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Potential association between allergic disease and risk of Alzheimer's disease: insight from genetic analysis

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Abstract

Backgroud Numerous evidence from observational studies indicated an association between allergic diseases and Alzheimer's Disease (AD). However, the causal association of this relationship remains unclear. To address this, we conducted a two-sample bidirectional Mendelian randomization (MR) analysis to investigate the potential causal impact of allergic diseases on AD.

Methods We used summary statistics for allergic diseases (allergic rhinitis, asthma, and atopic dermatitis) and AD from comprehensive genome-wide association studies (GWASs). Our primary analytical approach was inverse variance weighted (IVW) method, complemented by MR-Egger method and weighted median (WM) method.

Results In the forward MR analysis, our results indicate that age of onset of asthma is a protective factor against AD (OR = 0.824, 95% CI: 0.736–0.922, $P < 0.001$). However, we found no causal link between the age of onset of childhood onset asthma (OR = 1.023, 95% CI: 0.955–1.095, $P = 0.510$), allergic rhinitis (OR = 0.609, 95% CI: 0.188–1.973, $P = 0.408$) or atopic dermatitis (OR = 1.000, 95% CI: 0.995–1.005, $P = 0.902$) and AD risk. The sensitivity analysis confirms the robustness of our findings. In the reverse MR analysis, our results suggest that asthma has a bidirectional association with AD (OR = 0.994, 95% CI: 0.990–0.997, $P < 0.001$).

Conclusion Our study suggests that age of onset of asthma may reduce genetic susceptibility to AD. In addition, AD appear more likely to develop asthma risk. However, no significant genetic correlations were observed between allergic rhinitis or atopic dermatitis with AD risk.

Keywords Mendelian randomization, Causality, Allergic diseases, Asthma, Alzheimer's disease

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Introduction

Alzheimer's disease (AD), the leading prevalent cause of dementia, currently affects approximately 50 million individuals worldwide. Its incidence is rising rapidly, primarily due to the aging global population [1]. AD is a progressive neurodegenerative disorder characterized by cognitive decline, memory loss, and behavioral changes [2]. Although a growing body of research has identified multiple risk factors for AD, including genetics, age-related, and environmental factors, the precise mechanisms underlying the disease remain unclear [3]. This has led to an increasing interest in exploring potential novel risk factors, such as immune-related conditions, including allergic diseases.

The global prevalence of allergic diseases, which are immune-related and frequently co-occur in individuals, is steadily increasing. These conditions include life-threatening anaphylaxis, food allergies, certain types of asthma, rhinitis, conjunctivitis, angioedema, urticaria, eczema, and eosinophilic disorders [4]. Among these, asthma, allergic rhinitis, and atopic dermatitis are the most prevalent. Allergic diseases are characterized by an exaggerated immune response to otherwise harmless substances, leading to the release of pro-inflammatory cytokines and other biomarkers driven by immune activation. These pro-inflammatory agents are not only localized at the site of the allergic reaction but also circulate systemically, indicating widespread inflammation [5]. Despite this, research exploring the link between AD and allergic diseases remains limited, with results that are often inconsistent.

Mendelian randomization (MR) research has received much attention with the increased availability of genome-wide association studies (GWAS) databases. MR employs instrumental variables (IVs) to assess genetic causation between exposure and outcome, effectively emulating randomized controlled trials (RCTs) and offering a reliable statistical method [6–8]. Compared to traditional observational studies, MR analysis can not only avoid the issue of reverse causality but also mitigates residual confounding interference [9].

This study aimed to investigate the potential causal impact of allergic diseases, including allergic rhinitis, asthma, and atopic dermatitis, on AD using a two-sample bidirectional MR analysis. By using summary statistics from large-scale GWAS, we sought to determine whether the age of onset of asthma and other allergic conditions was associated with the risk of developing AD, and whether AD itself had a causal effect on the development of asthma. Our study aims to provide further insight into the relationship between allergic diseases and AD, which could have significant implications for understanding the pathophysiology of both conditions and potentially inform future therapeutic strategies.

Methods

Ethical approval

This MR research used only published or publicly available GWAS data. Each participant received ethical approval and informed consent for the respective study, as detailed in the original publication and consortium.

Study design

We employed the publicly accessible GWAS catalog to perform a two-sample MR study. The analysis was conducted using the two-sample MR software (version 0.5.5) and MR-Pleiotropy Residual Sum and Outlier (MR-PRESSO) (version 1.0) within the R environment (version 4.2.1).

The MR analysis is based on the following three core hypothesis: (1) The IVs selected must be significantly associated with the exposure (allergic diseases). (2) The selected IVs should not be linked to confounding factors affecting the outcome (AD). (3) The IVs influence the outcome solely through the specified exposure and not via alternative pathways [10, 11]. The study design is comprehensively illustrated in Fig. 1.

Selection of instrumental variables

Single nucleotide polymorphisms (SNPs) were extracted from the GWAS database, serving as IVs. To enhance the robustness of these genetic IVs, we applied a rigorous selection criterion: (1) We considered only those SNPs that achieved genome-wide significance ($P < 5 \times 10^{-8}$) and exhibited independence, as ascertained through linkage disequilibrium ($LDr^2 < 0.001$) [12]. (2) SNPs with an F-statistic greater than 10 were selected to mitigate bias arising from weak IVs [13]. (3) We excluded SNPs with a minor allele frequency (MAF) less than 0.01. (4) Ambiguous SNPs, characterized by non-concordant alleles, and palindromic SNPs with indeterminate strands were either corrected or eliminated from the selected instrumental SNPs during the harmonization process [14].

Database sources

Regarding exposure datasets, we sourced GWAS summary data for allergic rhinitis from the UK Biobank, comprising 26,107 cases and 436,826 controls from a European ancestry population. The forward MR analysis for asthma was conducted using summary statistics derived from the UK Biobank, which included 153,763 cases and 1,647,022 controls of European ancestry (https://www.ebi.ac.uk/gwas/publications/36778051) [15]. However, due to incomplete summary statistics, the reverse MR analysis for asthma was performed using data from 56,087 cases and 428,511 controls [16]. Moreover, summary-level GWAS data for atopic dermatitis were extracted from the FinnGen Consortium, which included 212,036 participants of European ancestry (7,024

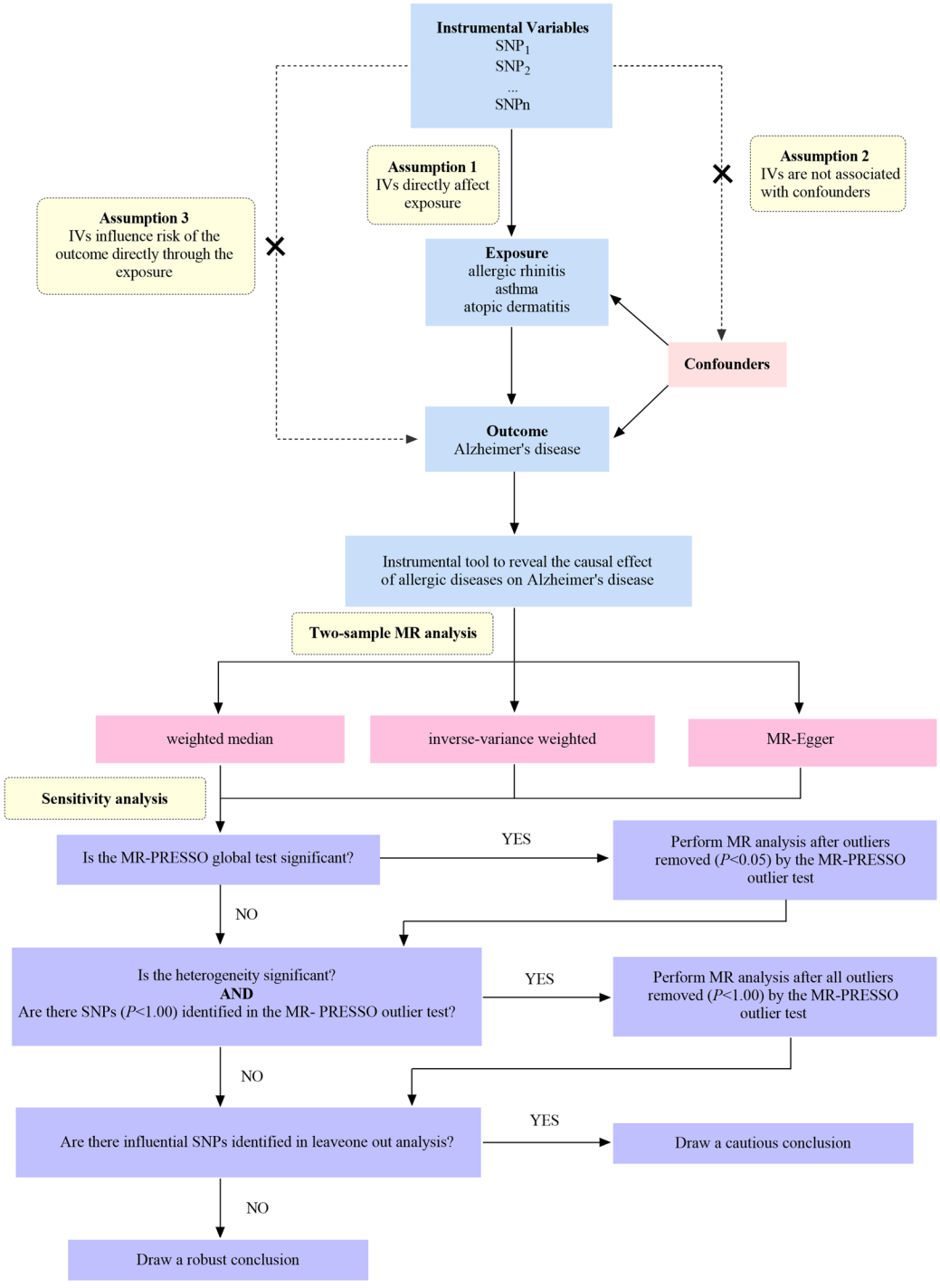

Fig. 1 Overview of Mendelian randomization study design on allergic diseases and Alzheimer's disease

cases and 198,740 controls). For the outcome datasets, genome-wide meta-analysis data on AD were extracted from an independent GWAS study, which included 75,024 cases and 397,844 controls of European ancestry [17]. The diagnostic criteria for AD adhered to the International Classification of Disease codes.

Statistical analysis

MR estimates for the association between allergic diseases and the risk of AD were calculated using three methods: the IVW, the WM, and the MR-Egger method [18]. The IVW method, serving as the primary MR analysis in our study, integrates the Wald ratios of individual SNPs through a meta-analysis approach. This method

presupposes that IVs influence outcomes solely via the specified exposure [19]. The WM and MR-Egger methods were employed to enhance the robustness of IVW estimates [20, 21]. These methods provide more reliable estimates across diverse scenarios despite having wider confidence intervals (CIs). Additionally, to further investigate the reverse causal association, we performed a MR analysis by reversing the roles of the exposure and outcome.

To evaluate potential heterogeneity and horizontal pleiotropy, a sensitivity analysis is crucial. We assessed the heterogeneity of effect sizes for selected genetic IVs using Cochran's Q test [22]. Horizontal pleiotropy was further evaluated using the intercept from MR-Egger regression [20]. The MR-PRESSO analysis was executed to detect outliers and to adjust for heterogeneity and horizontal pleiotropy [23]. Moreover, the leave-one-out analysis was performed to assess the impact of omitting each selected SNP on the overall findings [24].

Process of MR analysis

We initially harmonized the selected SNPs with the effect allele as identified in the GWAS database for AD. Following this, we will conduct MR estimates using the IVW method, WM method, and MR-Egger method. Should the global test P-value less than 0.05, SNPs exhibiting a P-value less than 0.05 in the MR-PRESSO outlier test will be excluded, followed by a re-analysis using the MR methods. In cases where significant heterogeneity remains, all outliers ($P < 1.00$) will be removed [25]. A robust conclusion is anticipated if the leave-one-out analysis does not identify any SNPs that could potentially compromise the stability of the outcomes [14, 23]. The MR process flow chart is illustrated in Fig. 1.

Results

Genetic instruments for allergic diseases

We extracted 60 significant and independent SNPs from the GWAS database to serve as genetic IVs. This selection comprised 34 SNPs for allergic rhinitis, 6 for asthma, and 20 for atopic dermatitis. Each SNP demonstrated an F-statistic greater than 10, confirming the absence of weak IVs in our study.

Forward MR analysis of allergic diseases on Alzheimer's disease

Genome-wide significant variants of allergic disease and their association with AD is listed in Table S2.

Our analysis showed no significant causal relationship between allergic rhinitis and the risk of AD [odds ratio (OR) = 0.609, 95% confidence interval (CI): 0.188–1.973, $P = 0.408$]. This observation was consistent with results using the WM method (OR = 0.551, 95% CI: 0.149–2.036, $P = 0.371$) and MR-Egger method (OR = 0.901, 95% CI: 0.017–48.291, $P = 0.959$), as displayed in Figs. 2A and 3A and detailed in Table 1. Notably, we detected no significant heterogeneity (Cochran's Q_$P = 0.193$) and horizontal pleiotropy (P for intercept = 0.606 and global test $P = 0.266$) in this MR analysis, and the leave-one-out analysis confirmed the stability of these results (Fig. 4A).

As for atopic dermatitis, we did not find a genetic association with AD (OR = 1.000, 95% CI: 0.995–1.005,

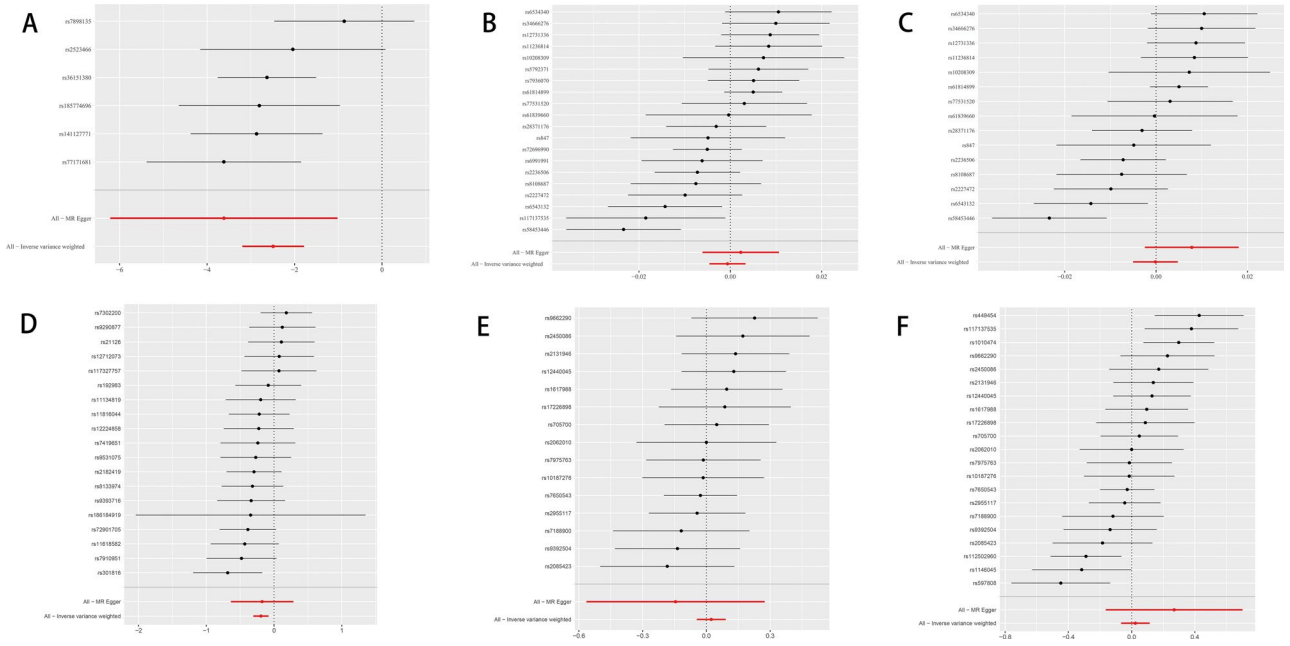

Fig. 2 MR estimates of the association between allergic diseases and Alzheimer's disease, including allergic rhinitis (**A**), atopic dermatitis (**B** [raw] and **C** [adjusted]), age of onset of childhood onset asthma (**D**), age of onset of childhood onset asthma (**E** [raw] and **F** [adjusted]), and Alzheimer's disease

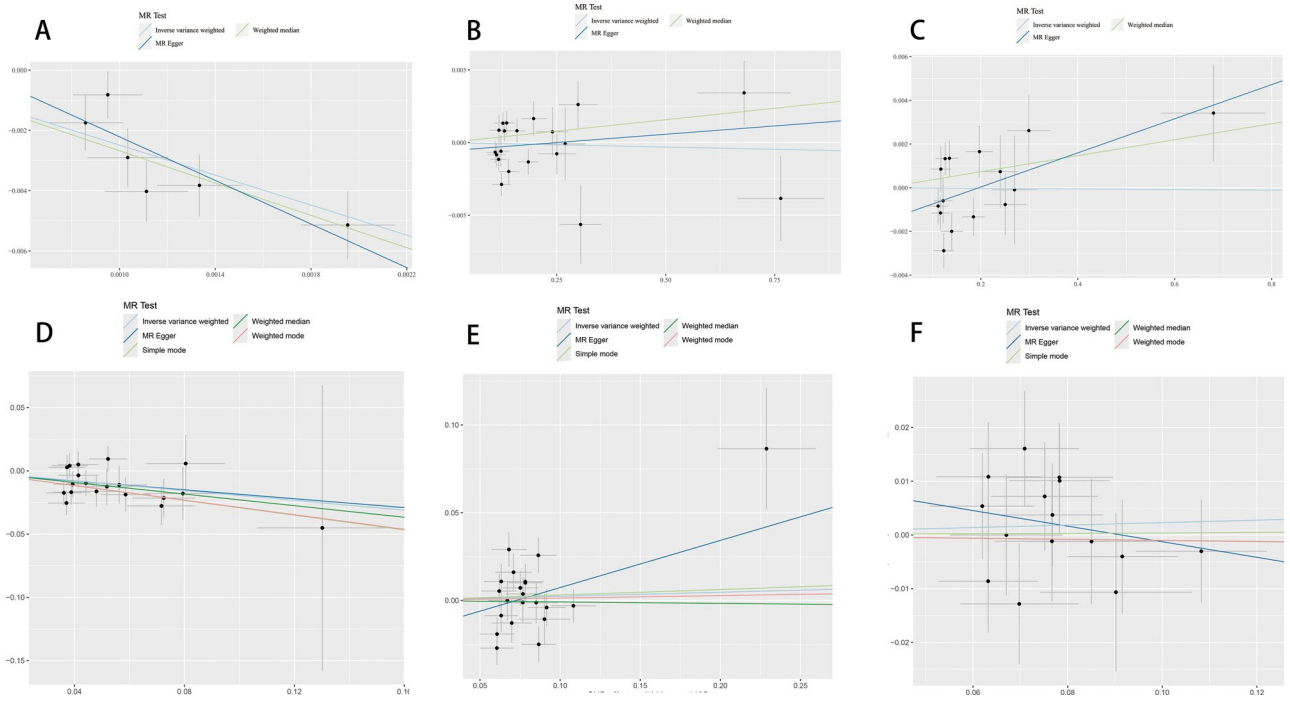

Fig. 3 Scatter plot of the association between allergic diseases and Alzheimer's disease, including allergic rhinitis (**A**), atopic dermatitis (**B** [raw] and **C** [adjusted]), age of onset of childhood onset asthma (**D**), age of onset of childhood onset asthma (E [raw] and F [adjusted]), and Alzheimer's disease

Table 1 The forward Mendelian randomization of allergic disease and AD

Exposure	SNPs	Method	OR	95% CI	*P* value	Q_P value	Intercept (*P* value)
		IVW	0.609	0.188–1.973	0.408	0.193	
allergic rhinitis	30	WM	0.551	0.149–2.036	0.371		
		MR-Egger	0.901	0.017–48.291	0.959	0.178	-0.00020 (0.606)
		IVW	0.999	0.995–1.003	0.759	< 0.001	
atopic dermatitis	20	WM	1.003	0.999–1.007	0.133		
(raw)		MR-Egger	1.002	0.994–1.011	0.599	< 0.001	-0.00057 (0.449)
		IVW	1.000	0.995–1.005	0.902	0.001	
atopic dermatitis	15	WM	1.004	0.999–1.008	0.072		
(adjusted)		MR-Egger	1.007	0.998–1.018	0.191	0.002	-0.00153 (0.114)
		IVW	0.824	0.736–0.922	< 0.001	0.564	
age of onset of asthma	19	WM	0.795	0.681–0.929	0.004		
		MR-Egger	0.839	0.528–1.331	0.466	0.495	-0.00088 (0.937)
		IVW	1.024	0.935–1.121	0.610	< 0.001	
age of onset of childhood onset asthma (raw)	21	WM	0.992	0.903–1.089	0.861		
		MR-Egger	1.308	0.849–2.0164	0.238	< 0.001	-0.019521 (0.270)
		IVW	1.023	0.955–1.095	0.510	0.831	
age of onset of childhood onset asthma (adjusted)	15	WM	0.990	0.903–1.085	0.828		
		MR-Egger	0.864	0.569–1.315	0.509	0.819	0.0132 (0.440)

SNPs, single nucleotide polymorphisms; OR, odds ratio; CI, confidence interval; IVW, inverse-variance weighted; WM, weight median; AD, Alzheimer's disease

$P = 0.902$). Similar results were shown on WM (OR = 1.004, 95% CI: 0.999–1.008, $P = 0.072$) and MR-Egger (OR = 1.007, 95%CI: 0.998–1.018, $P = 0.191$) (Figs. 2B and 3B) (Table 1). Our application of the MR-PRESSO test indicated the presence of outliers in our study (global test $P < 0.01$), leading us to remove rs58453446 ($P < 0.05$) and rerun the heterogeneity test. However, Cochran's Q test still detected significant heterogeneity. Consequently, we removed all SNPs (rs117137535, rs61814899, rs6534340, and rs6543132) with $P < 1.00$ to enhance precision. Even after rigorous adjustment, no causal association was found between allergic dermatitis and AD (OR = 1.000, 95% CI: 0.995–1.005, $P = 0.902$) (Figs. 2C and 3C). The leave-one-out

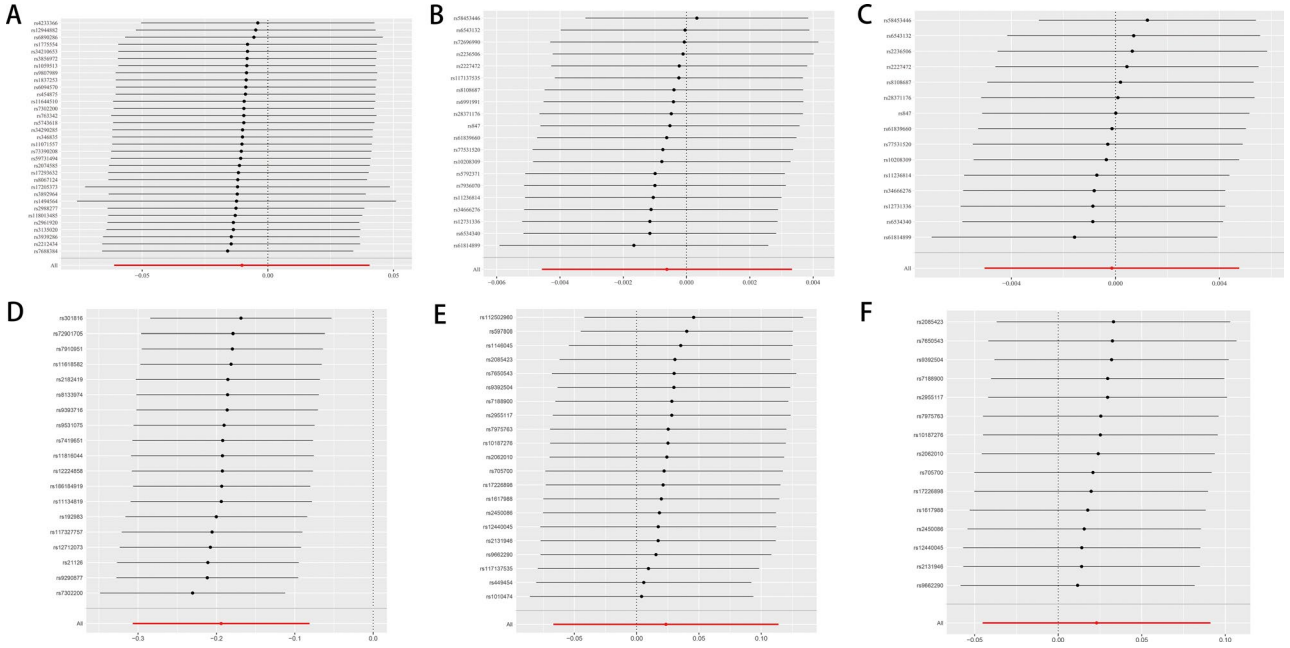

Fig. 4 Leave-one-out plots of allergic diseases and Alzheimer's disease, including allergic rhinitis (**A**), atopic dermatitis (**B** [raw] and **C** [adjusted]), age of onset of childhood onset asthma (**D**), age of onset of childhood onset asthma (E [raw] and F [adjusted]), and Alzheimer's disease

test reaffirmed the stability of the MR estimate upon the removal of individual SNPs (Fig. 4C). Lastly, funnel plots representing allergic diseases on AD are displayed in Fig. S1C.

For asthma, the IVW, WM, and MR-Egger methods produced varying conclusions. The IVW method indicated a significant causal genetic association between the age of asthma onset and AD risk (OR = 0.824, 95% CI: 0.736–0.922, $P < 0.001$), while the WM method demonstrated a significant genetic correlation between asthma and AD risk (OR = 0.795, 95% CI: 0.681–0.929, $P = 0.004$). In contrast, the MR-Egger method did not detect a significant association (OR = 0.839, 95% CI: 0.528–1.331, $P = 0.466$) (Figs. 2C and 3C; Table 1). The discrepancies among these methods may be attributed to residual horizontal pleiotropy detected by the MR-Egger approach; thus, the IVW result is considered more reliable. The leave-one-out analysis and funnel plot further supported the robustness of our findings (Fig. 4D and Fig. S1D). Conversely, no significant association was observed between the age of onset of childhood-onset asthma and AD risk (IVW: OR = 1.024, 95% CI: 0.935–1.121, $P = 0.610$) (Figs. 2E and 3E). Even after removing outliers using MR-PRESSO (rs1010474, rs112502960, rs1146045, rs117137535, rs449454, and rs597808), no significant association was detected (IVW: OR = 1.023, 95% CI: 0.955–1.095, $P = 0.510$) (Figs. 2F and 3F). The leave-one-out analysis and funnel plot confirmed the reliability of these findings (Fig. 4E and F and Fig. S1E, F).

Reverse MR analysis of allergic diseases on Alzheimer's disease

The reverse MR analysis follows the workflow illustrated in Fig. 1. Table 2 presents the results of the reverse MR analysis, demonstrating a significant causal association between asthma and AD (IVW raw: OR = 0.991, 95% CI: 0.983–0.999, $P = 0.040$). However, Cochran's Q test detected significant heterogeneity. After excluding outliers (rs116465569, rs141622900, rs157580, rs1878036, rs36096565, and rs679515), the association remained significant (IVW adjusted: OR = 0.994, 95% CI: 0.990–0.997, $P < 0.001$). However, no evidence of a causal relationship was found between allergic rhinitis or atopic dermatitis and AD. Sensitivity analysis confirmed the robustness of our results. Forest plots, scatter plots, leave-one-out analyses, and funnel plots are provided in Figures S2–S5.

Discussion

In this two-sample MR study, our results suggest a bidirectional association between asthma and AD, indicating that asthma may influence the development of AD. Furthermore, we identified that the age of asthma onset is a protective factor against AD, suggesting that a later onset of asthma may reduce AD risk. However, no causal associations were observed between the age of onset of childhood asthma, allergic rhinitis, or atopic dermatitis and AD risk, indicating that these atopic conditions do not contribute significantly to AD development through direct genetic mechanisms.

Our findings are consistent with prior epidemiological studies suggesting a potential link between asthma and

Table 2 The reverse Mendelian randomization of allergic disease and AD

Outcome	SNPs	Method	OR	95% CI	*P* value	Q_P value	Intercept (*P* value)
allergic rhinitis	35	IVW	1.001	0.998–1.003	0.589	0.123	
		WM	1.002	0.999–1.004	0.108		
		MR-Egger	1.000	0.997–1.004	0.699	0.176	-0.00002 (0.927)
atopic dermatitis	35	IVW	0.974	0.930–1.151	0.410	0.674	
		WM	0.958	0.872–1.053	0.374		
		MR-Egger	1.035	0.916–1.036	0.530	0.630	-0.00892 (0.183)
asthma (raw)	37	IVW	0.991	0.983–0.999	0.040	< 0.001	
		WM	0.996	0.992–0.999	0.020		
		MR-Egger	0.999	0.985–1.013	0.870	< 0.001	-0.00115 (0.193)
asthma (adjusted)	31	IVW	0.994	0.990–0.997	< 0.001	0.871	
		WM	0.994	0.989–0.998	0.003		
		MR-Egger	0.993	0.987–0.999	0.028	0.843	-0.000096 (0.749)

SNPs, single nucleotide polymorphisms; OR, odds ratio; CI, confidence interval; IVW, inverse-variance weighted; WM, weight median; AD, Alzheimer's disease

neurodegenerative diseases, including AD [26]. Some studies have proposed that chronic inflammation and immune dysregulation in asthma may contribute to neuroinflammation, a key mechanism in AD pathogenesis [27–30]. Additionally, systemic inflammation driven by allergic diseases has been implicated in cognitive decline [31–33]. However, our study provides genetic evidence supporting a bidirectional relationship, which has not been well established in previous observational studies.

The observed protective effect of asthma onset age on AD risk adds a novel perspective. Early-onset asthma may trigger a persistent pro-inflammatory stage, thereby increasing the risk of neurodegenerative diseases, whereas late-onset asthma may involve different immune pathways with a weaker long-term neuroinflammatory effect [34]. Previous cohort studies suggest that chronic inflammation in early life may increase the risk of neurodegenerative diseases in later life [35, 36].

Conversely, the absence of causal associations between childhood asthma onset, allergic rhinitis, or atopic dermatitis and the risk of AD suggests that not all allergic or atopic conditions contribute to the development of AD. This finding contrasts with some previous epidemiological reports that suggested an association between allergic diseases and cognitive decline [37]. Our results indicate that these associations may be driven by confounding factors or reverse causality rather than direct genetic mechanisms.

This study provides new insights into the complex interplay between asthma and AD, particularly emphasizing the role of asthma onset timing. The bidirectional nature of the association suggests that clinicians should consider potential neurological implications in patients with asthma. Additionally, these findings raise questions about whether targeting immune pathways involved in asthma could influence AD progression, potentially opening avenues for novel therapeutic interventions. Furthermore, our results highlight the importance of age-specific immune responses in determining AD risk. Further research should investigate the underlying immunological mechanisms.

The limitations of our study are as follows: Firstly, our two-sample MR analysis necessitated that the GWAS for exposure and outcome did not have overlapping participants. However, the extent of participant overlap in our study could not be estimated, which might influence the MR analysis. Secondly, as the GWAS data consist solely of individuals of European descent, the generalizability of our results to other ethnicities is limited; therefore, caution should be exercised when extrapolating our findings to other racial groups. Thirdly, although we employed the MR-PRESSO method to refine our MR estimates, the potential impact of heterogeneity on our results cannot be completely eliminated.

Conclusion

In conclusion, our research provides genetic evidence supporting a bidirectional relationship between asthma and AD, suggesting shared immune or inflammatory mechanisms. Additionally, we identified that the age of asthma onset is a protective factor, while childhood-onset asthma, allergic rhinitis, and atopic dermatitis do not appear to influence AD risk. These findings contribute to the growing understanding of the immune-neurodegeneration axis and highlight potential avenues for future research into the role of allergic diseases in AD pathogenesis.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12883-025-04192-7.

Supplementary Material 1

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Author contributions
Tianyu Jin and Wei Huang: present idea, perform MR analysis and manuscript writing.Yifan Cheng and Cao Zheng: manuscript writing and evaluate the quality of MR, data collection, figure and table drawing, search of the database and quality assessment.Shunyuan Guo: study supervision.Chunrong Li: study supervision and final approvement.

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Data availability
The datasets generated in this study, related to allergic rhinitis, can be accessed via the UK Biobank (https://gwas.mrcieu.ac.uk/datasets/ukb-b-16499/). Data on asthma is available at https://www.nature.com/articles/s43587-021-00051-5 and https://www.nature.com/articles/s41588-020-00776-w. Data related to atopic dermatitis is available at https://gwas.mrcieu.ac.uk/datasets/finn-b-L12_ATOPIC/. Furthermore, genome-wide meta-analysis data on atopic dermatitis can be accessed via https://www.nature.com/articles/s41588-020-00776-w. All datasets are available in publicly accessible GWAS databases.

Declarations

Ethics approval and consent to participate
Each participant received ethical approval and informed consent for the respective study, as detailed in the original publication and consortium.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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