G	A	-0.10888	0.004912	8.79E-109
TyG	rs57192995	G	C	-0.0199	0.003024	4.65E-11
TyG	rs58542926	C	T	-0.05205	0.002577	1.26E-90
TyG	rs188247550	C	T	-0.06447	0.006421	1.02E-23
TyG	rs62102718	A	T	0.011589	0.001527	3.22E-14
TyG	rs58895965	C	A	0.012724	0.001804	1.75E-12
TyG	rs541012177	G	T	0.024254	0.003536	6.94E-12
TyG	rs41290102	C	T	-0.03312	0.005888	1.86E-08
TyG	rs419925	G	C	-0.01304	0.001499	3.39E-18
TyG	rs483082	G	T	0.044675	0.001617	8.09E-168
TyG	rs79429216	G	A	0.037821	0.006299	1.92E-09
TyG	rs146390218	A	G	0.035524	0.004351	3.22E-16
TyG	rs62132802	C	T	-0.00912	0.001502	1.29E-09
TyG	rs12610709	G	A	0.013994	0.001833	2.24E-14
TyG	rs2207132	G	A	0.028323	0.003878	2.83E-13
TyG	rs2250900	C	T	0.008996	0.00164	4.10E-08
TyG	rs6073958	T	C	0.027409	0.001724	7.14E-57
TyG	rs4812995	T	C	0.009133	0.001617	1.64E-08
TyG	rs6066138	G	A	-0.00851	0.001523	2.36E-08
TyG	rs6090040	C	A	0.008917	0.001388	1.33E-10
TyG	rs2277844	A	G	-0.00908	0.001385	5.43E-11

SNP: single nucleotide polymorphism; TyG: triglyceride-glucose; SE: standard error.

Supplementary Table 2. SNPs of Triglyceride

Exposure	SNP	Other Allele	Effect Allele	Beta	SE	*P*
Triglyceride	rs114165349	G	C	0.084607	0.006823	2.59E-35
Triglyceride	rs880315	T	C	-0.01206	0.002176	3.01E-08
Triglyceride	rs72904737	G	A	-0.0261	0.003646	8.09E-13
Triglyceride	rs5005705	C	A	-0.0227	0.002757	1.84E-16
Triglyceride	rs12119979	C	G	0.0193	0.002058	6.77E-21
Triglyceride	rs61778883	T	C	0.019485	0.003079	2.47E-10
Triglyceride	rs10889334	C	G	-0.08094	0.002147	1.00E-200
Triglyceride	rs12749691	A	T	-0.01834	0.002263	5.25E-16
Triglyceride	rs4950877	A	G	-0.01288	0.002108	9.90E-10
Triglyceride	rs1494368	T	C	-0.01541	0.002306	2.34E-11
Triglyceride	rs11206374	G	A	0.026749	0.002456	1.25E-27
Triglyceride	rs213494	C	T	0.016422	0.00215	2.21E-14
Triglyceride	rs1365297	A	G	-0.0165	0.002646	4.54E-10
Triglyceride	rs141142383	C	T	-0.02666	0.003764	1.41E-12
Triglyceride	rs2842859	T	C	0.013303	0.002294	6.70E-09
Triglyceride	rs7539464	T	A	-0.01441	0.002071	3.49E-12
Triglyceride	rs10631642	C	CTTT	-0.01295	0.002268	1.13E-08
Triglyceride	rs907698	G	A	-0.01226	0.002091	4.60E-09
Triglyceride	rs11240358	G	A	0.013662	0.002101	7.85E-11
Triglyceride	rs11122450	T	G	-0.05017	0.002108	3.39E-125
Triglyceride	rs57929942	A	AT	0.015251	0.00265	8.70E-09
Triglyceride	rs114052230	C	T	-0.02121	0.00285	9.88E-14
Triglyceride	rs28489942	T	C	-0.02035	0.002154	3.61E-21
Triglyceride	rs6752845	G	C	-0.0144	0.00208	4.32E-12
Triglyceride	rs7424120	C	T	-0.01338	0.002107	2.15E-10
Triglyceride	rs1009360	T	C	-0.01876	0.002087	2.46E-19
Triglyceride	rs11688682	G	C	-0.0159	0.002391	2.93E-11
Triglyceride	rs3820897	T	C	0.020442	0.002703	3.91E-14
Triglyceride	rs4564803	G	T	-0.06872	0.002458	6.53E-172
Triglyceride	rs10172544	C	A	-0.01191	0.002091	1.21E-08
Triglyceride	rs6708784	A	G	-0.01345	0.002061	6.72E-11
Triglyceride	rs6432622	A	G	-0.01126	0.002057	4.32E-08
Triglyceride	rs2110690	A	G	0.011262	0.002059	4.50E-08
Triglyceride	rs4128205	A	C	0.012509	0.002072	1.56E-09
Triglyceride	rs13389219	C	T	-0.03812	0.002103	2.01E-73
Triglyceride	rs2943645	C	T	0.039947	0.002151	5.33E-77
Triglyceride	rs4675812	G	A	-0.01437	0.002088	5.78E-12
Triglyceride	rs1728918	A	G	-0.0823	0.00232	1.00E-200
Triglyceride	rs78058190	G	A	0.080843	0.005276	5.44E-53
Triglyceride	rs4665381	A	C	0.027301	0.002059	3.95E-40
Triglyceride	rs17326656	G	T	0.019274	0.002422	1.77E-15
Triglyceride	rs138033166	A	G	0.054578	0.008525	1.53E-10
Triglyceride	rs7563812	C	G	-0.0133	0.002171	9.05E-10
Triglyceride	rs3731696	A	G	0.022579	0.003151	7.74E-13
Triglyceride	rs6707559	C	T	-0.01287	0.002095	8.02E-10
Triglyceride	rs57074291	C	G	-0.0145	0.002343	6.07E-10
Triglyceride	rs9812100	G	A	-0.0141	0.00205	6.02E-12
Triglyceride	rs9831084	T	C	-0.01231	0.002056	2.14E-09
Triglyceride	rs13098603	G	A	0.011714	0.00213	3.82E-08

(*Continued*)

Supplementary Table 2. SNPs of Triglyceride (*Continued*)

Exposure	SNP	Other Allele	Effect Allele	Beta	SE	*P*
Triglyceride	rs76824303	A	C	-0.02015	0.003515	9.81E-09
Triglyceride	rs13066793	A	G	-0.01965	0.003574	3.86E-08
Triglyceride	rs7642634	T	C	-0.01767	0.003043	6.35E-09
Triglyceride	rs6792725	A	G	-0.01758	0.002284	1.39E-14
Triglyceride	rs79287178	G	A	0.056335	0.00618	7.86E-20
Triglyceride	rs1899951	C	T	-0.02806	0.003123	2.63E-19
Triglyceride	rs62271373	T	A	0.04357	0.004403	4.33E-23
Triglyceride	rs11919048	C	T	0.021181	0.002956	7.74E-13
Triglyceride	rs79141906	A	C	-0.01274	0.002187	5.63E-09
Triglyceride	rs17052058	A	G	-0.03007	0.002655	9.63E-30
Triglyceride	rs684773	A	C	0.030154	0.002419	1.16E-35
Triglyceride	rs7631606	T	G	-0.01291	0.002331	3.04E-08
Triglyceride	rs12513287	C	T	0.028639	0.002784	8.05E-25
Triglyceride	rs144586415	G	GTT	0.016549	0.002415	7.25E-12
Triglyceride	rs3775228	C	T	0.035561	0.002096	1.52E-64
Triglyceride	rs3852087	A	C	-0.01574	0.00284	2.96E-08
Triglyceride	rs10857292	A	C	-0.01345	0.002136	2.98E-10
Triglyceride	rs13108218	A	G	-0.03123	0.002124	6.10E-49
Triglyceride	rs13101719	T	A	0.01883	0.002462	2.06E-14
Triglyceride	rs7676961	T	C	-0.01146	0.002048	2.20E-08
Triglyceride	rs77361663	C	A	-0.01184	0.002172	4.92E-08
Triglyceride	rs78025076	C	T	0.050198	0.007183	2.78E-12
Triglyceride	rs385715	T	C	0.012966	0.002234	6.51E-09
Triglyceride	rs1902176	T	G	0.012027	0.002146	2.09E-08
Triglyceride	rs986545	T	C	-0.01127	0.002049	3.84E-08
Triglyceride	rs2870238	C	T	0.014209	0.002046	3.83E-12
Triglyceride	rs2035816	A	G	-0.02999	0.003726	8.31E-16
Triglyceride	rs457134	G	C	-0.01145	0.002071	3.18E-08
Triglyceride	rs1347188	A	G	0.013482	0.002382	1.52E-08
Triglyceride	rs71603401	A	G	0.026049	0.003017	5.86E-18
Triglyceride	rs7684939	G	A	-0.01297	0.002045	2.25E-10
Triglyceride	rs7666808	G	C	-0.01147	0.00209	4.07E-08
Triglyceride	rs181193678	C	T	-0.01507	0.002155	2.68E-12
Triglyceride	rs154735	G	A	0.024538	0.004215	5.84E-09
Triglyceride	rs192219	T	C	-0.01275	0.002273	2.03E-08
Triglyceride	rs7735249	C	G	0.025774	0.00325	2.19E-15
Triglyceride	rs11429307	G	GT	0.044123	0.002612	4.98E-64
Triglyceride	rs142047875	A	T	-0.01327	0.00209	2.14E-10
Triglyceride	rs4976033	A	G	0.018966	0.002114	2.90E-19
Triglyceride	rs7704653	A	G	0.015927	0.002312	5.62E-12
Triglyceride	rs10519336	G	A	0.012829	0.002333	3.82E-08
Triglyceride	rs5870855	A	AT	-0.02131	0.002322	4.51E-20
Triglyceride	rs72801474	G	A	-0.02933	0.003522	8.32E-17
Triglyceride	rs2963431	C	T	0.015838	0.002413	5.25E-11
Triglyceride	rs62397245	C	G	0.015346	0.002473	5.49E-10
Triglyceride	rs6882076	T	C	0.035833	0.002124	7.62E-64
Triglyceride	rs593979	T	C	-0.01584	0.002111	6.31E-14
Triglyceride	rs61093427	C	T	-0.01587	0.002453	9.88E-11
Triglyceride	rs970069	C	T	0.018388	0.002502	1.98E-13

(*Continued*)

Supplementary Table 2. SNPs of Triglyceride (*Continued*)

Exposure	SNP	Other Allele	Effect Allele	Beta	SE	*P*
Triglyceride	rs998584	C	A	0.040704	0.002055	2.42E-87
Triglyceride	rs2077111	A	G	-0.01971	0.002083	3.03E-21
Triglyceride	rs945890	A	T	0.013332	0.002273	4.50E-09
Triglyceride	rs186696265	C	T	-0.10902	0.008497	1.11E-37
Triglyceride	rs28359800	CAA	C	0.029221	0.002268	5.63E-38
Triglyceride	rs9353320	C	G	-0.01198	0.002091	1.00E-08
Triglyceride	rs72959041	G	A	0.06177	0.004752	1.22E-38
Triglyceride	rs73025562	G	A	0.014648	0.002389	8.70E-10
Triglyceride	rs35742417	C	A	-0.01595	0.002632	1.36E-09
Triglyceride	rs28383314	T	C	0.039203	0.002115	1.08E-76
Triglyceride	rs1064173	G	A	-0.0261	0.002373	3.83E-28
Triglyceride	rs9405533	A	G	-0.01181	0.002157	4.36E-08
Triglyceride	rs4710938	A	G	-0.01348	0.002054	5.38E-11
Triglyceride	rs28752924	T	C	0.031231	0.002133	1.48E-48
Triglyceride	rs707931	A	G	0.027323	0.004328	2.73E-10
Triglyceride	rs35834134	G	GA	-0.0154	0.002759	2.41E-08
Triglyceride	rs9264277	T	C	0.013956	0.002132	5.88E-11
Triglyceride	rs729761	T	G	0.016742	0.002282	2.19E-13
Triglyceride	rs62427982	C	T	-0.01465	0.002198	2.64E-11
Triglyceride	rs9480889	C	G	0.017568	0.002486	1.58E-12
Triglyceride	rs632057	T	G	-0.02933	0.002118	1.40E-43
Triglyceride	rs9403170	T	G	-0.01407	0.002547	3.31E-08
Triglyceride	rs77009508	A	G	0.048113	0.003882	2.77E-35
Triglyceride	rs38205	A	C	-0.01531	0.002134	7.15E-13
Triglyceride	rs4722551	T	C	-0.03778	0.002807	2.62E-41
Triglyceride	rs55896322	T	G	0.018535	0.003343	2.95E-08
Triglyceride	rs112182225	C	T	0.015304	0.002685	1.20E-08
Triglyceride	rs4731701	C	T	-0.03468	0.002057	9.54E-64
Triglyceride	rs56321085	G	A	0.021147	0.003699	1.08E-08
Triglyceride	rs34184329	C	T	0.018423	0.003093	2.58E-09
Triglyceride	rs852386	A	G	0.014142	0.002489	1.34E-08
Triglyceride	rs17138358	G	C	0.014704	0.002099	2.48E-12
Triglyceride	rs35797675	T	G	-0.09524	0.002507	1.00E-200
Triglyceride	rs6460043	T	C	-0.1076	0.008679	2.66E-35
Triglyceride	rs6465120	A	G	-0.01273	0.00205	5.28E-10
Triglyceride	rs2070971	G	T	0.026306	0.002989	1.36E-18
Triglyceride	rs183115140	T	A	0.079322	0.010382	2.17E-14
Triglyceride	rs12530679	A	G	-0.01145	0.002084	3.90E-08
Triglyceride	rs41785	C	A	-0.01435	0.002084	5.65E-12
Triglyceride	rs1406754	G	T	-0.02156	0.002105	1.24E-24
Triglyceride	rs2971669	C	T	0.016183	0.00249	8.08E-11
Triglyceride	rs4410790	T	C	0.017181	0.002132	7.73E-16
Triglyceride	rs62473520	T	C	-0.02193	0.003938	2.56E-08
Triglyceride	rs112206063	T	C	0.019665	0.002612	5.13E-14
Triglyceride	rs13269725	A	G	0.034846	0.003828	8.88E-20
Triglyceride	rs4500049	A	T	-0.0269	0.00207	1.29E-38
Triglyceride	rs1495743	G	C	-0.03779	0.002473	1.01E-52
Triglyceride	rs6999158	T	A	-0.08727	0.002276	1.00E-200
Triglyceride	rs12680217	T	C	-0.02555	0.004485	1.22E-08

(*Continued*)

Supplementary Table 2. SNPs of Triglyceride (*Continued*)

Exposure	SNP	Other Allele	Effect Allele	Beta	SE	*P*
Triglyceride	rs2081687	T	C	-0.02688	0.002184	8.24E-35
Triglyceride	rs13255619	T	C	-0.01306	0.002095	4.58E-10
Triglyceride	rs35859536	C	T	-0.01378	0.002231	6.58E-10
Triglyceride	rs7832515	A	G	-0.01685	0.002666	2.62E-10
Triglyceride	rs2035889	T	A	-0.03918	0.002269	8.19E-67
Triglyceride	rs10957299	T	G	-0.01139	0.002085	4.71E-08
Triglyceride	rs11461788	G	GT	0.014574	0.002571	1.45E-08
Triglyceride	rs11781439	C	A	0.01555	0.002642	3.98E-09
Triglyceride	rs2954010	A	C	-0.01349	0.002072	7.45E-11
Triglyceride	rs4537315	A	G	0.048164	0.002116	1.03E-114
Triglyceride	rs2980858	T	C	-0.08437	0.002247	1.00E-200
Triglyceride	rs1567353	C	G	0.014137	0.002222	1.98E-10
Triglyceride	rs613444	G	A	0.012245	0.0022	2.62E-08
Triglyceride	rs28712486	C	A	-0.02108	0.00244	5.60E-18
Triglyceride	rs550057	C	T	-0.01878	0.002347	1.21E-15
Triglyceride	rs581080	G	C	0.015668	0.002663	3.99E-09
Triglyceride	rs12350739	G	A	-0.01314	0.002111	4.86E-10
Triglyceride	rs10797119	T	C	0.016317	0.002062	2.52E-15
Triglyceride	rs62565259	C	T	-0.01717	0.002721	2.79E-10
Triglyceride	rs1800978	C	G	-0.02816	0.003129	2.26E-19
Triglyceride	rs34619169	G	A	0.013699	0.002218	6.53E-10
Triglyceride	rs10795464	G	A	0.011804	0.002108	2.16E-08
Triglyceride	rs2068888	G	A	-0.03136	0.002055	1.49E-52
Triglyceride	rs2773469	A	G	-0.01819	0.002326	5.30E-15
Triglyceride	rs71508062	G	A	0.044793	0.007146	3.66E-10
Triglyceride	rs71473777	A	G	0.020412	0.003157	1.01E-10
Triglyceride	rs75398587	C	G	-0.02776	0.00401	4.38E-12
Triglyceride	rs55767272	A	C	-0.0302	0.004135	2.80E-13
Triglyceride	rs10882098	C	T	-0.01281	0.002088	8.54E-10
Triglyceride	rs74563318	C	A	-0.04301	0.005574	1.20E-14
Triglyceride	rs1133400	A	G	0.013433	0.002461	4.78E-08
Triglyceride	rs10786114	C	T	-0.02884	0.003091	1.06E-20
Triglyceride	rs140107293	A	G	-0.02471	0.002823	2.04E-18
Triglyceride	rs10822163	C	G	-0.03076	0.002051	7.55E-51
Triglyceride	rs878409	G	A	-0.01145	0.002061	2.71E-08
Triglyceride	rs1765142	C	A	-0.01217	0.002175	2.21E-08
Triglyceride	rs12294913	C	G	0.056257	0.004972	1.12E-29
Triglyceride	rs4930352	G	T	-0.01199	0.002109	1.30E-08
Triglyceride	rs61905132	C	T	0.215164	0.006632	1.00E-200
Triglyceride	rs7927024	T	C	-0.04307	0.006504	3.54E-11
Triglyceride	rs6486122	C	T	0.019915	0.002239	5.75E-19
Triglyceride	rs118178067	C	T	0.024242	0.004198	7.68E-09
Triglyceride	rs11030102	C	G	0.01746	0.002348	1.03E-13
Triglyceride	rs10750766	C	A	0.020306	0.002287	6.78E-19
Triglyceride	rs61905077	C	A	-0.27794	0.007271	1.00E-200
Triglyceride	rs76814754	C	T	-0.0476	0.007236	4.76E-11
Triglyceride	rs79610135	T	C	-0.03763	0.005486	6.90E-12
Triglyceride	rs142958146	A	G	0.3028	0.012621	3.33E-127
Triglyceride	rs4080140	G	A	-0.05493	0.007794	1.82E-12

(*Continued*)

Supplementary Table 2. SNPs of Triglyceride (*Continued*)

Exposure	SNP	Other Allele	Effect Allele	Beta	SE	*P*
Triglyceride	rs141469619	A	G	0.33102	0.010872	1.00E-200
Triglyceride	rs11600815	G	A	-0.03257	0.00475	7.09E-12
Triglyceride	rs10838681	G	A	-0.028	0.002333	3.62E-33
Triglyceride	rs11229043	C	T	0.016726	0.003055	4.35E-08
Triglyceride	rs174574	A	C	-0.05084	0.002168	1.28E-121
Triglyceride	rs11237488	C	T	-0.01782	0.003143	1.43E-08
Triglyceride	rs45557239	C	T	-0.04759	0.00767	5.51E-10
Triglyceride	rs4909945	T	C	0.015415	0.002236	5.45E-12
Triglyceride	rs7117115	A	G	-0.01219	0.002109	7.33E-09
Triglyceride	rs141414463	C	T	0.214919	0.006915	1.00E-200
Triglyceride	rs74773964	T	C	-0.05154	0.007453	4.65E-12
Triglyceride	rs149137426	T	A	0.134098	0.008659	4.28E-54
Triglyceride	rs35192698	T	C	-0.06375	0.00777	2.31E-16
Triglyceride	rs142334475	G	A	-0.09266	0.009656	8.28E-22
Triglyceride	rs11057837	C	T	0.021433	0.003389	2.54E-10
Triglyceride	rs11064281	T	G	0.015914	0.002716	4.64E-09
Triglyceride	rs11045171	A	G	-0.0273	0.002585	4.48E-26
Triglyceride	rs11045866	A	C	0.025952	0.002885	2.38E-19
Triglyceride	rs36073309	G	A	-0.01307	0.002181	2.06E-09
Triglyceride	rs4760254	G	C	-0.02902	0.002384	4.19E-34
Triglyceride	rs12424054	G	A	0.020528	0.002418	2.08E-17
Triglyceride	rs76895963	T	G	-0.08957	0.007926	1.30E-29
Triglyceride	rs1032494	A	G	-0.01227	0.00222	3.23E-08
Triglyceride	rs1790099	C	T	0.015504	0.002262	7.15E-12
Triglyceride	rs4930724	T	C	-0.02631	0.002177	1.22E-33
Triglyceride	rs35763453	T	C	0.029112	0.004455	6.36E-11
Triglyceride	rs4761234	T	C	-0.01445	0.002053	1.95E-12
Triglyceride	rs863750	C	T	0.030684	0.002098	1.86E-48
Triglyceride	rs2182784	C	A	0.013591	0.00246	3.30E-08
Triglyceride	rs9561643	A	C	0.018173	0.002206	1.73E-16
Triglyceride	rs7140110	T	C	0.029471	0.002239	1.45E-39
Triglyceride	rs1340819	A	C	-0.01206	0.00215	2.03E-08
Triglyceride	rs41284816	G	T	-0.06123	0.007583	6.79E-16
Triglyceride	rs9604570	A	G	-0.02289	0.00264	4.26E-18
Triglyceride	rs1928496	C	T	0.018051	0.002336	1.09E-14
Triglyceride	rs10872918	C	A	0.015759	0.00289	4.96E-08
Triglyceride	rs12880341	T	C	0.022136	0.002814	3.65E-15
Triglyceride	rs2070341	C	T	0.011849	0.002092	1.47E-08
Triglyceride	rs61993685	T	C	-0.02531	0.003807	2.96E-11
Triglyceride	rs12891477	C	T	0.012957	0.002126	1.10E-09
Triglyceride	rs71413977	T	C	-0.0151	0.002573	4.37E-09
Triglyceride	rs11620989	A	G	0.012199	0.002102	6.47E-09
Triglyceride	rs1037117	G	A	0.019607	0.002361	1.01E-16
Triglyceride	rs7170463	A	G	-0.01508	0.002213	9.43E-12
Triglyceride	rs12442886	T	C	0.013672	0.002385	9.87E-09
Triglyceride	rs10152471	G	A	-0.01244	0.002107	3.55E-09
Triglyceride	rs139974673	T	C	0.146821	0.006565	8.95E-111
Triglyceride	rs1532085	A	G	-0.03201	0.002103	2.49E-52
Triglyceride	rs261334	G	C	-0.04617	0.002498	2.61E-76

(*Continued*)

Supplementary Table 2. SNPs of Triglyceride (*Continued*)

Exposure	SNP	Other Allele	Effect Allele	Beta	SE	*P*
Triglyceride	rs12591786	C	T	-0.01912	0.002849	1.92E-11
Triglyceride	rs62012775	A	T	0.023199	0.002693	7.00E-18
Triglyceride	rs2925979	T	C	-0.03225	0.002231	2.36E-47
Triglyceride	rs4471666	T	G	-0.02343	0.004106	1.16E-08
Triglyceride	rs28577186	G	A	-0.0142	0.002179	7.11E-11
Triglyceride	rs143076454	G	A	0.04289	0.007584	1.56E-08
Triglyceride	rs11644601	T	C	-0.02834	0.002242	1.31E-36
Triglyceride	rs3814883	C	T	0.015661	0.002054	2.46E-14
Triglyceride	rs247617	C	A	-0.03271	0.002188	1.62E-50
Triglyceride	rs2937124	C	T	-0.01847	0.002183	2.58E-17
Triglyceride	rs34682685	G	A	0.033122	0.003349	4.55E-23
Triglyceride	rs12600110	T	C	-0.01617	0.00211	1.84E-14
Triglyceride	rs4843754	A	G	0.012403	0.002052	1.50E-09
Triglyceride	rs8073177	T	C	-0.01592	0.002454	8.89E-11
Triglyceride	rs591939	A	G	0.020038	0.002364	2.33E-17
Triglyceride	rs1801689	A	C	-0.06139	0.006022	2.09E-24
Triglyceride	rs11078597	T	C	0.020974	0.002625	1.34E-15
Triglyceride	rs9904004	A	G	0.041163	0.004285	7.52E-22
Triglyceride	rs1468270	C	T	-0.01981	0.002563	1.08E-14
Triglyceride	rs60856912	G	T	0.025474	0.002789	6.59E-20
Triglyceride	rs9889402	G	A	0.014576	0.002309	2.75E-10
Triglyceride	rs4969179	T	G	-0.01707	0.002094	3.63E-16
Triglyceride	rs2304969	G	T	-0.01663	0.002937	1.50E-08
Triglyceride	rs72836561	C	T	0.138147	0.005812	6.78E-125
Triglyceride	rs12601665	C	G	-0.01481	0.002082	1.11E-12
Triglyceride	rs1292060	A	G	0.013757	0.002247	9.16E-10
Triglyceride	rs62070804	C	T	0.048037	0.007728	5.11E-10
Triglyceride	rs4121765	G	A	-0.01245	0.002227	2.25E-08
Triglyceride	rs867939	G	A	-0.01329	0.002079	1.61E-10
Triglyceride	rs2510344	T	C	-0.01677	0.002046	2.43E-16
Triglyceride	rs41292412	C	T	0.060419	0.009438	1.54E-10
Triglyceride	rs6506033	C	T	-0.02348	0.00396	3.07E-09
Triglyceride	rs34690548	C	CAAA	0.020392	0.00357	1.12E-08
Triglyceride	rs58542926	C	T	-0.1056	0.003891	3.58E-162
Triglyceride	rs12891	G	C	-0.01165	0.002083	2.22E-08
Triglyceride	rs55803162	C	T	-0.01318	0.002186	1.64E-09
Triglyceride	rs483082	G	T	0.088813	0.002416	1.00E-200
Triglyceride	rs5112	C	G	0.069518	0.002206	1.00E-200
Triglyceride	rs739320	T	C	-0.02195	0.00215	1.76E-24
Triglyceride	rs8102873	C	T	0.011841	0.002083	1.32E-08
Triglyceride	rs11878235	G	A	-0.01417	0.002115	2.07E-11
Triglyceride	rs116843064	G	A	-0.22586	0.007469	1.00E-200
Triglyceride	rs62117489	C	A	-0.04352	0.004525	6.70E-22
Triglyceride	rs188247550	C	T	-0.13795	0.009323	1.53E-49
Triglyceride	rs71368855	C	T	0.026048	0.003236	8.27E-16
Triglyceride	rs62112763	C	G	0.020101	0.002076	3.64E-22
Triglyceride	rs62118471	T	C	0.042229	0.006727	3.45E-10
Triglyceride	rs10422861	C	T	-0.02122	0.002182	2.33E-22
Triglyceride	rs897764	T	C	0.025428	0.004151	9.05E-10

(*Continued*)

Supplementary Table 2. SNPs of Triglyceride (*Continued*)

Exposure	SNP	Other Allele	Effect Allele	Beta	SE	*P*
Triglyceride	rs74698119	A	T	0.067123	0.008029	6.26E-17
Triglyceride	rs4809604	T	G	0.016007	0.002084	1.57E-14
Triglyceride	rs2738759	A	G	0.020959	0.003733	1.97E-08
Triglyceride	rs34587839	G	A	0.016788	0.002834	3.13E-09
Triglyceride	rs6063840	G	A	0.013111	0.002216	3.29E-09
Triglyceride	rs8126001	C	T	-0.01595	0.002052	7.82E-15
Triglyceride	rs151235402	C	T	0.05455	0.008279	4.42E-11
Triglyceride	rs6088889	C	A	0.01562	0.002861	4.76E-08
Triglyceride	rs2865390	T	C	0.016561	0.002085	2.00E-15
Triglyceride	rs146496844	G	A	0.059334	0.008471	2.48E-12
Triglyceride	rs6073958	T	C	0.055684	0.002567	2.40E-104
Triglyceride	rs8134638	T	C	0.013671	0.00211	9.32E-11
Triglyceride	rs5755799	C	G	0.012303	0.002055	2.13E-09
Triglyceride	rs2071887	T	A	0.016384	0.002153	2.75E-14
Triglyceride	rs140287	G	A	-0.0128	0.002085	8.18E-10
Triglyceride	rs134551	C	T	-0.01342	0.002167	5.89E-10
Triglyceride	rs2267373	C	T	0.02173	0.002074	1.11E-25
Triglyceride	rs9626823	G	A	0.023428	0.003254	6.07E-13

SNP: single nucleotide polymorphism; SE: standard error.

Supplementary Table 3. SNPs of Glucose

Exposure	SNP	Other Allele	Effect Allele	Beta	SE	*P*
Glucose	rs481443	G	C	0.021	0.0031	7.80E-12
Glucose	rs78444298	G	A	0.054	0.009	2.21E-09
Glucose	rs348330	G	A	-0.0159	0.0022	2.80E-13
Glucose	rs12139196	G	T	-0.015	0.0025	1.75E-09
Glucose	rs12089247	G	A	-0.0157	0.0023	1.04E-11
Glucose	rs3176447	T	A	-0.0186	0.0034	2.90E-08
Glucose	rs41276588	G	A	0.0222	0.0024	3.38E-20
Glucose	rs79687284	G	C	0.0818	0.0068	1.29E-33
Glucose	rs1260326	T	C	0.0362	0.002	7.50E-70
Glucose	rs115654069	C	T	0.0712	0.0124	9.67E-09
Glucose	rs12712928	G	C	0.041	0.0024	5.26E-64
Glucose	rs881309	C	A	0.0208	0.0033	2.59E-10
Glucose	rs2444769	C	A	-0.017	0.0028	1.33E-09
Glucose	rs560887	T	C	0.1491	0.0026	1.00E-200
Glucose	rs6743071	T	G	-0.0414	0.0041	1.18E-23
Glucose	rs143869345	A	G	0.1291	0.0099	3.75E-39
Glucose	rs2389615	T	C	0.0482	0.0037	6.50E-38
Glucose	rs7640470	G	A	0.0113	0.0021	4.47E-08
Glucose	rs9873618	G	A	-0.0549	0.0023	1.22E-124
Glucose	rs6808574	T	C	0.0196	0.0026	1.73E-14
Glucose	rs73174306	A	T	0.0475	0.0062	1.69E-14
Glucose	rs7650482	A	G	-0.0125	0.0021	5.24E-09
Glucose	rs11708067	A	G	-0.0509	0.0029	7.96E-70
Glucose	rs75206890	A	C	-0.0476	0.0058	4.13E-16
Glucose	rs73079003	G	A	-0.0208	0.0037	2.76E-08
Glucose	rs73018297	A	G	-0.0366	0.0065	1.76E-08
Glucose	rs11728350	A	G	0.0244	0.0037	3.24E-11
Glucose	rs376109082	G	GGTT	0.0169	0.0026	3.91E-11
Glucose	rs116401167	T	C	-0.0312	0.0036	6.61E-18
Glucose	rs1503884	T	G	0.0116	0.0021	2.55E-08
Glucose	rs4457054	G	C	-0.0203	0.0026	1.47E-14
Glucose	rs10476553	G	C	-0.0316	0.0028	1.76E-30
Glucose	rs6887717	A	T	0.0158	0.0025	2.37E-10
Glucose	rs392794	C	T	0.0125	0.0023	3.39E-08
Glucose	rs10223666	G	C	-0.0181	0.0024	4.50E-14
Glucose	rs9371670	C	G	0.0151	0.0021	6.28E-13
Glucose	rs693906	G	C	0.0202	0.003	3.34E-11
Glucose	rs727332	A	G	-0.0172	0.0024	1.13E-12
Glucose	rs57088429	G	A	-0.0169	0.0024	3.51E-12
Glucose	rs76823979	C	T	-0.0301	0.0032	2.28E-21
Glucose	rs7766070	C	A	0.027	0.0022	7.60E-35
Glucose	rs675495	C	T	-0.0161	0.0021	2.86E-14
Glucose	rs80097396	A	G	-0.0318	0.0046	3.13E-12
Glucose	rs188745922	C	T	0.038	0.0021	1.83E-71
Glucose	rs849133	C	T	-0.0131	0.0021	1.03E-09
Glucose	rs11763820	T	G	0.0138	0.0021	2.52E-11
Glucose	rs117892540	C	T	-0.0556	0.0082	1.36E-11
Glucose	rs221797	A	C	0.0279	0.0036	7.89E-15
Glucose	rs10265504	A	G	-0.0171	0.0022	2.47E-14
Glucose	rs76323047	A	G	0.0364	0.003	1.25E-33

(*Continued*)

Supplementary Table 3. SNPs of Glucose (*Continued*)

Exposure	SNP	Other Allele	Effect Allele	Beta	SE	*P*
Glucose	rs1985469	A	T	0.1079	0.0032	1.00E-200
Glucose	rs17168486	C	T	0.0311	0.0024	2.28E-38
Glucose	rs718336	C	A	-0.0598	0.0082	3.99E-13
Glucose	rs3757974	A	G	0.0148	0.0021	2.14E-12
Glucose	rs9987289	A	G	-0.0442	0.0042	3.42E-26
Glucose	rs896854	T	C	-0.0148	0.0021	7.89E-13
Glucose	rs9650069	C	T	-0.0427	0.0021	4.66E-88
Glucose	rs10811656	C	T	0.0127	0.0021	1.57E-09
Glucose	rs28533815	T	C	0.0248	0.0025	8.02E-23
Glucose	rs12335452	G	C	-0.0485	0.0081	2.21E-09
Glucose	rs115478735	A	T	0.0288	0.003	3.92E-22
Glucose	rs4237150	G	C	0.0211	0.002	7.93E-25
Glucose	rs10811660	G	A	-0.03	0.0024	3.28E-36
Glucose	rs831277	A	T	0.0184	0.0026	3.41E-12
Glucose	rs11257655	C	T	0.0231	0.0023	2.52E-23
Glucose	rs7075575	A	G	0.0136	0.0024	1.67E-08
Glucose	rs12244654	C	T	-0.0525	0.0043	1.36E-33
Glucose	rs34872471	T	C	0.0508	0.0026	2.75E-85
Glucose	rs11015026	G	C	-0.0216	0.0032	1.87E-11
Glucose	rs174600	T	C	-0.0185	0.0021	3.61E-18
Glucose	rs3750952	G	C	-0.0156	0.0021	2.41E-13
Glucose	rs11039165	A	G	-0.0321	0.0027	1.51E-31
Glucose	rs117720468	G	C	0.0553	0.0081	9.31E-12
Glucose	rs5215	C	T	-0.0166	0.0021	1.97E-15
Glucose	rs1552224	A	C	-0.0241	0.0032	5.13E-14
Glucose	rs3842753	T	G	-0.0245	0.0026	1.70E-20
Glucose	rs2237897	C	T	-0.0409	0.0036	6.31E-30
Glucose	rs721156	C	T	-0.0443	0.0053	5.88E-17
Glucose	rs12581677	A	G	-0.0201	0.0036	3.34E-08
Glucose	rs36098511	A	T	0.0162	0.0024	9.62E-12
Glucose	rs76895963	T	G	-0.1053	0.0095	2.56E-28
Glucose	rs71274822	C	CT	-0.0198	0.0025	4.38E-15
Glucose	rs3741414	C	T	-0.0163	0.0029	1.76E-08
Glucose	rs55657684	A	T	0.032	0.0053	1.94E-09
Glucose	rs7997912	T	C	0.0316	0.0028	8.70E-30
Glucose	rs9579131	A	G	-0.0196	0.0025	6.81E-15
Glucose	rs11616380	G	T	-0.0161	0.0022	9.01E-13
Glucose	rs11626777	T	C	-0.0255	0.0023	1.74E-27
Glucose	rs1535464	G	A	-0.0144	0.0026	2.14E-08
Glucose	rs79548680	G	C	0.0144	0.0025	1.55E-08
Glucose	rs189400382	A	G	0.0174	0.0025	7.00E-12
Glucose	rs67507374	T	A	-0.0172	0.0025	1.04E-11
Glucose	rs11633054	A	G	0.0181	0.0022	6.44E-17
Glucose	rs3743140	G	A	0.0153	0.0028	4.58E-08
Glucose	rs2239741	T	C	-0.026	0.0032	1.05E-15
Glucose	rs9937521	C	T	0.0136	0.0021	2.55E-10
Glucose	rs8614	C	A	-0.0168	0.0023	8.22E-13
Glucose	rs62076542	C	T	0.0178	0.0025	9.83E-13
Glucose	rs62075838	C	T	0.0124	0.0021	3.82E-09

(*Continued*)

Supplementary Table 3. SNPs of Glucose (*Continued*)

Exposure	SNP	Other Allele	Effect Allele	Beta	SE	*P*
Glucose	rs11418239	G	GA	0.0272	0.0036	2.15E-14
Glucose	rs4968204	C	T	-0.014	0.0024	7.83E-09
Glucose	rs1880900	T	C	-0.0128	0.002	3.89E-10
Glucose	rs11651755	C	T	-0.0172	0.0021	7.82E-17
Glucose	rs1808335	A	G	-0.019	0.0022	2.82E-17
Glucose	rs1964272	G	A	-0.0167	0.0025	2.08E-11
Glucose	rs3833331	A	AG	-0.0365	0.0036	1.35E-23
Glucose	rs8115194	C	T	-0.015	0.0026	8.00E-09
Glucose	rs7265519	C	T	-0.0156	0.0025	2.52E-10
Glucose	rs73155719	A	G	0.0139	0.0025	3.59E-08

SNP: single nucleotide polymorphism; SE: standard error.

Supplementary Table 4. SNPs of CAVS

Exposure	SNP	Other Allele	Effect Allele	Beta	SE	*P*
CAVS	rs1999383	A	G	-0.07351	0.013426	4.38E-08
CAVS	rs11166276	C	T	0.147265	0.013215	7.64E-29
CAVS	rs11204664	T	C	0.078853	0.014272	3.29E-08
CAVS	rs17550940	A	C	0.110605	0.013547	3.23E-16
CAVS	rs665770	G	A	0.09374	0.013421	2.85E-12
CAVS	rs3902193	C	A	0.131192	0.023733	3.24E-08
CAVS	rs309306	C	T	-0.10839	0.013382	5.52E-16
CAVS	rs10185667	C	T	-0.13494	0.014772	6.57E-20
CAVS	rs1706003	G	T	-0.07507	0.013323	1.75E-08
CAVS	rs9999406	T	C	0.074275	0.013264	2.14E-08
CAVS	rs61320297	G	A	0.090625	0.016123	1.90E-08
CAVS	rs9285863	T	C	-0.08617	0.014395	2.15E-09
CAVS	rs6595383	C	T	-0.09136	0.016644	4.05E-08
CAVS	rs3129945	G	A	0.08831	0.015158	5.68E-09
CAVS	rs1819631	G	T	-0.08008	0.013359	2.04E-09
CAVS	rs7804522	G	C	0.075625	0.013252	1.15E-08
CAVS	rs1800797	A	G	-0.11771	0.013237	5.97E-19
CAVS	rs99780	C	T	-0.09828	0.013426	2.48E-13
CAVS	rs12785633	T	C	0.168577	0.029699	1.38E-08
CAVS	rs10744645	T	C	0.097806	0.016684	4.56E-09
CAVS	rs10770612	A	G	-0.10568	0.015928	3.25E-11
CAVS	rs149168595	G	T	-0.17707	0.032278	4.12E-08
CAVS	rs12427600	T	C	0.085846	0.01498	1.00E-08
CAVS	rs17774047	C	T	-0.09985	0.01584	2.91E-10
CAVS	rs62012588	G	A	0.094335	0.014331	4.63E-11
CAVS	rs186779791	C	T	0.17143	0.029004	3.41E-09
CAVS	rs4887815	A	C	0.096026	0.013416	8.22E-13
CAVS	rs9896030	C	G	-0.10855	0.016069	1.43E-11
CAVS	rs16950448	G	A	0.086428	0.015781	4.34E-08
CAVS	rs61140632	G	A	-0.09039	0.014823	1.08E-09
CAVS	rs143466522	G	A	0.347348	0.050515	6.15E-12
CAVS	rs77464740	C	T	0.184277	0.030735	2.03E-09

SNP: single nucleotide polymorphism; CAVS: calcific aortic valve stenosis; SE: standard error.

Supplementary Table 5. Statistical analysis results of exposures associated with CAVS

Exposure	Method	Nsnp	OR (95% CI)	*p*	*p* for H	MR Egger_intercept	*p* for P
TyG	MR Egger	60	2.06 (1.22, 3.49)	9.22E-03	5.23E-04	-7.39E-03	1.60E-01
	Weighted median	60	1.24 (0.83, 1.85)	2.95E-01			
	IVW	60	1.50 (1.12, 2.02)	7.29E-03			
	Simple mode	60	2.00 (0.87, 4.61)	1.10E-01			
	Weighted mode	60	1.47 (0.98, 2.22)	6.91E-02			
Triglyceride	MR Egger	201	1.19 (0.99, 1.44)	7.27E-02	1.89E-07	2.60E-03	2.85E-01
	Weighted median	201	1.18 (0.99, 1.40)	5.77E-02			
	IVW	201	1.29 (1.15, 1.45)	1.15E-05			
	Simple mode	201	1.08 (0.73, 1.59)	6.97E-01			
	Weighted mode	201	1.20 (1.01, 1.43)	4.09E-02			
Glucose	MR Egger	78	1.08 (0.87, 1.34)	4.68E-01	1.23E-03	4.80E-03	1.78E-01
	Weighted median	78	1.07 (0.89, 1.28)	4.61E-01			
	IVW	78	1.21 (1.05, 1.40)	1.03E-02			
	Simple mode	78	1.81 (1.20, 2.71)	5.49E-03			
	Weighted mode	78	1.17 (0.99, 1.37)	7.04E-02			

TyG: triglyceride-glucose index; OR: Odds ratio; IVW: Inverse variance weighted; CAVS: calcific aortic valve stenosis; P: pleiotropy; H: heterogeneity.

Supplementary Table 6. MVMR statistical analysis results of exposures associated with CAVS

Exposure	Method	Nsnp	OR (95% CI)	*p*	*p* for H	MR Egger_intercept	*p* for P
TyG	MR Egger	150	2.18 (1.60, 2.96)	1.74E-06	9.75E-05	-4.98E-03	9.61E-02
(crude analysis)	Weighted median	150	1.68 (1.28, 2.22)	2.06E-04			
	IVW	150	1.77 (1.47, 2.12)	1.13E-09			
	Simple mode	150	1.76 (0.99, 3.12)	5.48E-02			
	Weighted mode	150	1.72 (1.29, 2.28)	2.79E-04			
(r^2<0.001)	IVW	85	1.70 (1.33, 2.17)	2.20E-05	2.46E-04	-5.17E-03	2.23E-01
Adjusted for confounders	IVW	86	1.64 (1.18, 2.28)	3.01E-03	0.00E-00	-1.00E-02	9.60E-02
Triglyceride	MR Egger	245	1.28 (1.09, 1.50)	3.18E-03	3.87E-10	1.50E-04	9.46E-01
	Weighted median	245	1.25 (1.10, 1.43)	8.54E-04			
	IVW	245	1.28 (1.16, 1.41)	5.14E-07			
	Simple mode	245	1.19 (0.89, 1.60)	2.35E-01			
	Weighted mode	245	1.27 (1.10, 1.47)	1.56E-03			
Adjusted for confounders	IVW	148	1.20 (1.07, 1.35)	2.45E-03	0.00E-00	-3.00E-03	5.10E-02
Glucose	MR Egger	92	1.03 (0.83, 1.28)	7.71E-01	2.46E-05	6.23E-03	7.98E-02
	Weighted median	92	1.07 (0.89, 1.28)	4.70E-01			
	IVW	92	1.20 (1.04, 1.38)	1.11E-02			
	Simple mode	92	1.65 (1.08, 2.53)	2.27E-02			
	Weighted mode	92	1.12 (0.96, 1.30)	1.51E-01			
Adjusted confounders	IVW	54	1.25 (1.05, 1.49)	1.35E-02	0.00E-00	0.00E-00	9.37E-01

TyG: triglyceride-glucose index; OR: Odds ratio; IVW: Inverse variance weighted; MVMR: multivariable mendelian randomization; CAVS: calcific aortic valve stenosis; P: pleiotropy; H: heterogeneity.

Supplementary Table 7. Reverse statistical analysis results of CAVS associated with outcomes

Outcome	Method	Nsnp	OR (95% CI)	*p*	*p* for H	MR Egger_intercept	*p* for P
Triglyceride	MR Egger	25	0.99 (0.93, 1.05)	6.84E-01	7.20E-05	2.56E-03	4.31E-01
	Weighted median	25	1.00 (0.99, 1.02)	7.34E-01			
	IVW	25	1.01 (1.00, 1.03)	1.29E-01			
	Simple mode	25	1.00 (0.97, 1.03)	8.25E-01			
	Weighted mode	25	1.00 (0.98, 1.02)	8.83E-01			
Glucose	MR Egger	30	1.01 (0.99, 1.03)	5.16E-01	1.12E-01	-1.25E-04	9.22E-01
	Weighted median	30	1.00 (0.99, 1.01)	7.01E-01			
	IVW	30	1.01 (1.00, 1.02)	1.88E-01			
	Simple mode	30	1.00 (0.98, 1.02)	7.84E-01			
	Weighted mode	30	1.00 (0.99, 1.02)	6.85E-01			

OR: Odds ratio; IVW: Inverse variance weighted; CAVS: calcific aortic valve stenosis; P: pleiotropy; H: heterogeneity.