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ORIGINAL RESEARCH - CLINICAL

Mendelian Randomization Suggests a Causal Link Between Glycemic Traits and Thoracic Aortic Structures and Diseases

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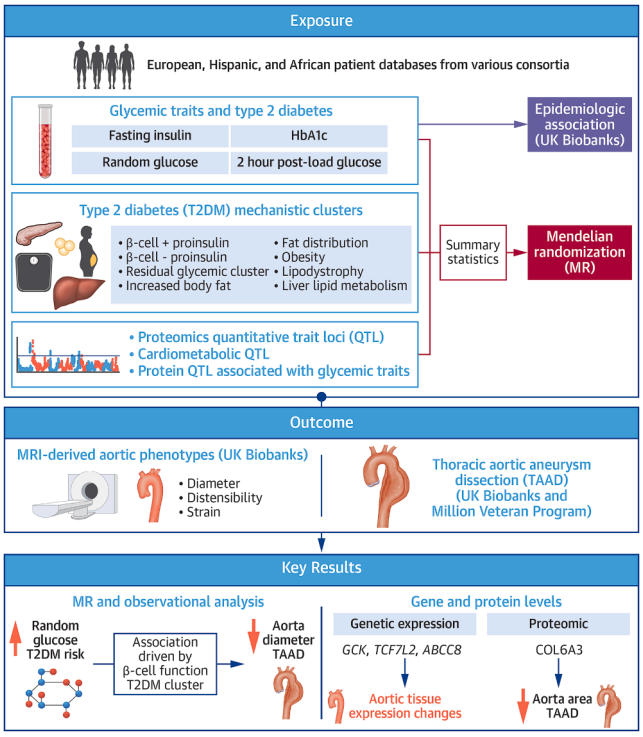
VISUAL ABSTRACT



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ABBREVIATIONS AND ACRONYMS

2hPG = 2-hour postload glucose

AAoD = ascending aortic diameter

AAoDis = ascending aortic distensibility

AAoSt = ascending aortic strain

AFR = African (populations)

AGEs = advanced glycation end products

AoDis = aortic distensibility

AoSt = aortic strain

DAoD = descending aortic diameter

DAoDis = descending aortic distensibility

DAoSt = descending aortic strain

eQTLs = expression quantitative trait loci

EUR = European (populations)

FDR = false discovery rate

FG = fasting glucose

FI = fasting insulin

GTs = glycemic traits

GWAS = genome-wide association study

HbA_{1c} = glycated hemoglobin

HEIDI = heterogeneity in dependent instruments

HIS = Hispanic (populations)

ICD-10 = International Classification of Diseases-Tenth Revision

IVs = instrumental variables

IVW = inverse-variance weighted

MR = mendelian randomization

MR-PRESSO = mendelian randomization pleiotropy residual sum and outlier

MRI = magnetic resonance imaging

MVMR = multivariable mendelian randomization

PI = proinsulin

pQTLs = protein quantitative trait loci

SMR = summary data–based mendelian randomization

SNP = single nucleotide polymorphism

SumStat = summary statistics

T2DM = type 2 diabetes mellitus

TAAD = thoracic aortic aneurysm and dissection

TWAS = transcriptome-wide association study

UKBB = UK Biobank

UMVR = univariable mendelian randomization

HIGHLIGHTS

- **In our study, we observed an inverse association between HbA_{1c} and MRI-derived aorta diameter, which was stronger among nondiabetic participants. This suggests that elevated HbA_{1c} level decreases aorta diameter and reduces the risk of a TAAD event at HbA_{1c} normal range or prediabetic state.**
- **Our MR analyses indicated that genetically predicted T2DM risk, higher HbA_{1c}, FG, and 2hPG levels are associated with smaller AAoD and DAoD and lower risk of TAAD, which remain consistent even after accounting for confounders such as blood pressure and lipid levels. This inverse association is also independent of diabetes status, suggesting that the impact of blood glucose on blood vessel occurs prior to development of diabetes, even in the normal range of blood glucose or at prediabetic state.**
- **In our proteomic MR, we found LRIG1 pQTLs associated with HbA_{1c} and AAoD, while 2hPG and DAoDis were associated with CTSS pQTLs. Eleven pQTLs were associated with aortic phenotypes but not GTs. Among them, COL6A3 was inversely associated with AAoD, DAoD, and TAAD, AGER with AAoD, and LTBP4 with DAoSt and DAoDis. Interestingly, AGER plays a crucial role in metabolizing AGEs, which accumulate in blood vessels in diabetes and high blood glucose contexts, suggesting their potential direct role in the relationship between blood glucose and vascular remodeling.**
- **Gene prioritization analysis highlights genes such as *TCF7L2, GCK, HFE, KHK,* and *AGER* that play a key role in these pathways involved in glucose metabolism and regulation. In addition, clustering-based MR suggested that among the drivers of the inverse association observed between T2D and aortic phenotypes are genetically predicted genes involved in beta-cell function. All together, we hypothesized that elevated blood glucose level and diabetes state may lead to fibrotic event and stiffness of the aortic vessel, thus the observed smaller aorta diameter and reduce risk of TAAD.**

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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SUMMARY

We investigate the relationship between glycemic traits—specifically type 2 diabetes mellitus, fasting glucose, fasting insulin, glycated hemoglobin, and 2-hour post-load glucose—and thoracic aortic morphology and diseases. The results indicate an inverse association between elevated glycemic traits and aortic morphology, as well as a reduced risk of thoracic aortic aneurysm. Genetic predictors related to beta-cell proinsulin mechanisms in type 2 diabetes mellitus drive these associations. Key genes such as *AGER*, *GLRX*, *TCF7L2*, and *GCK* are implicated, highlighting their potential as therapeutic targets for the prevention and treatment of thoracic aortic aneurysm, given their role in glycemic control medication.

Aortic aneurysm and dissection involve weakening or balloon-like dilation in the aorta's wall, often asymptomatic until dissection occurs. These dissections, associated with high mortality rates, result in death in over 90% of cases within 48 hours if untreated.[1] The only curative treatment available is surgical; drug-based preventive therapies are lacking, highlighting a huge unmet need for clinical practice. Thoracic aortic aneurysm and dissection (TAAD) is generally linked to genetic disorders of the extracellular matrix and the contractile apparatus but also shares cardiovascular risk factors including male, age, smoking, hypertension, and hyperlipidemia.[2] Moreover, genome-wide association studies (GWAS) on magnetic resonance imaging (MRI)-derived aortic measures[3] has led to the identification of genetic markers linked to aortic morphology and function.[4,5] These discoveries have enhanced our understanding of the biology and genetics of aortic aneurysms and dissections.[4,5]

Epidemiological studies have shown an intriguing inverse association between type 2 diabetes (T2DM) and TAAD.[6,7] On the other hand, current epidemiological studies have rarely investigated the comprehensive spectrum of glycemic disturbances associated with T2DM, including fasting insulin (FI) markers, glycated hemoglobin (HbA_{1c}), fasting blood glucose (FG), and 2-hour postload glucose (2hPG), and aortic structures. Nevertheless, the observational nature of epidemiological studies can be marred with various types of errors such as confounding, reverse causation, mediation bias, or inability to fully differentiate the direct effect of T2DM on aortic aneurysms independent of upstream factors such as obesity and hypertension.

To better understand the causal relationship between glycemic traits (GTs) and aortic structure and disease, previous studies have employed mendelian randomization ([MR], a method that leverages genetic variants associated with exposures to assess causal relationships while controlling for confounding factors[8]) approach to examine causal relationship involving T2DM and GTs and TAAD and imaging-based aortic structure that could inform on the earlier stages of aortic diseases processes among patients without overt clinical symptoms.[9-11]

For instance, Li et al[9] demonstrated an inverse association between GTs and aortic structures, though residual heterogeneity remained, suggesting potential unaccounted confounders even after pleiotropy correction and exclusion of single nucleotide polymorphisms (SNPs) related to blood pressure. Zhang et al[11] identified associations among T2DM, fasting glucose (FG), and aortic diameter, but not with TAAD, likely due to limited statistical power or residual heterogeneity hindering the association. In addition to the lack of comprehensive assessment of heterogeneity, these studies have limitations including a lack of in-depth investigation of genes driving these associations or their potential impact on aortic tissue, not exploring biological pathways/clusters involved in the observed association, and the focus on European-only populations.

In this study, we investigated whether T2DM and various glycemic traits (FG, FI, HbA_{1c}, and 2hPG) affect thoracic aortic structure and subsequently influence the development of TAAD using a comprehensive multiomic approach. This approach included an MR analysis across multiple populations, an innovative clustering-based MR analysis focusing on newly developed cluster for GTs or predefined T2DM-derived mechanistic cluster, proteomic MR, transcriptome-wide association study (TWAS) focusing on aortic tissue, and gene/pathway enrichment analysis.

METHODS

STUDY POPULATION. All epidemiological analyses were conducted using data from the UK Biobank (UKBB) under application 87255. We analyzed approximately 30,000 participants who had undergone cardiac magnetic resonance, from which aortic phenotypes were extracted. To examine the association with TAAD, we used the full cohort of UKBB participants (1,135 cases, 405,574 control subjects).

For the MR analysis, genetic summary statistics (SumStat) of associations between genetic variants and MRI-derived aortic phenotypes were obtained from approximately 39,000 UKBB participants from European populations (EUR)[4,12] (GWAS catalog: GCST90091050, GCST90094401, GCST90267386, GCST90267389). We sourced the SumStat for TAAD[13] from the Million Veteran Program for EUR (7,050 cases/330,610 control subjects), African (AFR) (1,266 cases/88,107 control subjects), and Hispanic (HIS) (310 cases/34,326 control subjects) populations. The GTs exposure SumStats were derived from the population-specific GWAS of body mass index-adjusted FG, FI, HbA_{1c}, or 2hPG in EUR, AFR, and HIS[14] (GWAS accession numbers: GCST90002226-34, GCST90002236-39, GCST90002242-46, GCST90002248). The GT GWAS were performed in participants with no diabetes diagnosis, no reported use of diabetes-relevant medication(s), and who had FG $\leq$ 7 mmol/L (126 mg/dL), 2hPG $\leq$11.1 mmol/L (200 mg/dL), or $HbA_{1c} \leq 6.5\%$. Instrumental variables (IVs) for T2DM were selected from EUR, HIS, and AFR-specific meta-analysis of T2DM adjusted on body mass index.[15,16] To avoid sample overlap, we assessed the association between T2DM and MRI-derived aortic phenotypes using EUR-only SumStat, which did not include the UKBB data. For the association between T2DM and TAAD, we employed T2DM population-specific SumStat for EUR, AFR, and HIS that did not include data from the Million Veteran Program. The GWAS sample size for GWAS for each trait within each population used in our MR is available in Supplemental Table ST1.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE. For the epidemiological analysis component of our study, ethical approval was obtained from the National Health Service National Research Ethics Service (reference 11/NW/0382) for the use of UKBB imaging and clinical data, along with consent from participants. Data use was subsequently approved under application 87255. The MR component of this study used SumStat only and, therefore, did not involve human participants, human data, or human tissue.

ASSOCIATION ANALYSIS OF AORTIC PHENOTYPES AND GTs. First, we examined the epidemiological association of GT and binary T2DM status, with aortic phenotypes including TAAD in the UKBB. We used blood glucose levels at enrollment, specifically random glucose instead of FG (due to the small number of UKBB participants with fasting glucose value) and HbA_{1c}, and defined T2DM using International Classification of Diseases-Tenth Revision (ICD-10) and ICD-9 codes, self-reported medical history, and/or self-reported diabetes related medication usage whether or not this was for diabetes treatment (Anatomical Therapeutic Chemical code) (Supplemental Table ST2). The MRI-derived aortic measures included the diameter of the ascending aorta (AAoD), descending aorta (DAoD), as well as the aortic strain (AoSt) and aortic distensibility (AoDis) of the ascending (AAoSt and AAoDis) and descending (DAoSt and DAoDis) aorta. These aortic phenotypes were derived using image segmentation of the transversal image of cardiac magnetic resonance, of over 1 million images obtained from ~39,000 UKBB participants.[4,12,17] TAAD was defined using ICD-9 and ICD-10 codes, Office of Population Censuses and Surveys codes, and self-reported medical history (Anatomical Therapeutic Chemical code) (Supplemental Table ST2).

The associations between GT and MRI-derived aortic phenotypes were assessed using multivariable linear regression models whereas the association between GTs and TAAD was assessed using multivariable logistic regression and presented in the tables using regression coefficient (β) for aortic phenotypes and ORs for TAAD. All analyses were adjusted for body surface area at imaging, sex acquired from the central registry at recruitment, lipid levels and blood pressure (measured at enrollment), and age at the time of imaging or at enrollment. To mitigate potential confounding by indication, adjustments were made for participants taking antihypertensive medication by adding 10 mm Hg to diastolic blood pressure and 15 mm Hg to systolic blood pressure.[18] For participants on lipid-lowering medications, raw low density lipoprotein values were divided by 0.7 to account for medication influence on lipid levels.[19] To further investigate the impact of GTs and T2DM on aortic area and TAAD independent of diabetes medication usage, we performed additional analyses: 1) analysis restricted to control subjects (participants without a diabetes diagnosis or any record of diabetes medication use); 2) analysis where cases were participants with a T2D diagnosis only, excluding participants who were taking any diabetes medications: and 3) analysis

where cases were defined as participants with T2D diagnosis and diabetes medication.

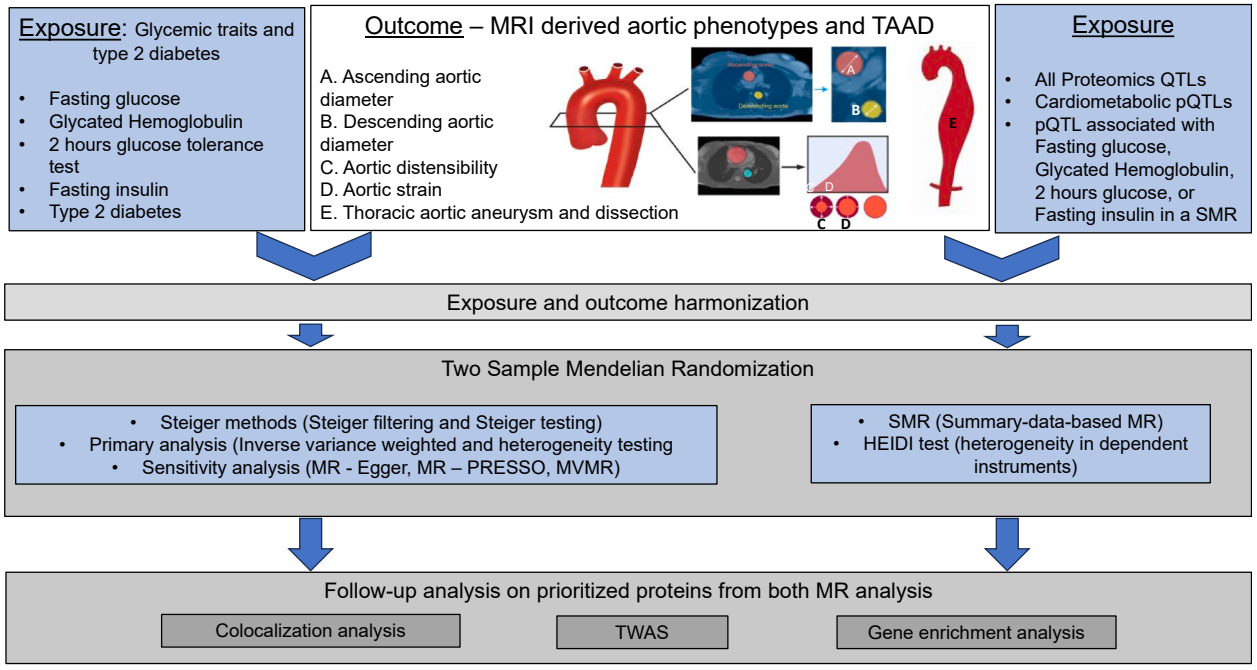
MR ANALYSES. Selection of IVs. The selection of IVs was in accordance with the 3 main hypotheses of MR. The IV was defined as SNP with minor allelic frequency >0.05, independently associated with the exposure at the GWAS significance ($P < 5 \times 10^{-08}$ and $R^2 < 0.001$). However, to overcome power issues due to the small sample size in GWAS among AFR and HIS, we lowered the *P*-value threshold for selecting the IV to a suggestive threshold of $P < 1 \times 10^{-05}$. In a second approach, we performed an MR using SNPs that were selected as IVs in EUR and that were nominally significant ($P < 0.05$) in non-EUR. Variants selected as instruments from the exposure GWAS SumStat were then matched to the outcome SumStat. SNPS selected as IV for each exposures and their overlap across exposures are present in Supplemental Figure S1. Given the lack of data available for aortic measures in non-EUR, we performed the MR of GTs and aortic measurements among EUR-only, whereas the MR between GTs and TAAD was performed independently in EUR, AFR, and HIS.

STATISTICAL ANALYSES. Figure 1 presents the analysis flowchart. For each exposure-outcome pair, the IV was harmonized to ensure consistency of the effect allele between the exposure and the outcome. An IV was excluded if its variance, as explained by the F-statistic, was <10 ($F < 10$ indicates a weak IV) if the minor allelic frequency was <0.05, or if the SNP appeared to be multiallelic. The F-statistic was calculated using the following formula: $F = [R^2 / (1 - R^2)] \times [(n - k - 1) / k]$, where R^2, n, and k represent, respectively, the proportion of variance in the exposure explained by the genetic instruments, the sample size, and the number of genetic instruments used.[20] Additionally, we used MR-Steiger filtering to exclude SNPs, indicating possible reverse causation or for which the effect on the outcome was larger than the exposure.[21] The inverse-variance weighted (IVW) method was used as the primary analytical approach to assess the relationship between each exposure-outcome pair. The IVW method is considered the most powerful because it depends on the validity of all IVs and can robustly detect associations.[22] To investigate heterogeneity and detect outliers, we used the Cochran Q method and the mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO). The MR-PRESSO test also identifies potential biases caused by horizontal pleiotropy. Using MR-PRESSO, we conducted an outlier-corrected causal estimate to assess the presence of heterogeneous SNPs, identify outliers, and correct for horizontal pleiotropy.[23] In sensitivity analyses, we employed MR-Egger, weighted median, and inverse-weighted median methods. The MR-Egger intercept test was specifically used to detect potential directional pleiotropy, where the MR-Egger intercept can be interpreted as an estimate of the average horizontal pleiotropic effect of the genetic variants.[24] All results were presented using the regression coefficient (β) of the MR association testing.

To address the high likelihood of pleiotropy between GT genetic variants (ie, variants affecting multiple GTs simultaneously), we conducted a multivariable MR analysis using multivariable mendelian randomization (MVMR) in R (R Foundation for Statistical Computing).[25] This analysis included all evaluated GTs (FG, FI, 2hPG, and HbA_{1c}) and T2DM for each outcome. Additionally, we performed MVMR incorporating all evaluated GTs and T2DM, along with blood pressure (systolic, diastolic) and lipid biomarkers (low-density lipoprotein, high-density lipoprotein) to account for potential confounders in the association between GTs and aortic phenotypes. For exposures and outcomes showing significant heterogeneity after pleiotropy assessment, reverse causation testing, and outlier correction, we employed a clustering approach with MR-Clust.[26] MR-Clust clusters genetic variants based on their causal effect estimates and define clusters assuming distinct causal mechanisms. To address the issue of multiple testing, we applied the false discovery rate (FDR) to every possible combination of exposures and outcomes in the univariable mendelian randomization (UVMR), MVMR, and the clustering MR approach.

To explore the potential biological mechanisms relevant to T2DM driving the observed inverse association with aortic phenotypes, we leveraged the T2DM mechanistic clusters defined by Suzuki et al[16] for MR. These T2DM mechanistic clusters were derived using a combination of dimension reduction and hard clustering of T2DM lead SNPs and their significant association with cardiometabolic traits such as FG, HbA_{1c}, body mass index, obesity, blood pressure, lipid biomarkers, and fat tissue percentage.[16] The defined clusters included beta-cell with proinsulin (+PI; 91 SNPs), beta-cell without PR (−PI; 89 SNPs), residual glycemic (389 SNPs), body fat (273 SNPs), metabolic syndrome (166 SNPs), obesity (233 SNPs), lipodystrophy (45 SNPs), and liver and lipid

FIGURE 1 Flowchart of MR Analysis Investigating the Causal Association Between GTs and Aortic Measurement and Diseases



Flowchart of mendelian randomization (MR) analysis investigating the causal association among glycemic traits (GTs) and aortic measurement and diseases. Sample size description for each summary statistic is presented in Supplemental Table ST2. HEIDI = heterogeneity in dependent instruments; MRI = magnetic resonance imaging; MR-PRESSO = mendelian randomization pleiotropy residual sum and outlier; MVMR = multivariable mendelian randomization; pQTLs = protein quantitative trait loci; QTLs = quantitative trait loci; SMR = summary data-based mendelian randomization; TAAD = thoracic aortic aneurysm and dissection; TWAS = transcriptome-wide association study.

metabolism (3 SNPs). For each of these clusters, we performed an MR analysis with MRI-derived aortic phenotypes and TAAD.

EVALUATION OF THE MR ASSUMPTION. Overall, to ensure that robust conclusions are derived, we rigorously tested the 3 core MR assumptions: relevance, exchangeability, and exclusion restriction. The relevance assumption was validated by assessing the strength of IVs by excluding instruments with an F-statistic below 10 to avoid weak instrument bias. The exchangeability assumption was addressed through multivariable MR analysis[25] to distinguish genuine gene-disease associations from spurious ones caused by confounding genetic variants.[27] Finally, the exclusion restriction assumption was examined using MR-Steiger filtering,[21] which helps confirm that the genetic predictors influenced the outcome solely through exposure. All statistical analyses were performed using the "TwoSampleMR" package (version 0.5.9) in R software (version 4.3.2). Additionally, we followed the strengthening the reporting of observational studies in epidemiology using MR (or STROBE-MR) checklist to ensure the transparent and comprehensive reporting of our MR study.[28]

MR OF pQTLs AND GTs AS WELL AS AORTIC PHENOTYPES. To investigate the colocalization of protein quantitative trait loci (pQTLs) and GTs as well as aortic phenotypes, we employed summary data-based mendelian randomization (SMR) and the heterogeneity in dependent instruments (HEIDI) test.[29] Our objectives were to investigate which pQTLs were associated with aortic structure and whether the pQTL-targeted genes were relevant for glycemic function. Additionally, we aimed to determine whether pQTLs associated with GTs and/or T2DM were also associated with aortic phenotypes. To do so, GWAS of 1,948 plasma proteins were sourced from the deCODE circulating proteins project (deCODE genetics).[30] *cis*-pQTLs were defined as SNPs located 1 Mb upstream and downstream of the protein-coding genes, demonstrating an association with plasma protein levels at $P < 5 \times 10^{-8}$. Multiallelic SNPs were excluded before the SMR analysis.

We conducted SMR analysis integrating GWAS with pQTL data from deCODE with GWAS of GTs, T2DM, and aortic phenotypes for EUR. The EUR population in the 1000 Genomes Project was used as the reference to estimate the linkage disequilibrium between SNPs. The HEIDI test was then applied to differentiate pleiotropic associations from those due to linkage.

To account for multiple testing, we adjusted the *P* values for the associations using the FDR method following Benjamini-Hochberg procedure. Associations passing the FDR-adjusted significance threshold of <0.05 ($P_{FDR} < 0.05$) in SMR analysis and the HEIDI $P > 0.05$ were considered robust evidence for association between pQTLs and GWAS.

FUNCTIONAL ANNOTATION OF IVs AND TWASs. To explore the biological implications of GT genetic variants, we first annotated each SNP selected as IV using various annotation tools including Phenoscanner,[31] SNPNexus,[32] and Haploreg.[33] These annotations include expression quantitative trait loci (eQTLs) expression look-up for each SNP in various tissues (such as aorta, arteries, heart, and fibroblasts), with eQTL data sourced from GTEx (Genotype-Tissue Expression Project) and STARNET.[34,35] A significant eQTL mapping was defined as an SNP with tissue eQTL $P < 1 \times 10^{-05}$. To further extend our eQTL mapping to genes targeted by our IVs, we performed a TWAS study on all GT traits GWAS using S-PrediXcan, a summary-statistics-based gene mapping method available in the MetaXcan software package.[36] The summary statistics were harmonized following the best practices on MetaXcan GitHub. Using a precomputed expression prediction model using the GTEx database, we inferred tissue-specific gene-trait associations.[35] Tissues tested include coronary artery, aorta, visceral and subcutaneous adipose, atrial appendage, left ventricle, liver, pancreas, whole blood, and Epstein-Barr virus-transformed lymphocyte cells. In sensitivity analyses, we used 2 different families of prediction models, elastic net-based and multivariate adaptive shrinkage (or MASHR)-based, a biologically informed model.[37] For each trait, FDR *P*-value adjustment was conducted both by tissue and across all tested tissues.

GENE ENRICHMENT ANALYSIS. Significant genes from S-PrediXcan that were also gene targets of the IVs in our MR were tested for gene ontology-term over-representation using the enrichGO function within the clusterProfiler package.[38] The analysis was performed for each ontology (molecular function, biological process, and cellular component) and significant genes from each trait-tissue pair separately. The universe of genes for each enrichment analysis was defined as genes present in the GTEx tissues summary statistic files. The *P* values were adjusted using the Benjamini-Hochberg method.

RESULTS

EPIDEMIOLOGICAL ASSOCIATION BETWEEN GTs AND AORTIC PHENOTYPES IN THE UKBB. The characteristics of our study population are presented in Supplemental Table ST3, whereas the epidemiological associations between aortic phenotypes and GTs (which include random glucose, HbA_{1c}, and T2DM) in the UKBB are outlined in **Table 1** and Supplemental Table ST4. In our analysis, we observed a strong negative association between HbA_{1c} levels and both AAoD and DAoD across all models with the inverse association stronger among the control group (**Table 1**, Supplemental Table ST4). When stratified by diabetes medication use, the negative associations among AAoD and DAoD and HbA_{1c} persisted in subgroup analyses (model in which T2DM is defined as participants with T2D diagnosis and/or with a record of diabetes medication and model in which T2DM is defined as diagnosis only without record of diabetes medication). Similarly, T2D case status was consistently associated with smaller aorta diameter across all models, but the effect estimates were stronger in control subjects as well as among participants with T2D diagnosis and under T2D medication (Supplemental Table ST4). For thoracic aortic aneurysm, the associations with HbA_{1c} and T2DM were less pronounced and often nonsignificant, probably due to lower sample size (**Table 1**, Supplemental Table ST4).

MR GTs AND AORTIC PHENOTYPES. Aorta diameter and thoracic aortic aneurysm. In univariable MR analyses using the IVW method, 2hPG, FG, HbA_{1c}, and T2DM were all inversely associated with AAoD and DaoD, but no associations were observed with FI (**Figure 2**, Supplemental Figure S2, and Supplemental Table ST5). Notably, the associations of 2hPG, FG, HbA_{1c}, and T2DM with AAoD were significant (**Figure 2**, Supplemental Table ST5), whereas only the associations of 2hPG and FG with DAoD were significant (**Figure 2**). We also observed a significant inverse association of 2hPG, FG, HbA_{1c}, and T2DM with TAAD (**Figure 2**, Supplemental Table ST6). These observed associations with TAAD in EUR were similarly present among AFR and HIS populations (Supplemental Figure S3, Supplemental Table ST6). However, only the association with T2DM in HIS reached statistical significance (OR: 0.70; 95% CI: 0.54-0.90; $P = 0.03$) (Supplemental Figure S3, Supplemental Table ST6). In sensitivity

TABLE 1 Association Between GTs and Aortic Phenotypes in the UKBB (Multivariable Regression Model With Adjustment for Age, Sex, Body Surface Area)

	Full Cohort[a]			T2D Cases[a]			T2D Control Subjects		
	β/OR[d]	SE	*P* Value	β/OR[d]	SE	*P* Value	β/OR[d]	SE	*P* Value
Ascending aorta maximum area									
No. of subjects or cases		29,219			1,449			27,770	
Random glucose	0.27	0.07	<0.001	0.26	0.12	0.03	0.18	0.08	0.03
HbA_{1c}	−1.80	0.24	<0.001	−0.95	0.51	0.06	−2.15	0.28	<0.001
T2D (case)	−24.45	5.15	<0.001						
Ascending aorta distensibility									
No. of subjects or cases		26,708			1,329			25,379	
Random glucose	<−0.001	<0.001	0.26	<−0.001	<0.001	0.41	<−0.001	<−0.001	0.92
HbA_{1c}	0.001	0.002	0.48	<−0.001	0.003	0.72	0.002	0.002	0.22
T2D (case)	1.00	0.04	0.92						
Descending aorta maximum area									
No. of subjects or cases		29,219			1,449			27,770	
Random glucose	0.03	0.03	0.37	0.06	0.06	0.27	0.003	0.04	0.94
HbA_{1c}	−0.79	0.11	<0.001	−0.79	0.25	0.001	−0.81	0.13	<0.001
T2D (case)	−14.58	2.33	<0.001						
Descending aorta distensibility									
No. of subjects or cases		26,708			1,329			25,379	
Random glucose	−0.001	<0.001	0.05	−0.002	<0.001	0.07	<−0.001	<0.001	0.38
HbA_{1c}	−0.001	0.002	0.54	<0.001	0.004	0.94	−0.001	0.003	0.61
T2D (case)	0.93	0.04	0.14						
Thoracic aortic aneurysm and dissection									
No. of subjects or cases		40,4447			34,352			370,095	
Random glucose	1.00	<0.001	0.02	1.00	<0.001	0.72	1.00	<0.001	0.02
HbA_{1c}	1.00	<0.001	0.02	1.00	<0.001	0.05	1.00	<0.001	0.28
T2D (case)	1.00	<0.001	0.03						

[a]T2D case (individuals on T2D medications or with ICD-9/ICD-10/OPCS diagnosis codes). [b]T2D case (individuals with ICD-9/ICD-10/OPCS diagnosis codes only). [c]T2D case (individuals on T2D medications and with ICD-9/ICD-10/OPCS diagnosis codes). [d]Random glucose and HbA_{1c} values are reported as β and T2D case values as OR, except for in the thoracic aortic aneurysm and dissection section, in which random glucose and HbA_{1c} values are reported as OR.

GTs = glycemic traits; HbA_{1c} = glycated hemoglobin; ICD-9/10 = International Classification of Diseases-Ninth/Tenth Revision; T2D = type 2 diabetes; OPCS = Office of Population Censuses and Surveys; UKBB = UK Biobank.

Continued on the next page

analyses, a consistent inverse association was observed using MR-Egger, weighted median, and weighted model approaches, which aligned with the aforementioned IVW results (Supplemental Figure S2, Supplemental Tables ST5 and ST6).

In MVMR analyses, the inverse associations remained significant for 2hPG and AAoD (β: −0.11, 95% CI: −0.16 to −0.06; p ≤ 0.001); HbA_{1c} and AAoD (β: −0.37; 95% CI: −0.59 to −0.14; $P = 0.01$); 2hPG and DAoD (β: −0.08; 95% CI: −0.12 to −0.03; $P = 0.005$); 2hPG and TAAD (OR: 0.79; 95% CI: 0.67-0.88; $P = 0.003$) (**Figure 1**, Supplemental Table ST7). It is noteworthy that some exposures had weak strength of the genetic instruments (F-statistics <10) (Supplemental Table ST7) due to a large number of SNPs used as IVs in for T2DM. In a sensitivity analysis using a different summary statistic with smaller number of genetic instruments for T2DM, we observed similar results with most exposures displaying stronger genetic instruments (Supplemental Table ST8).

In MVMR analyses accounting for blood pressure (systolic and diastolic) and lipids (low-density lipoprotein and high-density lipoproteins) we observed, after multiple testing correction, a persistent inverse association of 2hPG with AAoD (β: −0.11; 95% CI: −0.15 to −0.06; $P \leq 0.001$), DAoD (β: −0.07; 95% CI: −0.12 to −0.04; $P = 0.003$), and TAAD (OR: 0.79; 95% CI: 0.70-0.81; $P = 0.005$); FG with DAoD (β: −0.12; 95% CI: −0.2 to −0.04; $P = 0.03$); and HbA_{1c} with AAoD (β: −0.19; 95% CI: −0.33 to −0.06; $P = 0.04$) (Supplemental Table ST9).

AoSt and AoDis. In UVMR analyses using IVW, we observed that 2hPG exhibited an inverse association with both DAoDis and AAoDis (β: −0.12; 95% CI: −0.18 to −0.06; $P \leq 0.001$, and β: −0.11; 95% CI: −0.18 to −0.04; $P = 0.009$, respectively) (**Figure 2**, Supplemental Table ST5). FG and T2DM

TABLE 1 Continued

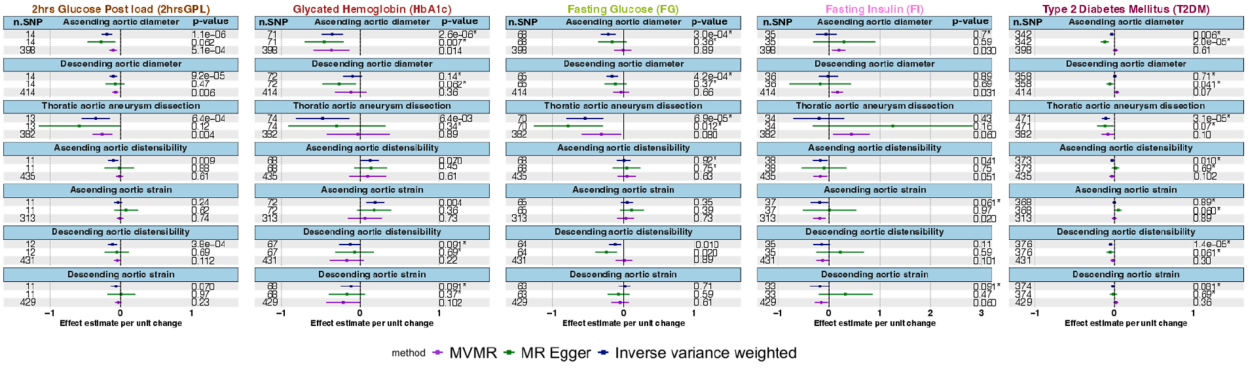
Full Cohort[b]			T2D Cases[b]			Full Cohort[c]			T2D Cases[c]		
β/OR[d]	SE	*P* Value	β/OR[d]	SE	*P* Value	β/OR[d]	SE	*P* Value	β/OR[d]	SE	*P* Value
Ascending aorta maximum area											
	28,262			492			28,451			681	
0.23	0.08	0.003	0.55	0.25	0.03	0.26	0.07	<0.001	0.31	0.15	0.03
−2.10	0.27	<0.001	−1.81	1.16	0.12	−1.90	0.26	<0.001	−0.93	0.66	0.16
−24.06	7.59	0.002				−27.58	7.42	<0.001			
Ascending aorta distensibility											
	25,834			455			26,003			624	
<−0.001	<0.001	0.49	−0.002	0.001	0.14	<0.001	<0.001	0.91	<0.001	<0.001	0.52
0.002	0.002	0.31	0.003	0.01	0.60	0.002	0.002	0.33	−0.002	0.004	0.66
1.03	0.06	0.64				0.98	0.05	0.69			
Descending aorta maximum area											
	28,262			492			28,451			681	
0.01	0.04	0.72	0.13	0.12	0.26	0.03	0.03	0.44	0.06	0.07	0.42
−0.85	0.12	<0.001	−1.42	0.56	0.01	−0.77	0.12	<0.001	−0.67	0.33	0.04
−11.51	3.44	<0.001				−18.48	3.36	<0.001			
Descending aorta distensibility											
	25,834			455			26,003			624	
−0.001	<0.001	0.12	−0.004	0.002	0.04	<−0.001	<0.001	0.33	<−0.001	0.001	0.93
−0.002	0.002	0.52	0.002	0.01	0.85	−0.002	0.002	0.50	−0.003	0.004	0.52
0.97	0.07	0.70				0.90	0.06	0.11			
Thoracic aortic aneurysm and dissection											
	390,638			20,543			381,760			11,665	
1.00	<0.001	0.01	1.00	<0.001	0.30	1.00	<0.001	0.14	1.00	<0.001	0.49
1.00	<0.001	0.22	1.00	<0.001	0.75	1.00	<0.001	0.25	1.00	<0.001	0.28
1.00	<0.001	<0.001				1.00	<0.001	0.19			

were significantly associated with DAoDis (β: −0.12; 95% CI: −0.19 to −0.04; $P = 0.01$, and OR: 0.95; 95% CI: −0.07 to −0.03; $P \leq 0.001$ for FG and T2DM, respectively). Regarding AoSt, FI and HbA_{1c} demonstrated a significant association with strain in the ascending aorta (**Figure 2**, Supplemental Table ST5). In MVMR analyses with and without blood pressure and lipids, none of the associations remained significant after multiple testing correction (**Figure 2**, Supplemental Tables ST7 and ST8).

HETEROGENEITY AND SENSITIVITY ANALYSIS. Significant variability was detected using the Q-statistic for the associations between DAoD and HbA_{1c}, TAAD and T2DM, and FI with both AAoD and DAoD (Supplemental Table ST5), despite addressing reverse causation, excluding weak instruments, correcting for horizontal pleiotropy and removing outliers. However, consistent directionality of effects was observed across MR-IWV, MR-Egger, weighted median, and weighted mode approaches for most exposure-outcome traits (Supplemental Figures S2 to S4, Supplemental Table ST5).

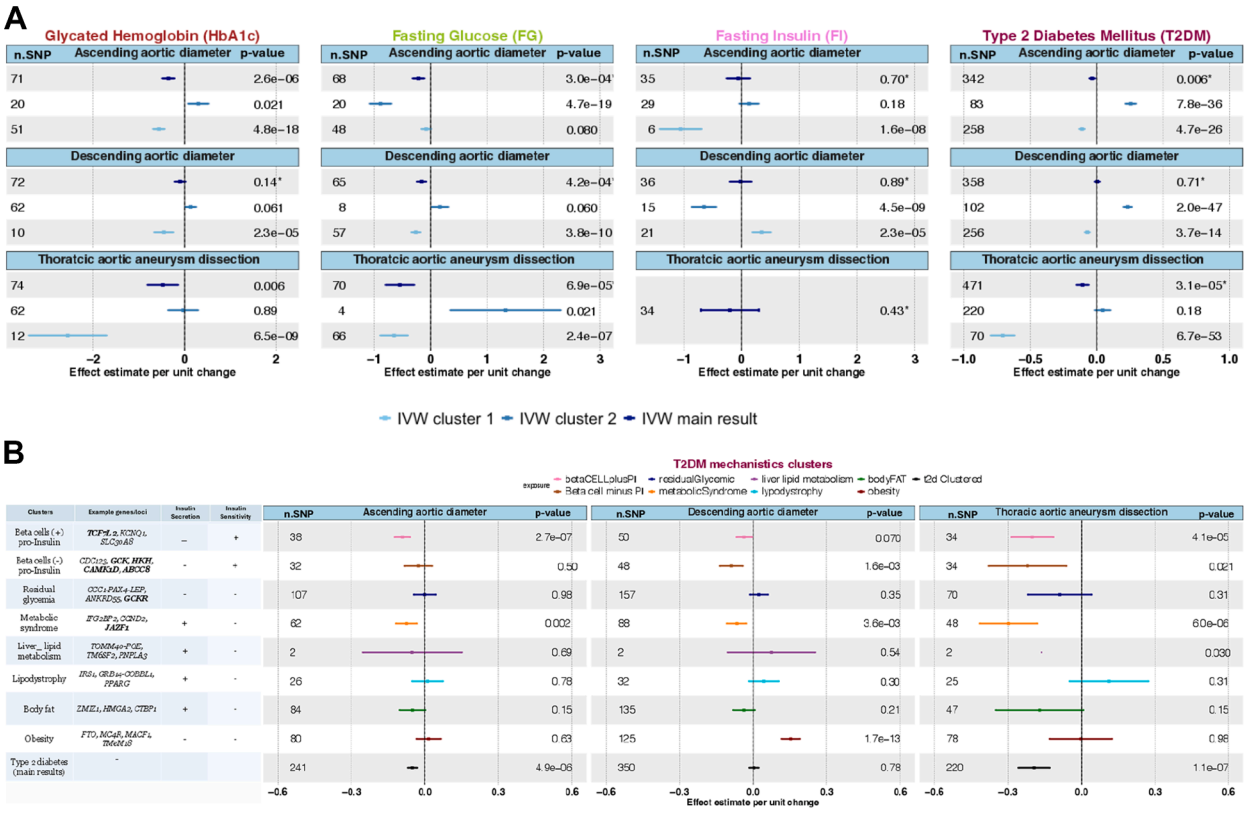
MR using the clustering approach. Given that the observed heterogeneity suggests a potential contradiction in the effect direction of the SNPs included in each analysis, we reclassified our IVs into more homogenous groups using a cluster analysis approach and conducted MR within each cluster. We identified, for the outcomes AAoD, DAoD, and TAAD, and the exposures HbA_{1c}, FG, and FI, respectively, 2 distinct clusters of associations (**Figure 3A**, Supplemental Table ST10). These clusters included either one with a positive association and another with a negative association, or 2 unique clusters with negative associations. For instance, the inverse relationship between FG and AAoD showcased 2 clusters with inverse associations, of which only 1 cluster, comprising 20 IVs, was significant (β: −0.88; $P = 4.75 \times 10^{-19}$) (**Figure 3A**), whereas the inverse association with the second cluster including 48 IVs was not significant (**Figure 3A**, Supplemental Table ST10). The associations between FI and both AAoD and DAoD, which were nonsignificant in our overall MR analysis, revealed 2 distinct clusters with significant associations. One cluster displayed a positive association, whereas the other showed an inverse association (**Figure 3A**). This indicates that a subset of insulin-related genetic instruments may contribute to an increase in aortic diameter, whereas another set may be linked to a decrease in aortic diameter. Similarly, we observed 2 distinct clusters

FIGURE 2 UVMR and MVMR Association Between GTs and Aortic Structure



Univariable mendelian randomization (UVMR) and MVMR of the association between GTs and aortic structure. The green and blue lines represent the UVMR for MR-Egger and inverse weighted variant, respectively, whereas the purple line represents the MVMR. *Phenotypes with significant heterogeneity even after MR-PRESSO and outlier removal. 2hPG = 2-hour postload glucose; FG = fasting glucose; FI = fasting insulin; HbA_{1c} = glycated hemoglobin; n.SNP = number of single nucleotide polymorphisms; T2DM = type 2 diabetes mellitus; other abbreviations as in Figure 1.

FIGURE 3 MR Results Using a Cluster of Genetic Instruments for GTs and T2DM



MR results using a cluster of genetic instruments for GTs (A) and T2DM (B). IVW = inverse-variance weighted; PI = proinsulin; other abbreviations as in Figures 1 and 2.

with significant associations in opposite directions for FG/TAAD and T2DM/TAAD exposure-outcome pairs. This suggests that the impact of FG or T2DM on TAAD may operate through distinct biological pathways, which are either protective or detrimental.

MR using T2DM predefined cluster. To further explore the biological processes linking T2DM to MRI-derived aortic phenotypes and TAAD, we conducted MR between aortic phenotypes and clusters of SNPs representing various biological processes implicated in T2DM pathophysiology, as recently described by Suzuki et al.[16] We found that the beta-cell + PI and the beta-cell − PI clusters, characterized by variants that reduce insulin secretion and enhance insulin sensitivity, were significantly inversely associated with AAoD, DAoD, and TAAD (**Figure 3B**, Supplemental Table ST11). These associations were most pronounced for the beta-cell − PI clusters. Furthermore, the metabolic syndrome cluster (dominated by FG, FI, visceral adipose tissues, and glutamine fructose-6-phosphate amidotransferase genes) was inversely associated with AAoD, DAoD, and TAAD, whereas the obesity cluster was significantly associated with larger DAoD (**Figure 3B**, Supplemental Table ST11). Additionally, the lipodystrophy cluster, enriched with body fat, lipid levels, and blood pressure, was associated with an increase in AAoD, DAoD, and TAAD (although the association was not significant) while decreasing strain and distensibility of both ascending and descending aorta (**Figure 3B**, Supplemental Figure S5).

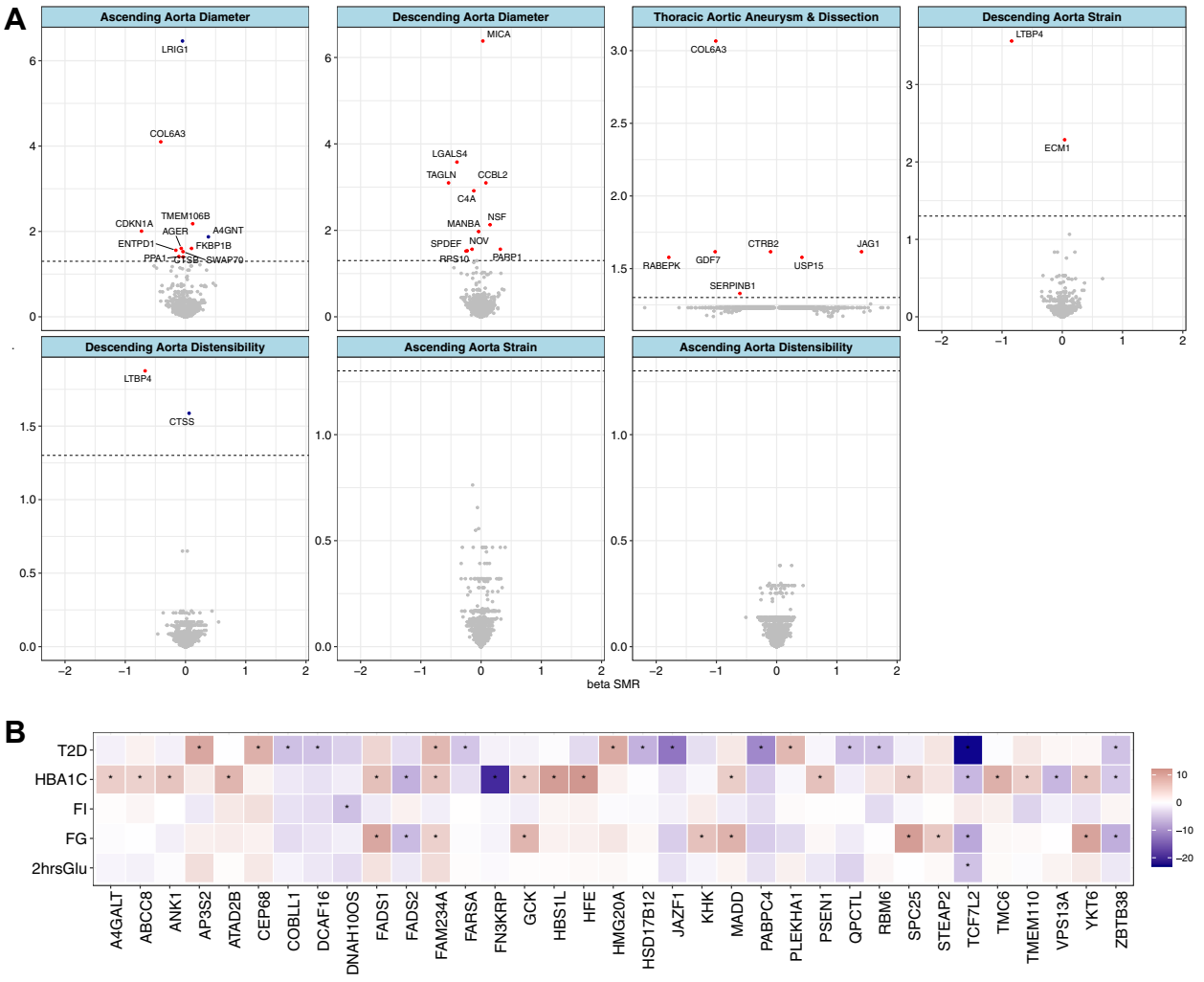
Proteomic MR. To investigate whether pQTLs associated with GTs are also associated with aortic phenotype, we performed SMR analysis for FG, 2hPG, FI, HbA_{1c}, as well as aortic phenotypes using ~1,940 pQTLs from deCODE.[30] We then checked whether some pQTLs significantly associated with GTs were also associated with aortic phenotypes. We identified 31 proteins associated with HbA_{1c}, 16 proteins associated with FG, 7 proteins for FI, and 1 protein for 2hPG (Supplemental Table ST12). Among these identified proteins, protein LRIG1, which was associated with HbA_{1c}, was also associated with AAoD and CTSS, which was associated with 2hPG, was associated with DAoDis (**Figure 4A**, Supplemental Table ST12). pQTLs were associated with aortic phenotypes but not GTs and included 11 pQTLs for AAoD, 12 pQTLs for DAoD, 7 pQTLs for TAAD, and 4 pQTLs for DAoDis and DAoSt (**Figure 4A**, Supplemental Figure S6, Supplemental Table ST12). Of these pQTLs, COL6A was inversely associated with AAoD, DAoD, and TAAD (**Figure 4A**); AGER was inversely associated with AAoD (**Figure 4A**); and LTBP4 was inversely associated with DAoSt and DAoDis, respectively (Supplemental Table ST14). When investigating whether these pQTL-associated genes have IVs in our MR, we found that SNPs in or near ECM1, CTSS, and *AGER* were present in the UVMR for AAoD, DAoD, and DAoDis phenotypes.

FUNCTIONAL ANNOTATION AND ENRICHMENT ANALYSIS OF SELECTED GENETIC INSTRUMENTS. Functional annotations of SNPs selected as IVs are available in Supplemental Tables S13 and S14. Overall, we observed that several of our IVs are located in regulatory regions such as promoter/enhancer histone marks, proteins bound, or altered transcription factors binding motifs. Several of our IVs were also missense (eg, rs267738 in *CESR2*, rs120326 in *GCKR*, and rs1800562 in *HFE*), nonsynonymous variants or variants located in 5'UTR of genes. We also observed that several IVs had significant eQTL changes in various heart-related tissues including the aorta (Supplemental Table S13). For instance, SNPs selected as IVs in *GCK*, *TCF7L2*, *HFE, ABCC8,* and *AGER* showed significant eQTLs in heart and aortic tissues (Supplemental Table S13). Our TWAS analysis unveiled a significant enrichment ($P < 1 \times 10^{-05}$) of genes surrounding our IVs for FG, HbA_{1c}, and T2DM across a range of tissues and cells including the aorta, tibial artery, heart, whole blood, and fibroblasts (Supplemental Table ST14). When specifically examining the TWAS in aortic tissues, we observed a significant association between various GTs and changes in gene expression of *GCK, CTSS, HFE, KHK, AGER,* and *TCF7L2* (**Figure 4B**, Supplemental Table ST15). Moreover, our gene ontology enrichment using gene targets by our IVs and with notable expression quantitative trait loci in aortic tissues showcased a significant enrichment in gene ontology pathways such as carbohydrate kinase activity, glucose homeostasis, intracellular glucose homeostasis, and positive regulation of hormone secretion (Supplemental Table ST16). Genes playing a key role in these pathways included *TCF7L2, GCK, HFE, KHK,* and *AGER*.

DISCUSSION

In this study, we assessed the relationship between GTs and aortic phenotypes, using an epidemiological approach, followed by an MR across multiple populations, a multiomic analysis, and a proteomic-based MR. In our epidemiological assessment, we observed a strong inverse association between HbA_{1c} and aorta diameter with stronger effect among control subjects, suggesting that elevated HbA1c level decreases aorta diameter and reduces the risk of

FIGURE 4 SMR and Colocalization Results Using pQTL and eQLTs



(A) SMR and colocalization analysis of pQTLs from decode with all aortic phenotypes. In red are significant pQTLs for aortic phenotypes only and in blue are pQTLs that are significant for both aortic phenotypes and GTs. (B) TWAS results of GTs' genetic association in the aorta tissue for genes targeted by the instrumental variables included in our MR. Abbreviations as in Figures 1 and 2.

TAAD event at HbA_{1c} normal range and prediabetic state. These findings are concordant with previous studies.[39-41] For instance, increased arterial stiffness; reduced aortic elasticity; and lower rates of development, progression, and mortality from aortic aneurysms have been noted among individuals with prediabetes or diabetes.[39-41] Furthermore, among men, an inverse relationship has been observed between high FG levels and infrarenal-aortic diameter on one hand, and the risk of abdominal aortic aneurysm progression on the other hand.[42] Furthermore, we showed that the inverse association of HbA_{1c} and T2D with aortic size was also stronger among diabetes participants on diabetes medication when compared to T2D cases with no report of taking diabetes medication. These findings suggest that diabetes medication may confer additional protective effect on aorta enlargement but do not fully explain the decrease in aorta enlargement or reduced risk of TAAD.

Our MR analyses indicated that genetically predicted T2DM risk, higher HbA_{1c}, FG, and 2hPG levels are associated with smaller AAoD, DAoD, and lower risk of TAAD; these are consistent with previously reported MR studies that examined the impact of GTs on TAAD and MRI-derived aortic structure.[9]

Furthermore, the genetic instruments used in our analysis for HbA_{1c}, FG, and 2hPG were derived from participants with normal or prediabetic status, suggesting, as reported in our epidemiological analysis, that the potential causal impact of these blood glucose levels on aortic area occurs prior to development of diabetes, even in the normal range of blood glucose or prediabetic state. Additionally, our MVMR analysis revealed that the decrease in aorta diameter associated genetically with predicted increase of FG and HbA_{1c}, is independent of blood pressure and lipids levels, which, are risk factors for aortic aneurysm. We also showed, for the first time, an inverse association between GTs and TAAD among AFR and HIS populations. However, the association was only significant for T2DM in an HIS subgroup, probably due to a lack of power driven by low sample size in the AFR ancestry-specific GWAS.

With regard to AoSt and AoDis, we observed overall, that genetic predictors of increase in HbA_{1c}, FG, 2hPG, and T2DM were associated with a decrease in both ascending and descending AoSt and AoDis which, is consistent with our reported MR for aorta diameter as, a decrease in AoSt and AoDis will result in a decrease in enlargement of the aorta due to increased stiffness while an increase in AoSt and AoDis are often associated with higher risk of aneurysm.[43]

A novel aspect of our MR analysis, in contrast to previous work,[9-11] is the use of MR-Clust, a method that clusters genetic variants into homogeneous groups to discern clusters of genetic variants exhibiting homogeneous effects. This methodology facilitates the testing of the hypothesis that multiple directional effects may coexist within the IVs, potentially indicative of distinct biological mechanisms mediating the association between the genetic variants of the exposure and the outcome. Our approach revealed that certain IVs associated with FG, FI, and HbA_{1c} may correlate with an increased in aortic diameter and TAAD risk. Conversely, other IVs associated with these GTs, were associated with a decreased in aortic diameter and TAAD risk. For instance, within the cluster of genetic variants showing an inverse association for FG and HbA_{1c}, we identified variants in genes such as *GCK* and *TCF7L2*. Indeed, prior studies have suggested that variants in *TCF7L2* and *GCK* are linked to a decreased risk of aortic aneurysm or macrovascular disease.[13,44,45] On the other hand, among variants in the FI cluster associated with a larger aorta diameter or higher risk of TAAD, we noted the variant rs284585 in *VEGF*, a vascular endothelial growth factor. VEGF is a well-known protein that causes vascular endothelial cells to proliferate, migrate, and become more permeable.[46] Moreover, findings suggested that insulin's action may enhance angiogenesis through *VEGF* and promote vasodilation[47] thus possibly increasing the risk of TAAD.

We also used the T2D mechanistic clusters defined by Suzuki et al[16] to investigate the relationship between various aspects of the T2DM metabolic profile and aortic phenotypes. We showed that clusters associated with beta-cell dysfunction, specifically those with a positive (beta-cell + PI) and a negative (beta-cell − PI) association with PI, were inversely associated with aorta diameter and TAAD. Notably, the beta-cell − PI cluster exhibited even stronger associations. Of note, the beta-cell cluster was dominated by genes/loci increasing FG, 2hPG, and HbA_{1c}, suggesting that factors affecting glucose homeostasis have a greater impact on aortic structure and function.

We enhanced our MR analysis by incorporating a proteomic MR (SMR) approach, which provides additional insights into the proteins involved and potential mechanisms linking GTs to aortic structure and disease. Our SMR analysis identified several proteomic biomarkers associated with aortic phenotypes among which LRIG1, which was associated with increased HbA_{1c} level in SMR, was also associated with decreased AAoD. LRIG1 is a protein known to promote stem cell formation, signaling, differentiation, and migration.[48] Studies have suggested that LRIG1 may play a role in regulating vascular smooth muscle cells, which are crucial in maintaining the structural integrity of the aorta. Previous studies have also suggested that LRIG1 is regulated by TGFB1,[48] a transcription factor playing a crucial role in the pathophysiology of thoracic aortic aneurysm.[49,50] Mutation in LRIG1 is strongly associated with increased body mass index by regulating adipogenesis.[51] However, it remains unclear whether LRIG1 may affect aortic structure through glucose regulation or whether the observed association of LRIG1 pQTLs with aorta diameter and HbA_{1C} is simply a pleiotropic effect and requires further investigation. It is possible that LRIG1's involvement in reducing aortic enlargement is more about its broad role in vascular biology and cell signaling, rather than a specific link through diabetes or high glucose level. Another TGFB signaling regulatory gene identified in our pQTL analysis is LTBP4, which was associated with a decrease in both ascending and descending AoSt and AoDis. LTBP4 is a protein that plays a pivotal role in the activation and regulation of TGFB signaling. As previously mentioned, this signaling pathway is crucial for various biological processes,

including development, tissue repair, fibrosis, and immune regulation.[49,50] Dysregulation of this pathway has been linked to the development of TAAD. Therefore, it is plausible that the role of LTBP4 in AoSt and AoDis is connected to the dysregulation of the TGFB signaling pathway. Moreover, LTBP4 was previously associated with a decrease in thoracic and abdominal aortic aneurysmal growth.[52]

Other notable associations with pQTLs observed in our analysis include *COL6A3* pQTL, which was inversely associated with AAoD, DAoD, and TAAD, and AGER pQTL, which was inversely associated with AAoD. AGER (or RAGE) is a receptor that binds to advanced glycation end products (AGEs) for degradation. Chronic hyperglycemia leads to the formation of AGEs, which stabilize collagen networks, increase resistance to protease degradation, and reduce aortic wall stress.[7,47,53,54] In abdominal aortic aneurysm tissues from individuals with diabetes, increased cross-linking AGEs such as pentosidine correlate with smaller abdominal aortic aneurysm diameters, indicating a protective role due to collagen network stabilization.[7,54] Genetic variants near AGER also contributed as IVs in the inverse association observed with our MR for HbA_{1c} and T2D, further consolidating our pQTL SMR findings. COL6A3 is a core component of COL6, which assembles into microfibrils, forming a scaffold within the extracellular matrix, thus supporting the aortic tissue structure by providing tensile strength and resilience against mechanical stress. COL6A3 can undergo glycation in the setting of hyperglycemia. AGE-modified COL6A3 in the aortic wall could contribute to increased vascular stiffness, influencing blood flow dynamics and vessel function.[55-57] Further studies are needed to better understand the relationship between these protein biomarkers and aortic phenotypes in hyperglycemic conditions.

Functional annotation of IVs revealed an enrichment of functional impact for multiple SNPs. This includes the presence of missense variants among our IVs, SNPs located in regulatory elements such as transcription factor binding sites, enhancers, and promotors active in aortic tissues. This includes SNPs in genes such as *GCK* that also show significant enrichment in aortic tissues from our TWAS. *GCK* is a glucokinase linked to maturity-onset diabetes of the young, a rare monogenic diabetes where elevated blood glucose levels remain stable without worsening glycemic control.[46,58] Studies have suggested that patients with GCK maturity-onset diabetes of the young exhibit a lower risk of diabetes-related microvascular and macrovascular complications.[45,46] Glucokinase activation, targeting *GCK*, has recently emerged as a potential diabetes therapy, which either is U.S. Food and Drug Administration-approved (tofogliflozin) or being tested in phase II or III clinical trials (eg, GKA-50 and dorzagliatin).[59-61] In our study, SNPs in *GCK* were included as IVs for the HbA_{1c}, FG, and the T2DM beta-cell − PI cluster. Molecules targeting *GCK* in diabetes treatment could be good candidates for repurposing to TAAD treatment and prevention given the impact of *GCK* on decreasing the aorta diameter.

Another interesting finding provided by MR, functional annotation, and TWAS analysis in aortic tissue is the evidence to support the causal effect of *TCF7L2* gene on adverse aortic phenotypes. An inverse association between *TCF7L2* locus and thoracic aortic aneurysm was previously described by Roychowdhury et al.[44] However, in the latter study, the inverse association observed at the locus was driven by a set of variants also independently associated with an increased risk of diabetes. They suggested that the inverse association between T2DM and TAAD at this locus reflects independent gene-level horizontal pleiotropy.[44] In our TWAS, *TCF7L2* expression in aortic tissues was inversely associated with HbA_{1c}, FG, 2hPG, and T2DM. Furthermore, SNPs in *TCF7L2* including rs7903146 were IVs for 2hGP, HbA_{1c} − association cluster, FG − association cluster as well as in the T2D beta-cell + PI cluster. Indeed, rs7903146 is a known diabetes candidate SNP.[62] In our analysis, rs7903146 showed an inverse association with 2hPG, FG, HbA_{1c}, and T2DM with the directionality of the effect consistent with the association of TCF7L2 variants rs4077257 reported by Roychowdhury et al.[44] We found that the square coefficient of correlation (R^2), which measures linkage disequilibrium between rs7903146 and rs4077257, was 0.46, indicating a moderate level of correlation between the 2 SNPs. Based on these findings, we hypothesize that the observed inverse association between *TCF7L2* and aortic phenotypes may be mediated through glucose levels, independent of diabetes status. Further research is warranted to investigate this hypothesis in greater detail.

Our pathway analyses identified several pathways with high enrichment of genes targeted by the IVs in our MR study. These pathways include carbohydrate kinase activity, glucose homeostasis, response to intracellular glucose homeostasis, response to monosaccharides, regulation of the glycolytic process, peptide secretion, and response to carbohydrates. Key genes involved are *GCK*, *TCF7L2*, *KHK*, *HFE*, and *AGER*. These interconnected pathways are crucial for maintaining glucose balance and cellular energy management. For example, carbohydrate

kinase activity and glucose homeostasis regulate glucose levels and limit AGE formation. As mentioned previously, accumulation of AGEs affects the extracellular matrix remodeling of the aortic wall by cross-linking with ECM proteins, such as collagen and elastin, which could increase aortic wall stiffness,[7] and thus possibly contributing to the observed decreased risk of aortic aneurysm in diabetes and hyperglycemia.

STUDY STRENGTHS AND LIMITATIONS. To our knowledge, our study is the first to investigate the role of GTs on TAAD among non-EUR populations. Furthermore, this is the first comprehensive study to assess the relationship between GTs/diabetes and aortic phenotypes using a multiomic approach that includes MR, clustering MR analysis, proteomic MR, TWAS, and gene/pathway enrichment analysis. The validity and robustness of our findings are supported using a 2-sample MR technique with the latest GWAS summary statistics data available for exposure-outcome traits, supplemented by MR cluster analysis. A limitation of our study is that we could not assess the causal relationship between glycemic traits and aortic structure in non-EU populations. However, our results showing an inverse association between glycemic traits and thoracic aortic aneurysm suggest that the direction of these associations is consistent across different ancestries.

CONCLUSIONS

Genetic predictors associated with high FG, HbA_{1c}, 2hPG, and T2DM risk are causally linked to a decrease in aortic size and a reduced risk of TAAD. The inverse association with T2DM may be driven by genetic variants associated with beta-cell function. The study highlights the potential involvement of glucose regulation genes such as *GCK* and *TCF7L2*. Hence, drugs targeting GCK such as glucokinase activators, or interacting with TCF7L2 such as metformin, could be good candidates to be repurposed for treating and preventing TAAD. Future preclinical/clinical research is needed to better understand this opportunity.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Our study expands current understanding of vascular disease in diabetes by demonstrating a causal and inverse relationship involving GTs and thoracic aortic area and TAAD risk. It underscores that a modestly elevated blood glucose event (in normoglycemic or prediabetic states) may influence vascular remodeling in a way that reduces aortic dilatation risk—highlighting heterogeneous pathophysiologic pathways in vascular complications of diabetes.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Our findings support individualized vascular risk assessment in patients with elevated GTs, even before the onset of diabetes. Clinicians may consider glycemic parameters as modifiers of aortic disease risk, potentially influencing the monitoring frequency or imaging strategy for patients at risk for TAAD, particularly those with high predisposition to elevated blood glucose levels. In the same vein, it is crucial to acknowledge the greater risk of microvascular diseases, such as peripheral blood vessel diseases and coronary artery diseases, which should be prioritized in terms of risk assessment and prevention compared to large vessel diseases such as aortic aneurysm in these patients with predisposition to elevated blood glucose levels.

TRANSLATIONAL OUTLOOK: Our results support the development of precision cardiovascular risk models that consider GTs across the full continuum, not just overt diabetes. The identification of variant clusters (eg, involving TCF7L2, GCK, VEGFA) via MR-Clust highlights distinct genetic pathways that may mediate divergent effects of glycemic control on aortic structure. This could inform targeted therapeutic strategies, such as glucose-lowering interventions tailored to vascular phenotype or genotype, to reduce TAAD risk or leveraging the physiological impact of blood glucose on vasculature to develop new drugs targeting aortic aneurysmal treatment. A disease for which no treatment other than surgical intervention exists.

REFERENCES

1. Elefteriades JA, Sang A, Kuzmik G, Hornick M. Guilt by association: paradigm for detecting a silent killer (thoracic aortic aneurysm). *Open Heart*. 2015;2(1):e000169. https://doi.org/10.1136/openhrt-2014-000169

2. Pinard A, Jones GT, Milewicz DM. Genetics of thoracic and abdominal aortic diseases. *Circ Res*. 2019;124(4):588–606. https://doi.org/10.1161/CIRCRESAHA.118.312436

3. Petersen SE, Matthews PM, Francis JM, et al. UK Biobank's cardiovascular magnetic resonance protocol. *J Cardiovasc Magn Reson*. 2016;18:8. https://doi.org/10.1186/s12968-016-0227-4

4. Pirruccello JP, Chaffin MD, Chou EL, et al. Deep learning enables genetic analysis of the human thoracic aorta. *Nat Genet*. 2022;54(1):40–51. https://doi.org/10.1038/s41588-021-00962-4

5. Benjamins JW, Yeung MW, Van De Vegte YJ, et al. Genomic insights in ascending aortic size and distensibility. *EBioMedicine*. 2022;75:103783. https://doi.org/10.1016/j.ebiom.2021.103783

6. D'cruz RT, Wee IJY, Syn NL, Choong AMTL. The association between diabetes and thoracic aortic aneurysms. *J Vasc Surg*. 2019;69(1):263–268.e1. https://doi.org/10.1016/j.jvs.2018.07.031

7. Raffort J, Lareyre F, Clément M, Hassen-Khodja R, Chinetti G, Mallat Z. Diabetes and aortic aneurysm: current state of the art. *Cardiovasc Res*. 2018;114(13):1702–1713. https://doi.org/10.1093/cvr/cvy174

8. Minelli C, Del Greco MF, van der Plaat DA, Bowden J, Sheehan NA, Thompson J. The use of two-sample methods for Mendelian randomization analyses on single large datasets. *Int J Epidemiol*. 2021;50(5):1651–1659. https://doi.org/10.1093/ije/dyab084

9. Li Z, Xiong J, Guo Y, et al. Effects of diabetes mellitus and glycemic traits on cardiovascular morpho-functional phenotypes. *Cardiovasc Diabetol*. 2023;22(1):336. https://doi.org/10.1186/s12933-023-02079-w

10. Bai W, Suzuki H, Huang J, et al. A population-based phenome-wide association study of cardiac and aortic structure and function. *Nat Med*. 2020;26(10):1654–1662. https://doi.org/10.1038/s41591-020-1009-y

11. Zhang Y, Li Y, Dai X, Lin H, Ma L. Type 2 diabetes has a protective causal association with thoracic aortic aneurysm: a Mendelian randomization study. *Diabetol Metab Syndr*. 2023;15(1):120. https://doi.org/10.1186/s13098-023-01101-1

12. Tcheandjieu C, Xiao K, Tejeda H, et al. High heritability of ascending aortic diameter and trans-ancestry prediction of thoracic aortic disease. *Nat Genet*. 2022;54(6):772–782. https://doi.org/10.1038/s41588-022-01070-7

13. Klarin D, Devineni P, Sendamarai AK, et al. Genome-wide association study of thoracic aortic aneurysm and dissection in the Million Veteran Program. *Nat Genet*. 2023;55(7):1106–1115. https://doi.org/10.1038/s41588-023-01420-z

14. Chen J, Spracklen CN, Marenne G, et al. MAGIC. The trans-ancestral genomic architecture of glycemic traits. *Nat Genet*. 2021;53(6):840–860. https://doi.org/10.1038/s41588-021-00852-9

15. Mahajan A, Spracklen CN, Zhang W, et al. Multi-ancestry genetic study of type 2 diabetes highlights the power of diverse populations for discovery and translation. *Nat Genet*. 2022;54(5):560–572. https://doi.org/10.1038/s41588-022-01058-3

16. Suzuki K, Hatzikotoulas K, Southam L, et al. Genetic drivers of heterogeneity in type 2 diabetes pathophysiology. *Nature*. 2024;627(8003):347–357. https://doi.org/10.1038/s41586-024-07019-6

17. Pirruccello JP, Rämö JT, Choi SH, et al. The genetic determinants of aortic distention. *J Am Coll Cardiol*. 2023;81(14):1320–1335. https://doi.org/10.1016/j.jacc.2023.01.044

18. Surendran P, Feofanova EV, Lahrouchi N, et al. Discovery of rare variants associated with blood pressure regulation through meta-analysis of 1.3 million individuals. *Nat Genet*. 2020;52(12):1314–1332. https://doi.org/10.1038/s41588-020-00713-x

19. Graham SE, Clarke SL, Wu KHH, et al. The power of genetic diversity in genome-wide association studies of lipids. *Nature*. 2021;600(7890):675–679. https://doi.org/10.1038/s41586-021-04064-3

20. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol*. 2015;44(2):512–525. https://doi.org/10.1093/ije/dyv080

21. Hemani G, Tilling K, Davey Smith G. Orienting the causal relationship between imprecisely measured traits using GWAS summary data. *PLoS Genet*. 2017;13(11):e1007081. https://doi.org/10.1371/journal.pgen.1007081

22. Nikolakopoulou A, Mavridis D, Salanti G. How to interpret meta-analysis models: fixed effect and random effects meta-analyses. *Evid Based Ment Health*. 2014;17(2):64. https://doi.org/10.1136/eb-2014-101794

23. Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nat Genet*. 2018;50(5):693–698. https://doi.org/10.1038/s41588-018-0099-7

24. Burgess S, Thompson SG. Interpreting findings from Mendelian randomization using the MR-Egger method. *Eur J Epidemiol*. 2017;32(5):377–389. https://doi.org/10.1007/s10654-017-0255-x

25. Sanderson E, Davey Smith G, Windmeijer F, Bowden J. An examination of multivariable Mendelian randomization in the single-sample and two-sample summary data settings. *Int J Epidemiol*. 2019;48(3):713–727. https://doi.org/10.1093/ije/dyy262

26. Foley CN, Mason AM, Kirk PDW, Burgess S. MR-Clust: clustering of genetic variants in Mendelian randomization with similar causal estimates. *Bioinformatics*. 2021;37(4):531–541. https://doi.org/10.1093/bioinformatics/btaa778

27. Zheng J, Haberland V, Baird D, et al. Phenome-wide Mendelian randomization mapping the influence of the plasma proteome on complex diseases. *Nat Genet*. 2020;52(10):1122–1131. https://doi.org/10.1038/s41588-020-0682-6

28. Skrivankova VW, Richmond RC, Woolf BAR, et al. Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization: the STROBE-MR statement. *JAMA*. 2021;326(16):1614. https://doi.org/10.1001/jama.2021.18236

29. Sun BB, Chiou J, Traylor M, et al. Plasma proteomic associations with genetics and health in the UK Biobank. *Nature*. 2023;622(7982):329–338. https://doi.org/10.1038/s41586-023-06592-6

30. Ferkingstad E, Sulem P, Atlason BA, et al. Large-scale integration of the plasma proteome with genetics and disease. *Nat Genet*. 2021;53(12):1712–1721. https://doi.org/10.1038/s41588-021-00978-w

31. Kamat MA, Blackshaw JA, Young R, et al. PhenoScanner V2: an expanded tool for searching human genotype-phenotype associations. *Bioinformatics*. 2019;35(22):4851–4853. https://doi.org/10.1093/bioinformatics/btz469

32. Oscanoa J, Sivapalan L, Gadaleta E, Dayem Ullah AZ, Lemoine NR, Chelala C. SNPnexus: a web server for functional annotation of human genome sequence variation (2020 update). *Nucleic Acids Res*. 2020;48(W1):W185–W192. https://doi.org/10.1093/nar/gkaa420

33. Ward LD, Kellis M. HaploReg v4: systematic mining of putative causal variants, cell types, regulators and target genes for human complex traits and disease. *Nucleic Acids Res*. 2016;44(D1):D877–D881. https://doi.org/10.1093/nar/gkv1340

34. Jupiter D, Chen H, VanBuren V. STARNET 2: a web-based tool for accelerating discovery of gene regulatory networks using microarray co-expression data. *BMC Bioinformatics*. 2009;10:332. https://doi.org/10.1186/1471-2105-10-332

35. Wheeler HE, Shah KP, Brenner J, et al. GTEx Consortium. Survey of the heritability and sparse architecture of gene expression traits across human tissues. *PLoS Genet*. 2016;12(11):e1006423. https://doi.org/10.1371/journal.pgen.1006423

36. Barbeira AN, Dickinson SP, Bonazzola R, et al. Exploring the phenotypic consequences of tissue specific gene expression variation inferred from GWAS summary statistics. *Nat Commun*. 2018;9(1):1825. https://doi.org/10.1038/s41467-018-03621-1

37. Araujo DS, Nguyen C, Hu X, et al. Multivariate adaptive shrinkage improves cross-population transcriptome prediction for transcriptome-wide association studies in underrepresented

populations. *bioRxiv*. Published online May 20, 2023. https://doi.org/10.1101/2023.02.09.527747

38. Wu T, Hu E, Xu S, et al. clusterProfiler 4.0: A universal enrichment tool for interpreting omics data. *Innovation (Camb)*. 2021;2(3):100141. https://doi.org/10.1016/j.xinn.2021.100141

39. Aslan AN, Ayhan H, Çiçek ÖF, et al. Relationship between aortic stiffness and the left ventricular function in patients with prediabetes. *Intern Med*. 2014;53(14):1477-1484. https://doi.org/10.2169/internalmedicine.53.1720

40. Dec-Gilowska M, Trojnar M, Makaruk B, Mosiewicz-Madejska B, Dzida G, Mosiewicz J. Local elasticity of the aorta in patients with type 2 diabetes mellitus. *J Int Med Res*. 2020;48(9): 300060520952643. https://doi.org/10.1177/0300060520952643

41. Prakash SK, Pedroza C, Khalil YA, Milewicz DM. Diabetes and reduced risk for thoracic aortic aneurysms and dissections: a nationwide case-control study. *J Am Heart Assoc*. 2012;1(2):jah3-e000323. https://doi.org/10.1161/JAHA.111.000323

42. Le MTQ, Jamrozik K, Davis TME, Norman PE. Negative association between infra-renal aortic diameter and glycaemia: the Health In Men Study. *Eur J Vasc Endovasc Surg*. 2007;33(5):599-604. https://doi.org/10.1016/j.ejvs.2006.12.017

43. Chiu P, Lee HP, Dalal AR, et al. Relative strain is a novel predictor of aneurysmal degeneration of the thoracic aorta: An ex vivo mechanical study. *JVS Vasc Sci*. 2021;2:235-246. https://doi.org/10.1016/j.jvssci.2021.08.003

44. Roychowdhury T, Lu H, Hornsby WE, et al. Regulatory variants in TCF7L2 are associated with thoracic aortic aneurysm. *Am J Hum Genet*. 2021;108(9):1578-1589. https://doi.org/10.1016/j.ajhg.2021.06.016

45. Steele AM, Shields BM, Wensley KJ, Colclough K, Ellard S, Hattersley AT. Prevalence of vascular complications among patients with glucokinase mutations and prolonged, mild hyperglycemia. *JAMA*. 2014;311(3):279-286. https://doi.org/10.1001/jama.2013.283980

46. Aiello LP, Wong JS. Role of vascular endothelial growth factor in diabetic vascular complications. *Kidney Int Suppl*. 2000;77:S113-S119. https://doi.org/10.1046/j.1523-1755.2000.07718.x

47. Fu J, Yu MG, Li Q, Park K, King GL. Insulin's actions on vascular tissues: physiological effects and pathophysiological contributions to vascular complications of diabetes. *Mol Metab*. 2021;52: 101236. https://doi.org/10.1016/j.molmet.2021.101236

48. Abdullah A, Herdenberg C, Hedman H. Ligand-specific regulation of transforming growth factor beta superfamily factors by leucine-rich repeats and immunoglobulin-like domains proteins. *PLoS One*. 2023;18(8):e0289726. https://doi.org/10.1371/journal.pone.0289726

49. Rocchiccioli S, Cecchettini A, Panesi P, et al. Hypothesis-free secretome analysis of thoracic aortic aneurysm reinforces the central role of TGF-β cascade in patients with bicuspid aortic valve. *J Cardiol*. 2017;69(3):570-576. https://doi.org/10.1016/j.jjcc.2016.05.007

50. Perrotta S, Carnevale D, Lembo G. TGF-β signalling: the Dr Jekyll and Mr Hyde of the aortic aneurysms. *Cardiovasc Res*. 2024;120(17):2160-2162. https://doi.org/10.1093/cvr/cvae245

51. Herdenberg C, Mutie PM, Billing O, et al. LRIG proteins regulate lipid metabolism via BMP signaling and affect the risk of type 2 diabetes. *Commun Biol*. 2021;4(1):90. https://doi.org/10.1038/s42003-020-01613-w

52. Thompson AR, Cooper JA, Jones GT, et al. Assessment of the association between genetic polymorphisms in transforming growth factor beta, and its binding protein (LTBP), and the presence, and expansion, of abdominal aortic aneurysm. *Atherosclerosis*. 2010;209(2):367-373. https://doi.org/10.1016/j.atherosclerosis.2009.09.073

53. Zieman SJ, Kass DA. Advanced glycation end product cross-linking: pathophysiologic role and therapeutic target in cardiovascular disease. *Congest Heart Fail*. 2004;10(3):144-151. https://doi.org/10.1111/j.1527-5299.2004.03223.x

54. Golledge J, Karan M, Moran CS, et al. Reduced expansion rate of abdominal aortic aneurysms in patients with diabetes may be related to aberrant monocyte-matrix interactions. *Eur Heart J*. 2008;29(5):665-672. https://doi.org/10.1093/eurheartj/ehm557

55. Singh SN, Vats P, Suri S, et al. Effect of an antidiabetic extract of Catharanthus roseus on enzymic activities in streptozotocin induced diabetic rats. *J Ethnopharmacol*. 2001;76(3): 269-277. https://doi.org/10.1016/S0378-8741(01)00254-9

56. Bosco C, Alegana V, Bird T, et al. Exploring the high-resolution mapping of gender-disaggregated development indicators. *J R Soc Interface*. 2017;14(129):20160825. https://doi.org/10.1098/rsif.2016.0825

57. Sakai M, Troutman TD, Seidman JS, et al. Liver-derived signals sequentially reprogram myeloid enhancers to initiate and maintain Kupffer cell identity. *Immunity*. 2019;51(4):655-670.e8. https://doi.org/10.1016/j.immuni.2019.09.002

58. Fendler W, Rizzo M, Borowiec M, et al. Less but better: cardioprotective lipid profile of patients with GCK-MODY despite lower HDL cholesterol level. *Acta Diabetol*. 2014;51(4):625-632. https://doi.org/10.1007/s00592-014-0567-1

59. Ren Y, Li L, Wan L, Huang Y, Cao S. Glucokinase as an emerging anti-diabetes target and recent progress in the development of its agonists. *J Enzyme Inhib Med Chem*. 2022;37(1): 606-615. https://doi.org/10.1080/14756366.2021.2025362

60. Ikeda S, Takano Y, Cynshi O, et al. A novel and selective sodium-glucose cotransporter-2 inhibitor, tofogliflozin, improves glycaemic control and lowers body weight in patients with type 2 diabetes mellitus. *Diabetes Obes Metab*. 2015;17(10): 984-993. https://doi.org/10.1111/dom.12538

61. Zhu D, Li X, Ma J, et al. Dorzagliatin in drug-naïve patients with type 2 diabetes: a randomized, double-blind, placebo-controlled phase 3 trial. *Nat Med*. 2022;28(5):965-973. https://doi.org/10.1038/s41591-022-01802-6

62. Cropano C, Santoro N, Groop L, et al. The rs7903146 variant in the TCF7L2 gene increases the risk of prediabetes/type 2 diabetes in obese adolescents by impairing β-cell function and hepatic insulin sensitivity. *Diabetes Care*. 2017;40(8):1082-1089. https://doi.org/10.2337/dc17-0290

KEYS WORDS **aortic aneurysm, aortic tissue expression, glycemic traits, mendelian randomization, type 2 diabetes**

APPENDIX **For supplemental methods, results, references, figures, and tables, please see the online version of this paper.**