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Causal association of allergic diseases, eosinophils, and osteoporosis: A Mendelian randomization study

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ABSTRACT

Background: The association between allergic diseases and osteoporosis remains controversial. We hypothesize that this discrepancy may be due to a mediator that plays a role in the pathogenesis of both allergic diseases and osteoporosis. To test this hypothesis, we used Mendelian randomization (MR) analysis to investigate the relationships among allergic diseases, eosinophils, and osteoporosis.

Method: This study utilized data from publicly available GWAS databases, including 3 allergic diseases: asthma, allergic rhinitis, and eczema. We conducted bidirectional MR analyses on the relationships between allergic diseases and eosinophils (including eosinophil counts and percentage), allergic diseases and osteoporosis, and eosinophils and osteoporosis, respectively. We conducted sensitivity analyses for results with significance, validated the findings using multivariable Mendelian randomization (MVMR) analysis to ensure the reliability of the significant results.

Results: Two-sample MR analysis revealed significant bidirectional causal relationships between the 3 allergic diseases and eosinophils. A unidirectional causal relationship was found between eosinophils and osteoporosis, with eosinophil counts associated with osteoporosis (OR: 1.194; 95% CI 1.064 to 1.339; Pivw $<$0.001) and eosinophil percentage associated with osteoporosis (OR: 1.187; 95% CI 1.057 to 1.332; Pivw $<$0.001). Sensitivity analyses indicated no pleiotropy, However, the association between eosinophil percentage and osteoporosis was no longer significant after multivariable (MVMR) analysis. Additionally, no causal effects were observed from allergic diseases to osteoporosis, from osteoporosis to allergic diseases, or from osteoporosis to eosinophils.

Conclusions: 1.) There is a significant bidirectional potential causal relationship between the 3 allergic diseases (asthma, allergic rhinitis, eczema) and eosinophils. 2.) There is no evidence to support a causal relationship between the 3 allergic diseases and osteoporosis, and vice versa. 3.) There is a unidirectional causal relationship may exist from eosinophil counts to osteoporosis.

Keywords: Asthma, Allergic diseases, Osteoporosis, Eosinophils, Allergy, Eczema, Allergic rhinitis

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INTRODUCTION

Allergic diseases are a complex group of chronic conditions with diverse symptoms that can affect multiple organs and systems throughout the body. In recent decades, the global prevalence of allergic diseases has risen significantly, becoming a major public health concern. Approximately 400 million people worldwide suffer from allergic rhinitis, 260 million from asthma, and 15%–20% of children and 6%–10% of adults from atopic dermatitis[1] These diseases severely impact patients' physical and mental health, increase healthcare costs, and elevate the risk of other conditions such as fractures and osteoporosis.[2] Previous studies have shown a close relationship between osteoporosis and various allergic diseases, including atopic dermatitis, hay fever, and food allergies. However, the mechanisms underlying this association remain unclear. On the other hand, some research suggests that there is no association between allergic diseases and osteoporosis.

It is certain that the relationship between allergic diseases and bone metabolism, including osteoporosis, is complex and sophisticated. The prevailing view is that there is a connection between immune cells and bones, and that interactions within the bone microenvironment, involving T cells and other immune cell subsets, regulate bone homeostasis and affect bone remodeling through cytokine secretion.[3] In recent reviews, researchers have explored the pathophysiological connections between allergies and osteoporosis, as well as between eosinophils and osteoporosis.[2,4] Eosinophils play a central role in the pathogenesis of allergic diseases, participating in immune and inflammatory responses and serving as key biomarkers for diagnosing and monitoring these conditions.[5,6] As a type of white blood cell, eosinophils do not directly participate in bone metabolism, but they may influence bone loss and skeletal health through immune and inflammatory responses.[7]

MR is an effective method for investigating causal relationships, utilizing the natural random distribution of genetic variations in individuals to mimic the effects of randomized controlled trials. This approach minimizes the influence of confounding factors and reverse causality.[8] Consequently, this study aims to employ MR analysis to explore the relationships among allergic diseases, eosinophils, and osteoporosis, ultimately providing preventive recommendations for clinical practice.

METHOD

Study design and data sources

We employed a two-sample MR analysis to assess the causal effects among allergic diseases, eosinophils, and osteoporosis. Before conducting MR analysis, we considered the following 3 core assumptions:[9,10] 1) there is a robust association between the instrumental variables (IVs) and the exposure factors; 2) the IVs are not related to confounding factors that influence the exposure-outcome relationship; and 3) the IVs affect the outcome solely through the exposure factors and not through any other pathways.

We used data from publicly available IEU GWAS, GWAS Catalog, and FINNGEN datasets. We selected 3 common allergic diseases, including asthma, allergic rhinitis, and eczema. Eosinophils were represented by eosinophil counts and eosinophil percentage. Details are provided in Table 1. The population involved in this study consists of individuals of European descent. For specific sample sources, please refer to the Supplementary Table 1.

Selection of IVs

In MR analysis, IVs serve as intermediaries between exposure factors and outcomes to explore causal relationships. Single nucleotide polymorphisms (SNPs) are the most commonly used IVs. For this study, SNPs were selected using a default threshold of $P < 5 \times 10^{-8}$, (except for the two-sample MR analyses of osteoporosis-allergic diseases and osteoporosis-eosinophils, where the threshold was $P < 5 \times 10^{-6}$). The clump window was set at 10,000 kb, and the linkage disequilibrium level was $r^2 < 0.001$. We calculated the F-statistic for each SNP ($F = \beta^2/se^2$) and selected SNPs with an F-value greater than 10 to ensure the strength of each instrumental variable.[11] Detailed results of F-value can be found in the supplementary file SNP.xlsx of the article.

GWAS ID	Year	Trait	Sample size	SNPs
Two-sample MR dataset				
Ebi-a-GCST90018795	2021	Asthma	449,500	24,162,338
Ebi-a-GCST90013920	2021	Allergic rhinitis	407,746	11,039,206
Ebi-a-GCST90029017	2018	Eczema	461,199	11,973,148
Ebi-a-GCST90002381	2020	Eosinophil counts	408,112	40,311,874
Ebi-a-GCST90002382	2020	Eosinophil percentage	408,112	40,312,065
Finn-b-M13_OSTEOPOROSIS	2021	Osteoporosis	212,778	16,380,452
Multivariable MR dataset				
Ebi-a-GCST90029014	2018	Smoking status	468,170	11,973,425
Ukb-b-5779	2018	Alcohol intake frequency	462,346	9,851,867
Ebi-a-GCST90000618	2020	Serum 25-Hydroxyvitamin D levels	496,946	6,896,093
Ebi-a-GCST006867	2018	Type 2 diabetes	655,666	5,030,727
Ebi-a-GCST90019000	2021	Medication use (glucocorticoids)	205,700	14,256,400

Table 1. Data sources and details of this study

Statistical analysis

Two-sample MR

In our preliminary analysis, we observed noticeable heterogeneity in some results. Therefore, we employed MR PRESSO[12] and Radial MR[13] to remove outliers before conducting the two-sample MR analysis. We used 5 MR methods–Inverse Variance Weighted (IVW), MR Egger, Weighted Median, Simple Mode, and Weighted Mode–to evaluate the bidirectional causal relationships between allergic diseases and eosinophils, allergic diseases and osteoporosis, and eosinophils and osteoporosis. For results that showed significance, we further analyzed their heterogeneity and pleiotropy.

Multivariable (MV) MR

We used MVMR[14] to test the reliability of results with statistical significance. In MVMR, we included current smoking status, alcohol consumption frequency, serum vitamin D levels,[4,15] type 2 diabetes[16] and use of glucocorticoids as confounding factors to determine if the two-sample MR results remained statistically significant. All statistical analyses in this study were performed using the "TwoSampleMR" (version 0.6.10), "MRPRESSO" (version 1.0), and "RadialMR" (version 1.0) packages in R (version 4.3.0).

RESULTS

Two-sample MR

The results of the two-sample MR analysis (see Fig. 1) showed that: 1) There are significant bidirectional causal relationships between the 3 allergic diseases (asthma, allergic rhinitis, eczema) and eosinophils. Notably, in the MR analysis of allergic diseases-eosinophils, the effect size of eczema on eosinophils was particularly significant: eczema-eosinophil counts (β: 1.561; 95% CI 1.445 to 1.676; $P_{ivw} < 0.001$), and eczema-eosinophil percentage (β: 1.525; 95% CI 1.394 to 1.656; $P_{ivw} < 0.001$). However, the effect of eosinophils on eczema was less pronounced. 2) There is no causal relationship between the 3 allergic diseases and osteoporosis (or osteoporosis-allergic diseases). 3) There is a unidirectional causal relationship from eosinophils to osteoporosis: eosinophil counts-osteoporosis (OR: 1.194; 95% CI 1.064 to 1.339; $P_{ivw} < 0.001$) and eosinophil percentage-osteoporosis (OR: 1.187; 95% CI 1.057 to 1.332; $P_{ivw} < 0.001$).

The results of MR analysis (IVW)

Exposure	Outcome	nSNP	SE	β(95%CI)	OR(95%CI)	P.value
Allergic diseases on Eosinophils						
Asthma	Eosinophil counts	15	0.01	0.354(0.334 to 0.374)	1.425(1.396 - 1.454)	**<0.001**
	Eosinophil percentage	15	0.011	0.338(0.316 to 0.359)	1.402(1.372 - 1.432)	**<0.001**
Allergic rhinitis	Eosinophil counts	36	0.011	0.196(0.174 to 0.218)	1.216(1.190 - 1.243)	**<0.001**
	Eosinophil percentage	34	0.011	0.205(0.182 to 0.227)	1.227(1.200 - 1.255)	**<0.001**
Eczema	Eosinophil counts	35	0.059	1.561(1.445 to 1.676)	4.762(4.244 - 5.343)	**<0.001**
	Eosinophil percentage	40	0.067	1.525(1.394 to 1.656)	4.595(4.032 - 5.236)	**<0.001**
Eosinophils on Allergic diseases						
Eosinophil counts	Asthma	280	0.023	0.452(0.406 to 0.497)	1.571(1.501 - 1.643)	**<0.001**
	Allergic rhinitis	230	0.018	0.346(0.312 to 0.381)	1.414(1.366 - 1.464)	**<0.001**
	Eczema	209	0.003	0.059(0.053 to 0.065)	1.061(1.055 - 1.067)	**<0.001**
Eosinophil percentage	Asthma	249	0.025	0.446(0.398 to 0.494)	1.562(1.488 - 1.639)	**<0.001**
	Allergic rhinitis	213	0.019	0.404(0.367 to 0.440)	1.497(1.443 - 1.553)	**<0.001**
	Eczema	203	0.003	0.067(0.061 to 0.073)	1.069(1.063 - 1.076)	**<0.001**
Allergic diseases on Osteoporosis						
Asthma	Osteoporosis	56	0.06	0.074(-0.044 to 0.193)	1.077(0.957 - 1.213)	0.218
Allergic rhinitis	Osteoporosis	112	0.059	0.075(-0.040 to 0.190)	1.078(0.961 - 1.209)	0.203
Eczema	Osteoporosis	129	0.319	0.181(-0.444 to 0.806)	1.198(0.641 - 2.239)	0.57
Osteoporosis Allergic diseases						
Osteoporosis	Asthma	21	0.012	-0.004(-0.027 to 0.019)	0.996(0.973 - 1.020)	0.738
	Allergic rhinitis	19	0.009	0.010(-0.009 to 0.028)	1.010(0.991 - 1.029)	0.308
	Eczema	18	0.002	-0.001(-0.004 to 0.002)	0.999(0.996 - 1.002)	0.563
Eosinophils on Osteoporosis						
Eosinophil counts	Osteoporosis	355	0.059	0.177(0.062 to 0.292)	1.194(1.064 - 1.339)	**0.002**
Eosinophil percentage	Osteoporosis	349	0.059	0.171(0.056 to 0.287)	1.187(1.057 - 1.332)	**0.004**
Osteoporosis on Eosinophils						
Osteoporosis	Eosinophil counts	17	0.004	-0.002(-0.010 to 0.006)	0.998(0.990 - 1.006)	0.599
	Eosinophil percentage	16	0.004	-0.003(-0.011 to 0.004)	0.997(0.989 - 1.004)	0.389

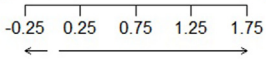

Fig. 1 The results of Two-sample MR analysis (IVW)

For all significant results, the direction of the beta values across the 5 methods remained consistent. Complete analysis results can be found in the Supplementary Figs. 1–6.

Subsequently, we conducted sensitivity analyses on the significant results, and no pleiotropy was detected, as shown in Table 2. We also performed scatter plot and leave-one-out analyses for all significant results, which are presented in the Supplementary Figs. 7–20.

MVMR

Figs. 2 and 3 display the MVMR analysis results of eosinophil counts and eosinophil percentage on osteoporosis, respectively. MVMR results indicated that the association between eosinophil count and osteoporosis remained significant after adjusting for current smoking status, alcohol consumption frequency, serum vitamin D levels, type-2 diabetes, and use of glucocorticoids. However, the association between eosinophil percentage and osteoporosis became non-significant after adjusting for use of glucocorticoids. The multivariable MR analysis results for allergic diseases and eosinophils are provided in the Supplementary Tables 2–13. All results remain stable.

DISCUSSION

This study used human genome-wide association summary data and MR analysis to explore the relationships among 3 allergic diseases (asthma, allergic rhinitis, and eczema), eosinophils (including eosinophil counts and eosinophil percentage), and osteoporosis. The MR analysis revealed significant bidirectional potential causal relationships between allergic diseases and eosinophils, no direct evidence to support a causal relationship between allergic diseases and osteoporosis (or osteoporosis-allergic diseases), and eosinophil counts may have a unidirectional causal relationship with osteoporosis. These specific associations are illustrated in Fig. 4.

Exposure	Outcome	Method	Heterogeneity		Pleiotropy				
			Q	Q_pval	Egger _intercept	SE	P.value	Global test RSSobs	Global testP.value
Asthma	Eosinophil counts	MR Egger	15.057	0.304	**−0.003**	0.002	**0.222**	19.296	**0.931**
	Eosinophil counts	IVW	16.966	0.258					
	Eosinophil percentage	MR Egger	20.298	0.088	**−0.001**	0.002	**0.801**	24.514	**0.789**
	Eosinophil percentage	IVW	20.402	0.118					
Allergic rhinitis	Eosinophil counts	MR Egger	43.402	0.130	**0.002**	0.002	**0.352**	46.937	**0.409**
	Eosinophil counts	IVW	44.538	0.130					
	Eosinophil percentage	MR Egger	45.479	0.058	**−0.001**	0.002	**0.737**	48.604	**0.314**
	Eosinophil percentage	IVW	45.642	0.070					
Eczema	Eosinophil counts	MR Egger	35.131	0.367	**−0.001**	0.002	**0.451**	38.054	**0.854**
	Eosinophil counts	IVW	35.751	0.386					
	Eosinophil percentage	MR Egger	57.172	0.024	**0.001**	0.002	**0.402**	61.665	**0.318**
	Eosinophil percentage	IVW	58.255	0.024					
Eosinophil counts	Asthma	MR Egger	270.447	0.616	**0.001**	0.001	**0.426**	273.287	**0.664**
	Asthma	IVW	271.084	0.622					
	Allergic rhinitis	MR Egger	234.963	0.362	**0.002**	0.001	**0.046**	241.247	**0.400**
	Allergic rhinitis	IVW	239.099	0.310					
	Eczema	MR Egger	213.789	0.358	**0.000**	0.000	**0.274**	217.009	**0.398**
	Eczema	IVW	215.031	0.354					
Eosinophil percentage	Asthma	MR Egger	257.626	0.308	**0.001**	0.001	**0.281**	260.947	**0.385**
	Asthma	IVW	258.842	0.305					
	Allergic rhinitis	MR Egger	229.311	0.184	**0.001**	0.001	**0.200**	234.069	**0.234**
	Allergic rhinitis	IVW	231.108	0.175					
	Eczema	MR Egger	208.294	0.347	**0.000**	0.000	**0.089**	213.400	**0.406**
	Eczema	IVW	211.330	0.312					
Eosinophil counts	Osteoporosis	MR Egger	279.055	0.999	**0.001**	0.003	**0.693**	280.819	**1.000**
	Osteoporosis	IVW	279.210	0.999					
Eosinophil percentage	Osteoporosis	MR Egger	255.612	0.999	**−0.005**	0.003	**0.150**	259.378	**0.998**
	Osteoporosis	IVW	257.692	0.999					

Table 2. Sensitivity analysis of significant results. (Bold text highlights the results of the pleiotropy analysis.)

The results of MVMR analysis of Eosinophil counts on Osteoporosis

Exposure	Outcome	nSNP	SE	OR(95%CI)	P.value
Adjust for Smoking status					
Eosinophil counts	Osteoporosis	342	0.059	1.138(1.013 - 1.277)	**0.029**
Smoking status	Osteoporosis	47	0.354	1.666(0.832 - 3.333)	0.149
Plus Alcohol intake frequency					
Eosinophil counts	Osteoporosis	335	0.059	1.141(1.016 - 1.282)	**0.026**
Smoking status	Osteoporosis	44	0.363	1.268(0.623 - 2.583)	0.512
Alcohol intake frequency	Osteoporosis	30	0.181	0.496(0.347 - 0.707)	0.001
Plus serum 25-Hydroxyvitamin D levels					
Eosinophil counts	Osteoporosis	278	0.061	1.138(1.009 - 1.284)	**0.035**
Smoking status	Osteoporosis	40	0.363	1.418(0.696 - 2.891)	0.337
Alcohol intake frequency	Osteoporosis	29	0.183	0.532(0.371 - 0.761)	0.001
vitamin D levels	Osteoporosis	47	0.119	1.150(0.910 - 1.453)	0.242
Plus Type 2 diabetes					
Eosinophil counts	Osteoporosis	211	0.069	1.173(1.024 - 1.343)	**0.021**
Smoking status	Osteoporosis	32	0.411	2.565(1.146 - 5.740)	0.022
Alcohol intake frequency	Osteoporosis	25	0.196	0.530(0.361 - 0.779)	0.001
vitamin D levels	Osteoporosis	36	0.137	1.133(0.866 - 1.481)	0.363
Type 2 diabetes	Osteoporosis	33	0.053	0.863(0.778 - 0.958)	0.006
Plus Medication use (glucocorticoids)					
Eosinophil counts	Osteoporosis	211	0.071	1.171(1.019 - 1.346)	**0.026**
Smoking status	Osteoporosis	31	0.428	1.970(0.852 - 4.555)	0.113
Alcohol intake frequency	Osteoporosis	25	0.196	0.538(0.367 - 0.791)	0.002
vitamin D levels	Osteoporosis	36	0.136	1.134(0.868 - 1.481)	0.358
Type 2 diabetes	Osteoporosis	33	0.053	0.864(0.779 - 0.959)	0.006
Medication use (glucocorticoids)	Osteoporosis	8	0.033	1.003(0.941 - 1.071)	0.917

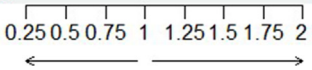

Fig. 2 The results of MVMR analysis of Eosinophil counts on Osteoporosis

First, the close association between allergic diseases and eosinophils has been widely confirmed, but the bidirectional causal relationship between eosinophils and allergic diseases has not been fully elucidated before this study. Eosinophils regulate immune and inflammatory responses, and their accumulation in blood and tissues is strongly associated with various inflammatory diseases.[17] Upon binding to the high-affinity receptor FcεRI on the cell surface, IgE-mediated activation causes eosinophils to degranulate and release a range of inflammatory mediators, including major basic protein (MBP) and eosinophil cationic protein (ECP). This release of mediators exacerbates the symptoms and progression of allergic diseases such as asthma and allergic rhinitis.[5] For certain allergic diseases, such as asthma, allergic rhinitis, and eczema, eosinophils both increase the risk of these diseases and are further produced in greater numbers due to these diseases, leading to disease exacerbation. This bidirectional causal relationship between these allergic diseases and eosinophils may partly explain the close association observed among different allergic diseases.[18,19] This correlation may originate from the analogous immune regulatory and inflammatory roles of eosinophils in diverse allergic reactions, consequently causing an intersection and overlap in the clinical manifestations and pathophysiological mechanisms of various allergic diseases. However, it is important to note that this bidirectional relationship does not apply to all allergic diseases. For instance, previous studies have shown that there is only a unidirectional causal relationship from eosinophils to atopic dermatitis,[20] which is 1 reason why atopic dermatitis was not included in this study.

The results of MVMR analysis of Eosinophil percentage on Osteoporosis

Exposure	Outcome	nSNP	SE	OR(95%CI)	P.value
Adjust for Smoking status					
Eosinophil percentage	Osteoporosis	315	0.061	1.148(1.018 - 1.295)	**0.024**
Smoking status	Osteoporosis	47	0.356	1.626(0.809 - 3.268)	0.172
Plus Alcohol intake frequency					
Eosinophil percentage	Osteoporosis	308	0.062	1.163(1.030 - 1.314)	**0.015**
Smoking status	Osteoporosis	43	0.368	1.377(0.669 - 2.836)	0.385
Alcohol intake frequency	Osteoporosis	36	0.182	0.535(0.375 - 0.764)	0.001
Plus serum 25-Hydroxyvitamin D levels					
Eosinophil percentage	Osteoporosis	255	0.065	1.170(1.031 - 1.329)	**0.015**
Smoking status	Osteoporosis	40	0.370	1.461(0.707 - 3.020)	0.306
Alcohol intake frequency	Osteoporosis	33	0.185	0.634(0.441 - 0.911)	0.014
vitamin D levels	Osteoporosis	53	0.120	1.119(0.884 - 1.417)	0.348
Plus Type 2 diabetes					
Eosinophil percentage	Osteoporosis	200	0.073	1.191(1.033 - 1.373)	**0.016**
Smoking status	Osteoporosis	33	0.412	2.204(0.983 - 4.943)	0.055
Alcohol intake frequency	Osteoporosis	28	0.198	0.592(0.402 - 0.872)	0.008
vitamin D levels	Osteoporosis	38	0.139	1.104(0.840 - 1.451)	0.477
Type 2 diabetes	Osteoporosis	36	0.054	0.874(0.787 - 0.971)	0.012
Plus Medication use (glucocorticoids)					
Eosinophil percentage	Osteoporosis	200	0.081	1.161(0.991 - 1.360)	**0.065**
Smoking status	Osteoporosis	32	0.428	1.707(0.738 - 3.950)	0.211
Alcohol intake frequency	Osteoporosis	28	0.198	0.593(0.402 - 0.875)	0.008
vitamin D levels	Osteoporosis	38	0.139	1.100(0.838 - 1.443)	0.494
Type 2 diabetes	Osteoporosis	36	0.053	0.876(0.789 - 0.973)	0.013
Medication use (glucocorticoids)	Osteoporosis	7	0.082	1.060(0.902 - 1.246)	0.481

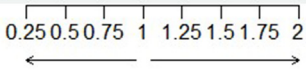

Fig. 3 The results of MVMR analysis of Eosinophil percentage on Osteoporosis

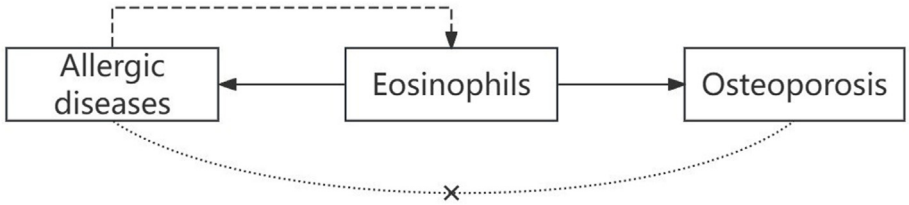

Fig. 4 The causal relationships among allergic diseases, eosinophils, and osteoporosis. Notes:The causal relationship from allergic diseases to eosinophils does not apply to all allergic diseases; therefore, we used a dashed line in the figure

Second, the association between allergic diseases and osteoporosis remains a controversial topic, which is the primary issue this study aims to resolve. Initially, this connection between allergic diseases and osteoporosis was primarily attributed to the use of glucocorticoids. However, growing evidence suggests that the relationship extends beyond glucocorticoid use. Although studies have suggested that the pathophysiological connection between allergic diseases and osteoporosis may involve multiple factors, including the immune system, inflammatory processes, and bone morphogenetic proteins,[4] previous research has not reached a consensus on whether there is a definitive association between allergic diseases and osteoporosis. For example, studies by Nachshon et al[21] and Lowe et al[22] have supported associations between milk allergy and osteoporosis, and between eczema and fractures, respectively. Multiple studies have also confirmed a clear association between asthma and osteoporosis,[23,24] though these studies often

focus on the use of steroid medications rather than asthma itself; additionally, a meta-analysis on atopic dermatitis and bone health[25] included 15 relevant studies, but their results were inconsistent, some studies found a significant correlation between atopic dermatitis and the risk of osteoporosis and fractures, while others did not find any association. Therefore, researchers speculate that there may be a common mediator involved in the development of both allergic diseases and osteoporosis. Earlier studies suggested that vitamin D could be the mediator linking allergic diseases and osteoporosis both clinically and biologically.[4,15] However, subsequent research refuted this hypothesis.[26,27] Moreover, 2 recent MR studies have indicated a causal association between asthma and osteoporosis,[28,29] which conflicts with our findings. We propose several potential reasons for this discrepancy: 1) sample bias, and 2) different research methodologies. To provide more reliable results, we employed 5 MR analysis methods and performed sensitivity analyses on statistically significant results, as well as MVMR analyses, which these 2 studies did not incorporate. Our more comprehensive results and high-quality evidence further support our conclusion that there is no genetic causal relationship between the 3 allergic diseases (asthma, allergic rhinitis, and eczema) and osteoporosis. Although our genetic analysis found no direct link between allergic diseases and osteoporosis, we do not rule out the possibility of other biological associations between them.

3) The specific mechanisms linking eosinophils and osteoporosis require further investigation, with inflammation being 1 potential mechanism. Eosinophils are a component of the innate immune system and belong to the granulocyte lineage. They develop in the bone marrow and differentiate from myeloid progenitor cells under the influence of the transcription factor GATA-1.[30] Recent studies have shown that eosinophils regulate osteoclast activity by secreting eosinophil peroxidase (EPX) under both normal and pathological conditions, thereby playing a role in maintaining bone homeostasis.[31] This suggests that eosinophils may be involved in bone metabolism and the regulation of osteoporosis. Furthermore, inflammation can definitively link eosinophils and osteoporosis. Eosinophils can produce various inflammatory mediators, such as interleukin-5 (IL-5) and tumor necrosis factor-alpha (TNF-α). These cytokines can regulate bone metabolism, promoting bone resorption and inhibiting bone formation.[32] Recently, Sirufo[4,33] constructed a model involving the bone, allergic diseases, and the IL-33/IL-31 axis to explain the complex overlapping mechanisms between allergies and osteoporosis. IL-31 and IL-33 are 2 key inflammatory cytokines involved in inflammatory responses and immune regulation. Their interaction and effects are thought to play crucial roles in various diseases, including cancer, autoimmune diseases, allergies, and osteoporosis.[34] It has been reported that serum levels of IL-31 increase with age in postmenopausal women with reduced bone mineral density,[35] while IL-33, a protective cytokine for bones, is significantly decreased in the serum of postmenopausal women with osteoporosis.[36] Eosinophils, as common targets of both IL-33 and IL-31, are likely to play an important role in inflammation and immune regulation, thereby contributing significantly to the development and progression of osteoporosis.

Our study further revealed the potential causal relationships among allergic diseases, eosinophils, and osteoporosis. However, more research is needed to verify and refine these causal relationships, particularly regarding their applicability across different populations and environments.

The limitations of this study are as follows: First, the populations involved are all of European descent, so the generalizability of the findings to other populations requires further investigation. Second, the Mendelian randomization dataset is complex, and there may be incidental results due to sample biases that should be considered. Lastly, the persuasive power of a single Mendelian randomization study remains limited, and further validation through other types of studies, such as clinical research, is necessary. Therefore, the results of this study should be interpreted with caution.

CONCLUSION

This study used MR analysis to elucidate the bidirectional potential causal relationship between the 3 allergic diseases (asthma, allergic rhinitis, and eczema) and eosinophils, and found a

unidirectional causal relationship may exist from eosinophil counts to osteoporosis. These findings provide new perspectives for further research into the pathophysiology of allergic diseases and osteoporosis.

Abbreviations

MR, Mendelian randomization (MR); MVMR, multivariable Mendelian randomization; IVs, instrumental variables; SNP, Single nucleotide polymorphism; IVW, Inverse Variance Weighted; MBP, major basic protein; ECP, eosinophil cationic protein; EPX, eosinophil peroxidase; IL-5, interleukin-5; TNF-α, tumor necrosis factor-alpha.

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Data availability statement

The datasets presented in this study can be found in article/supplementary material. They can also be downloaded from the IEU Open GWAS (https://gwas.mrcieu.ac.uk/datasets/), GWAS Catalog (https://www.ebi.ac.uk/gwas/) and FINNGEN (https://www.finngen.fi/en) project.

Author contributions

The study was designed by XH Y and SS S. Statistical analyses were performed by XH Y, SM Y, and T F. The manuscript was written by XH Y and HF L. All authors contributed to the interpretation of data and commented on the manuscript. All authors contributed to the article and approved the submitted version.

Author's consent for publication

All authors have approved the manuscript and agree with its submission to World Allergy Organization Journal.

Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. All authors have no conflicts of interest to declare.

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Ethics statement

The GWAS summary data used in this study were publicly available for download, and each original study received the appropriate ethical approval. Therefore, no additional ethical approval or informed consent was required for this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2025.101039.

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REFERENCES

1. Wang Z, Li Y, Gao Y, et al. Global, regional, and national burden of asthma and its attributable risk factors from 1990 to 2019: a systematic analysis for the Global Burden of Disease Study 2019. *Respir Res*. 2023;24(1):169.
2. Gatti D, Senna G, Viapiana O, et al. Allergy and the bone: unexpected relationships. *Ann Allergy Asthma Immunol*. 2011;107(3):202–206.
3. Saxena Y, Routh S, Mukhopadhaya A. Immunoporosis: role of innate immune cells in osteoporosis. *Front Immunol*. 2021;12, 687037.
4. Sirufo MM, Suppa M, Ginaldi L, et al. Does allergy break bones? Osteoporosis and its connection to allergy. *Int J Mol Sci*. 2020;21(3).
5. Wechsler ME, Munitz A, Ackerman SJ, et al. Eosinophils in health and disease: a state-of-the-art review. *Mayo Clin Proc*. 2021;96(10):2694–2707.
6. Gigon L, Fettrelet T, Yousefi S, et al. Eosinophils from A to Z. *Allergy*. 2023;78(7):1810–1846.
7. Fischer V, Haffner-Luntzer M. Interaction between bone and immune cells: implications for postmenopausal osteoporosis. *Semin Cell Dev Biol*. 2022;123:14–21.
8. Larsson SC, Butterworth AS, Burgess S. Mendelian randomization for cardiovascular diseases: principles and applications. *Eur Heart J*. 2023;44(47):4913–4924.
9. Skrivankova VW, Richmond RC, Woolf BAR, et al. Strengthening the reporting of observational studies in epidemiology using mendelian randomization: the STROBE-MR statement. *JAMA*. 2021;326(16):1614–1621.
10. Spiga F, Gibson M, Dawson S, et al. Tools for assessing quality and risk of bias in Mendelian randomization studies: a systematic review. *Int J Epidemiol*. 2023;52(1):227–249.

11. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol*. 2015;44(2):512–525.
12. Verbanck M, Chen C, Neale B, et al. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nat Genet*. 2018;50(5):693–698.
13. Bowden J, Spiller W, Del Greco MF, et al. Improving the visualization, interpretation and analysis of two-sample summary data Mendelian randomization via the Radial plot and Radial regression. *Int J Epidemiol*. 2018;47(4):1264–1278.
14. Sanderson E. Multivariable mendelian randomization and mediation. *Cold Spring Harb Perspect Med*. 2021;11(2).
15. Murdaca G, Allegra A, Tonacci A, et al. Mast cells and vitamin D status: a clinical and biological link in the onset of allergy and bone diseases. *Biomedicines*. 2022;10(8).
16. Cheng L, Wang S, Tang H. Type 2 diabetes mellitus plays a protective role against osteoporosis: mendelian randomization analysis. *BMC Muscoskelet Disord*. 2023;24(1):444.
17. Fulkerson PC, Rothenberg ME. Targeting eosinophils in allergy, inflammation and beyond. *Nat Rev Drug Discov*. 2013;12(2):117–129.
18. Ahn K, Penn RB, Rattan S, et al. Mendelian randomization analysis reveals a complex genetic interplay among atopic dermatitis, asthma, and gastroesophageal reflux disease. *Am J Respir Crit Care Med*. 2023;207(2):130–137.
19. Zhao J, Zhang M, Li Z. Association between immune-related disease and allergic rhinitis: a two-sample mendelian randomization study. *Am J Rhinol Allergy*. 2024;38(1):31–37.
20. Zeng-Yun-Ou Z, Zhong-Yu J, Wei L. Bidirectional associations between eosinophils, basophils, and lymphocytes with atopic dermatitis: a multivariable Mendelian randomization study. *Front Immunol*. 2022;13, 1001911.
21. Nachshon L, Goldberg MR, Schwartz N, et al. Decreased bone mineral density in young adult IgE-mediated cow's milk-allergic patients. *J Allergy Clin Immunol*. 2014;134(5):1108–1113.
22. Lowe KE, Mansfield KE, Delmestri A, et al. Atopic eczema and fracture risk in adults: a population-based cohort study. *J Allergy Clin Immunol*. 2020;145(2):563–571.
23. Chalitsios CV, McKeever TM, Shaw DE. Incidence of osteoporosis and fragility fractures in asthma: a UK population-based matched cohort study. *Eur Respir J*. 2021;57(1).
24. Chalitsios CV, Shaw DE, McKeever TM. Corticosteroids and bone health in people with asthma: a systematic review and meta-analysis. *Respir Med*. 2021;181, 106374.
25. Mukovozov IM, Morra DE, Giustini D, et al. Atopic dermatitis and bone health: a systematic review. *J Eur Acad Dermatol Venereol*. 2021;35(3):615–628.
26. Sun J, Zhao M, Hou Y, et al. Circulating serum vitamin D levels and total body bone mineral density: a Mendelian randomization study. *J Cell Mol Med*. 2019;23(3):2268–2271.
27. Feng Q, Bønnelykke K, Ek WE, et al. Null association between serum 25-hydroxyvitamin D levels with allergic rhinitis, allergic sensitization and non-allergic rhinitis: a Mendelian randomization study. *Clin Exp Allergy*. 2021;51(1):78–86.
28. Chen L, Li C, Chen H, et al. Cross-sectional studies of the causal link between asthma and osteoporosis: insights from Mendelian randomization and bioinformatics analysis. *Osteoporos Int*. 2024;35(6):1007–1017.
29. Ding W, Huang Y, Li G, et al. Higher risk of osteoporosis in adult-onset asthma than childhood-onset asthma: from genetic and prospective evidence. *Osteoporos Int*. 2024;35(4):659–668.
30. Drissen R, Buza-Vidas N, Woll P, et al. Distinct myeloid progenitor-differentiation pathways identified through single-cell RNA sequencing. *Nat Immunol*. 2016;17(6):666–676.
31. Andreev D, Kachler K, Liu M, et al. Eosinophils preserve bone homeostasis by inhibiting excessive osteoclast formation and activity via eosinophil peroxidase. *Nat Commun*. 2024;15(1):1067.
32. Iantomasi T, Romagnoli C, Palmini G, et al. Oxidative stress and inflammation in osteoporosis: molecular mechanisms involved and the relationship with microRNAs. *Int J Mol Sci*. 2023;24(4).
33. Sirufo MM, De Pietro F, Catalogna A, et al. The microbiota-bone-allergy interplay. *Int J Environ Res Publ Health*. 2021;19(1).
34. Murdaca G, Greco M, Tonacci A, et al. IL-33/IL-31 Axis in immune-mediated and allergic diseases. *Int J Mol Sci*. 2019;20(23).
35. Ginaldi L, De Martinis M, Ciccarelli F, et al. Increased levels of interleukin 31 (IL-31) in osteoporosis. *BMC Immunol*. 2015;16:60.
36. Ginaldi L, De Martinis M, Saitta S, et al. Interleukin-33 serum levels in postmenopausal women with osteoporosis. *Sci Rep*. 2019;9(1):3786.