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Allergic Diseases and Cardiovascular Diseases: A Mendelian Randomization Study

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Abstract

Background: Prior observational and experimental research has established an association between allergic diseases and cardiovascular diseases (CVDs), yet the causal relationship remains elusive. Our study utilized Mendelian randomization (MR) to investigate the potential causality between allergic diseases and CVDs.

Methods: The exposure and outcome datasets were sourced from the IEU Open GWAS project (https://gwas.mrcieu.ac. uk/). The exposure dataset comprised data on allergic diseases, including allergic rhinitis, childhood-onset asthma, adult-onset asthma, dermatitis and eczema. The outcome dataset consisted of data on CVDs, specifically coronary artery disease (CAD), ischemic stroke (IS), and congestive heart failure (CHF). The primary analysis employed the Inverse Variance Weighted (IVW) method, complemented by sensitivity analyses including MR-Egger, Cochrane's Q test, MR-PRESSO, and leave-one-out to enhance the results' reliability.

Result: Utilizing the IVW method, the MR analysis unveiled a genetically predicted association between allergic rhinitis and CVDs (OR=0.989; 95% CI =0.980-0.999, P=0.031), as well as coronary artery disease (CAD) (OR=0.944; 95% CI =0.8914-0.9995, P=0.048). Similarly, a significant association emerged between childhood-onset asthma and CVDs (OR=0.99993; 95% CI =0.9989-0.9998, P=0.003) and CAD (OR=0.996; 95% CI =0.993-0.999, P=0.023).

Conclusion: This study offers preliminary evidence indicating a slight reduction in CADs risk associated with specific allergies. Additional studies are necessary to confirm these preliminary results and to investigate their significance for the prevention of CVDs.

Keywords: allergic diseases, cardiovascular diseases, mendelian randomization, GWAS, single nucleotide polymorphisms

Introduction:

Cardiovascular diseases (CVDs) are the leading cause of death worldwide, responsible for approximately one-third of all yearly fatalities. This is an increasingly serious public health problem.(Cieza et al., 2021; Roth et al., 2020) Recent research has pointed to a complex relationship between allergic diseases and cardiovascular diseases (CVDs), where the nature and extent of their connection to CVDs risk remains to be fully elucidated.(Fearon & Fearon, 2008; Fernandez-Gallego et al., 2022; Hariharan et al., 2022; Martinez-Hervas & Gonzalez-Navarro, 2019; Roifman et al., 2011; Vuong et al., 2022)

While chronic inflammation is acknowledged as contributing to cardiovascular diseases, the specific impact of allergic diseases, characterized by both acute and late-phase inflammatory responses, on atherosclerosis and cardiovascular health is not well-defined, indicating a multifaceted relationship. Allergic conditions, including allergic asthma, rhinitis, eczema, and some dermatitides, encompass a range of inflammatory disorders that interact intricately with cardiovascular health, potentially affecting endothelial function and the progression of atherosclerosis. Researchers such as Patterson(Patterson et al., 2010) have highlighted the systemic inflammatory effects of allergic diseases, which can impact the development and progression of atherosclerosis through various mechanisms. Additionally, studies by Marone et al.(Marone et al., 2014) have demonstrated that the heart can be both a site and a target of allergic reactions in cases of anaphylactic shock. Kounis et al.(Kounis et al., 2015) have also found evidence that severe allergic reactions can directly attack the heart and coronary arteries, leading to myocardial infarction. Similarly, research has also suggested that asthma may indirectly elevate the risk of coronary artery disease through mechanisms such as cardiac remodeling(Geng et al., 2022). Prospective studies, such as the one conducted by Yoko Nishida et al.(Nishida et al., 2019), have shown a significant relationship between the frequency of eczema and the risk of death from coronary heart disease. However, there are also studies indicating that allergic rhinitis may be associated with a reduced risk of coronary heart disease, cardiovascular disease, and overall mortality(Pandher et al., 2022). The relationship between rhinitis, specific dermatitis, and the risk of CVDs remains controversial, as noted by Pandher et al.(Pandher et al., 2022) Despite these findings, the specific relationship between allergic conditions and cardiovascular health is still a subject of debate, with the causal links remaining unclear. Understanding the underlying causal relationship between allergic diseases and CVDs is crucial for the prevention and treatment of CVDs.

To address potential confounding factors inherent in observational studies, Mendelian randomization (MR) offers an effective approach. This method incorporates instrumental variables, which serve as proxies, to analyze the causal associations between exposure factors and outcomes. By employing summarized genome-wide association study (GWAS) data, we aim to investigate the potential causal relationship between allergic diseases and CVDs. Utilizing a two-sample MR framework, we seek to clarify the direction and nature of this association, providing insights into the underlying causality between allergic diseases and CVDs, thereby informing strategies for CVDs prevention and treatment.

Method

Study Design

We conducted the current study using a two-sample Mendelian randomization (MR) analysis, extracting instrumental variables from exposure and outcome associations in two independent, non-overlapping participant sets. Employing a two-sample MR method, we evaluated the potential causal link between allergic diseases and CVDs. Result reliability was ensured through sensitivity analysis. The MR approach relied on three key assumptions: (1) Strong association of genetic variants used as

instrumental variables with exposure; (2) No association of genetic variants with any confounders; (3) Absence of a direct correlation between genetic variation and the outcome, except through exposure(Glymour et al., 2012). As all data used were publicly available, no additional ethical approval was required. The specific study design is depicted in Fig. 1.

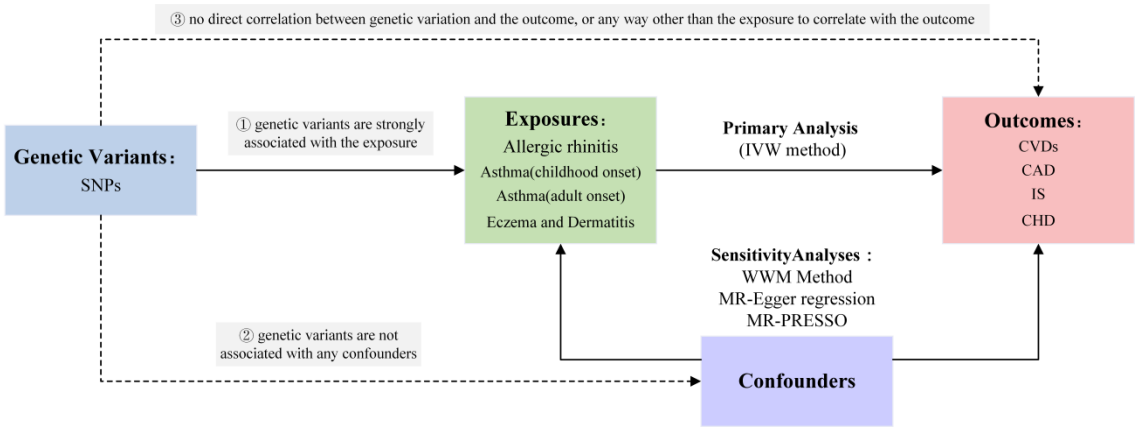

Figure 1. The Mendelian randomization study design

Allergic diseases GWAS sources

Herein, IVs of four allergic diseases were selected from GWAS, including allergic rhinitis, asthma (childhood onset), asthma(adult onset), dermatitis and eczema. Genetic association data for allergic rhinitis were derived from the research of Joelle Mbatchou et al.(Mbatchou et al., 2021), involving 407746 cases. The genetic association data for asthma (childhood onset) and asthma (adult onset)were derived from the study of Manuel A.R. Ferreira et al.(Ferreira et al., 2019), involving 40,544 cases（childhood onset 13,962 and adult onset 26,582）and 300,671 controls. The GWAS summary-level data of dermatitis and eczema was extracted from FinnGen biobank by the IEU open GWAS project studied 20,052 cases and 198,740 controls. The majority of the study population was of European descent, and estimates of genetic associations were gender-adjusted. Table 1 presents comprehensive information regarding the sources of GWAS used in this work.

CVDs GWAS sources

The GWAS summary-level data of CVDs were extracted directly from UK Biobank by the IEU Open GWAS project. More information about the exposure and outcome datasets is presented in Table 1. The genetic association data for IS and CHF were extracted from study of Sakaue S(Sakaue et al., 2021), involving 11,929 cases and 472,192 controls of IS, 14262 cases and 471,898 controls of CHF. The summary statistics for CAD were obtained from the IEU Open GWAS project (https://gwas.mrcieu.ac.uk/), which included 352,063 European individuals. The sample characteristics of the study population are described in Table 1.

Table 1 Details on GWAS of IVs used in Mendelian randomization analyses

Traits	IEU GWAS ID	Study or Consortium	Sample size	Population studied	Year
CVDs	ebi-a-GCST90038595	Donertas, H. M	484,598	European	2021
CAD	ebi-a-GCST90013864	UK Biobank	352,063	European	2021
IS	ebi-a-GCST90018877	Sakaue S	484,121	European	2021
CHF	ebi-a-GCST90018806	Sakaue S	486,160	European	2021
Allergic rhinitis	ebi-a-GCST90013970	UK Biobank	407,746	European	2021

Asthma (childhood onset)	ebi-a-GCST007800	Ferreira et al.	314,633	European	2019
Asthma (adult onset)	ebi-a-GCST007799	Ferreira et al.	327,253	European	2019
Dermatitis and Eczema	finn-b-L12_DERMATITISECZEMA	FinnGen biobank	218792	European	2021

Abbreviations: cardiovascular diseases = CVDs; Coronary artery disease = CAD; Ischemic stroke = IS; Chronic heart failure = CHF

The selection of IVs

In our Mendelian randomization analysis, we employed instrumental variables (IVs) as tools to discern the causal relationships between exposure factors and outcomes. IVs are typically genetic variants, with SNPs being the variant of choice for their commonality. To reliably associate SNPs with exposure, we only included those meeting stringent criteria: genome-wide significance ($p < 5\times10^{-8}$), a substantial clumping window over 10,000 kb, and minimal linkage disequilibrium ($r^2 < 0.001$), as these measures ensure the SNPs' independence(Palmer et al., 2012). Detailed SNP information is provided in Table 1. Concurrently, we scrutinized the Phenoscanner database to confirm that our selected SNPs were not associated with any known confounders. Moreover, to affirm the robustness of the association between IVs and the exposure, we utilized the F statistic as a gauge of validity(Burgess & Thompson, 2011). In this study, the inclusion criteria for SNPs demanded F values exceeding 10, thus minimizing the risk of weak instrument bias. Palindromic SNPs, specifically those with A/T or G/C alleles, were systematically identified and excluded to prevent the ambiguity they can cause regarding the effect allele in GWAS studies of both exposure and outcome. To address and rectify the presence of horizontal pleiotropy, we employed the Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) tool for both global and outlier analyses, rooting out SNPs exhibiting such effects(Verbanck et al., 2018). Finally, 145 SNPs for allergic rhinitis, 103 SNPs for asthma (childhood onset), 46 SNPs for asthma (adult onset), 14 SNPs for Dermatitis and Eczema were selected. The SNPs are shown in Supplementary Table S1, Table S2, Table S3, and Table S4.

Statistical analysis

To estimate the causal effect, we utilized the inverse variance weighted (IVW) method as our primary analytical approach. The IVW model is particularly potent for detecting causality within the framework of two-sample MR analysis(Hartwig et al., 2017). We translated our findings into odds ratios (ORs) and their corresponding 95% confidence intervals (CIs). Heterogeneity within the IVW estimates was evaluated using Cochran's Q test, where a p-value less than 0.05 signified heterogeneity. Nevertheless, heterogeneity does not inherently invalidate the IVW model. Given the diversity in causal estimates from different variants, the multiplicative random effects model was deemed preferable to the fixed effects model, and was therefore adopted for our main analysis.

Furthermore, we employed the MR-PRESSO method to identify and correct for outliers in the IVW linear regression(Verbanck et al., 2018). The MR-Egger method, which accommodates non-zero intercepts, was applied to check for the presence of directional pleiotropy. We also conducted leave-one-out analyses to determine the influence of individual SNPs on our results. Using MR-PRESSO, we were vigilant in detecting and excluding outliers promptly. Following outlier removal, the MR analyses were revisited. All computations and statistical analyses were facilitated by the R software (version 4.3.2), utilizing the TwoSampleMR package.

Results

Allergic rhinitis

After removing palindromic SNPs rs10950805, rs10979387, rs11539209, rs11924625, rs192254932, rs2746438, rs35441874, rs3933376, rs4660 71, rs61774728, rs62375550, rs72774901, rs72823641, rs73042197, rs7861040, rs8067124, we used a random-effects model to estimate the

causal effect estimates for allergic rhinitis and CVDs, taking into account the substantial heterogeneity of the SNPs. Based on the IVW method, the genetic prediction results showed that the allergic rhinitis was linked to a decreased risk of CVDs (OR=0.989; 95% CI =0.980-0.999, P=0.031) and CAD (OR=0.944; 95% CI =0.8914-0.9995, P=0.048). This suggests that the presence of allergic rhinitis may be associated with a slightly decreased risk of CVDs and CAD. Sensitivity tests demonstrated that the MR-Egger intercept did not demonstrate imbalanced horizontal pleiotropy for CVDs (P = 0.731) and CAD (P = 0.917). The MR analysis showed that genetically predicted allergic diseases decreased the risk of CVDs. All sensitivity analysis results are included in Supplementary Tables S5 and S6, while Supplementary Fig. S3 and Fig. S4 show the forest plots and scatter plots. By using the MR-PRESSO test, 5 outliers of CAD (rs6177 4728, rs11690149, rs2070642, rs3918226, rs793 6323), 1outliers of IS (rs7925585), 3 outliers of CHF (rs7925585, rs11626205, rs6089970) were detected, which were corrected for possible outliers.

Table 2 Odds ratios for the associations between genetically predicted allergic rhinitis and risk of CVDs

Exposure	Outcome	No. of SNPs	Method	OR (95% CI)	P
Allergic Rhinitis	CVDs	125	IVW	0.989 (0.980-0.999)	0.031
			Weighted median	0.994 (0.987-1.000)	0.056
			MR Egger	0.993 (0.968-1.020)	0.624
	CAD	129	IVW	0.944 (0.8914-0.9995)	0.048
			Weighted median	0.983 (0.923-1.046)	0.579
			MR Egger	0.951 (0.816-1.108)	0.522
	IS	128	IVW	0.985 (0.937-1.034)	0.537
			Weighted median	0.970 (0.909-1.035)	0.359
			MR Egger	0.994 (0.870-1.136)	0.935
	CHF	128	IVW	1.009 (0.950-1.072)	0.772
			Weighted median	1.053 (0.981-1.130)	0.152
			MR Egger	1.035 (0.879-1.220)	0.680

Abbreviations: Abbreviations: cardiovascular diseases = CVDs; Coronary artery disease = CAD; Ischemic stroke = IS; Chronic heart failure = CHF; No. of SNPs = the number of SNPs used as instrumental variables; P = P-value of the causal estimate; OR = odds ratio; CI = confidence interval

Childhood and adult onset Asthma

After removing palindromic SNPs rs10737105, rs11121240, rs11658582, rs142716649, rs16903574, rs1806656, rs1887704, rs1893380, rs2428494, rs4722758, rs61584523, rs6927172, rs71421264, rs72823641, rs7626218, based on the IVW method, childhood onset asthma was associated with a decreased risk of CVDs (OR=0.99993; 95% CI =0.9989-0.9998, P=0.003) and CAD (OR=0.996; 95% CI =0.993-0.999, P=0.023), adult onset asthma was associated with a decreased risk of IS (OR=0.9959; 95% CI =0.9919-0.9999, P=0.46). The IVM method showed that exposure to childhood onset asthma was not associated with IS and CHF, exposure to adult-onset asthma was not associated with CVDs, CAD and CHF. 5 outlier SNPs of CVDs (rs12023876, rs12750027, rs3856439, rs1837253, rs6954667, rs4795399), 3 outlier SNPs of CAD (rs12750027, rs4792846, rs4795399), 1 outlier SNP of IS (rs12750027), and 2 outlier SNP of CHF (rs12750027, rs12657787) were detected through the MR-PRESSO test. After correcting for possible outliers, the results of all these associations were proven valid. Leave one out plot

showed no substantial change in genetically predicted risk (supplementary Figs 5 and 9). The MR-Egger intercept identified a notable imbalance in horizontal pleiotropy when considering adult-onset asthma as the exposure and ischemic stroke (IS) as the outcome (P = 0.031). All Sensitivity analysis and heterogeneity analysis of childhood onset and adult-onset asthma are shown in Supplemental Tables S5 and S6.

Table 3 Odds ratios for the associations between genetically predicted asthma and risk of CVDs

Exposure	Outcome	No. of SNPs	Method	OR (95% CI)	P
Asthma (childhood onset)	CVDs	100	IVW	0.9993(0.9989-0.9998)	0.003
			Weighted median	0.9996(0.9993-1.0000)	0.053
			MR Egger	0.998(0.999-1.002)	0.413
	CAD	87	IVW	0.996 (0.993-0.999)	0.023
			Weighted median	0.997 (0.994-1.000)	0.097
			MR Egger	0.994 (0.967-1.023)	0.698
	IS	97	IVW	1.000 (0.998-1.003)	0.786
			Weighted median	1.000 (0.997-1.004)	0.763
			MR Egger	0.989 (0.966-1.014)	0.386
	CHF	97	IVW	0.999 (0.996-1.002)	0.491
			Weighted median	0.999 (0.995-1.003)	0.578
			MR Egger	1.003 (0.976-1.030)	0.795
Asthma (adult onset)	CVDs	46	IVW	0.9997(0.9992-1.0000)	0.333
			Weighted median	0.9997(0.9993-1.0001)	0.169
			MR Egger	1.002(0.994-1.009)	0.607
	CAD	40	IVW	0.999 (0.995-1.003)	0.535
			Weighted median	0.996 (0.992-1.001)	0.107
			MR Egger	0.991 (0.935-1.051)	0.765
	IS	45	IVW	0.9959(0.9919-0.9999)	0.046
			Weighted median	0.996 (0.991-1.001)	0.088
			MR Egger	0.936 (0.887-0.989)	0.022
	CHF	45	IVW	0.9989 (0.995-1.003)	0.546
			Weighted median	1.000 (0.995-1.005)	0.972
			MR Egger	0.987 (0.938-1.040)	0.630

Abbreviations: Abbreviations: cardiovascular diseases = CVDs; Coronary artery disease = CAD; Ischemic stroke = IS; Chronic heart failure = CHF; No. of SNPs = the number of SNPs used as instrumental variables; P = P-value of the causal estimate; OR = odds ratio; CI = confidence interval

Dermatitis and Eczema

Dermatitis and Eczema showed no remarkable influence on CVDs, CAD, IS and CHF based on the IVW, weighted median, and MR-Egger analyses (Table 2). The estimated effect sizes of exposure (Dermatitis and Eczema) on outcome (CVDs, CAD, IS and CHF) are shown in the scatter plot (Supplementary Figure S12). The funnel plot provides a simple method for detecting directional-level pleiotropic tests, as shown in Supplementary Figures S14. The forest plot reflects the results estimated by a single SNP using the Wald ratio method and is shown in the Supplementary Figures S13. 2 outlier SNP of IS (rs61839660, rs7925585), and 2 outlier SNP of CHF (rs12750027, rs12657787) were detected through the MR-PRESSO test. After correcting for possible outliers, the results of all these associations were proven valid. We found no substantial evidence of horizontal pleiotropy from the MR-Egger intercept (intercept P > 0.05). Sensitivity analysis and heterogeneity analysis are shown in Supplementary Table S5 and S6.

Table 4 Odds ratios for the associations between genetically predicted dermatitis and eczema and risk of CVDs

Exposure	Outcome	No. of SNPs	Method	OR (95% CI)	P
Eczema and Dermatitis	CVDs	13	IVW	1.017(0.999-1.035)	0.0691
			Weighted median	1.005(0.9941.016)	0.360
			MR Egger	0.995(0.944-1.049)	0.869
	CAD	11	IVW	1.048(0.880-1.247)	0.601
			Weighted median	0.937(0.831-1.057)	0.291
			MR Egger	0.849(0.514-1.403)	0.539
	IS	14	IVW	1.032(0.917-1.161)	0.601
			Weighted median	1.10(0.966-1.246)	0.154
			MR Egger	1.367(0.895-2.09)	0.173
	CHF	14	IVW	1.048 (0.945-1.161)	0.376
			Weighted median	1.073 (0.946-1.218)	0.272
			MR Egger	0.983 (0.685-1.410)	0.926

Abbreviations: Abbreviations: cardiovascular diseases = CVDs; Coronary artery disease = CAD; Ischemic stroke = IS; Chronic heart failure = CHF; No. of SNPs = the number of SNPs used as instrumental variables; P = P-value of the causal estimate; OR = odds ratio; CI = confidence interval

Discussion

This study conducted the most comprehensive Mendelian Randomization (MR) analysis so far to investigate the link between allergic diseases and the risk of CVDs. In this study, we systematically evaluated the connections between five different allergic conditions and a wide range of CVDs, including three representative cardiovascular conditions. Our MR analysis results suggest that patients with allergic rhinitis and childhood onset asthma have a reduced risk of CVDs and CAD. Moreover, these associations were found to be robust and reliable even in sensitivity analysis.

Importantly, none of the instrumental variables used in this study substantially influenced the outcome variable, further reinforcing the validity of our findings.

The unexpected discovery of a protective association between allergic diseases and CVDs in our study is noteworthy. Importantly, this observation is supported by findings from several other observational studies. A retrospective, population-based, matched cohort study showed that the presence of allergic rhinitis was associated with decreased CHD, CVDs, and all-cause mortality(Crans et al., 2016). A cross-sectional study found that patients with positive sIgE test results were less likely to have had a history of MI(Jaramillo et al., 2013). A study, utilizing ross-sectional analysis of baseline data from the Canadian Partnership for Tomorrow Project, revealed a negative association between atopic dermatitis (AD) and subsequent occurrences of hypertension, type 2 diabetes, myocardial infarction, and stroke. These findings provide evidence that allergic rhinitis and atopic dermatitis might not be major risk factors for CVDs.

The potential mechanisms contributing to this observed cardiovascular protection in allergic populations may involve:①Treg cells play a central role in the immune response, secreting anti-inflammatory cytokines such as TGF-β and IL-10. These cytokines inhibit T-cell and macrophage activation, promoting vascular smooth muscle cell proliferation and plaque stability, thereby contributing to atheroprotection(Gao et al., 2020; Grainger, 2004; Lin et al., 2010).The T-cell identity in allergy and atherosclerosis suggests an atheroprotective role for Th2 cells, countering Th1 responses(Fernandez-Gallego et al., 2022). ②Regulatory T cells (Treg) promote the transformation of macrophages from a pro-inflammatory to an anti-inflammatory phenotype by secreting IL-10, thereby enhancing their atheroprotective effec; some studies suggest that IL-17 may play a protective role in atherosclerosis by promoting Type I collagen production, contributing to plaque stability(Danzaki et al., 2012). Co-administration of IL-33 with anti-IL-5 prevents plaque size reduction(Miller et al., 2008). ③IgE promotes M1 macrophage polarization in plaques, a process not fully understood but potentially linked to atherosclerosis(Fernandez-Gallego et al., 2022). Formation of oxLDL immune complexes by serum IgM and IgG1 clears harmful substances, exerting anti-atherosclerotic effects(de Vries et al., 2021; Schiopu et al., 2007). ④Chronic inflammation resulting from CD70 overexpression surprisingly exhibits atheroprotective effects, emphasizing the multifaceted nature of the CD27/CD70 pathway in macrophage function and plaque stability(Winkels, Meiler, & Lievens et al., 2017; Winkels, Meiler, & Smeets et al., 2017).

However, the results of this study are not completely consistent with the results of previous observational studies, which may be attributed to the following reasons: First, most of the previous studies came from observational studies and cohort studies, and the results might be influenced by confounding factors and reverse causation. Second, the previous researches have the problem of small research scale and sample size.

The research highlights several strengths. First and foremost, the application of Mendelian Randomization (MR) effectively curtails the biases linked to confounders and reverse causation that are typically present in observational research. In addition, this study draws upon the most extensive publicly accessible GWAS datasets currently available for both exposure and outcome variables, ensuring that the F-statistics are sufficiently large to diminish weak instrument bias. The use of GWAS data with considerable sample sizes not only bolsters statistical power but also reduces the influence of weak instrumental variables. Finally, the reliability of our findings is further solidified by an exhaustive suite of sensitivity analyses that corroborate the robustness of our results.

Previous Mendelian randomization studies have positioned asthma as a primary risk factor for atrial fibrillation(Wang et al., 2023), while both asthma and atopic dermatitis have been implicated as causal factors for heart failure(Guo et al., 2022). Diverging from these earlier findings, our investigation significantly broadens the scope by incorporating allergic rhinitis, a widespread allergic condition. Our data reveal a correlation with slightly lower risks of CVDs and CAD among individuals presenting with allergic rhinitis. Our nuanced analysis further stratifies

asthma by the age of onset, revealing a novel association: a reduced risk of CVDs and CAD in cases of childhood-onset asthma. Additionally, our approach capitalizes on the robustness offered by the large sample sizes and the extensive catalog of SNPs from contemporary GWAS datasets, which likely increases the precision of our genetic instruments.

This study also has some shortcomings. Firstly, the reliance on European ancestry for pooled data restricts the generalizability of findings to non-European populations. Furthermore, although the IVW random effects model was applied to SNPs exhibiting heterogeneity, heterogeneity exhibited by the Cochrane's Q test may have reduced the potency of our study. Lastly, a small sample overlap between exposure and outcomes could potentially diminish the quality of the data. Despite this, the extensive UK Biobank dataset with over 300,000 participants ensures that methods like IVW used in our study remain robust than one-sample MR methods, even in the presence of confounding factors(Burgess et al., 2016). The whole-genome arrays, focusing solely on common alleles, efficiently capture the genetic variations associated with diseases.

Conclusion

In conclusion, our study has yielded preliminary evidence for a modestly reduced risk of CVDs associated with certain allergic conditions. Given the substantial morbidity and mortality attributed to CVDs globally, the potential public health implications of an inverse relationship between allergic diseases and CVDs risk warrant serious consideration. Our data suggest that immune system dynamics, altered by the presence of allergic diseases, may confer some degree of protective effect against the development of CVDs. This novel insight could inform future cardiovascular risk stratification and prevention strategies.

Although our study suggests a potential protective effect of allergic conditions against cardiovascular disease, these findings must be approached with caution due to inherent limitations of Mendelian Randomization, including the possibility of residual confounding and heterogeneity. Future research should employ a broader set of instrumental variables and delve into the biological mechanisms to substantiate the observed association. Comprehensive multidisciplinary studies are crucial to confirm these preliminary insights and their implications for CVDs prevention.

Ethics statement

Ethical review and approval was not required for this study in accordance with the local legislation and institutional requirements.

Conflict of interest

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

Supplementary Figures

Figure Sl: Leave-one-out inverse-variance weighted mendelian randomization analyses of allergic rhinitis on different kinds of cardiovascular diseases:(A) CVDs; (B) CAD; (C) IS; (D) CHF

Figure S2: Funnel plot on allergic rhinitis and different kinds of cardiovascular diseases:(A) CVDs; (B) CAD; (C) IS; (D) CHF

Figure S3: Forest plots for association of allergic rhinitis with different kinds of cardiovascular diseases:(A) CVDs; (B) CAD; (C) IS; (D) CHF

Figure S4: Scatter plot of the causal effect of for association of allergic rhinitis with different kinds of cardiovascular diseases:(A) CVDs; (B) CAD; (C) IS; (D) CHF

Figure S5: Leave-one-out inverse-variance weighted mendelian randomization analyses of childhood-onset asthma on different kinds of cardiovascular diseases:(A) CVDs; (B) CAD; (C) IS; (D)CHF

Figure S6: Funnel plot on childhood-onset asthma and different kinds of cardiovascular diseases:(A) CVDs; (B) CAD; (C) IS; (D) CHF

Figure S7: Forest plots for association of childhood-onset asthma with different kinds of cardiovascular diseases:(A) CVDs; (B) CAD; (C) IS; (D) CHF

Figure S8: Scatterl plot on childhood-onset asthma and different kinds of cardiovascular diseases:(A) CVDs; (B) CAD; (C) IS; (D) CHF

Figure S9: Leave-one-out inverse-variance weighted mendelian randomization analyses of adult onset asthma on different kinds of cardiovascular diseases:(A) CVDs; (B) CAD; (C) IS; (D) CHF

Figure S10: Funnel plot on adult onset asthma and different kinds of cardiovascular diseases:(A) CVDs; (B) CAD; (C) IS; (D) CHF

Figure S11: Forest plots for association of adult-onset asthma with different kinds of cardiovascular diseases:(A) CVDs; (B) CAD; (C) IS; (D) CHF

Figure S12: Scatterl plot on childhood-onset asthma with different kinds of cardiovascular diseases:(A) CVDs; (B) CAD; (C) IS; (D) CHF

Figure S13: Leave-one-out inverse-variance weighted mendelian randomization analyses of dermatitis and eczema on different kinds of cardiovascular diseases:(A) CVDs; (B) CAD; (C) IS; (D) CHF

Figure S14: Funnel plot on dermatitis and eczema with different kinds of cardiovascular diseases:(A) CVDs; (B) CAD; (C) IS; (D) CHF

Figure S15: Forest plots for association of dermatitis and eczema asthma with different kinds of cardiovascular diseases:(A) CVDs; (B) CAD; (C) IS; (D) CHF

Figure S16: Scatter plots on association of dermatitis and eczema asthma with different kinds of cardiovascular diseases:(A) CVDs; (B) CAD; (C) IS; (D) CHF

Supplementary Table

Table S1: The single nucleotide polymorphism selected for allergic rhinitis to perform Mendelian randomization analysis.

Table S2: The single nucleotide polymorphism selected for childhood onset asthma to perform Mendelian randomization analysis.

Table S3: The single nucleotide polymorphism selected for adult onset asthma to perform Mendelian randomization analysis.

Table S4: The single nucleotide polymorphism selected for dermatitis and eczema to perform Mendelian randomization analysis.

Table S5: Pleiotropy analysis of mendelian randomization analysis.

Table S6: Heterogeneity analysis of mendelian randomization analysis.

Table S7: The SNPs associated with confounders.

References

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