Original Article

Exploring the causal association between congenital heart disease and stroke based on two-sample Mendelian randomization

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Background: Research into common pathological mechanisms and genetic factors is essential for better understanding, prevention and management of cardiovascular disease in congenital heart disease (CHD) survivors. This study aims to explore the possible causal associations between CHD and acquired cardiovascular diseases with the help of genetic instruments.

Methods: This study utilized summary data from genome-wide association studies (GWASs) of CHD (including congenital anomalies of great vessels and heart septal defect) and seven different cardiovascular diseases, employing a two-sample Mendelian randomization (MR) design. Analysis was conducted using the inverse variance weighted method (IVW), weighted median, weighted mode, and MR-Egger regression methods. Sensitivity analysis included MR-Egger, MR-PRESO, Cochran's Q, and leave-one-out.

Results: In this study, 15 instrumental variables related to CHD were selected [F-statistic =23.55 (21.27, 28.84)]. The IVW MR analysis revealed potential association between genetically predicted congenital anomalies of great vessels and higher risk of atrial fibrillation [odds ratio (OR) =1.07, 95% confidence interval (CI): 1.02–1.12, P=0.004], unspecified stroke (OR =1.07, 95% CI: 1.02–1.12, P=0.008) and ischemic stroke (OR =1.07, 95% CI: 1.01–1.14, P=0.02). No significant associations were observed between other factors. The MR-Egger regression results indicated that these analyses were not affected by horizontal pleiotropy. Leave-one-out analysis showed that the causal effects were not driven by any single mutation.

Conclusions: This study found a potential causal association between exposure to congenital anomalies of great vessels and higher risk of atrial fibrillation, stroke and ischemic stroke. Discussed genetic factors might potentially help to identify a higher risk of stroke and other cardiovascular diseases.

Keywords: Congenital heart defects; atrial fibrillation; ischemic stroke; Mendelian randomization (MR)

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Introduction

Cardiovascular diseases, such as coronary artery disease, heart failure, atrial fibrillation (AF), stroke, myocardial infarction, hypertension and others, is an umbrella term covering various conditions that develop during a person's lifetime as opposed to congenital heart disease (CHD) (1,2). Conditions classified as cardiovascular diseases vary in morbidity and mortality, but are undeniably the leading cause of death globally, as well as a significant economic burden (3). Despite heterogeneity, common risk factors have been reported for many cardiovascular diseases, while outcomes additionally depend on the presence of comorbidities and disease modifiers (4,5). Usually, both the heart and the vasculature are affected by the interplay between remodeling of the heart muscle, arrhythmias and

underlying immune processes, with the specific risk factors, including hypertension, obesity and metabolic diseases (4,6). However, even in the 21st century, mechanisms underlying cardiovascular disease development have not been completely understood, especially in elderly patients.

In contrast, CHD is the major cause of morbidity and mortality in infants, affecting 10 out of every 1,000 newborns (2). With recent advances in surgical and management technologies, most of the CHD patients could live through childhood; as they now reaching advanced age, in many countries adult CHD has become a healthcare concern comparable to infant CHD (7). Patients surviving CHD typically exhibit unique anatomical and functional changes in the heart region, thus the higher possibility of later diagnosed cardiovascular diseases has become the focus of recent studies (8). In particular, Brida *et al.* (9) in 2023 reported that the disease burden in adult CHD is shifting from congenital to acquired, primarily atherosclerotic cardiovascular disease. A recent meta-analysis of cohort studies found an association of CHD with increased risk of cardiovascular diseases in later life, but the meta-analysis cannot determine whether this association is confounded by a risk factor profile in CHD survivors or CHD is an independent risk factor (10). In addition, mutations in genes such as *MYH7*, *GATA4*, *NKX2-5*, *TBX5*, and *TBX20*, traditionally known as causative for CHD, have been shown to be associated with the development of cardiomyopathy and arrhythmias (11-13).

With currently only a few studies and no available guidelines, the research into common pathological mechanisms and genetic factors is essential for better understanding, prevention and management of cardiovascular disease in CHD survivors. Mendelian randomization (MR) is an instrumental method to access the inherent properties of single-nucleotide polymorphisms (SNPs) and/or modifiable environmental factors of interest and explore the potential causal relationships between them, proposing the alternative to observational studies and randomized trials (14,15). Two-sample MR analysis uses genetic variants from independent genome-wide association studies (GWASs), previously shown to be associated with health outcomes (such as mutations commonly found in CHD and cardiovascular disease), and combines them into a single causal estimate (16). In this manner the random allocation of genetic variants could be viewed as a tool to randomize participants into different groups not influenced by other confounding factors (17). As the number of GWASs on CHD is growing, large-scale MR study has the advantage of improved statistical power by minimizing bias due to confounding factors and reverse causality (18).

In this study, we employed a two-sample MR design to examine the potential relationship between CHD as exposure and cardiovascular disease as the outcome, including datasets on coronary artery disease, heart failure, AF, stroke, myocardial infarction and ischemic heart diseases. All analyses are presented in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology using MR (STROBE-MR) reporting checklist (available at https://cdt.amegroups.com/article/view/10.21037/cdt-24-422/rc).

Highlight box

Key findings

- This study establishes a causal link between congenital heart disease (CHD) and an increased risk of atrial fibrillation, stroke, and ischemic stroke, as predicted by genetic factors. Using a two-sample Mendelian randomization approach, we identified 15 instrumental variables associated with CHD, revealing a potential association with higher risks of acquired heart diseases.

What is known and what is new?

- Prior research has suggested associations between CHD and cardiovascular diseases, but this study offers robust genetic evidence in support of potential causal relationship. While the genetic contribution to CHD and its implications for acquired conditions have been recognized, this manuscript provides new insights into specific cardiovascular outcomes linked to CHD.

What is the implication, and what should change now?

- These findings underscore the importance of genetic screening for individuals with CHD to identify those at higher risk for developing atrial fibrillation and stroke. Enhanced monitoring and early intervention strategies may be warranted to mitigate these risks in patients with congenital heart anomalies. Future research should focus on exploring the mechanisms underpinning these associations and developing targeted preventive approaches for at-risk populations.

Methods

Study design

For this two-sample MR analysis GWAS statistics were obtained from the publicly available NHGRI-EBI GWAS Catalog for genetic studies (https://www.ebi.ac.uk/gwas/home) and FinnGen study data catalog (https://www.finngen.fi/en). A diagram of the study design is presented in *Figure 1*. This study was conducted in accordance with

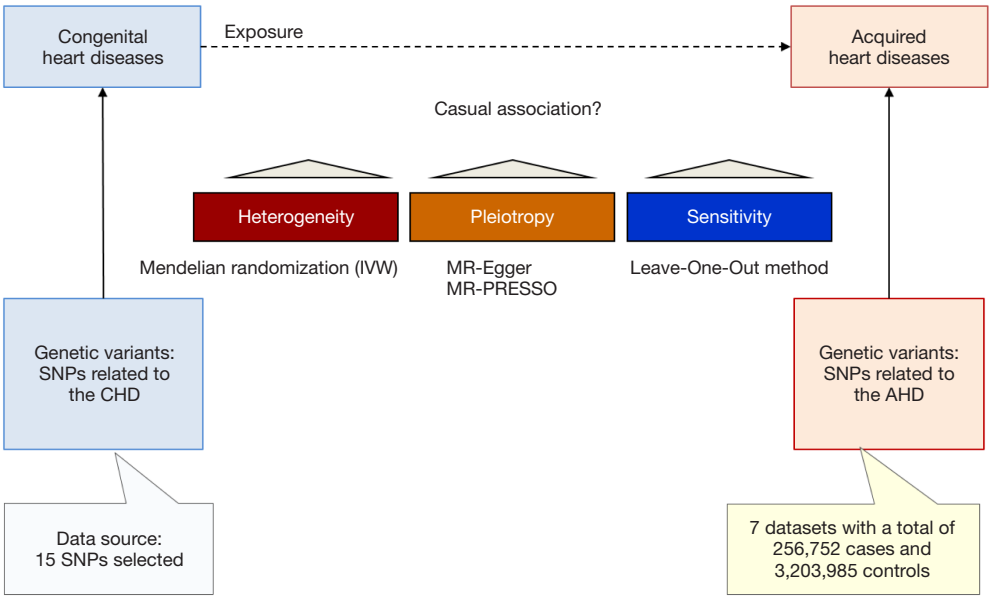


Figure 1 Description of the study design, hypothesis and SNPs selection process for this two-factor Mendelian randomization study. SNPs, single nucleotide polymorphisms; AHD, acquired heart diseases; CHD, congenital heart diseases; MR, mendelian randomization; IVW, inverse variance weighted method; PRESSO, pleiotropy RESidual Sum and Outlier.

the Declaration of Helsinki (as revised in 2013). FinnGen is an anonymous health registry that provides genomic data for research while protecting the privacy and integrity of participants. The UK Biobank has approval from the North West Multi-centre Research Ethics Committee (MREC) as a Research Tissue Bank (RTB), reference number 21/NW0157; studies using data from UK Biobank do not require separate ethical clearance and can operate under the RTB approval. To ensure the consistency of recourse materials all genetic data were downloaded on the same day, March 1, 2024.

Exposure data

The SNPs related to the CHD life-long exposure were downloaded from NHGRI-EBI GWAS Catalog, for studies GCST90044604 and GCST90044603 (19), utilizing all eligible cases under the diagnosis based on PheCode. First was a genome-wide genotyping array for congenital anomalies of great vessels (PheCode 747.13), including data from 919 cases, and 455,429 controls of European (U.K.) ancestry. Second was a genome-wide genotyping array for cardiac shunt/heart septal defect (PheCode 747.11), including data from 392 European ancestry cases, and 455,956 European ancestry controls.

Outcome data

The following datasets were selected as outcome data as classified according to International Classification of Diseases (ICD)-10, based on Hospital Discharge registry or Cause of Death registry: (I) coronary artery disease (GCST005194) with 34,541 European ancestry cases, 261,984 European ancestry controls (20); (II) heart failure (GCST009541) with 47,309 European ancestry cases, 930,014 European ancestry controls (21); (III) AF (GCST006414) with 60,620 European ancestry cases, 970,216 European ancestry controls (22); (IV) stroke (all strokes, GCST006906) with 40,585 European ancestry cases, 406,111 European ancestry controls (23); (V) ischemic stroke (GCST006908) with 34,217 European ancestry cases, 406,111 European ancestry controls (23); (VI) acute myocardial infarction (GCST90043954) with 8,528 European ancestry cases, 447,820 European ancestry controls (19); and (VII) data on ischemic heart diseases was extracted from the FinnGen study (finn-b-I9_ISCHHEART) with 30,952 European ancestry cases and 187,840 European ancestry controls (24).

Instrumental variable (IV) selection

Selection of IVs for further analysis was performed based

on the criteria of Mendelian randomization (STROBE-MR) guidelines (25). Firstly, SNPs significantly associated with the exposure factor were selected (meeting $P<5\times10^{-8}$); if nothing was found, the criteria were relaxed to select $P<5\times10^{-6}$. Among selected SNPs, those with a minimum minor allele frequency (MAF) >0.01 (26) were included; according to the standard of $R^2<0.001$ and window size =10,000 kb linkage disequilibrium (LD) between SNPs was removed (for SNPs that are inconsistent or cannot be matched between the exposure and outcome datasets and palindromic SNPs (those with inconsistent allele directions between exposure and outcome), SNPs with high LD ($R^2>0.8$) (27) were used to replace them). To evaluate the strength of the IV and exclude the possibility of a weak instrument the F value was calculated for each SNP in the IV dataset, according to the formula: $F = R^2*(N-2)/(1-R^2)$, where R^2 is the proportion of exposure variance explained by the SNP in the IV, and the requirement for the F value was >10 (26).

Statistical analyses

The main MR approach used to evaluate the possibility of causal association between CHD and cardiovascular diseases was the inverse variance weighted method (IVW); for interpreting MR results the weighted average of effect sizes was used with the inverse variance of each SNP as weights (27). To test the robustness of the results and estimate the presence of outliers and pleiotropic bias MR-Egger, MR-PRESSO and leave-one-out methods were used. Cochran's Q test was used to assess heterogeneity, MR Egger and MR-PRESSO were employed to evaluate pleiotropy, and the leave-one-out method was utilized for sensitivity analysis (28,29). All analyses in this study were conducted using the R version 4.3.0 along with the "Two-sample MR" package. The MR analysis results included odds ratios (OR) with their 95% confidence intervals (CIs) and P values. The results were presented using four different methods: tables, scatter plots, forest plots, and funnel plots; P values associated with the observed associations were subjected to multiple testing correction using the false discovery rate (FDR) method. Associations with a corrected P (P_{FDR}) less than 0.05 were considered statistically significant.

Results

IV selection

In this study, 15 IVs related to CHD were selected. The mean F-statistic for IVs was 23.55, with a minimum value of 21.27 and a maximum value of 28.84. Of selected IVs, conducting MR with congenital anomalies of great vessels as the exposure, one weak IV (rs9570679) was excluded, seven independent SNPs were associated with the outcomes [F-statistic =24.68 (21.46, 28.84)]; for coronary artery disease and ischemic heart diseases two SNPs (rs9590977, rs9570679) were not matched in the summary data, rs9570679 was replaced by rs9570685 as a proxy SNP ($R^2=4.783678\times10^{-5}$). Conducting MR with heart septal defect as the exposure, eight independent SNPs were associated with the outcomes [F-statistic =22.56 (21.27, 25.00)]; for coronary artery disease as the outcome, two SNPs (rs140732201, rs142621120) were not matched in the summary data. Detailed information for IVs used in this study is presented in available online https://cdn.amegroups.cn/static/public/cdt-24-422-1.xlsx.

Potential causal effects of CHD exposure on the development of cardiovascular disease

The results of IVW MR analysis, demonstrated in *Table 1*, showed that exposure to congenital anomalies of great vessels was potentially associated with a higher risk of AF (OR =1.07, 95% CI: 1.02–1.12, P=0.004) (*Figure 2A*). The results of MR-Egger regression method were consistent with those of the IVW method. The exposure to congenital anomalies of great vessels was also casually associated with all strokes (OR =1.07, 95% CI: 1.02–1.12, P=0.008) and Ischemic stroke (OR =1.07, 95% CI: 1.01–1.14, P=0.02) (*Figure 2B,2C*). The results of the Weighted Median and weighted Mode were consistent with those of the IVW method. The MR-Egger regression results indicated that this analysis was not affected by horizontal pleiotropy (*Table 2*). The effect sizes and confidence intervals for all outcomes were demonstrated in forest plots (*Figure 3*). There was no significant association uncovered in this study between genetic variants associated with congenital anomalies of great vessels and acute myocardial infarction, heart failure or ischemic heart diseases; between heart septal defect and all outcomes (*Table 1*).

Sensitivity analysis

According to the IVW there was no statistically significant association found between congenital anomalies of great vessels as the exposure and acute myocardial infarction as the outcome, but MR-PRESSO analysis suggested

Table 1 MR analysis of causal association between congenital heart diseases and cardiovascular diseases

Exposure	Outcome	Significant of SNP	No. of SNPs	Methods	OR (95% CI)	P	FDR adjusted P value
Congenital anomalies of great vessels	Coronary artery disease	5×10^{-6}	5	IVW	1.12 (0.86–1.45)	0.39	0.64
			5	MR-Egger	2.00 (0.79–5.04)	0.24	0.58
			5	Weighted median	0.99 (0.96–1.02)	0.52	0.69
			5	Weighted mode	0.99 (0.96–1.02)	0.53	0.69
	Atrial fibrillation	5×10^{-6}	6	IVW	1.07 (1.02–1.12)	0.004	0.055
			6	MR-Egger	1.07 (0.89–1.30)	0.52	0.69
			6	Weighted median	1.06 (1.02–1.10)	0.005	0.055
			6	Weighted mode	1.04 (0.97–1.11)	0.33	0.60
	Stroke	5×10^{-6}	6	IVW	1.07 (1.02–1.12)	0.01	0.06
			6	MR-Egger	1.09 (0.88–1.36)	0.48	0.69
			6	Weighted median	1.08 (1.03–1.13)	0.001	0.02
			6	Weighted mode	1.08 (1.02–1.14)	0.05	0.25
	Ischemic stroke	5×10^{-6}	6	IVW	1.07 (1.01–1.14)	0.02	0.11
			6	MR-Egger	1.11 (0.86–1.44)	0.47	0.69
			6	Weighted median	1.09 (1.04–1.14)	<0.001	0.02
			6	Weighted mode	1.10 (1.04–1.16)	0.03	0.14
	Heart failure	5×10^{-6}	4	IVW	1.02 (0.98–1.06)	0.29	0.58
			4	MR-Egger	1.04 (0.89–1.20)	0.69	0.80
			4	Weighted median	1.03 (0.99–1.07)	0.20	0.58
			4	Weighted mode	1.04 (0.98–1.10)	0.32	0.60
	Ischemic heart diseases	5×10^{-6}	2	IVW	1.06 (0.96–1.16)	0.27	0.58
	Acute myocardial infarction	5×10^{-6}	3	IVW	1.07 (0.99–1.15)	0.08	0.39
			3	MR-Egger	1.03 (0.75–1.43)	0.88	0.89
			3	Weighted median	1.06 (0.96–1.16)	0.27	0.58
			3	Weighted mode	1.05 (0.94–1.17)	0.50	0.69
Heart septal defect	Coronary artery disease	5×10^{-6}	6	IVW	1.01 (1.00–1.02)	0.14	0.58
			6	MR-Egger	1.01 (0.98–1.04)	0.45	0.69
			6	Weighted median	1.01 (1.00–1.03)	0.16	0.58
			6	Weighted mode	1.01 (0.99–1.03)	0.30	0.60
	Atrial fibrillation	5×10^{-6}	7	IVW	1.00 (0.99–1.02)	0.82	0.85
			7	MR-Egger	0.99 (0.96–1.02)	0.67	0.80
			7	Weighted Median	1.00 (0.98–1.01)	0.71	0.80
			7	Weighted Mode	1.00 (0.97–1.02)	0.78	0.82
	Stroke	5×10^{-6}	8	IVW	0.99 (0.96–1.01)	0.28	0.58
			8	MR-Egger	1.02 (0.97–1.07)	0.46	0.69
			8	Weighted median	1.00 (0.97–1.02)	0.76	0.82
			8	Weighted mode	1.00 (0.97–1.04)	0.82	0.85
	Ischemic stroke	5×10^{-6}	8	IVW	0.98 (0.95–1.01)	0.25	0.58
			8	MR-Egger	1.02 (0.97–1.09)	0.45	0.69

Table 1 (*continued*)

Table 1 (*continued*)

Exposure	Outcome	Significant of SNP	No. of SNPs	Methods	OR (95% CI)	P	FDR adjusted P value
			8	Weighted median	1.00 (0.97–1.03)	0.96	0.96
			8	Weighted mode	1.01 (0.97–1.04)	0.76	0.82
	Heart failure	5×10^{-6}	7	IVW	1.01 (0.99–1.03)	0.21	0.58
			7	MR-Egger	1.03 (0.99–1.08)	0.19	0.58
			7	Weighted median	1.01 (0.99–1.04)	0.21	0.58
			7	Weighted mode	1.02 (0.99–1.05)	0.26	0.58
	Ischemic heart diseases	5×10^{-6}	8	IVW	1.01 (0.99–1.02)	0.33	0.60
			8	MR-Egger	1.01 (0.98–1.05)	0.57	0.71
			8	Weighted median	1.01 (0.99–1.03)	0.37	0.64
			8	Weighted mode	1.01 (0.98–1.04)	0.50	0.69
	Acute myocardial infarction	5×10^{-6}	8	IVW	1.01 (0.98–1.04)	0.71	0.80
			8	MR-Egger	0.98 (0.92–1.05)	0.61	0.75
			8	Weighted median	1.01 (0.97–1.06)	0.49	0.69
			8	Weighted mode	1.03 (0.97–1.10)	0.37	0.64

MR, Mendelian randomization; SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval; FDR, false discovery rate; IVW, inverse variance weighted method.

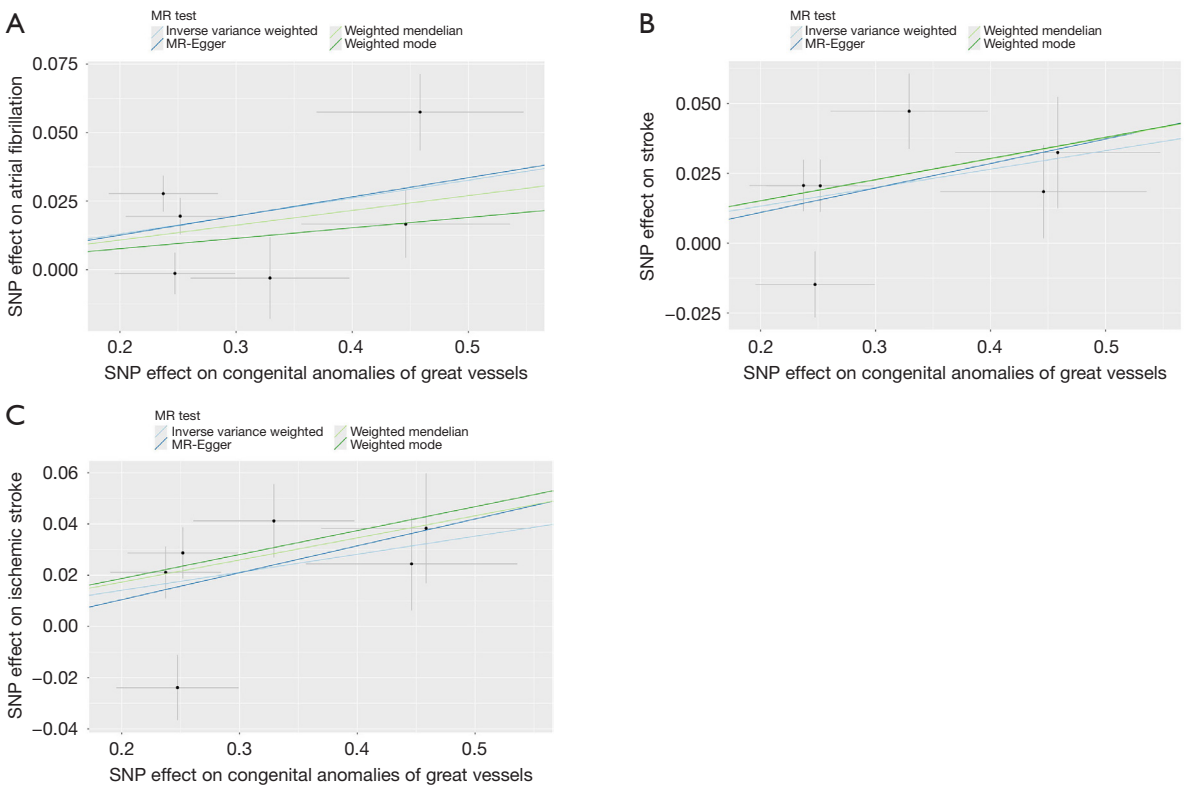


Figure 2 Scatter graphs of Mendelian randomization analysis, demonstrating casual effects of congenital anomalies of great vessels on the development of atrial fibrillation (A), all strokes (B), and ischemic stroke (C). MR, Mendelian randomization; SNP, single nucleotide polymorphism.

Table 2 Potential outliners according to the MR-PRESSO multiplicity analysis

Exposure	Outcome	Raw		Outlier corrected		Global P	Number of outliers	Distortion P
		OR (95% CI)	P	OR (95% CI)	P			
Heart septal defect	Coronary artery disease	1.01 (1.00–1.02)	0.04	NA	NA	0.94	NA	NA
Congenital anomalies of great vessels	Coronary artery disease	1.12 (0.86–1.45)	0.44	NA	NA	<0.001	NA	NA
Congenital anomalies of great vessels	Atrial fibrillation	1.07 (1.02–1.12)	0.03	NA	NA	0.04	NA	NA
Heart septal defect	Atrial fibrillation	1.00 (0.99–1.01)	0.78	NA	NA	0.72	NA	NA
Heart septal defect	Stroke	0.99 (0.96–1.01)	0.31	NA	NA	0.13	NA	NA
Congenital anomalies of great vessels	Stroke	1.07 (1.02–1.12)	0.05	NA	NA	0.10	NA	NA
Congenital anomalies of great vessels	Ischemic stroke	1.07 (1.01–1.14)	0.06	NA	NA	0.051	NA	NA
Heart septal defect	Ischemic stroke	0.98 (0.95–1.01)	0.29	NA	NA	0.09	NA	NA
Congenital anomalies of great vessels	Heart failure	1.05 (0.97–1.13)	0.29	1.02 (0.99–1.05)	0.25	<0.001	2 (rs10455872, rs944339)	<0.001
Heart septal defect	Heart failure	1.01 (0.99–1.03)	0.26	NA	NA	0.33	NA	NA
Congenital anomalies of great vessels	Ischemic heart diseases	1.10 (0.90–1.34)	0.42	1.06 (0.96–1.16)	0.47	<0.001	3 (rs10455872, rs650707, rs76899956)	<0.001
Heart septal defect	Ischemic heart diseases	1.01 (1.00–1.02)	0.21	NA	NA	0.86	NA	NA
Congenital anomalies of great vessels	Acute myocardial infarction	1.17 (0.91–1.50)	0.28	1.07 (1.02–1.12)	0.11	<0.001	3 (rs10455872, rs650707, rs944339)	<0.001
Heart septal defect	Acute myocardial infarction	1.01 (0.98–1.04)	0.72	NA	NA	0.37	NA	NA

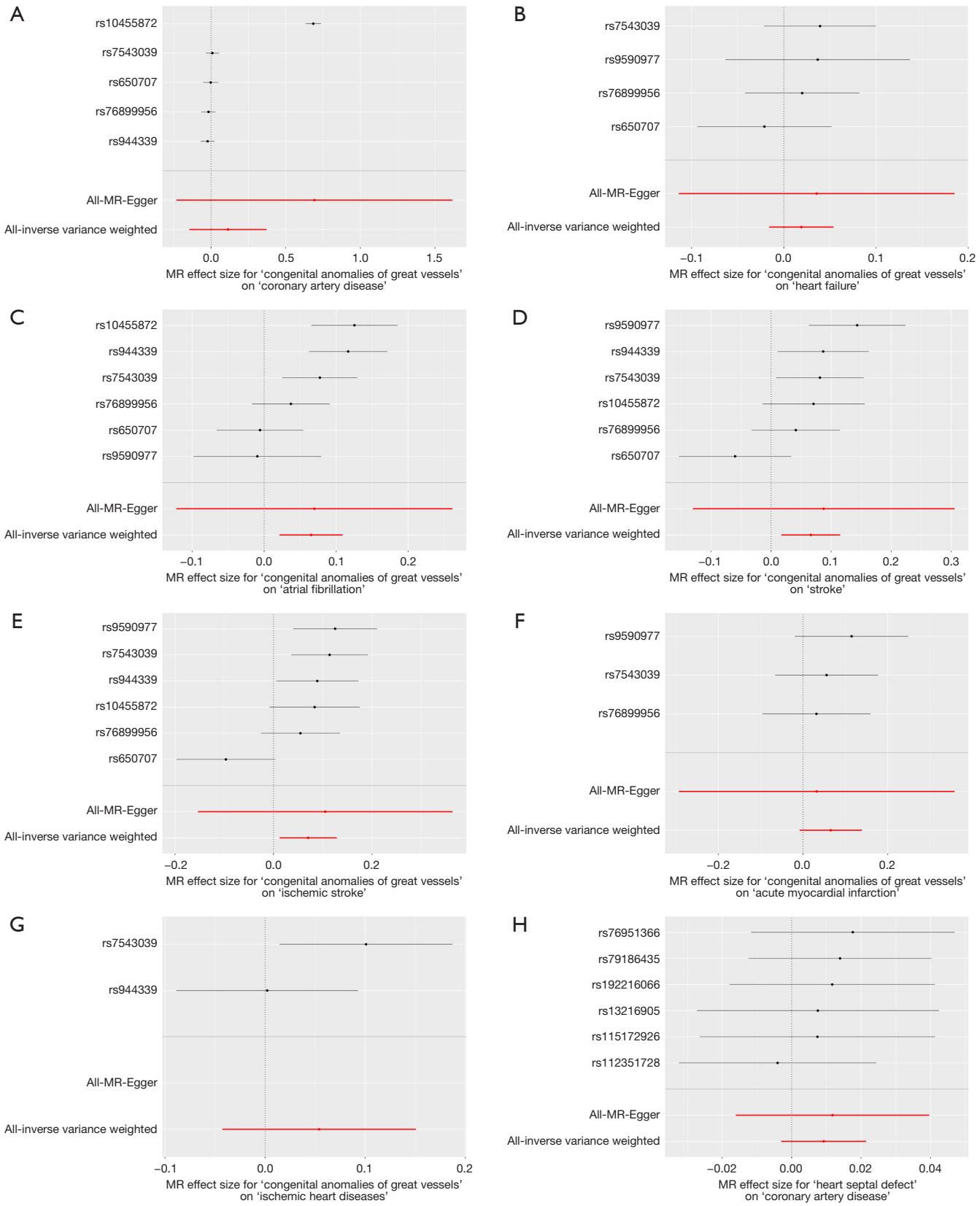
MR, Mendelian randomization; OR, odds ratio; CI, confidence interval; NA, not applicable.

the presence of three outliers (rs10455872, rs650707, rs944339); after their removal the association remained insignificant. For heart failure, MR-PRESSO analysis also suggested the presence of two outliers (rs10455872, rs944339), but even after their removal, the association between congenital anomalies of great vessels and heart failure remained insignificant. Similarly, for ischemic heart diseases, MR-PRESSO suggested the presence of three outliers (rs10455872, rs650707, rs76899956), but even after their removal, the association remained insignificant (*Table 2*, *Figure 4*).

The results of sensitivity analysis are demonstrated in *Table 3*. Cochran's Q test revealed considerable heterogeneity for congenital anomalies of great vessels and no heterogeneity in heart septal defect dataset. The MR-Egger regression results indicate that all analyses were not affected by horizontal pleiotropy. Leave-one-out analysis indicated that the causal effects were not driven by any single SNP (*Figure 5*).

Discussion

In this study, exposure to congenital anomalies of great vessels was found to be associated with a higher risk of AF, stroke in general and ischemic stroke in particular. The results of this study provide novel insights into the association between congenital anomalies of great vessels and various cardiovascular outcomes, utilizing MR analysis. By employing a rigorous methodological approach and examining multiple outcomes, this study contributes to the



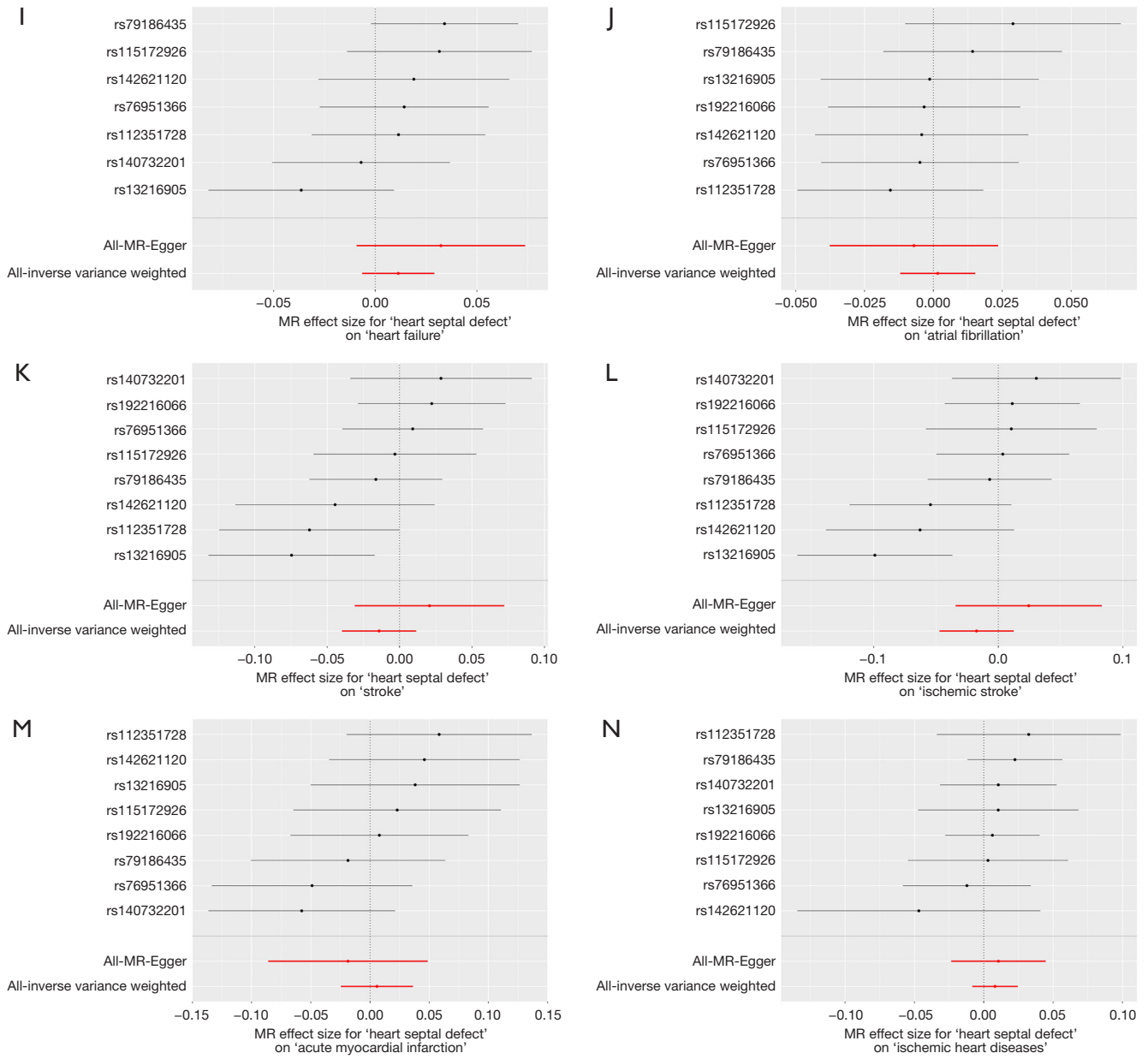
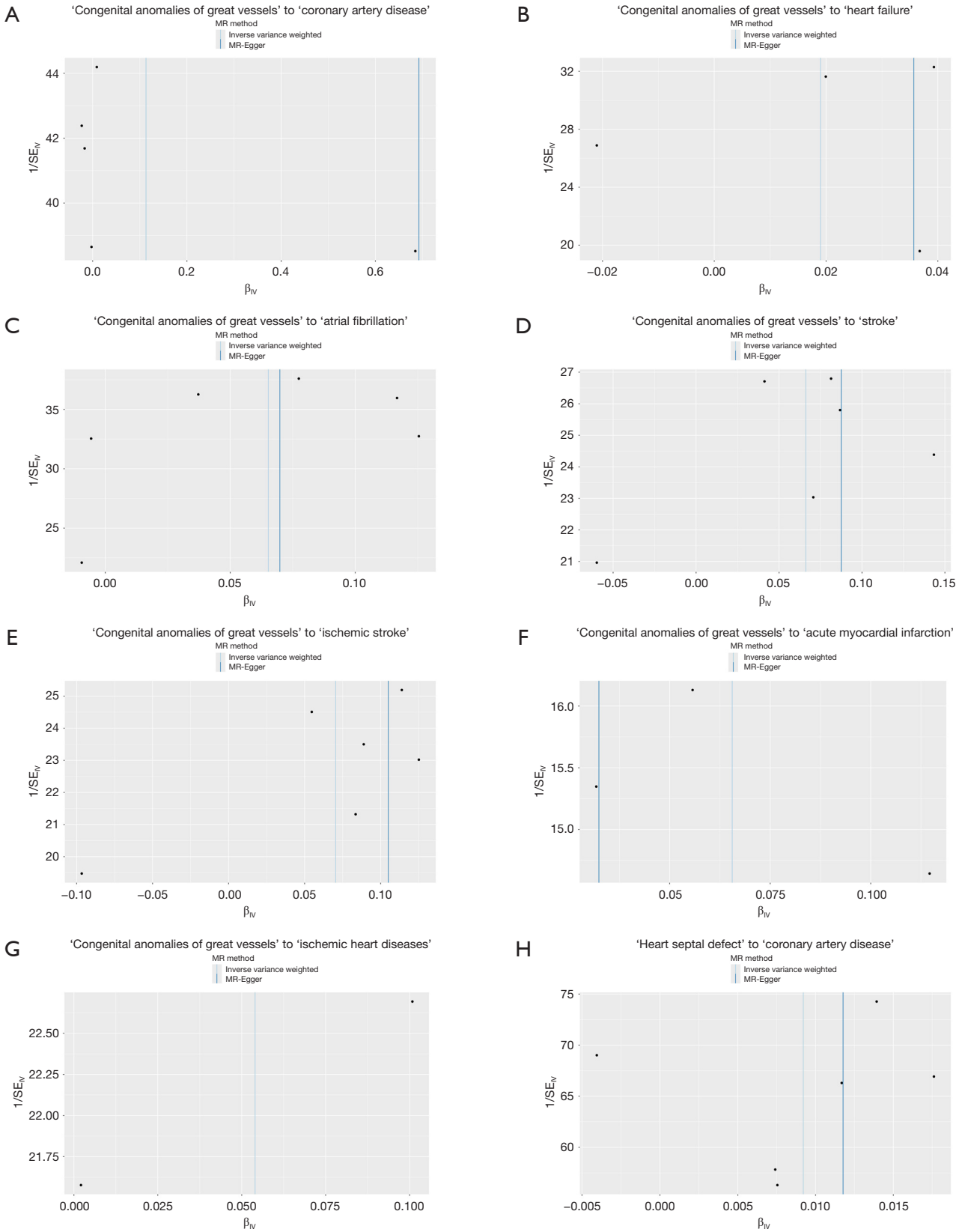


Figure 3 Effect size for selected single nucleotide polymorphisms on the development of cardiovascular disease estimated by MR-Egger and inverse variance weighted method. Congenital anomalies of great vessels on coronary artery disease (A), heart failure (B), atrial fibrillation (C), all strokes (D), ischemic stroke (E), acute myocardial infarction (F) and ischemic heart diseases (G). Heart septal defect on coronary artery disease (H), heart failure (I), atrial fibrillation (J), all strokes (K), ischemic stroke (L), acute myocardial infarction (M) and ischemic heart diseases (N). MR, Mendelian randomization.

understanding of the genetic determinants of cardiovascular diseases. The main findings of our study are summarized in *Figure 6*.

Previous clinical studies and meta-analyses have yielded mixed results regarding the association between congenital anomalies of great vessels and cardiovascular outcomes (11,29,30). These discrepancies underscore the need for further investigation using robust methodologies such as MR. In this study, exposure to congenital anomalies of great vessels was casually associated with AF, in line with the



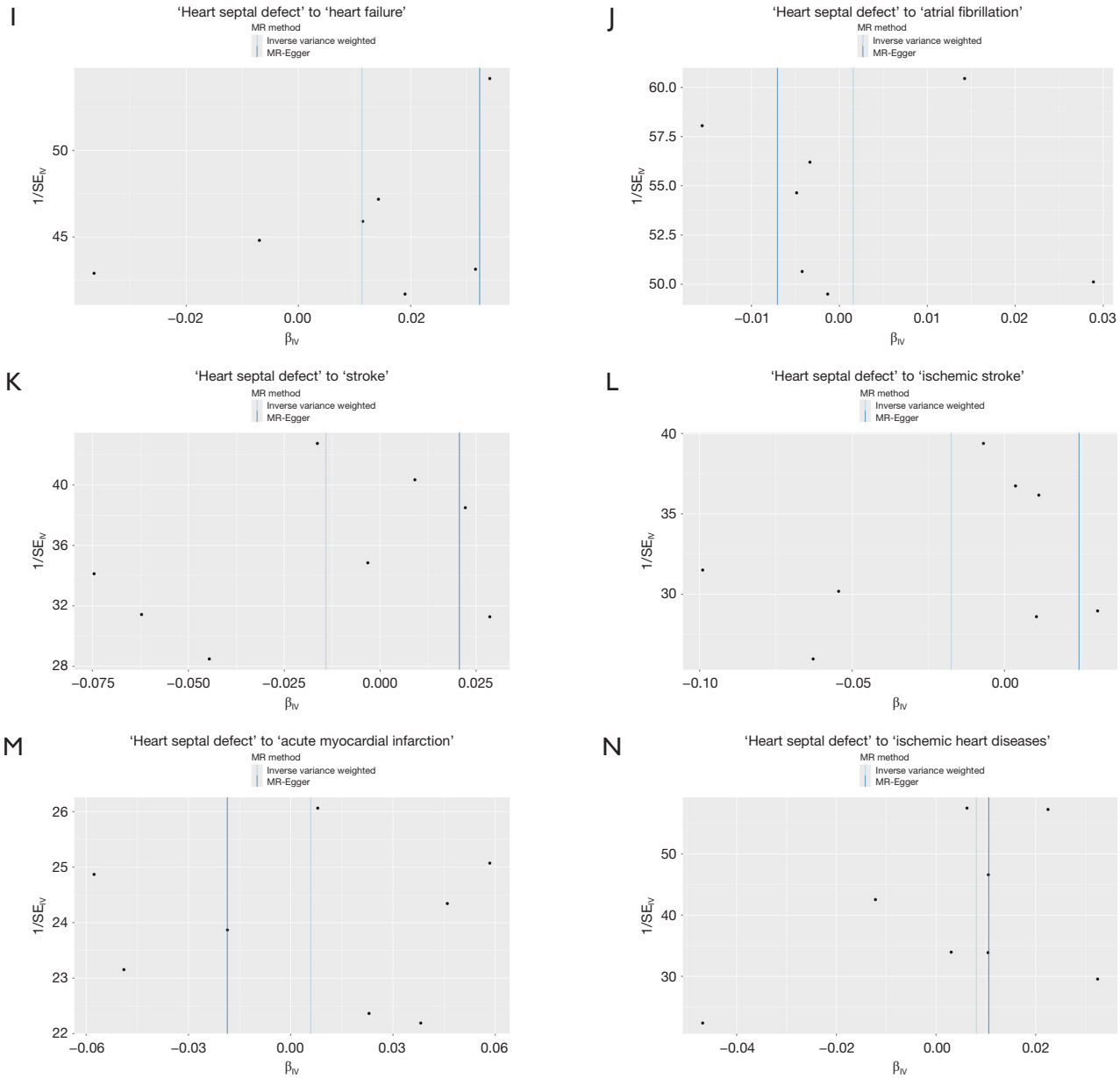


Figure 4 The funnel graphs demonstrating the impact of horizontal pleiotropy on the casual association between congenital heart disease exposure and the development of cardiovascular disease. Congenital anomalies of great vessels on coronary artery disease (A), heart failure (B), atrial fibrillation (C), all strokes (D), ischemic stroke (E), acute myocardial infarction (F) and ischemic heart diseases (G). Heart septal defect on coronary artery disease (H), heart failure (I), atrial fibrillation (J), all strokes (K), ischemic stroke (L), acute myocardial infarction (M) and ischemic heart diseases (N). MR, Mendelian randomization.

recently reported increasing prevalence of AF in adult CHD patients, being the leading cause of morbidity and hospital admissions (31,32). In particular, specific anatomical anomalies such as tetralogy of Fallot, transposition of great arteries, and coarctation of the aorta have been shown to correlate with higher rates of arrhythmias, highlighting the significance of understanding these structural differences in our cohort (33). The influence of studied genetic variants in the development of heart/great vessels could lead to changes in the electrophysiological components of the heart, with

Table 3 Results of sensitivity and heterogeneity analyses

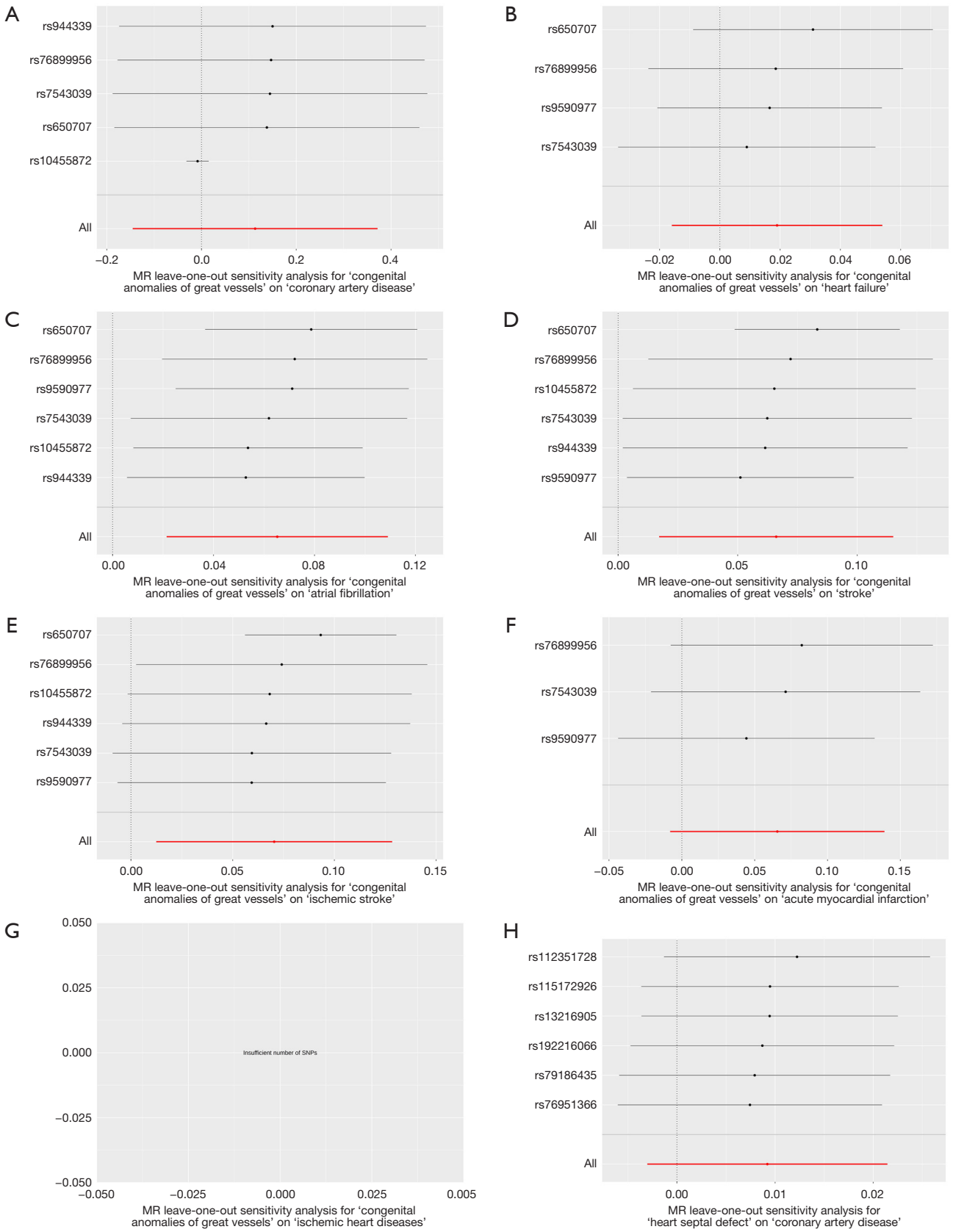
Exposure	Outcome	Heterogeneity		Pleiotropy	
		Q statistic (IVW)	P value	MR-Egger Intercept	P value
Congenital anomalies of great vessels	Coronary artery disease	588.57	<0.001	0.17	0.29
	Atrial fibrillation	16.6	0.005	0.001	0.96
	Stroke	11.42	0.04	0.007	0.85
	Ischemic stroke	13.79	0.02	0.01	0.8
	Heart failure	38.27	<0.001	0.07	0.16
	Ischemic heart diseases	92.33	<0.001	0.10	0.46
	Acute myocardial infarction	113.57	<0.001	0.22	0.17
Heart septal defect	Coronary artery disease	1.32	0.93	0.002	0.85
	Atrial fibrillation	3.76	0.71	0.008	0.56
	Stroke	12.06	0.10	0.03	0.19
	Ischemic stroke	13.64	0.06	0.04	0.17
	Heart failure	7.27	0.30	0.02	0.32
	Ischemic heart diseases	3.51	0.84	0.003	0.88
	Acute myocardial infarction	7.8	0.35	0.02	0.45

IVW, inverse variance weighted method; MR, Mendelian randomization.

pulmonary veins considering to be the primary source of AF and atypical atrial flutter in CHD survivors (34). Moreover, one of the analyzed SNPs (rs7543039) was previously reported to have a significant effect on cardiac electrophysiology (35), suggesting the genetic basis of the association between cardiac conduction and heart disease, further confirmed by the present study. Furthermore, the increased risk of stroke in these patients, particularly due to AF and atypical atrial flutter (36), emphasizes the need for ongoing monitoring and intervention. The uncovered link might manifest in vessel to atrial rhythm interface in CHD patients as they age, which is one of the most clinically significant findings of the present study. It is therefore important to take it into account in the development of guidelines for follow-up in patients with CHD diagnosis.

One of the predicted findings was the casual association between congenital anomalies of great vessels and stroke/ischemic stroke—according to the most recent study, compared to other patients, CHD survivors develop stroke more often (OR =1.15, 95% CI: 1.06–1.24) (37,38). Although recent retrospective cohort studies discussed an increase of coronary artery disease (CAD) risk in subjects with adult CHD (39), in this study genetically predicted heart septal defect and anomalies of great vessels were not casually associated with CAD. In addition to physiological differences, the discrepancy might be at least partly explained by the insufficient power to detect weak associations (29). Still, the calculated F-statistics for selected IVs exceeded 10, suggesting the absence of instrument bias in our analysis, and results make a positive contribution to the genetics of cardiovascular diseases, allowing a better understanding of CHD-specific risk factors, which might potentially help to identify higher risk of stroke and other cardiovascular diseases.

No statistically significant genetic links were confirmed in this study between CHD (both congenital anomalies of great vessels and heart septal defect) and acute myocardial infarction, heart failure or ischemic heart diseases, despite clinical evidence of such associations (9,10). It might be at least partly explained by the lower number of common SNPs found at this date: in particular, original study utilized as the GWAS source for heart failure outcomes (21) rigorously analyzed genetic data from Heart Failure Consortium and found 12 SNPs, of which only 4 were matched in the summary data for CHD—and after application of MR methods no significant association was found. It is quite possible that common SNPs still exist and could be found in the near future. On the other hand,



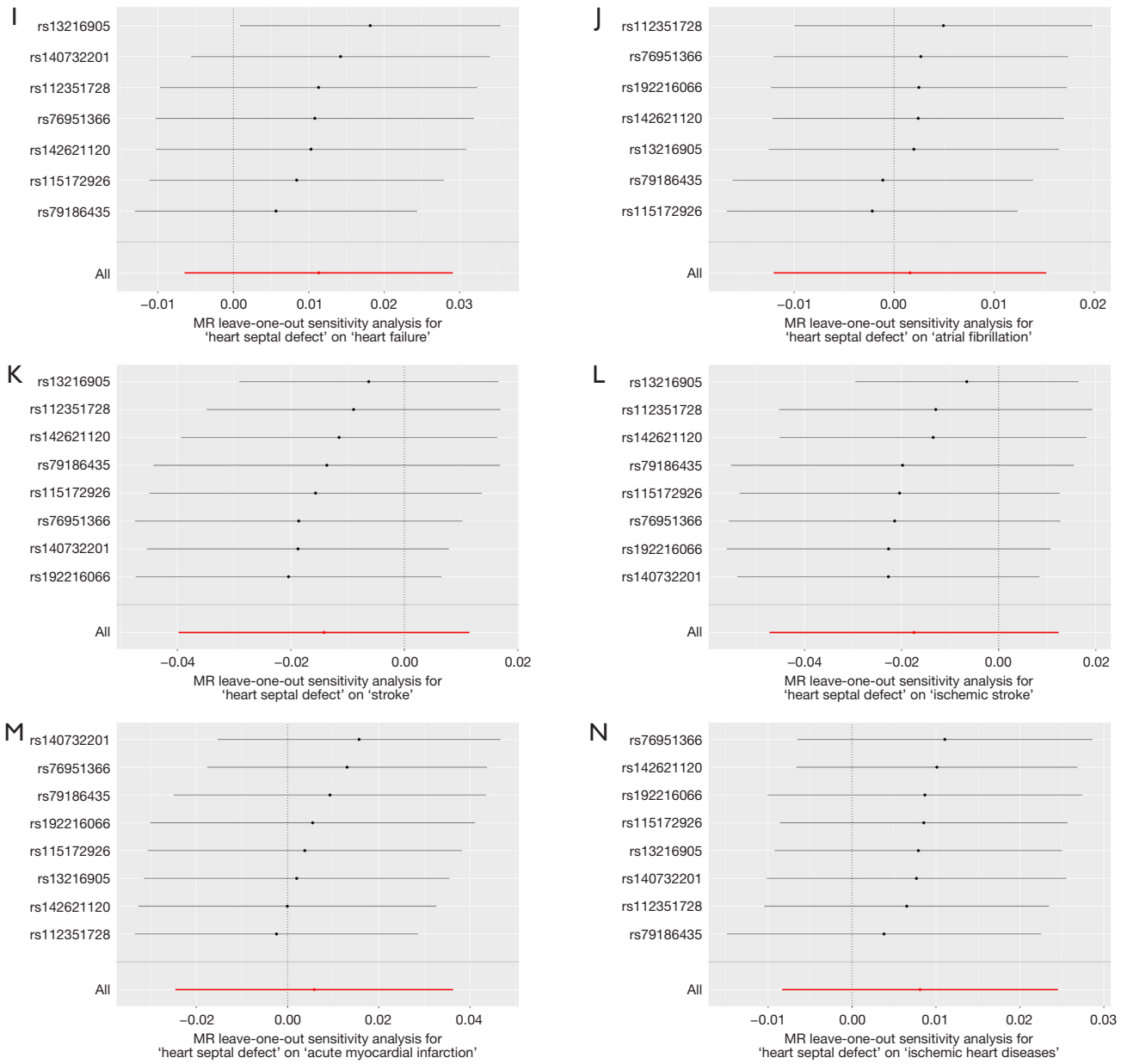


Figure 5 Results of sensitivity analysis by leave-one-out method, indicating that the observed causal effects were not driven by any single factor. Congenital anomalies of great vessels on coronary artery disease (A), heart failure (B), atrial fibrillation (C), all strokes (D), ischemic stroke (E), acute myocardial infarction (F) and ischemic heart diseases (G). Heart septal defect on coronary artery disease (H), heart failure (I), atrial fibrillation (J), all strokes (K), ischemic stroke (L), acute myocardial infarction (M) and ischemic heart diseases (N). MR, Mendelian randomization.

these associations may include shared genetic pathways and common risk factors, but develop under the influence of a wider number of factors besides underlying anatomic defect, such as haemodynamic changes, systemic or pulmonary hypertension, myocardial ischaemia and arrhythmias (9). A variety of biological mechanisms were not fully captured in the current analysis, and further evidence from molecular studies or animal models may shed light on the underlying relationship between congenital anomalies of great vessels and other cardiovascular outcomes.

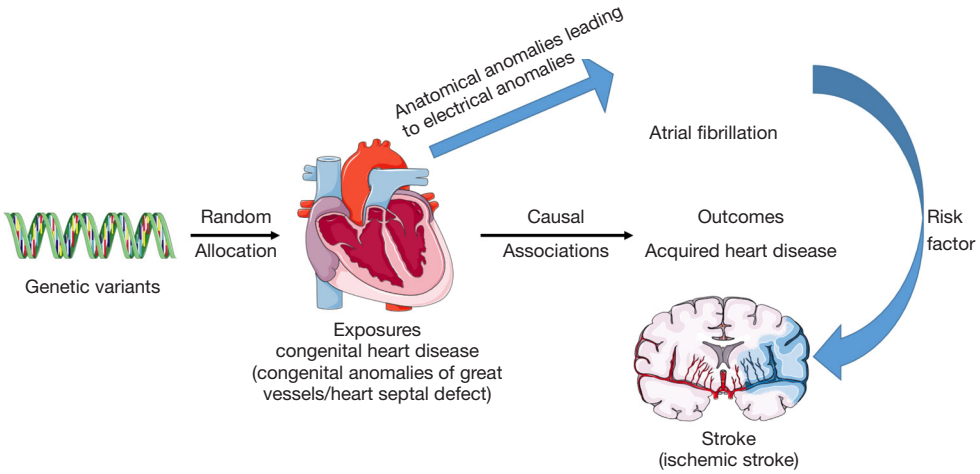


Figure 6 Main findings of Mendelian randomization study. We investigate that congenital anomalies of great vessels are associated with a higher risk of atrial fibrillation, overall stroke, and particularly ischemic stroke. We hypothesize that changes in the heart's electrophysiology, driven by genetic variants and structural heart anomalies, increase susceptibility to arrhythmias and stroke, especially as congenital heart disease patients age. The figure was generated partly using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license, and partly using Heart Beat Icon Vectors by Vecteezy (Vector illustration credit: https://www.vecteezy.com/free-vector/heart-beat-icon).

The strengths of this study lie in its utilization of MR, a powerful method for assessing causality in observational studies. By leveraging genetic variants as IVs, this study minimizes confounding and reverse causation biases commonly encountered in traditional observational studies. Additionally, the inclusion of multiple cardiovascular outcomes enhances the comprehensiveness of the analysis. However, several limitations should be considered when interpreting the findings. Firstly, the MR analysis relies on several assumptions, including the validity of IVs and the absence of horizontal pleiotropy. Although efforts were made to address these assumptions through sensitivity analyses, and MR-Egger regression results indicate that the above results were not affected by horizontal pleiotropy, residual confounding cannot be entirely ruled out. Secondly, the generalizability of the findings may be limited by the predominantly European ancestry of the study population. Thirdly, a variety of factors that might have influenced the development of heart condition (such as medication use, type of surgical procedure, etc.) were not validated due to the MR design specifics. Moreover, GWAS data did not include individual clinical information, such as disease severity, limiting the stratification possibilities. Future studies in more diverse populations with more detailed outcome data are warranted to validate the results. Finally, as with any observational study, causal inference is inherently limited, and further research, including experimental studies, is needed to confirm the observed associations.

Conclusions

In conclusion, this study found a potential causal association between genetically predicated exposure to congenital anomalies of great vessels and a higher risk of AF, unspecified strokes and ischemic stroke. The genetic factors discussed herein might potentially help to identify a higher risk of stroke and other cardiovascular diseases.

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Footnote

Reporting Checklist: The authors have completed the STROBE-MR reporting checklist. Available at https://cdt.amegroups.com/article/view/10.21037/cdt-24-422/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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