Original Article

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Mendelian randomization evidence for lung function mediates the association between childhood allergies (age <16 years) and essential hypertension

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Abstract

Objective: This study aimed to investigate the influence of lung function on the relationship between allergies and hypertension, thereby elucidating significant potential mechanisms from a genetic standpoint. We investigated the causal relationship between childhood allergies (age <16 years) and essential hypertension and identified and quantified the role of lung function (forced vital capacity [FVC] and forced expiratory volume in the first second/forced vital capacity [FEV1/FVC]) as potential mediators.

Methods: Using data from a genome-wide association study and the Fenn Genn consortium, a two-sample Mendelian randomization (MR) analysis of genetically predicted childhood allergies (7128 cases and 211,703 controls) and essential hypertension (116,714 cases and 1,032,659 controls) was performed. Furthermore, we used two-step MR to quantify the effect of lung function-mediated childhood allergies on essential hypertension. The FVC and FEV1/FV sample size was 371,898.

Results: Childhood allergies were associated with increased odds of developing essential hypertension (odds ratio [*OR*] = 1.0900, 95% confidence interval [*CI*] = 1.0034–1.1842, *P* = 0.0414). No strong evidence that genetically predicted essential hypertension affected childhood allergy risk was identified (*OR* = 1.0631, 95% *CI* = 0.9829–1.1498, *P* = 0.1264). The proportion of genetically predicted childhood allergies mediated only by FVC was 5.67% (95% *CI*, 5.13%–5.73%).

Conclusion: A causal relationship between childhood allergies and essential hypertension was identified, with a proportion of the effect mediated by FVC. Therefore, implementing early interventions in children with allergies is imperative to mitigate the long-term risk of developing hypertension. Further research is required to identify additional risk factors as potential mediators.

Keywords: Mendelian randomization, Childhood allergy (age <16 years), Essential hypertension, Forced vital capacity, Forced expiratory volume in the first second/forced vital capacity

Introduction

High blood pressure can develop during childhood, and it significantly contributes to organ damage in children and cardiovascular disease (CVD) in adults[1]. Hypertension affects four of every 100 young individuals[2]. Several studies have demonstrated a strong connection between allergy or immune-related conditions and the likelihood of developing CVD[3–5]. Meanwhile, a growing occurrence of CVD has been reported among adolescents[6], with some studies indicating a potential link to childhood asthma[7], dermatitis[8], food allergy[9], and other autoimmune diseases[10]. Nevertheless, Mendelian randomization (MR) analyses on the correlation between childhood allergy exposure and CVD outcomes are scarce. Furthermore, the association between childhood allergies and essential hypertension remains unclear.

A recent MR analysis has suggested a genetic link between immune diseases and essential hypertension[11]. Although immune diseases are linked to essential hypertension, no genetic correlation has been identified between the specific subtypes of asthma and essential hypertension. Another bidirectional MR study has suggested a genetic link between exposure factors, such as forced vital capacity (FVC) and forced expiratory volume in the first second (FEV1) and CVD outcomes[12]. Furthermore, the developmental course of lung function may be associated with cardiovascular risk, and other allergies, such as early developmental food allergy[13], are linked to reduced lung function. Therefore, lung function is closely linked to asthma, and MR studies have suggested that lung function may serve as an intermediate factor between immune diseases and essential hypertension.

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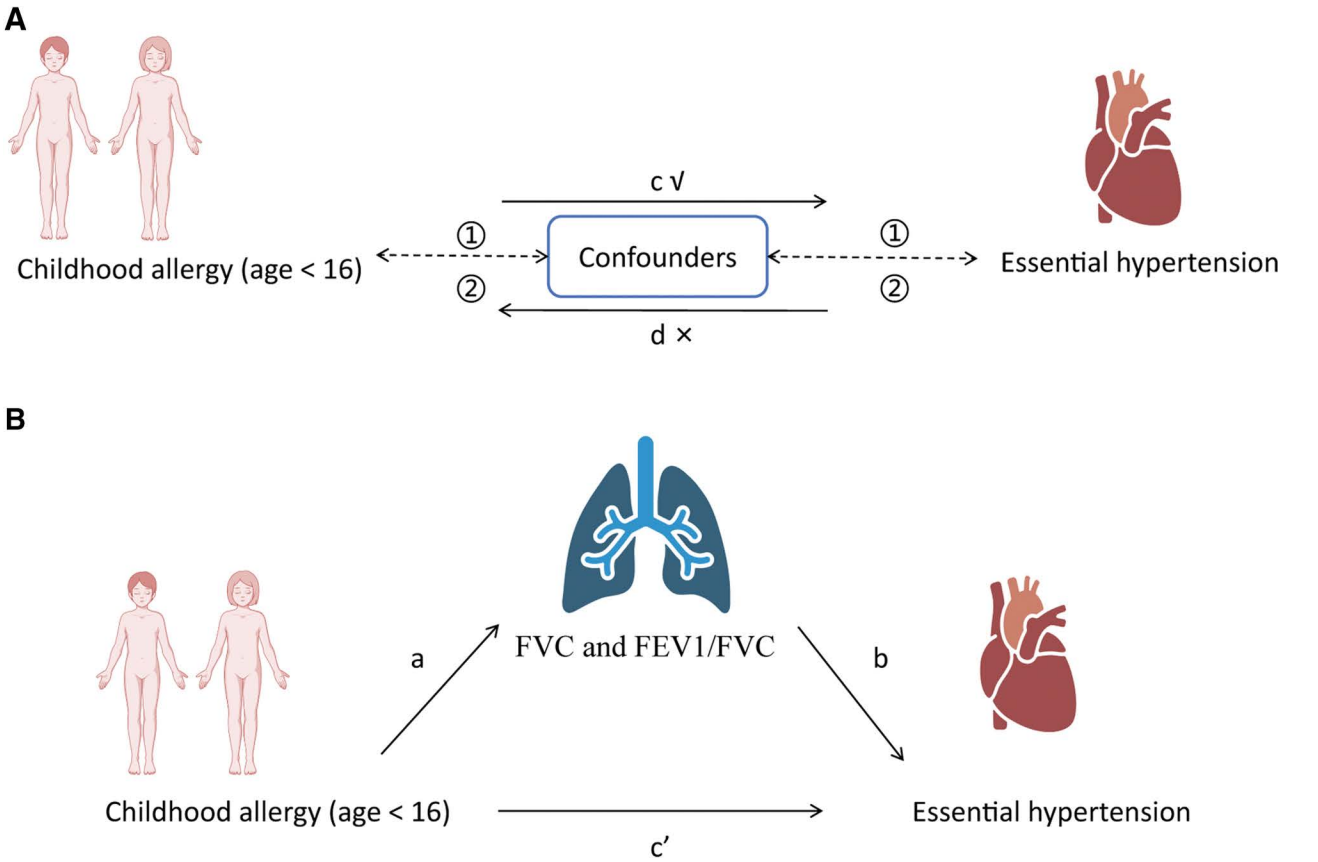

Fig. 1. Relationships investigated in this research. (A) The overall impact between childhood allergies (age <16 years) and essential hypertension. Herein, *c* represents the total effect utilizing genetically predicted childhood allergies (age <16 years) as the exposure and essential hypertension as the outcome, whereas *d* signifies the total effect using genetically predicted essential hypertension as the exposure and childhood allergies (age <16 years) as the outcome. (B) Breaks down the total effect into (i) an indirect effect *via* a two-step process (where *a* is the total effect of childhood allergies [age <16 years] on lung function [FVC and FEV1/FVC], and *b* is the impact of lung function [FVC and FEV1/FVC] on essential hypertension) using the product method ($a \times b$) and (ii) a direct effect ($c' = c - a \times b$). The proportion mediated is determined by dividing the indirect effect by the total effect. Two criteria are essential for these variants. First, it should be independent of confounding factors influencing the exposure–outcome relationship. Second, they should affect the outcome solely through the exposure pathway, excluding other biological pathways. Solid paths indicate significance, whereas dashed paths are not applicable in this study. FEV: forced expiratory volume; FVC: forced vital capacity.

Briefly, the potential mechanisms linking childhood allergies (age <16 years) and essential hypertension have not been explored. Lung function could potentially serve as a mediator between childhood allergies (age <16 years) and essential hypertension.

MR is used to establish causal relationships using genetic variation as an instrumental variable (IV) to assess the impact of exposure factors on outcomes derived from observational data[14]. MR can mitigate the effects of measurement errors or confounding variables, while preventing reverse causality through Mendelian inheritance principles, making it a crucial tool in CVD research[15]. Therefore, this study aimed to (1) identify a causal link between childhood allergies (age <16 years) and essential hypertension and (2) assess the extent to which lung function mediates the relationship between childhood allergies (age <16 years) and essential hypertension.

Materials and methods

Study design

The data used in our analysis were sourced from publicly available datasets and were approved by the institutional review boards of the respective studies. No additional approvals were obtained for this study. All generated outcomes are detailed in the main article and accompanying supplements.

This research explored the bidirectional causal connection between childhood allergies (age <16 years) and essential hypertension through two-sample MR analyses. In this investigation, single nucleotide polymorphisms (SNPs) were designated as IVs[16].

This illustrates the overall relationship between childhood allergies (age <16 years) and essential hypertension (Fig. 1). Herein, *c* represents the total effect of genetically predicted childhood allergies as the exposure and essential hypertension as the outcome, whereas *d* denotes the total effect of genetically predicted essential hypertension as the exposure and childhood allergies as the outcome. The total effect is decomposed into (1) an indirect effect via a two-step process, where *a* is the total effect of childhood allergies on lung function (FVC and FEV1/FVC), and *b* is the effect of lung function on essential hypertension, calculated using the product method ($a \times b$) and (2) a direct effect ($c' = c - a \times b$). The mediated proportion was calculated by dividing the indirect effect by the total effect. Two criteria are essential for these pathways: ① independence from confounding factors affecting the exposure–outcome relationship and ② that they influence the outcome exclusively through the exposure pathway, excluding other biological pathways. Solid lines indicate significant relationships, and dashed lines denote non-applicable pathways.

Genome-wide association study (GWAS) summary data sources

The data used in our study were publicly available, and the participants in the GWAS were of European ancestry. The genetic associations between childhood allergies (age <16 years) and essential hypertension were derived from the FennGenn consortium, which included childhood allergies (age <16 years) (7128 cases and 211,703 controls) and essential hypertension (116,714 cases and 1,032,659 controls). Only 0.18% of the children with allergies were affected by essential hypertension. Lung function data comprising FVC and FEV1/FVC metrics[17] were obtained from gwasmrcieu.ac.uk, with detailed information available for individual access at https://gwas.mrcieu.ac.uk/ and https://www.finngen.fi/en. Lung function GWAS data were obtained from different consortia or organizations; thus, no sample overlap was observed. Additional details are provided in Table S1, http://links.lww.com/RDM/A81.

IV selection and data harmonization

We incorporated SNPs that reached genome-wide significance ($P < 5 \times 10^{-8}$). In cases where no significant genome-wide SNPs were identified as IVs, SNPs with a significance level below the genome-wide significance level ($P < 5 \times 10^{-6}$) were considered potential IVs. Subsequently, these SNPs were grouped based on linkage disequilibrium (LD) (window size = 10,000 kb, $r^2 < 0.001$). The estimated LD levels were derived from the 1000 Genomes Project using European samples[18]. When a specific exposed SNP was absent from the outcome dataset, proxy SNPs were used through LD tagging. Palindromic and ambiguous SNPs were excluded from the IVs for MR analysis[19]. The *F* statistic was determined based on the variance explained by SNPs for each exposure, given by $\left(\frac{\left(\frac{N-K-1}{K}\right)}{\frac{R2}{1-R2}}\right)$, where *K* represents the number of genetic variants and *N* indicates the sample size. We eliminated ineffective IVs with *F* statistics below 10[20].

Statistical analysis

The MR analysis was conducted using the R software (version 4.4.1, http://www.r-project.org) and the "two-sample MR" package (version 0.6.6)[21]. The MR-Pleiotropy RESidual Sum and Outlier (MR-PRESSO) and robust adjusted profile score (MR.RAPS) analyses were conducted using the R packages "MRPRESSO" and "MR.raps," respectively. Statistical power calculations for the MR were performed using mRnd (https://cnsgenomics.shinyapps.io/mRnd/). Subsequently, all SNPs linked to childhood allergies (age <16 years) and essential hypertension were individually scrutinized in the Phenoscanner database (http://www.phenoscanner.medschl.cam.ac.uk/) to assess their associations with potential confounding variables or direct impacts on outcomes (Table S2, http://links.lww.com/RDM/A81).

Primary analysis

Fig. 1 presents a schematic overview of the analysis. Two-sample bidirectional MR was performed to assess the reciprocal causation between childhood allergies (age <16 years) and essential hypertension (Fig. 1A), referred to as the total effect.

Inverse variance weighting (IVW) uses meta-analysis to combine the Wald ratios of causal effects for each SNP[22]. Subsequently, MR-Egger[23] and weighted median[24] approaches were used in conjunction with IVW to enhance the robustness of the analyses. Various methods tailored to specific validity assumptions have been employed to derive the MR estimates. The IVW method assumes that all SNPs serve as valid IVs, thereby ensuring accurate outcomes. MR-Egger evaluates directional pleiotropy within IVs, with the intercept serving as an indicator of the average pleiotropic effects of genetic variation. Conversely, the weighted median method offers increased precision (lower standard deviation) compared with the MR-Egger analysis. In scenarios involving horizontal pleiotropy, the weighted median approach delivers consistent estimates, even if half of the genetic variants are deemed invalid IVs[25].

Mediation analysis

We conducted a mediation analysis using a two-step MR design to investigate whether lung function acts as a mediator in the causal pathway from childhood allergies (age <16 years) to the development of essential hypertension (Fig. 1B). The overall effect can be classified as an indirect (mediated by lung function) or a direct effect (not mediated by lung function)[26]. The total influence of childhood allergies (age <16 years) on essential hypertension was divided into two components as follows: (1) the direct impact of childhood allergies on essential hypertension (c' in Fig. 1B) and (2) the indirect effects mediated by childhood allergies through lung function ($a \times b$ in Fig. 1B). The proportion of mediation was determined by dividing the indirect effect by the total effect. In addition, we calculated 95% confidence intervals (*CI*) using the delta method[27].

Sensitivity analysis

The causal direction of each selected SNP with respect to exposure and outcome was assessed using MR Steiger filtering[28]. This approach computes the variance explained in exposure and outcomes by instrumental SNPs and evaluates whether the variance in outcomes is lower than that in exposure. "TRUE" and "FALSE" MR Steiger outcomes suggest causality in the anticipated and opposite directions, respectively. SNPs yielding "FALSE" results were omitted, indicating a substantial impact on outcomes rather than exposure.

Variability among the SNPs was evaluated using Cochran's *Q* statistics and funnel plots[29,30]. Horizontal pleiotropy was detected using the MR-Egger intercept[23] and MR-PRESSO methods[31]. If outliers were detected, they were removed, and the MR causal estimates were re-evaluated. If heterogeneity remained high after removal, the stability of the results was assessed using a random-effects model, which is less susceptible to weaker SNP exposure associations. Finally, a leave-one-out analysis was performed to validate the effect of each SNP on the overall causal estimates.

Results

Association of childhood allergies (age <16 years) with essential hypertension

After excluding palindromic and ambiguous SNPs, SNPs lacking proxies, and those with incorrect causal directions identified through MR Steiger filtering, 12 SNPs were retained as IVs for childhood allergies (age <16 years), whereas 188 SNPs were selected for essential hypertension (Tables S3 and S4, http://links.lww.com/RDM/A81). Only SNPs that achieved genome-wide significance ($P < 5 \times 10^{-8}$) were used as IVs. Subsequently,

SNPs missing from the outcome GWAS and those identified as distorted by MR-PRESSO and the "leave-one-out" test were removed, leaving the remaining SNPs as IVs for childhood allergies (age <16 years). The outcomes of the "leave-one-out" test for the final set of SNPs are presented in Fig. S1, http://links.lww.com/RDM/A82.

We used IVW, MR-Egger, and weighted median regression techniques to assess the potential causal link between genetically predicted childhood allergies (age <16 years) and essential hypertension (Figs. 2 and 3). Our analyses across all three MR methods consistently supported a positive association between childhood allergies (age <16 years) and essential hypertension. The IVW odds ratio (*OR*) per standard deviation increase in childhood allergies (age <16 years) was 1.0900 (95% *CI*, 1.0034–1.1842; *P* = 0.0414), the MR-Egger OR was 1.1120 (95% *CI*, 0.7499–1.6490; *P* = 0.6102), and the weighted median *OR* was 1.0067 (95% *CI*, 0.9618–1.0538; *P* = 0.7735). Importantly, our MR analysis did not reveal any evidence of reverse causality, indicating that genetically predicted essential hypertension did not cause childhood allergies (age <16 years), with an *OR* of 1.0631 (95% *CI*, 0.9829–1.1498; *P* = 0.1264) using the IVW method (Fig. 3).

Association of childhood allergies (age <16 years) with lung function

We identified 272 genome-wide significant SNPs in FVC and 346 SNPs in FEV1/FVC as IVs after excluding palindromic and ambiguous SNPs and SNPs with incorrect causal direction identified through MR Steiger filtering (Tables S5 and S6, http://links.lww.com/RDM/A81). Using the IVW, MR-Egger, and weighted median methods, we observed a positive association between genetically predicted childhood allergies (age <16 years) and the risk of lung function impairment. Specifically, for FVC, the IVW method yielded an *OR* of 0.9692 (95% *CI*, 0.9540–0.9845; *P* <0.001), the MR-Egger method produced an *OR* of 0.9684 (95% *CI*, 0.9100–1.0307; *P* = 0.3517), and the weighted median method yielded an *OR* of 0.9666 (95% *CI*, 0.9489–0.9846; *P* <0.001). For FEV1/FVC, the IVW method showed an *OR* of 0.9373 (95% *CI*, 0.9131–0.9620; *P* <0.001), the MR-Egger method displayed an *OR* of 0.9694 (95% *CI*, 0.8778–1.0706; *P* = 0.562), and the weighted median method showed an *OR* of 0.9543 (95% *CI*, 0.9338–0.9752; *P* <0.001) (Fig. 3).

Association of lung function with essential hypertension

As depicted in Fig. 3, genetically predicted lung function exhibited a significant positive correlation with essential hypertension using the IVW method (FVC: *OR* = 0.8556, 95% *CI*, 0.7920–0.9242; *P* <0.001; FEV1/FVC: *OR* = 1.0274, 95% *CI*, 0.9712–1.0868; *P* = 0.3462). Except for the genetic association between FVC and essential hypertension, no significant results were observed for FEV1/FVC using the IVW, MR-Egger, or weighted median methods.

Proportion of the association between childhood allergies (age <16 years) and essential hypertension mediated by FVC

In our analysis, we examined FVC as a mediator in the pathway linking childhood allergies (age <16 years) to essential

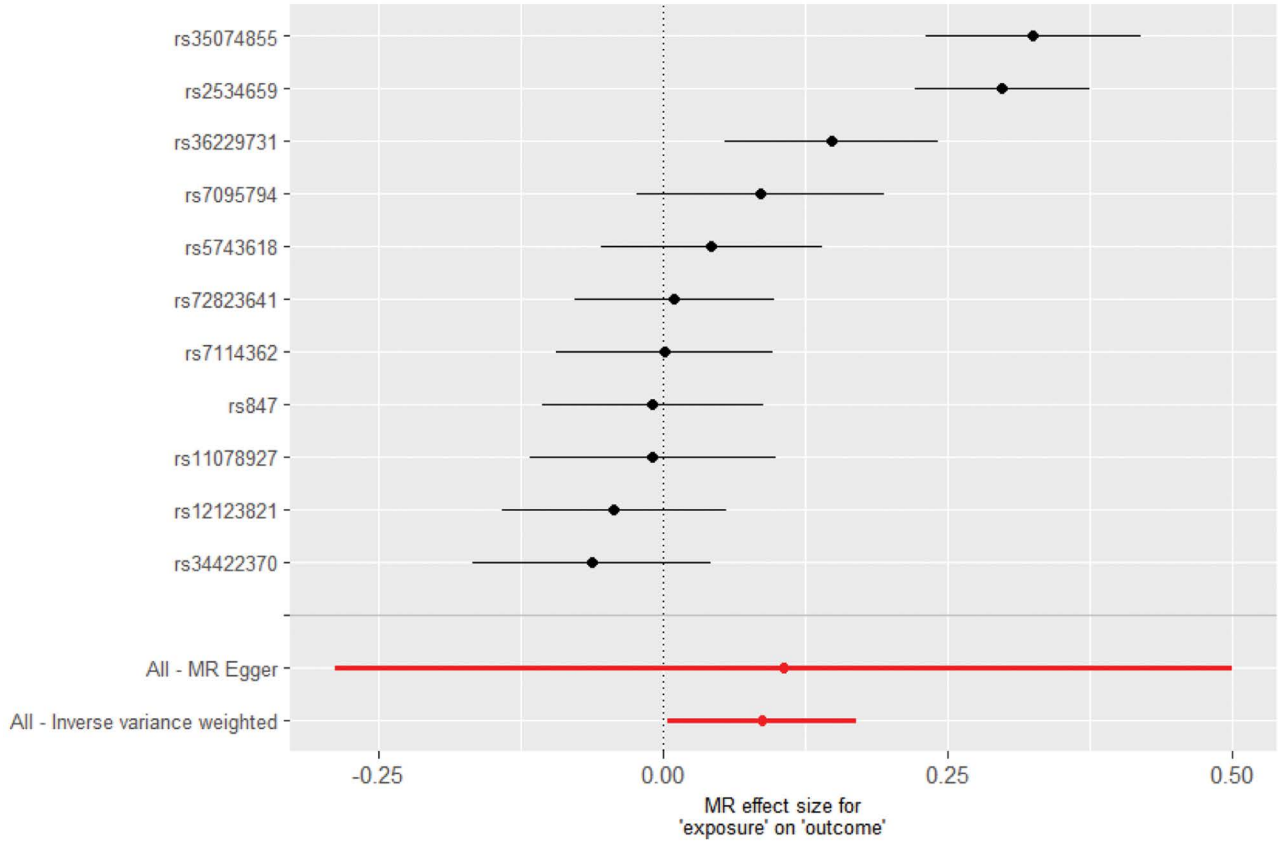

Fig. 2. Forest plot visualizing the causal effect of each single nucleotide polymorphism on total essential hypertension risk. Exposure: childhood allergies (age <16 years). Outcome: essential hypertension. MR: Mendelian randomization.

Exposure	MR.method	NO.of.SNPs	P.value	OR (95% CI)
Childhood allergy (age < 16) on essential hypertension	MR Egger	11	0.6102	1.1120 (0.7499 - 1.6490)
	Weighted median	11	0.7735	1.0067 (0.9618 - 1.0538)
	Inverse variance weighted	11	0.0414	1.0900 (1.0034 - 1.1842)
Childhood allergy (age < 16) on FVC	MR Egger	8	0.3517	0.9684 (0.9100 - 1.0307)
	Weighted median	8	<0.001	0.9666 (0.9489 - 0.9846)
	Inverse variance weighted	8	<0.001	0.9692 (0.9540 - 0.9845)
Childhood allergy (age < 16) on FEV1/FVC	MR Egger	8	0.5620	0.9694 (0.8778 - 1.0706)
	Weighted median	8	<0.001	0.9543 (0.9338 - 0.9752)
	Inverse variance weighted	8	<0.001	0.9373 (0.9131 - 0.9620)
Essential hypertension on childhood allergy (age < 16)	MR Egger	183	0.7297	1.0408 (0.8299 - 1.3052)
	Weighted median	183	0.9711	1.0019 (0.9053 - 1.1087)
	Inverse variance weighted	183	0.1264	1.0631 (0.9829 - 1.1498)
FVC on essential hypertension	MR Egger	268	0.5983	0.9308 (0.7132 - 1.2149)
	Weighted median	268	<0.001	0.8807 (0.8167 - 0.9496)
	Inverse variance weighted	268	<0.001	0.8556 (0.7920 - 0.9242)
FEV1/FVC on essential hypertension	MR Egger	337	0.2666	0.9355 (0.8319 - 1.0520)
	Weighted median	337	0.8162	1.0071 (0.9487 - 1.0692)
	Inverse variance weighted	337	0.3462	1.0274 (0.9712 - 1.0868)

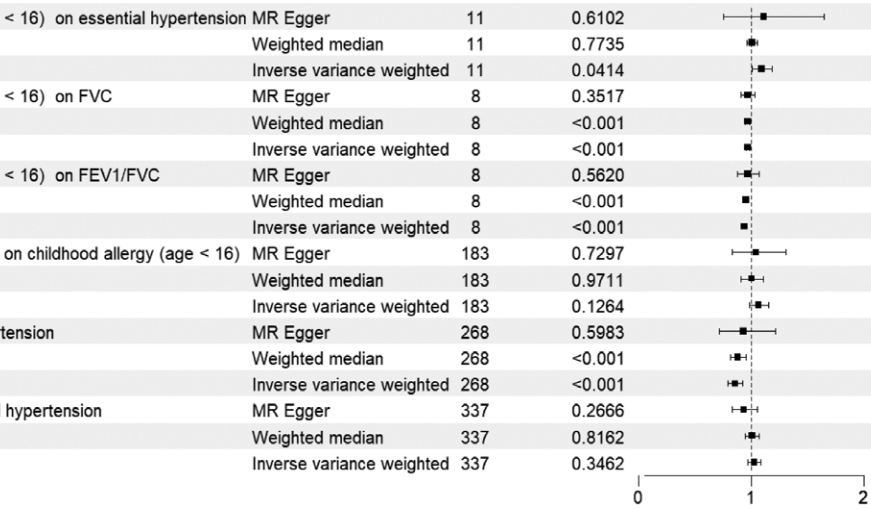

Fig. 3. Forest plot visualizing the causal effects of forced vital capacity with childhood allergies (age <16) and essential hypertension. *CI*: confidence interval; FEV: forced expiratory volume; FVC: forced vital capacity; MR: Mendelian randomization; *OR*: odds ratio; SNP: single nucleotide polymorphism.

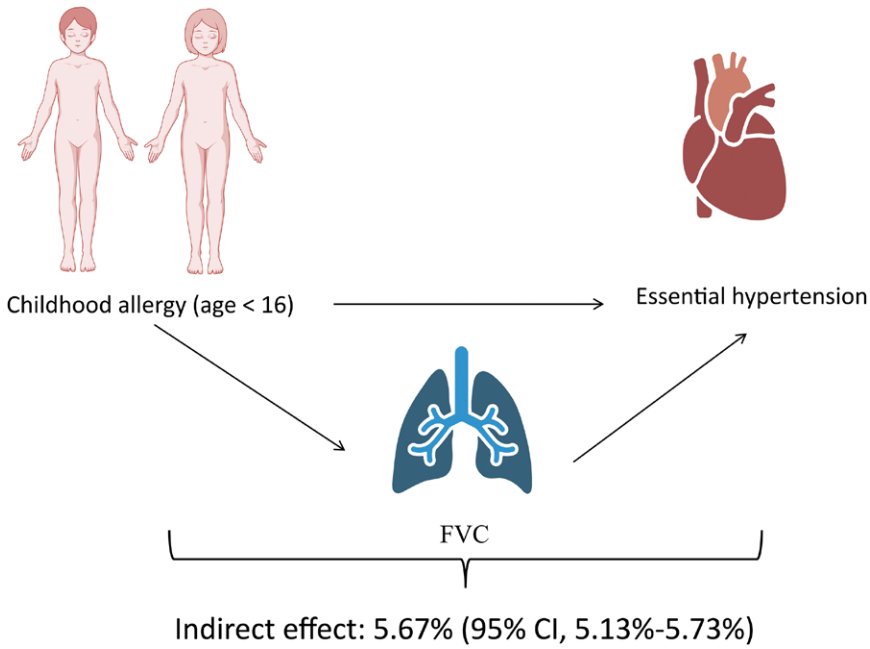

Fig. 4. Schematic diagram of the FVC mediation effect. *CI*: confidence interval; FVC: forced vital capacity.

hypertension. Our findings revealed that childhood allergies (age <16 years) were linked to reduced FVC, which, in turn, was linked to an increased risk of essential hypertension. FVC contributed to 5.67% of the elevated risk of essential hypertension associated with childhood allergies (age <16 years) (indirect effect: 5.67%, 95% *CI*, 5.13%–5.73%) (Fig. 4).

Sensitivity analysis

The MR-PRESSO global test identified potential horizontal pleiotropy (Table S7, http://links.lww.com/RDM/A81). Tables S8–S11, http://links.lww.com/RDM/A81, illustrate the causal effects among childhood allergies, lung function, and essential hypertension. Several sensitivity analyses were conducted to explore and adjust potential pleiotropy in the causal estimates. The impact of each SNP on the overall causal estimates was validated using a leave-one-out analysis (Fig. S1, http://links.lww.com/RDM/A82). In our study, heterogeneity and asymmetry in the causal relationships among these SNPs were observed using Cochran's test and funnel plots (Fig. S2, http://links.lww.com/RDM/A82). The MR-Egger intercept did not indicate any pleiotropy at the directional level of the instrument for childhood allergies (age <16 years) (Fig. S3, http://links.lww.com/RDM/A82). For more detailed information on MR-Egger, Cochran's test, and funnel plots, please refer to Tables S12–S13, http://links.lww.com/RDM/A81. By systematically reanalyzing the MR data after excluding each SNP, consistent results were obtained, indicating that all SNPs played a significant role in establishing causal relationships.

Discussion

Bidirectional MR analysis established a link between childhood allergies (age <16 years) and essential hypertension. However, the reverse study did not demonstrate a robust causal relationship. In addition, only FVC demonstrated a mediating effect on the genetic association. Recent studies have explored the association between immune system irregularities and essential hypertension[32–34]. Nevertheless, existing evidence is primarily based on observational and animal studies, which may be susceptible to the effects of confounding variables. Our findings indicated that genetically predicted childhood allergies (age <16 years) were associated with a higher likelihood of essential hypertension (approximately a 10% increased risk of essential hypertension for each one standard deviation increase in childhood allergies [age <16 years]), with 5.67% of this effect being mediated by FVC.

By analyzing the distribution of our data sources, we observed that childhood allergies predominantly affected the respiratory tract and skin. Among these, bronchial inflammation was the most common, primarily manifesting as asthma (35.69%) and rhinitis (16.16%). Therefore, respiratory function impairment due to childhood allergies should be considered a mediating factor in the development of essential hypertension. Although respiratory dysfunction can lead to pulmonary arterial hypertension, the incidence in our cohort was relatively low, with only 34 cases, compared with 1027 cases (3.31%) of essential hypertension. Thus, hypertension in children may be more likely to be attributable to immune system disorders that cause vascular damage and abnormal systolic and diastolic functions, resulting in elevated blood pressure. Moreover, asthma and rhinitis can trigger other allergic responses such as dermatitis and food allergies. Our findings indicate that respiratory inflammation in children mediates the impairment of respiratory function associated with essential hypertension. Respiratory function contributed to essential hypertension by approximately 5.67%, and a significant reduction in FVC was observed. Thus, chronic respiratory allergies may pose a risk for essential hypertension.

Epidemiological studies have suggested that the overall prevalence of hypertension in children is between 2% and 5%, with essential hypertension being the predominant type, particularly in adolescence[35]. However, the genetic correlation between childhood allergies and the decline in lung function remains unclear. Our study identified a mediating effect of childhood allergies and essential hypertension on the decline in lung function. Concurrently, younger individuals exhibit a cardiovascular risk[36]. Specifically, childhood allergies are significantly correlated with lung function. However, our study identified only FVC as a mediating factor. Furthermore, a previous epidemiological study has indicated that FVC is a stronger predictor of overall survival than FEV1[37], with limited clinical evidence supporting a causal relationship between FEV1 and the risk of CVD-related obstruction[38]. Compared with FEV1/FVC, FVC decreased from the peak average age of 29.4–35 years, suggesting an increased incidence of hypertension between the ages of 35 and 45 years according to another prospective cohort study[39,40]. A large-scale cardiovascular cohort study has revealed that both FEV1 and FVC strongly correlated with cardiovascular outcomes and served as significant protective factors, whereas the FEV1/FVC ratio showed no significant association[41,42]. Clinical studies examining the trajectory of lung function in children have also failed to identify a correlation between FEV1/FVC and hypertension characteristics[43]. Furthermore, another genetic correlation study has indicated that diastolic and systolic blood pressures were negatively correlated with FEV1 and FVC and positively correlated with the FEV1/FVC ratio. However, the MR analysis did not reveal any significant correlation between blood pressure traits and FEV1/FVC[44]. Both cardiovascular genetic studies and clinical investigations provide insufficient evidence for an association between the FEV1/FVC ratio and CVD risk. In particular, evidence supporting a genetic link between essential hypertension and FEV1/FVC is lacking. Currently, public databases provide data only on FVC and FEV1/FVC but not on FEV1. Consequently, evidence from MR and large clinical cohort studies suggesting an association between FEV1/FVC decline and increased essential hypertension risk remains limited, which is consistent with the findings of our research. However, the precise mechanisms linking lung function and essential hypertension remain unclear. However, clinical cohort and genetic research studies have suggested that childhood lung function trajectories may predict not only the development of future lung diseases but also the risk of CVD in adulthood.

To the best of our knowledge, this is the first study to explore the causal link between childhood allergies and vulnerability to essential hypertension instability using the MR method, while highlighting FVC as a mediator. Our results are consistent with findings reported in recent studies. Kony *et al.*[45] have reported that men with rhinitis have a higher likelihood of developing hypertension than those without rhinitis (OR = 2.6, 95% CI = 1.14–5.91). Our findings reinforce the link between rhinitis, a type of allergic disease, and essential hypertension as well as the mediating role of impaired respiratory function in cardiovascular risk factors such as hypertension. However, the MONICA/KORA-study[46] has indicated no significant relationships between rhinitis and adjusted blood pressure averages or hypertension in women. Although sex disparities have been noted in observational studies, the connection between childhood allergies (age <16 years) and hypertension can still be deduced, considering that the proportion of women with allergy who experienced childhood allergies (age <16 years) was almost twice than that of men. Moreover, the Bogalusa Heart Study[47] has indicated a robust association between history of childhood asthma and elevated blood pressure in young individuals. However, these studies had an observational design. The response rates of the two groups were low. Moreover, their findings were more susceptible to the influence of reverse causality or other potential confounding effects than the MR analysis.

Respiratory infections are prevalent among infants and young children[48] and often cause frequent episodes of asthma[49] and respiratory distress[50]. They are the leading causes of hospitalization in children aged <5 years[51]. In addition, respiratory infections are common respiratory ailments in children and can trigger uncontrolled systemic inflammatory responses that can lead to multi-organ failure and damage[52]. Reduced lung function is also associated with recurrent wheezing and severe asthma[53]. Although most studies on allergy mechanisms in infancy were conducted in mice, advancements in technology have enabled detailed analysis of immune cells at the molecular level, providing insights into the typical trajectory of immune development in childhood[54]. Understanding this trajectory is crucial for recognizing deviations that may affect respiratory health. Evidence suggests that lung function may not fully recover after the first 5 years of life, and sustained low lung

function is associated with an increased risk of early mortality[54]. Our study indicates that childhood immune abnormalities leading to lung dysfunction can increase the risk of CVD. Our results are the first to show that a decline in FVC induced by childhood allergies acts as a mediating factor for an increased risk of essential hypertension.

Pulmonary arterial hypertension is a form of high blood pressure characterized by a persistent elevation in pulmonary artery pressure due to various causes[55]. Pulmonary arterial hypertension and systemic hypertension have a fundamental distinction. Although both conditions result from an increased blood vessel pressure, they occur in different parts of the circulatory system and lead to significant differences in outcomes. Systemic hypertension stems from elevated arterial pressure in systemic circulation, which is typically measured using a blood pressure cuff. By contrast, pulmonary arterial hypertension involves heightened pressure in the arteries of pulmonary circulation, necessitating methods such as cardiac ultrasound or right heart catheterization for accurate assessment. The decline in lung function is closely linked to pulmonary hypertension induced by oxygen deprivation[56]. Various immune cells, such as T lymphocytes[57], B lymphocytes[58], macrophages[59], mast cells[60], dendritic cells[61], and neutrophils[62] contribute to hypertension's pathogenesis. Some immune cells not only engage in immune surveillance but also influence vascular remodeling[63]. Further research is required to elucidate the precise mechanisms underlying this process. This study also proposes a genetic connection between childhood allergies and essential hypertension, with FVC serving as a mediator between genetic connections. This implies that essential and pulmonary arterial hypertension share common immune factors that drive the development of hypertension.

Inflammatory response plays a crucial role in the initiation and progression of hypertension. Immune cells migrate, infiltrate, and cluster in response to various stimuli, such as injury and inflammation, releasing various inflammatory mediators and cytokines[64]. They form intricate signaling pathways with diverse effector cells, such as endothelial cells[65], smooth muscle cells[66], and fibroblasts[67], ultimately leading to vasoconstriction and remodeling of the vasculature, resulting in elevated blood pressure. Although animal experiments have confirmed the impact of certain immune cells on the development of hypertension[68–70], inflammatory responses have notable variations across different types of hypertension[71–73]. Moreover, the specific molecular mechanisms underlying their involvement in the pathophysiology of hypertension remain unclear. Therefore, investigating the inflammatory response in various types of hypertension may offer tailored and precise therapeutic approaches for managing blood pressure. In addition, our study suggests that in clinical practice, monitoring the decline in FVC due to childhood allergies could potentially increase the risk of CVD in adolescents or adults, particularly in cases of essential hypertension.

This study had some limitations. First, our analysis was conducted on a European population, which limits its generalizability. Second, despite efforts to identify and remove outlier variants, we cannot rule out the possibility that horizontal pleiotropy influenced the results. Third, we relied on summary-level statistics rather than on individual-level data, preventing further exploration of causal relationships within subgroups such as sexes. Finally, the genetic prediction of childhood allergies (age <16 years) mediated by FVC was only 5.67%, suggesting a relatively low mediation effect. Further research is required to assess the effects of other potential mediators.

Conclusion

Childhood allergies (age <16 years) were associated with essential hypertension, with a portion of the effect attributable to FVC mediation. However, the effect of childhood allergies (age <16 years) on essential hypertension remains unclear. Further investigations of additional risk factors as potential mediators are warranted. In clinical practice, heightened vigilance is advised to manage essential hypertension in pediatric patients with allergies (aged <16 years).

Supplemental materials

Supplementary information is linked to the online version of the paper on the *Reproductive and Developmental Medicine* website.

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Author contributions

All authors were involved in the design of this work. Y.H.L, J.S.S., and B.K.Z. obtained and analyzed the data. F.G., C.F., and L.Y.H. drafted the manuscript. Y.H.L., J.S.S., Y.Z.H., L.G., and F.G. critically revised the manuscript. L.G. and H.F.H. contributed to the discussion and edited the manuscript. H.F.H. is the guarantor of this work and, as such, had full access to all data in the study and takes responsibility for the integrity and accuracy of data analysis. All authors have reviewed and approved this manuscript in its final form. All authors contributed to the article and approved the submitted version.

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Conflicts of interest

All authors declare no conflicts of interest. He-Feng Huang is an Editorial Board member of Reproductive and Developmental

Medicine. The article was subject to the journal's standard procedures, with peer review handled independently of this Editorial Board member and their research groups.

Ethics approval

Some images were sourced from Biorender and were used with permission. The authorization file is provided in the Supplementary Material. No specific ethical approval or patient involvement was obtained for this study.

Informed consent statement

We are grateful to the participants in the UK Biobank and other cohorts as well as all the researchers who collected data.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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