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Mediating Mendelian randomization in the proteome identified potential drug targets for obesity-related allergic asthma

Jiannan Lin[1*], Shuwen Lu[1] and Xiaoyu Zhao[1]

Abstract

Background With the development of the economy, the number of obese patients has been increasing annually worldwide. The proportion of asthma patients associated with obesity is also gradually rising. However, the pathogenesis of obesity-related asthma remains incompletely understood, and conventional pharmacological treatments generally show limited efficacy.

Objective This study aims to explore the causal relationship between obesity and allergic asthma, elucidate the pathogenesis of obesity-related asthma, and identify the plasma proteins involved in its development, providing new insights for clinical interventions.

Methods In this study, we employed a two-step approach for mediation Mendelian randomization (MR) analysis, utilizing stringent selection criteria to identify instrumental variables (IVs). This approach was used to assess the causal impact of obesity on allergic asthma and to validate the plasma proteins identified as mediating factors. We further explored the functions and enriched pathways of the mediating proteins using Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses. Finally, we conducted drug-targeted MR analysis to evaluate the potential of each mediator plasma proteins as a drug target gene. If significant heterogeneity remained among the IVs, we applied the weighted median method as the primary analytical tool. Otherwise, we utilized the inverse variance weighted (IVW) method as the main analytical approach. Additionally, we conducted various sensitivity analyses and statistical tests to further illustrate the robustness of the observed associations.

Results The research findings indicate a causal relationship between obesity and allergic asthma. Plasma proteins such as TPST1, ROR1, and DAPK1 mediate this relationship, with TPST1 accounting for over 10% of the mediation effect. GO and KEGG analyses show that the genes corresponding to these mediator proteins are primarily enriched in pathways related to responses to stimuli, carbohydrate synthesis and metabolism, regulation of certain protein activities, and synaptic connections. The drug-targeted MR analysis suggests that SIGLEC12, BOLA1, HOMER2, and TPST1 all have the potential to be drug target genes.

Conclusion This study suggests that obese patients defined by BMI may promote the development of allergic asthma by influencing the expression of plasma proteins such as TPST1, ROR1, and DAPK1. Furthermore, some of

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these plasma proteins, including TPST1, could potentially serve as therapeutic targets for treating allergic asthma in these patients. However, further research is needed to explore their therapeutic potential and the mechanisms underlying their effects.

Clinical trial number Not applicable.

Keywords Allergic asthma, Obesity-related asthma, Plasma proteins, Mendelian randomization analysis

Introduction

Asthma is a chronic inflammatory disease of the airways, characterized by reversible airflow obstruction and airway hyperresponsiveness. It typically worsens and becomes more symptomatic at night and in the early morning hours, often triggered by infections. Clinically, the main symptoms include wheezing, chest tightness, and coughing. Severe asthma attacks can be life-threatening [1]. In recent years, the prevalence of asthma has been steadily increasing. The global prevalence of asthma is approximately 10%, with significant differences in prevalence rates across countries with varying income levels [2].This rising incidence places a considerable burden on both families and society. Asthma manifests in various phenotypes, generally classified as allergic and non-allergic asthma, with allergic asthma accounting for the majority of cases [3].

Obesity has become an increasingly pressing social issue, with its prevalence rising steadily in tandem with economic development. In the United States, the incidence of obesity among children and adolescents surged from 3.6% in 1980 to 19.3% in 2018 [4]. Recent studies have demonstrated a significant link between obesity and both the onset and exacerbation of asthma [5]. Obese children are more likely to be diagnosed with asthma, experience more frequent attacks, and present with more severe symptoms during these episodes. Furthermore, they tend to exhibit a reduced response to systemic corticosteroids [6]. However, the exact mechanisms driving this association remain poorly understood.

Current research suggests that obesity-related asthma is primarily characterized by neutrophilic inflammation and is typically classified as a non-allergic type of asthma [7]. However, it has been frequently observed in clinical practice that some obese children, particularly among pediatric patients, present with features typical of allergic asthma [8]. Furthermore, conventional corticosteroid treatments often prove less effective, making asthma management even more challenging in these cases [9]. Therefore, this study aims to further clarify the pathogenesis of obesity-related asthma, focusing on exploring biomarkers that may act as intermediaries. The ultimate goal is to provide a scientific basis for more effective clinical interventions and management strategies for obesity-related asthma.

However, in practice, numerous confounding factors and reverse causality often make it challenging to derive definitive conclusions from observational studies. The MR is a research method used to explore potential causal relationships between exposure and outcome by selecting appropriate instrumental variables to substitute for the exposure and then analyzing their association with the outcome. Due to the random nature of genetic inheritance, this method closely mirrors the design of randomized controlled trials [10]. As such, it offers distinct advantages in investigating causal links between two traits.

Materials and methods

Study design

In this study, we employed a two-step approach for mediation MR analysis. First, we investigated the causal relationship between plasma proteins and allergic asthma. Next, we explored the causal relationship between body mass index (BMI), used as a proxy for obesity, and plasma proteins that have potential mediating roles. After identifying the mediating plasma proteins, we first calculated the causal effect of BMI on these mediators (β_1). In the second step, we assessed the causal effect of the mediating plasma proteins on allergic asthma (β_2). We applied the delta method to evaluate the significance of the mediation effect ($\beta_1 \times \beta_2$) and determined the proportion of the mediation effect within the total effect. Next, we conducted GO and KEGG analyses on the mediating plasma proteins to explore their functional roles. Finally, after identifying the mediator proteins, we conducted drug-targeted MR analysis to evaluate the potential of each mediator plasma proteins as a drug target gene.

The MR employs genetic variations as proxies for risk factors; therefore, effective instrumental variables in causal inference must satisfy three key assumptions: (1) The relevance assumption: genetic variations are directly associated with the exposure. (2) The independence assumption: genetic variations are independent of any confounding factors that may affect both the exposure and the outcome. (3) The exclusion assumption: genetic variations influence the outcome solely through the exposure, without any alternative pathways (Fig. 1).

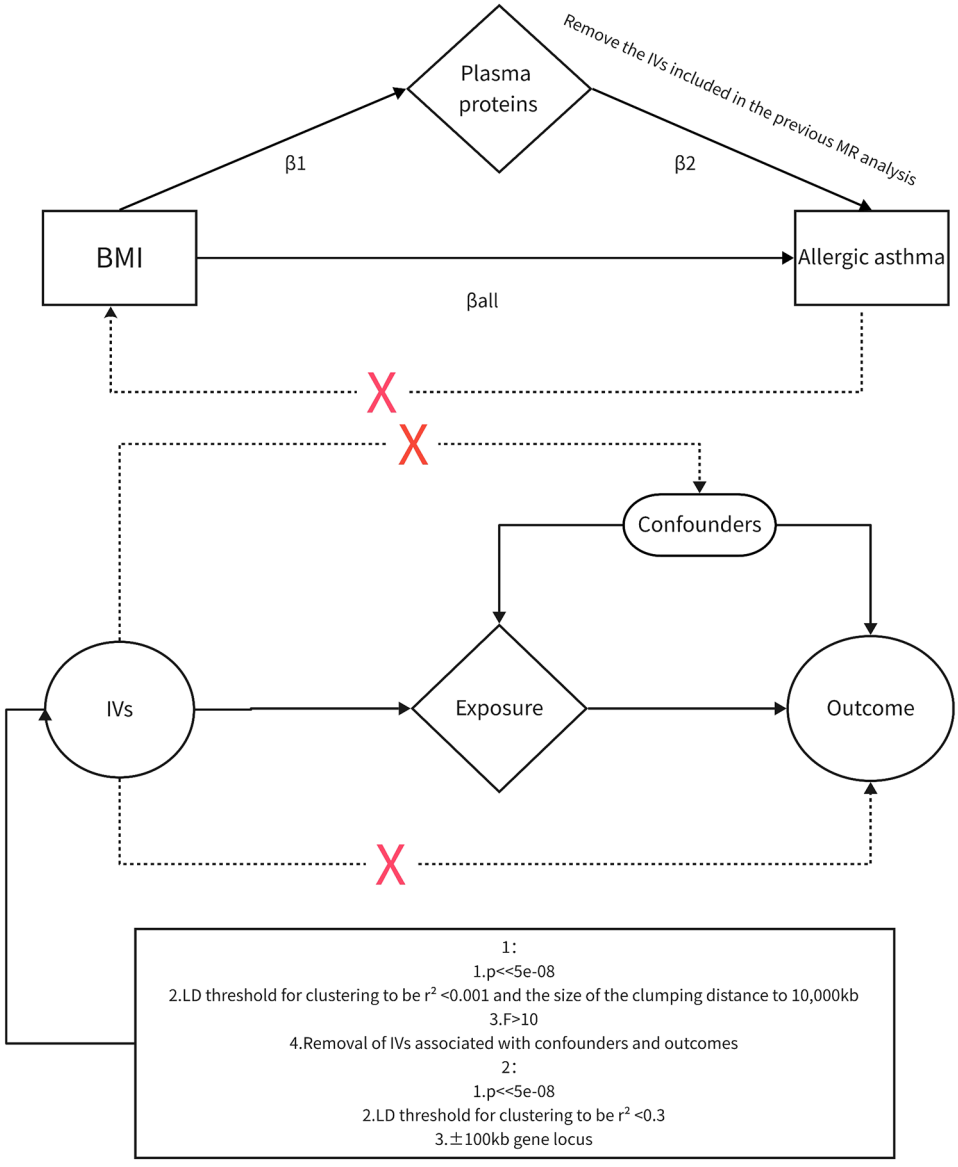

Fig. 1 Mendelian randomization flowchart

Table 1 Details of exposure and outcome GWAS datasets

Dataset type	Consortium	Population	Sample size	PMID
BMI	Barton AR et al.	European	457,756	34,226,706
Plasma protein	Ferkingstad et al.	European	35,559	34,857,953
Allergic asthma	FinnGen	European	260,128	-

Data sources

In this study, the exposure data were sourced from the research findings of Barton AR et al.(accession numbers: ebi-a-GCST90025994) [11]. The plasma protein data were obtained from the aggregated dataset provided by Ferkingstad et al. in the Decode database (https://www.decode.com/summarydata/) [12]. The outcome data were derived from summary statistics related to allergic asthma in the FinnGen database (version r11; https://www.finngen.fi/en) [13]. Detailed information about the data can be found in Table 1.

Instrumental variables selection

The selected IVs had to meet the following criteria: (1) To ensure robust results, a p-value threshold of $< 5 \times 10^{-8}$ was used. (2) To maintain the independence of each IV, a linkage disequilibrium (LD) threshold of $r^2 < 0.001$ was applied for clustering, with a clustering distance set at 10,000 kb. (3) The F-statistic for each IV was calculated to assess weak instrument bias, with IVs selected if $F > 10$. (4) The GWAS Catalog database (https://www.ebi.ac.u

k/gwas/) was utilized to exclude instrumental variables associated with confounding factors and outcomes.

GO and KEGG analysis

We utilized the "clusterProfiler" and "enrichplot" packages to conduct GO enrichment analysis and KEGG pathway enrichment analysis on the genes corresponding to the identified intermediate proteins. In this analysis, gene annotation was performed using "org.Hs.eg.db" packages.

The drug-targeted MR

After identifying the mediator proteins, we conducted drug-targeted MR analysis to evaluate the potential of each mediator protein as a drug target gene. The selection of instrumental variables met the following criteria: (1) $p < 5 \times 10$^-8; (2) IVWs were located within ± 100 kb of the target gene locus; (3) LD threshold ($r^2 < 0.3$).

Statistical analyses

To assess the stability of causal relationships and the validity of the hypotheses, we conducted various sensitivity analyses and statistical tests. To evaluate the heterogeneity and pleiotropy among the IVs, we employed Cochran's Q statistic and the MR-Egger intercept test. The "leave-one-out" method, along with scatter plots and funnel plots, can be used to ensure the robustness of the results. We removed any unstable results from our analysis.

If significant heterogeneity among the instrumental variables was detected, we adopted the weighted median method as the primary analytical approach. Conversely, if no heterogeneity was observed among the IVs, we applied the IVW method as the main analysis technique. All analyses were performed using R software, along with the MR (Version 4.4.1). Given the exploratory nature of the study, we did not apply the FDR correction, setting the significance threshold at $p < 0.05$ [14, 15].

Results

Based on the selection criteria established for our IVs, we first identified IVs closely related to BMI, followed by those associated with plasma proteins, and finally, those linked to allergic asthma. Using the GWAS Catalog database (https://www.ebi.ac.uk/gwas/), we excluded IVs that were related to confounding factors and outcomes in their respective MR analyses.

The impact of BMI on allergic asthma

Initially, we performed a MR analysis to examine the causal relationship between BMI and allergic asthma. The findings revealed a significant causal link, with an OR of 1.239 (95% CI: 1.055–1.455, $p = 0.009$) (Fig. 2). In contrast, reverse MR analysis indicated no causal relationship between allergic asthma and BMI ($P > 0.05$) (Fig. 2). Furthermore, the Cochran's Q statistic indicated significant heterogeneity in the results (Supplementary Material 1). Therefore, we used the weighted median method as the primary analytical approach for this study. Additionally, the MR-Egger intercept test indicated that our MR analysis was not affected by horizontal pleiotropy (Supplementary Material 1). Scatter plots, funnel plots, and leave-one-out analysis further illustrated the robustness of the correlations (Supplementary Materials 1).

The impact of plasma proteins on asthma

In our MR analysis investigating the relationship between plasma proteins and allergic asthma, we used the MR-Egger intercept test to eliminate results affected by horizontal pleiotropy. Ultimately, we identified 67 plasma proteins that exhibit a causal relationship with allergic asthma. Among these, 33 plasma proteins were found to serve as protective factors, while 34 were identified as detrimental factors for allergic asthma. The specific results can be seen in Fig. 3. Cochran's Q statistic assessments revealed significant heterogeneity in the MR results for IL1R2, CPB1, and IL1RL1. Consequently, we utilized the weighted median method for the analysis of IL1R2, CPB1, and IL1RL1, while the IVW method was applied as the primary analytical approach for the remaining plasma proteins (Supplementary Materials 2). Scatter plots, funnel plots, and leave-one-out analyses further demonstrated the robustness of these associations (Supplementary Materials 1).

The impact of BMI on plasma proteins

In our MR analysis investigating the relationship between BMI and the selected plasma proteins, we used the MR-Egger intercept test to eliminate results affected by horizontal pleiotropy. Ultimately, we identified a total of 40 plasma proteins with potential mediating factor roles, as illustrated in the accompanying figure (Fig. 4). Cochran's Q statistic evaluation indicated significant heterogeneity in the MR results for ATF6B, TST, TP53I11, IL6R, ALKBH3, ROR1, CFD, CNTN1, MMP12, PCSK9,

exposure	outcome	nsnp	method	pval	OR(95% CI)
Body mass index	Allergic asthma	356	Weighted median	**0.009**	1.239 (1.055 to 1.455)
Allergic asthma	Body mass index	10	Weighted median	0.879	1.002 (0.981 to 1.023)

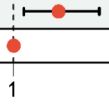

Fig. 2 The results of Mendelian randomization for BMI and allergic asthma

exposure	outcome	nsnp	method	pval	OR(95% CI)
SIGLEC12	Allergic asthma	10	Inverse variance weighted	**0.003**	0.907 (0.850 to 0.968)
GNRH2	Allergic asthma	3	Inverse variance weighted	**0.022**	1.194 (1.026 to 1.389)
KRT5	Allergic asthma	8	Inverse variance weighted	**0.006**	0.812 (0.699 to 0.943)
LRRN1	Allergic asthma	4	Inverse variance weighted	**0.033**	0.921 (0.855 to 0.993)
ADH7	Allergic asthma	5	Inverse variance weighted	**0.039**	0.915 (0.840 to 0.996)
ATF6B	Allergic asthma	6	Inverse variance weighted	**0.018**	1.237 (1.038 to 1.475)
TAPBP	Allergic asthma	7	Inverse variance weighted	**0.034**	1.090 (1.007 to 1.180)
TST	Allergic asthma	20	Inverse variance weighted	**0.023**	1.077 (1.010 to 1.148)
HOMER2	Allergic asthma	4	Inverse variance weighted	**0.008**	0.778 (0.646 to 0.938)
TP53I11	Allergic asthma	8	Inverse variance weighted	**0.022**	1.111 (1.015 to 1.217)
FSTL1	Allergic asthma	3	Inverse variance weighted	**0.026**	0.808 (0.670 to 0.974)
MAN1C1	Allergic asthma	8	Inverse variance weighted	**0.014**	1.170 (1.033 to 1.326)
SULT1A3	Allergic asthma	6	Inverse variance weighted	**0.015**	1.222 (1.039 to 1.437)
DAPK1	Allergic asthma	5	Inverse variance weighted	**0.022**	0.871 (0.774 to 0.981)
IL1RAP	Allergic asthma	8	Inverse variance weighted	**0.020**	0.948 (0.906 to 0.991)
IL1R2	Allergic asthma	12	Weighted median	**0.014**	0.857 (0.758 to 0.969)
VPS29	Allergic asthma	4	Inverse variance weighted	**0.030**	0.923 (0.858 to 0.992)
BOLA1	Allergic asthma	14	Inverse variance weighted	**0.008**	0.913 (0.853 to 0.976)
CPB1	Allergic asthma	13	Weighted median	**0.048**	0.892 (0.797 to 0.999)
ENPEP	Allergic asthma	8	Inverse variance weighted	**0.001**	0.868 (0.797 to 0.945)
IL6R	Allergic asthma	14	Inverse variance weighted	**0.003**	1.078 (1.026 to 1.132)
EPHA4	Allergic asthma	9	Inverse variance weighted	**0.013**	0.922 (0.864 to 0.983)
ALKBH3	Allergic asthma	4	Inverse variance weighted	**0.012**	1.147 (1.031 to 1.277)
ADK	Allergic asthma	5	Inverse variance weighted	**0.020**	1.269 (1.039 to 1.551)
GMPR2	Allergic asthma	5	Inverse variance weighted	**0.012**	1.157 (1.033 to 1.296)
PLXND1	Allergic asthma	12	Inverse variance weighted	**0.020**	0.917 (0.853 to 0.986)
ROR1	Allergic asthma	5	Inverse variance weighted	**0.003**	1.146 (1.047 to 1.254)
CFD	Allergic asthma	7	Inverse variance weighted	**0.037**	1.222 (1.012 to 1.475)
CNTN1	Allergic asthma	7	Inverse variance weighted	**0.018**	0.899 (0.823 to 0.982)
IL19	Allergic asthma	8	Inverse variance weighted	**0.044**	0.963 (0.928 to 0.999)
IDS	Allergic asthma	3	Inverse variance weighted	**0.038**	1.227 (1.012 to 1.488)
TGFBI	Allergic asthma	8	Inverse variance weighted	**0.041**	1.092 (1.003 to 1.188)
FCER2	Allergic asthma	20	Inverse variance weighted	**0.001**	1.139 (1.052 to 1.234)
TPSB2	Allergic asthma	20	Inverse variance weighted	**0.049**	1.040 (1.000 to 1.081)
ACP1	Allergic asthma	9	Inverse variance weighted	**0.010**	0.943 (0.902 to 0.986)
GZMB	Allergic asthma	3	Inverse variance weighted	**<0.001**	0.721 (0.622 to 0.837)
TNC	Allergic asthma	12	Inverse variance weighted	**0.004**	1.109 (1.034 to 1.190)
IL1RL1	Allergic asthma	30	Weighted median	**<0.001**	0.892 (0.836 to 0.952)
MMP12	Allergic asthma	9	Inverse variance weighted	**<0.001**	1.090 (1.037 to 1.144)
TFF3	Allergic asthma	7	Inverse variance weighted	**0.004**	1.235 (1.069 to 1.428)
GOT1	Allergic asthma	3	Inverse variance weighted	**0.005**	1.495 (1.126 to 1.984)
CD55	Allergic asthma	5	Inverse variance weighted	**0.035**	0.909 (0.832 to 0.993)
RTN4R	Allergic asthma	5	Inverse variance weighted	**0.040**	1.081 (1.004 to 1.164)
PCSK9	Allergic asthma	6	Inverse variance weighted	**<0.001**	1.292 (1.129 to 1.479)
MINPP1	Allergic asthma	4	Inverse variance weighted	**0.024**	1.130 (1.016 to 1.257)
PGLYRP2	Allergic asthma	8	Inverse variance weighted	**0.036**	0.909 (0.832 to 0.994)
SEMA4D	Allergic asthma	7	Inverse variance weighted	**0.043**	0.954 (0.911 to 0.999)
THPO	Allergic asthma	3	Inverse variance weighted	**0.020**	1.484 (1.063 to 2.072)
VWA1	Allergic asthma	9	Inverse variance weighted	**0.018**	0.931 (0.877 to 0.988)
RPN1	Allergic asthma	5	Inverse variance weighted	**0.007**	1.119 (1.032 to 1.213)
SERPINA12	Allergic asthma	5	Inverse variance weighted	**0.025**	1.069 (1.008 to 1.133)
LRP11	Allergic asthma	11	Inverse variance weighted	**0.009**	1.075 (1.018 to 1.135)
ITIH3	Allergic asthma	13	Inverse variance weighted	**0.045**	0.944 (0.892 to 0.999)
NFASC	Allergic asthma	4	Inverse variance weighted	**0.027**	0.918 (0.851 to 0.990)
TPST1	Allergic asthma	16	Inverse variance weighted	**0.031**	1.095 (1.008 to 1.188)
DRGX	Allergic asthma	9	Inverse variance weighted	**0.022**	1.093 (1.013 to 1.179)
PEAR1	Allergic asthma	7	Inverse variance weighted	**0.014**	0.833 (0.721 to 0.964)
PTPRU	Allergic asthma	6	Inverse variance weighted	**0.020**	0.858 (0.754 to 0.976)
CILP2	Allergic asthma	3	Inverse variance weighted	**0.024**	0.747 (0.579 to 0.962)
TMCC3	Allergic asthma	3	Inverse variance weighted	**0.013**	1.133 (1.027 to 1.251)
COL15A1	Allergic asthma	6	Inverse variance weighted	**0.028**	1.150 (1.015 to 1.304)
THBS3	Allergic asthma	9	Inverse variance weighted	**0.012**	0.824 (0.709 to 0.958)
MARCO	Allergic asthma	3	Inverse variance weighted	**0.041**	0.810 (0.662 to 0.991)
MAN2B2	Allergic asthma	9	Inverse variance weighted	**0.010**	1.083 (1.019 to 1.151)
IGSF3	Allergic asthma	5	Inverse variance weighted	**0.036**	1.347 (1.020 to 1.780)
NFKB1	Allergic asthma	3	Inverse variance weighted	**0.014**	0.776 (0.635 to 0.949)
SPOCK3	Allergic asthma	19	Inverse variance weighted	**0.019**	0.941 (0.895 to 0.990)

Fig. 3 The results of Mendelian randomization for plasma proteins and allergic asthma

exposure	outcome	nsnp	method	pval	OR(95% CI)
Body mass index	SIGLEC12	354	Inverse variance weighted	**<0.001**	1.120 (1.062 to 1.180)
Body mass index	GNRH2	354	Inverse variance weighted	**0.004**	1.080 (1.025 to 1.137)
Body mass index	ATF6B	354	Weighted median	**<0.001**	1.329 (1.212 to 1.458)
Body mass index	TST	354	Weighted median	**0.014**	1.107 (1.020 to 1.201)
Body mass index	HOMER2	354	Inverse variance weighted	**0.001**	1.096 (1.036 to 1.159)
Body mass index	TP53I11	354	Weighted median	**<0.001**	1.174 (1.069 to 1.290)
Body mass index	DAPK1	354	Inverse variance weighted	**<0.001**	1.132 (1.074 to 1.193)
Body mass index	BOLA1	354	Inverse variance weighted	**<0.001**	1.155 (1.097 to 1.216)
Body mass index	IL6R	354	Weighted median	**0.013**	1.117 (1.023 to 1.219)
Body mass index	ALKBH3	354	Weighted median	**0.033**	1.114 (1.009 to 1.231)
Body mass index	ADK	354	Inverse variance weighted	**<0.001**	1.127 (1.069 to 1.189)
Body mass index	PLXND1	354	Inverse variance weighted	**<0.001**	1.124 (1.063 to 1.188)
Body mass index	ROR1	354	Weighted median	**0.002**	0.856 (0.778 to 0.943)
Body mass index	CFD	354	Weighted median	**<0.001**	1.334 (1.211 to 1.469)
Body mass index	CNTN1	354	Weighted median	**<0.001**	0.801 (0.724 to 0.887)
Body mass index	IDS	354	Inverse variance weighted	**0.003**	0.922 (0.874 to 0.973)
Body mass index	TGFBI	354	Inverse variance weighted	**0.004**	1.080 (1.024 to 1.139)
Body mass index	TPSB2	354	Inverse variance weighted	**<0.001**	1.102 (1.052 to 1.155)
Body mass index	GZMB	354	Inverse variance weighted	**0.002**	1.088 (1.031 to 1.147)
Body mass index	MMP12	354	Weighted median	**0.002**	1.188 (1.066 to 1.325)
Body mass index	GOT1	354	Inverse variance weighted	**<0.001**	1.184 (1.122 to 1.249)
Body mass index	PCSK9	354	Weighted median	**<0.001**	1.216 (1.100 to 1.345)
Body mass index	MINPP1	354	Inverse variance weighted	**<0.001**	1.101 (1.044 to 1.162)
Body mass index	PGLYRP2	354	Weighted median	**0.014**	1.130 (1.025 to 1.245)
Body mass index	SEMA4D	354	Weighted median	**0.009**	1.142 (1.035 to 1.262)
Body mass index	THPO	354	Inverse variance weighted	**<0.001**	1.118 (1.059 to 1.180)
Body mass index	VWA1	354	Inverse variance weighted	**<0.001**	1.177 (1.113 to 1.245)
Body mass index	RPN1	354	Inverse variance weighted	**<0.001**	1.113 (1.056 to 1.174)
Body mass index	LRP11	354	Inverse variance weighted	**<0.001**	1.154 (1.099 to 1.212)
Body mass index	NFASC	354	Inverse variance weighted	**<0.001**	1.198 (1.132 to 1.268)
Body mass index	TPST1	354	Weighted median	**<0.001**	1.225 (1.115 to 1.346)
Body mass index	DRGX	354	Weighted median	**0.007**	1.144 (1.037 to 1.263)
Body mass index	PTPRU	354	Weighted median	**<0.001**	1.489 (1.362 to 1.629)
Body mass index	CILP2	354	Inverse variance weighted	**<0.001**	0.831 (0.784 to 0.879)
Body mass index	TMCC3	354	Weighted median	**0.002**	1.179 (1.065 to 1.305)
Body mass index	THBS3	354	Weighted median	**0.002**	1.151 (1.054 to 1.257)
Body mass index	MARCO	354	Inverse variance weighted	**<0.001**	1.193 (1.130 to 1.259)
Body mass index	MAN2B2	354	Inverse variance weighted	**<0.001**	1.148 (1.085 to 1.214)
Body mass index	NFKB1	354	Inverse variance weighted	**<0.001**	1.105 (1.048 to 1.165)
Body mass index	SPOCK3	354	Inverse variance weighted	**0.007**	1.075 (1.020 to 1.133)

Fig. 4 The results of Mendelian randomization for BMI and plasma proteins

PGLYRP2, SEMA4D, TPST1, DRGX, PTPRU, TMCC3, and THBS3 (Supplementary Materials 3). Consequently, we applied the weighted median method for the analysis of these specific plasma proteins, while the IVW method was utilized as the primary analytical approach for the remaining plasma proteins. Scatter plots, funnel plots, and leave-one-out analyses further supported the robustness of these associations (Supplementary Materials 3).

Mediation results

We utilized a two-step approach for mediation MR to study the plasma proteins identified as having mediator factor potential. In this analysis, we used the MR-Egger intercept test to eliminate results affected by horizontal pleiotropy. Ultimately, we identified 23 significant mediator factors and recalculated the β2 results, as detailed in Fig. 5. In the second step of mediation MR,

exposure	outcome	nsnp	method	pval	OR(95% CI)
SIGLEC12	Allergic asthma	12	Inverse variance weighted	**0.002**	0.906 (0.851 to 0.965)
TST	Allergic asthma	28	Inverse variance weighted	**0.032**	1.051 (1.004 to 1.100)
HOMER2	Allergic asthma	12	Inverse variance weighted	**0.005**	0.904 (0.842 to 0.970)
DAPK1	Allergic asthma	7	Inverse variance weighted	**0.005**	0.862 (0.776 to 0.957)
BOLA1	Allergic asthma	16	Inverse variance weighted	**0.008**	0.914 (0.855 to 0.977)
IL6R	Allergic asthma	15	Inverse variance weighted	**0.003**	1.077 (1.026 to 1.131)
ALKBH3	Allergic asthma	6	Inverse variance weighted	**0.022**	1.130 (1.018 to 1.254)
ROR1	Allergic asthma	8	Inverse variance weighted	**0.003**	1.136 (1.045 to 1.235)
CNTN1	Allergic asthma	9	Inverse variance weighted	**0.038**	0.931 (0.870 to 0.996)
IDS	Allergic asthma	5	Inverse variance weighted	**0.044**	1.202 (1.005 to 1.439)
TGFBI	Allergic asthma	10	Weighted median	**0.028**	1.117 (1.012 to 1.233)
GZMB	Allergic asthma	4	Inverse variance weighted	**<0.001**	0.716 (0.619 to 0.828)
MMP12	Allergic asthma	10	Inverse variance weighted	**<0.001**	1.092 (1.040 to 1.147)
PGLYRP2	Allergic asthma	8	Inverse variance weighted	**0.036**	0.909 (0.832 to 0.994)
SEMA4D	Allergic asthma	12	Inverse variance weighted	**0.035**	0.954 (0.913 to 0.997)
THPO	Allergic asthma	6	Inverse variance weighted	**0.017**	1.302 (1.049 to 1.617)
VWA1	Allergic asthma	12	Inverse variance weighted	**0.016**	0.931 (0.879 to 0.987)
LRP11	Allergic asthma	13	Inverse variance weighted	**0.006**	1.079 (1.022 to 1.138)
TPST1	Allergic asthma	21	Weighted median	**0.011**	1.126 (1.028 to 1.232)
DRGX	Allergic asthma	9	Inverse variance weighted	**0.022**	1.093 (1.013 to 1.179)
MAN2B2	Allergic asthma	13	Inverse variance weighted	**0.030**	1.063 (1.006 to 1.124)
NFKB1	Allergic asthma	4	Inverse variance weighted	**0.013**	0.785 (0.649 to 0.951)
SPOCK3	Allergic asthma	23	Inverse variance weighted	**0.041**	0.950 (0.905 to 0.998)

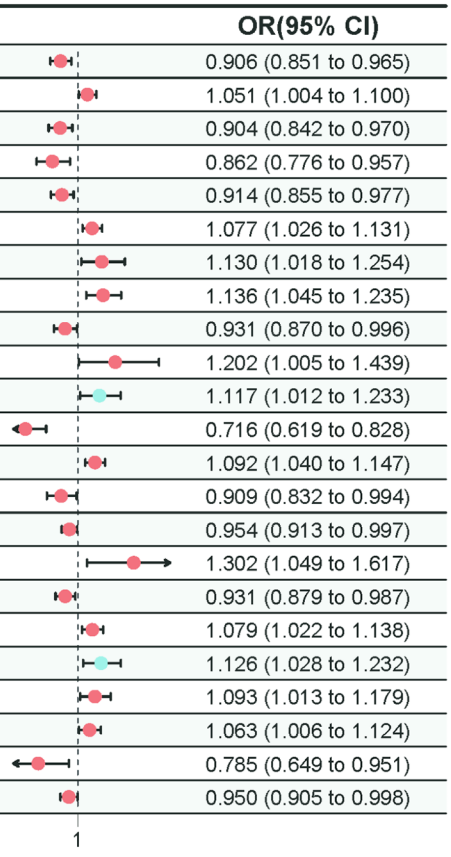

Fig. 5 The results of Mendelian randomization for mediating plasma proteins and allergic asthma

Table 2 The results of the mediating mendelian randomization analysis

Exposure	Metabolite	Outcome	Mediated_effect	Mediated_proportion	*p* value
BMI	SIGLEC12	Allergic asthma	-0.0112(-0.0198, -0.00253)	-5.2%(-9.22%, -1.18%)	0.01123966
BMI	HOMER2	Allergic asthma	-0.00927(-0.0181, -0.000466)	-4.32%(-8.43%, -0.217%)	0.039049369
BMI	DAPK1	Allergic asthma	-0.0184(-0.0353, -0.00155)	-8.58%(-16.4%, -0.721%)	0.032366324
BMI	BOLA1	Allergic asthma	-0.013(-0.0226, -0.00345)	-6.06%(-10.5%, -1.61%)	0.007652693
BMI	ROR1	Allergic asthma	-0.0198(-0.038, -0.00151)	-9.22%(-17.7%, -0.705%)	0.033811865
BMI	VWA1	Allergic asthma	-0.0116(-0.0217, -0.00158)	-5.42%(-10.1%, -0.736%)	0.023326572
BMI	LRP11	Allergic asthma	0.0109(0.00278, 0.0189)	5.06%(1.3%, 8.82%)	0.008415302
BMI	TPST1	Allergic asthma	0.024(0.0021, 0.046)	11.2%(0.979%, 21.4%)	0.031740497
BMI	MAN2B2	Allergic asthma	0.00848(1.09e-05, 0.0169)	3.95%(0.00507%, 7.9%)	0.049702042

when recalculating the β2 results, the Cochran's Q statistic assessment indicated significant heterogeneity in the MR results for TGFBI and TPST1 (Supplementary Material 4). Therefore, we applied the weighted median method for the analysis of these specific plasma proteins, while the IVW method was used as the primary analysis method for the remaining plasma proteins. Scatter plots, funnel plots, and leave-one-out analyses further supported the robustness of these associations (Supplementary Materials 4). By assessing the calculated β1 and β2 results, we evaluated the significance of the mediation effect (β1 × β2) and determined the proportion of the mediation effect within the total effect. Notably, the mediation effects of SIGLEC12, HOMER2, DAPK1, BOLA1, ROR1, VWA1, LRP11, TPST1, and MAN2B2 were found to be significant. Detailed results are presented in Table 2.

GO and KEGG analyses

To further explore the functions and enriched pathways of the genes corresponding to these plasma proteins, we performed GO and KEGG analyses. The results indicated that these genes are primarily enriched in pathways related to responses to stimuli, carbohydrate synthesis and metabolism, regulation of certain protein activities, and synaptic connections (Fig. 6).

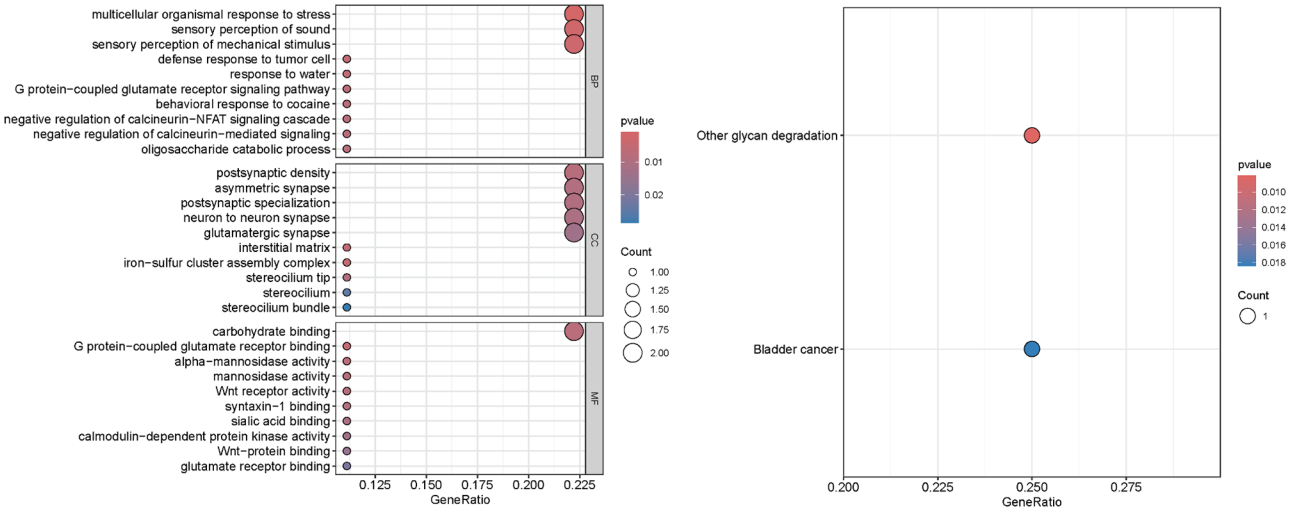

Fig. 6 (**A**) The results of GO analyses. (**b**) The results of KEGG analyses

exposure	outcome	nsnp	method	pval	OR(95% CI)
SIGLEC12	Allergic asthma	28	Inverse variance weighted	**<0.001**	0.926 (0.899 to 0.954)
BOLA1	Allergic asthma	12	Inverse variance weighted	**0.024**	0.881 (0.790 to 0.983)
HOMER2	Allergic asthma	23	Inverse variance weighted	**0.007**	0.930 (0.883 to 0.980)
TPST1	Allergic asthma	49	Inverse variance weighted	**0.001**	1.032 (1.012 to 1.053)

1

Fig. 7 The results of drug-targeted Mendelian randomization

The drug-targeted MR

We conducted drug-targeted MR analysis on the selected mediator plasma proteins. The results showed the following: SIGLEC12 (OR = 0.93, 95% CI = 0.90–0.95, $p < 0.01$), BOLA1 (OR = 0.88, 95% CI = 0.79–0.98, $p = 0.02$), HOMER2 (OR = 0.93, 95% CI = 0.88–0.98, $p < 0.01$), and TPST1 (OR = 1.03, 95% CI = 1.01–1.05, $p < 0.01$) (Fig. 7). Furthermore, the Cochran's Q statistic indicated that there is no heterogeneity in the results (Supplementary Material 5). Therefore, we used the IVW method as the primary analytical approach for this study. Additionally, the MR-Egger intercept test indicated that our MR analysis was not affected by horizontal pleiotropy (Supplementary Material 5). Scatter plots, funnel plots, and leave-one-out analysis further illustrated the robustness of the correlations (Supplementary Materials 5).

Discussion

Obesity-related asthma is widely recognized as a neutrophilic, non-allergic type of asthma. However, the relationship between obesity-related asthma and allergic asthma has garnered limited discussion. In this study, we used BMI as a surrogate for obesity and conducted a two-step mediation MR analysis to further clarify the underlying mechanisms of obesity-related asthma. Our goal was to investigate the causal relationship between obesity-related asthma and allergic asthma while identifying plasma proteins that may serve as mediators in this context. This approach aims to provide new insights for the treatment of obesity-related asthma.

Recent studies have demonstrated that obesity is not only an independent risk factor for asthma but also affects the phenotype and clinical manifestations of the disease [16]. Asthma that is closely associated with obesity is clinically defined as obesity-related asthma. This type of asthma is characterized by more frequent attacks, more severe symptoms, and higher mortality rates compared to other forms of asthma [17]. The pathogenesis of obesity-related asthma appears to be related to the inflammatory effects of lipids and the mechanical alterations in the airways [18]. However, the specific mechanisms underlying this condition remain unclear. Current pharmacological treatments often show limited efficacy in managing obesity-related asthma [19].

Based on existing literature, asthma can be broadly categorized into allergic and non-allergic types. The former is characterized by eosinophilic airway inflammation, whereas the latter is associated with neutrophilic inflammation. Among these, a distinctive form known as obesity-related asthma has emerged. Most studies unequivocally report that airway inflammation in obesity-related asthma is predominantly neutrophilic,

which suggests its classification as a non-allergic asthma [20]. However, a minority of studies have indicated that obesity-related asthma may also exhibit eosinophilic inflammation [21, 22]. This discrepancy raises an intriguing question: Should obesity-related asthma be classified as allergic or non-allergic? This question is particularly significant as it directly influences treatment strategies. Allergic asthma typically shows a favorable response to corticosteroids, resulting in considerable symptom improvement under standardized treatment regimens. In contrast, non-allergic asthma is often resistant to corticosteroids, leading to persistent symptoms that necessitate additional therapeutic approaches [23]. Our study's findings indicate a causal relationship between obesity and allergic asthma, suggesting that, under certain conditions, obesity may lead to the development of allergic asthma in individuals. Integrating prior research, it appears that the immunological profile of obesity-related asthma may not be fixed; it has the potential to manifest as either allergic or non-allergic asthma. The variability in how obesity triggers different asthma phenotypes may be linked to disease progression or patient age. However, the precise mechanisms remain to be elucidated. This variability in immune imbalance may partly explain the difficulties in achieving effective treatment for obesity-related asthma. Given the possibility of diverse immunological profiles, a standardized pharmacological approach may be ineffective.

The results of this study indicate that plasma proteins such as TPST1, ROR1, and DAPK1 may mediate the relationship between obesity and allergic asthma. Notably, the mediation effect of TPST1 exceeds 10%, underscoring its significant clinical relevance. GO analysis suggests that these genes are primarily involved in responses to stimuli, carbohydrate synthesis and metabolism, regulation of certain protein activities, and synaptic connections. Furthermore, KEGG analysis reveals that these genes are predominantly associated with pathways related to carbohydrate metabolism and bladder cancer. It is hypothesized that some genes may influence carbohydrate synthesis and metabolism, altering energy supply mechanisms and contributing to obesity. Additionally, abnormalities in synaptic connections between neurons may impair the function of the pulmonary autonomic nervous system, thereby affecting normal lung physiology.

Tyrosyl sulfotransferase 1 (TPST1) is an enzyme responsible for the sulfation modification of substrates, specifically by transferring sulfate groups to tyrosine residues, thus facilitating the sulfation of tyrosine. This sulfation process occurs throughout the body and is closely linked to not only normal physiological functions but also various pathological conditions. Research has indicated that the sulfation of heparan sulfate and chondroitin sulfate chains can significantly impact multiple aspects of inflammation, playing a crucial role in T-cell infiltration [24, 25]. N-acetylglucosamine (GlcNAc) 6-O sulfation has been shown to protect gut microbiota and modulate immune responses [26]. Additionally, sterol sulfate has been found to alleviate insulin resistance and systemic inflammation in obese mice, suggesting that TPST1 may also influence obesity-related asthma [27]. Therefore, a deeper exploration of the specific mechanisms by which sulfation contributes to inflammation is of great significance for developing novel anti-inflammatory therapeutic strategies.

The drug-targeted MR analysis indicated that SIGLEC12, BOLA1, HOMER2, and TPST1 all have the potential to be drug target genes. However, a search of the DrugBank database revealed that there are currently no approved drugs targeting these genes. Future research is anticipated to explore this potential further.

However, this study has several limitations. First, the use of BMI to define obesity has inherent limitations, as BMI does not accurately reflect the distribution of body fat. Future research should aim to utilize more comprehensive indicators to represent different types of obese populations, enhancing the generalizability of the conclusions drawn. Second, the sample was exclusively drawn from a European population, raising concerns about the general applicability of the findings in a global context, which still needs validation. Future directions should involve collecting data from diverse geographic regions for further verification. Third, we did not employ multiple comparison controls in this study in order to explore a wider range of plasma proteins with potential as drug targets, thus providing more hypotheses and possibilities for future research. Nevertheless, the clinical relevance of the identified drug target proteins requires further experimental validation. Our next research plan includes establishing corresponding gene amplification expression and knockout models of obese asthmatic mice to test our hypotheses and extend our findings. Lastly, although Mendelian Randomization analysis has advantages in controlling for known confounding factors, there remains a risk that undetected confounding variables may influence the study outcomes.

Future research should delve deeper into the mechanisms underlying obesity-related asthma and explore the mediating factors involved in its pathogenesis. Furthermore, it is advisable to conduct multi-center, large-scale studies to validate and expand upon the findings of this study, thereby enhancing the generalizability and reliability of the results.

Conclusion

This study suggests that obese patients defined by BMI may promote the development of allergic asthma by influencing the expression of plasma proteins such as TPST1, ROR1, and DAPK1. Furthermore, some of these plasma proteins, including TPST1, could potentially serve as therapeutic targets for treating allergic asthma in these patients. However, further research is needed to explore their therapeutic potential and the mechanisms underlying their effects.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41065-025-00376-w.

Supplementary Material 1: Supplementary Materials 1. The MR results of BMI and allergic asthma. Supplementary Materials 2. The MR results of plasma proteins and allergic asthma. Supplementary Materials 3. The MR results of BMI and plasma proteins. Supplementary Materials 4. The MR results of mediation factor plasma proteins and allergic asthma. Supplementary Materials 5. The results of drug-targeted MR

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Author contributions
The main writing of the manuscript was carried out by J.L., who also took responsibility for subsequent revisions. The editing and grammar corrections of the article were handled by S.L. Data organization and reference management were overseen by X.Z.

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Data availability
The data for allergic asthma was obtained from the FinnGen database (https://storage.googleapis.com/finngen-public-data-r11/summary_stats/finngen_R11_ALLERG_ASTHMA.gz).The BMI data was sourced from the IEU-OpenGWAS project (https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90025994/).The plasma protein data were obtained from the aggregated dataset provided by Ferkingstad et al. in the Decode database (https://www.decode.com/summarydata/).

Declarations

Ethics approval and consent to participate
The data used in our study were sourced from public databases, where the participating patients have given ethical approval. Users can freely download the relevant data for research purposes and publish related papers. Since our research is based on open-source data, there are no ethical concerns or conflicts of interest.

Consent for publication
We all agree to publish in the Hereditas.

Competing interests
The authors declare no competing interests.

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