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Investigating the causal association between heme oxygenase-1 and asthma: A bidirectional two-sample Mendelian randomization analysis in a European population

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ABSTRACT

Background: The association between heme oxygenase-1 (HO-1) and asthma has been a subject of debate in both observational and experimental studies. We aimed to evaluate the potential causal relationship between HO-1 and asthma.

Materials and methods: A bidirectional two-sample Mendelian randomization (TSMR) study was conducted to examine the causal relationship between HO-1 and asthma. In the forward Mendelian randomization (MR) analyses, HO-1 was considered as the exposure, while asthma as the outcome. Conversely, in the reverse MR analyses, asthma was regarded as the exposure, and HO-1 as the outcome. Data for HO-1 and asthma were obtained from publicly accessible genome-wide association studies (GWAS). These causal relationships were identified through 5 MR methods, namely MR-Egger, weighted median, inverse-variance weighted (IVW), simple mode, and weighted mode. Additionally, sensitivity tests were conducted to assess the robustness of MR study. Finally, additional asthma datasets and childhood asthma were selected to validate the findings.

Results: In the forward MR analyses, according to the IVW method, genetically predicted HO-1 displays a negative correlation with the risk of asthma (OR 0.947, 95% CI 0.905–0.990). It was not found any SNP overly sensitive or disproportionately responsible for the outcome. No evidence of heterogeneity and pleiotropy between SNPs was observed. Genetically predicted asthma was not associated with HO-1 in reverse MR analyses using the IVW method. The same results were validated in additional asthma datasets and in childhood asthma.

Conclusion: The results of MR analysis revealed heme oxygenase-1 as a protective factor for asthma.

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INTRODUCTION

Asthma, a chronic respiratory disease, exhibits a significant global prevalence and is distinguished by airway hyperresponsiveness (AHR), airway inflammation, and airway remodeling.[1] The estimated global population affected by asthma currently stands at 300 million, and this figure is projected to rise exponentially, with an additional 100 million individuals anticipated to be impacted by asthma by 2025.[2] Given the escalating burden of this condition, there is an imperative need to actively pursue efficacious preventive measures. Despite recent advancements in the understanding of the pathogenesis of asthma, the diagnosis process, and the availability of medication,[3] there remains a subset of asthma patients who experience inadequate control despite receiving the highest level of treatment.[4] Consequently, there is an urgent need to elucidate the underlying mechanisms of asthma and identify efficacious intervention strategies for its treatment.

Heme oxygenase-1 (HO-1), an inducible type of heme oxygenase, serves as the initial enzyme in the rate-limiting step of heme degradation, resulting in the production of free iron, biliverdin, and carbon monoxide (CO).[5] The lung protective effects of HO-1 and its enzymatic reaction products have been demonstrated in numerous in vitro and in vivo models of lung diseases.[6] Although recent studies have reported a connection between heme oxygenase-1 and asthma, the precise nature of this relationship remains a subject of controversy. The majority of studies have demonstrated that heme oxygenase-1 has a reducing effect on asthma.[7-9] HO-1 demonstrates a protective effect on airway epithelial cells by inhibiting apoptosis and preserving airway epithelial homeostasis in both asthmatic mouse models and in vitro studies of airway epithelial cells. Upregulation of HO-1 has been shown to diminish inflammatory cell infiltration in a mouse model of asthma, as well as decrease levels of T-cell factor 2 and immunoglobulin E. However, a minority of studies have indicated that heme oxygenase-1 actually promotes asthma inflammation and immune response.[10,11] The upregulation of HO-1 expression was observed in the context of allergic airway inflammation in a murine model of asthma sensitized with ovalbumin. The majority of investigations on this topic have been carried out using animal models of asthma, revealing inconsistencies. Further research utilizing higher levels of evidence is necessary to elucidate the causal association between HO-1 and asthma.

Mendelian randomization (MR) analysis is a novel study design in genetic epidemiology. This approach utilizes genetic variation in a risk factor to evaluate causal relationships between the risk factor and disease.[12] By employing genetic variables as instrumental variables instead of relying on exposure to outcomes, this method offers enhanced causal inference capabilities for estimating causal associations.[13] In terms of conceptualization, Mendelian randomization can be compared to prospective randomized controlled trials (RCTs), while the methods employed in Mendelian randomization can be conducted retrospectively.[14] Nevertheless, Mendelian randomization offers an advantage due to the random nature of genotypes at conception, which renders them unaffected by confounding factors related to lifestyle and eliminates the possibility of reverse causal relationships. The utilization of genome-wide association studies (GWAS) and Mendelian randomization has enabled the evaluation of causal relationships between risk factors and disease outcomes.[15] Analysis of GWAS data for Mendelian randomization can be conducted using the R package within the R programming language.

Since the causal relationship between HO-1 and asthma is unclear, we conducted a bidirectional two-sample Mendelian randomization (TSMR) analysis to explore the causal relationship between heme oxygenase-1 and asthma, and selected

additional asthma datasets and childhood asthma for external validation.

MATERIALS AND METHODS

Study design

A bidirectional two-sample Mendelian randomization approach was employed to investigate the causal relationship between heme oxygenase 1 and asthma (Fig. 1). Bidirectional Mendelian randomization can eliminate any analysis of reverse causality. In the forward MR analyses, heme oxygenase-1 was treated as the exposure, while asthma was considered as the outcome. Conversely, in the reverse MR analyses, asthma was treated as the exposure, and heme oxygenase-1 was considered as the outcome. Finally, additional asthma datasets and childhood asthma were selected to validate the findings. In the context of the MR study, adherence to 3 primary assumptions is imperative.[16] Firstly, it is crucial that the SNPs variants exhibit a strong correlation with the exposure being investigated. Secondly, the SNPs should be unaffected by any other established confounding factors. Lastly, the impact of the SNPs on the outcome should solely be mediated by the exposure under scrutiny.

Data sources

Publicly available data on heme oxygenase 1 and asthma were derived from genome-wide association studies (GWAS). The specific characteristics of these traits are presented in Table 1. Heme oxygenase-1 data were obtained from 10,780 individuals of European ancestry using blood protein measurement to obtain genome-wide genotyping arrays.[17] The data concerning asthma were sourced from the UK Biobank, encompassing a broad definition of asthma with 56,167 cases and 352,255 controls.

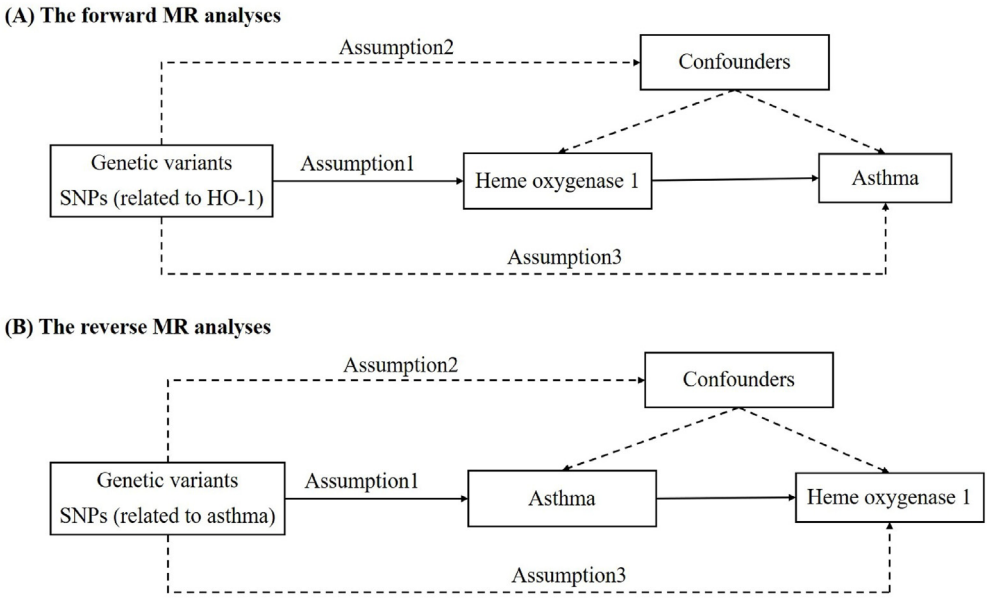

Fig. 1 The overview and assumptions of the MR study design. Assumption 1: SNPs variants should be closely associated with exposure (forward: HO-1, reverse: asthma). Assumption 2: SNPs should be independent of other known confounders. Assumption 3: SNPs should affect the risk of outcome (forward: asthma, reverse: HO-1) only through exposure (forward: HO-1, reverse: asthma).

Trait	id	Year	Population	Sample size	*n*SNPs
Heme oxygenase 1	ebi-a-GCST90019406	2020	European	10708	15567739
Asthma	ebi-a-GCST90014325	2021	European	408442	34551291
Asthma (Validation)	finn-b-J10_ASTHMA	2021	European	156078	16380176
Childhood asthma	finn-b-ASTHMA_CHILD	2021	European	138474	16379865

Table 1. Baseline characteristics of the genome-wide association studies included in the MR study

exposure	outcome	nsnp	method	pval	OR(95% CI)
Heme oxygenase 1	Asthma	10	MR Egger	0.084	0.905 (0.819 to 0.999)
		10	Weighted median	**0.026**	0.947 (0.902 to 0.993)
		10	Inverse variance weighted	**0.016**	0.947 (0.905 to 0.990)
		10	Simple mode	0.123	0.942 (0.878 to 1.009)
		10	Weighted mode	0.251	0.960 (0.898 to 1.025)
Asthma	Heme oxygenase 1	73	MR Egger	0.577	0.957 (0.822 to 1.115)
		73	Weighted median	0.377	0.962 (0.882 to 1.049)
		73	Inverse variance weighted	0.587	0.984 (0.927 to 1.044)
		73	Simple mode	0.603	0.950 (0.784 to 1.151)
		73	Weighted mode	0.149	0.883 (0.747 to 1.044)

Fig. 2 The results of MR analysis to indicate causal association between heme oxygenase-1 and asthma. nsnp, number of snp; OR, odds ratio.

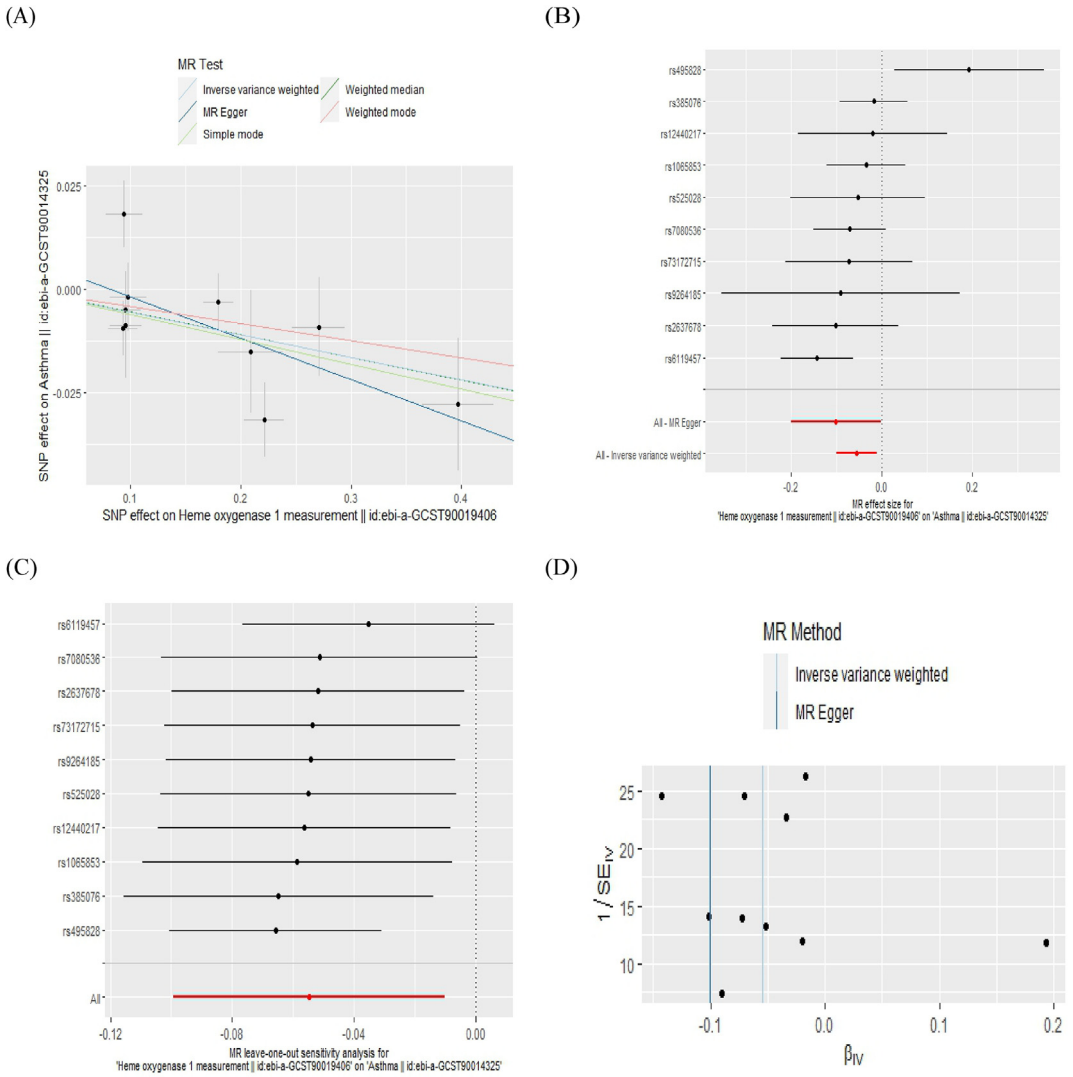

Fig. 3 Graphical results of forward MR analysis. (A) Scatter plot. (B) Forest plot. (C) Leave-one-out analysis. (D) funnel plot.

The case group exhibited a mean age of 56.5 years, comprising 42.5% males and 57.5% females, while the control group had an average age of 57.0 years, with 46.4% male and 53.6% female participants.[18] Data on asthma in the validation group and childhood asthma were sourced from FinnGen Release 5 (https://www.finngen.fi/en), a collaborative initiative aimed at gathering and

examining genomic and health information from 500,000 individuals in the Finnish biobank. The validation group for asthma comprised 20,629 cases and 135,449 controls. Within the case group, there were 12,679 females and 7950 males, with a mean age at first event of 43.94 years, 43.50 years for females, and 44.66 years for males. Childhood asthma was operationally defined as individuals with asthma aged 16 years or younger, resulting in 3025 cases and 135,449 controls in this subgroup. Among the cases, there were 1684 females and 1341 males, with a mean age at first event of 7.37 years, 7.86 years for females, and 6.76 years for males. Since this study solely utilized publicly accessible summary-level data from GWAS, there was no requirement for additional ethical approval.

Selection of instrumental variables for heme oxygenase-1

Genetic variants were employed as instrumental variables in Mendelian randomization (MR) analyses to investigate the causal relationship between exposure and outcome.[13] In our study, we selected single nucleotide polymorphisms (SNPs) that represent the global human genetic variation as instrumental variables (IVs). The exposure of interest in the forward MR analyses was heme oxygenase-1, while the outcome was asthma. SNPs that exhibited strong associations with heme oxygenase-1 reached a genome-wide significance level ($p < 5 \times 10^{-8}$). Subsequently, these SNPs were subjected to clumping based on linkage disequilibrium (LD), with a threshold of $r2 < 0.001$ within 10,000 kb windows. The F statistic was employed to confirm the robust correlation between independent variables (IVs) and exposure.[19] SNPs with an F statistic exceeding 10 were chosen. For each SNP, the corresponding phenotype was queried on the Ensembl website (https://useast.ensembl.org/index.html), and any SNP associated with asthma-related confounders was subsequently excluded. Prior to conducting Mendelian randomization (MR) analysis, we harmonized the data to ensure that the impact of SNPs on both exposure and outcome could be attributed to the same allele. The minor effect allele frequency was established at 0.42. We aimed to deduce positive strand alleles by utilizing allele frequencies for palindromes.

Selection of instrumental variables for asthma

In the reverse MR analyses, asthma was regarded as the exposure, while heme oxygenase-1 was considered as the outcome. The method was the same as described in"Selection of instrumental variables for heme oxygenase-1".

Exposure	Outcome	Heterogeneity test				Pleiotropy test		
		MR Egger		IVW		MR Egger		MR-PRESSO
		Cochran's Q	*p* Value	Cochran's Q	*p* Value	Egger intercept	*p* Value	Global *p* Value
HO-1	Asthma	13.678	0.091	15.392	0.081	0.008	0.346	0.097
Asthma	HO-1	87.450	0.090	87.625	0.102	0.002	0.707	0.083
HO-1	Asthma (Validation)	9.773	0.202	10.144	0.255	0.007	0.622	0.362
Asthma (Validation)	HO-1	17.423	0.234	21.373	0.125	−0.041	0.097	0.153
HO-1	Childhood asthma	5.553	0.475	6.954	0.434	0.036	0.281	0.47
Childhood asthma	HO-1	1.283	0.733	1.733	0.785	−0.018	0.550	0.713

Table 2. Tests of heterogeneity and pleiotropy

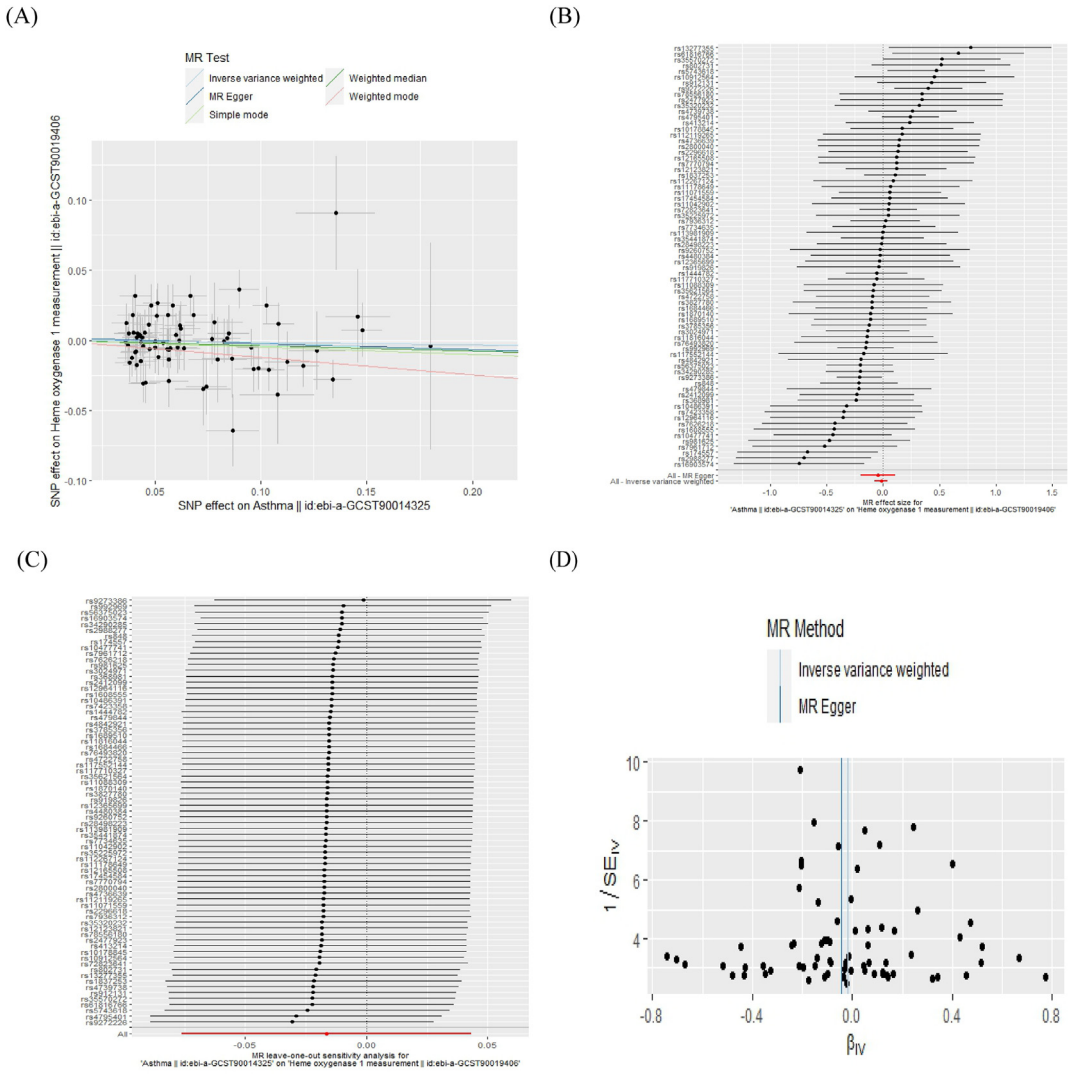

Fig. 4 Graphical results of reverse MR analysis. (A) Scatter plot. (B) Forest plot. (C) Leave-one-out analysis. (D) funnel plot.

Statistical analysis

The MR pleiotropy residual sum and outlier (MR-PRESSO) test, with a Nb Distribution of 1000 and a Significant Threshold of 0.05, was used to detect outlier SNPs. This analysis was performed using the MR-PRESSO packages in R software version 4.2.0. Both forward and reverse MR analyses were conducted using the TwoSampleMR packages in R software. In order to elucidate the causal association between heme oxygenase-1 and asthma, this study employed 5 different MR analysis techniques, namely MR-Egger, weighted median, inverse-variance weighted (IVW), simple mode, and weighted mode. To assess the robustness of the findings, sensitivity analyses were conducted by examining heterogeneity using Cochran's Q statistics and funnel plots for the IVW and MR-Egger methods. If the p-value for these 2 methods exceeded 0.05, it indicated the absence of heterogeneity. Additionally, the presence of horizontal pleiotropy was assessed using the MR-Egger and MR-PRESSO methods. When p-value for the 2 methods >0.05, there was no horizontal pleiotropy. In the leave-one-out analysis, the sensitivity of SNPs was assessed to determine if any of them exhibited disproportionate influence on the outcome. If the p-value for the IVW method in the MR analysis is less than 0.05, and all 5 methods of the MR analysis go in the same direction without any indication of horizontal pleiotropy, the obtained result can be considered statistically significant.

Mendelian randomization of validation group asthma and childhood asthma

The identical bidirectional two-sample Mendelian randomization approach was employed to confirm the causal association between heme oxygenase 1 and asthma in the validation cohort, as well as the causal relationship between heme oxygenase 1 and childhood asthma.

RESULTS

The role of heme oxygenase-1 in asthma

In the forward MR analyses, we selected 10 SNPs from heme oxygenase-1 as instrumental variables (Supplement 1). No proxies SNPs were found in outcome. The effect of each SNP on the exposure and the outcome attributed to the same allele. Results of the 5 MR analysis methods were displayed in Fig. 2. Result of IVW method showed that there was a negative association between genetically predicted heme oxygenase-1 with risk of asthma (OR 0.947, 95% CI 0.905–0.990). The 5 methods of the MR analysis go in the same direction. These results were also showed in the scatter plot (Fig. 3A) and forest plot (Fig. 3B). There was no SNP that was oversensitive and disproportionately responsible for the outcome (Fig. 3C). No evidence of heterogeneity and pleiotropy between SNPs was observed (Table 2, Fig. 3D).

The role of asthma on heme oxygenase-1

In the reverse MR analyses, we selected 80 independent SNPs from GWAS on asthma (Supplement 2), then we found 6 proxies SNPs in heme oxygenase 1 and removed them. When we harmonize the data, we found 1 SNP (rs13099273) for being palindromic with intermediate allele frequencies and removed it. Finally, 73 SNPs significantly associated with asthma in our study were used as instrumental variables. The results of the 5 MR analysis methods were showed in Fig. 2. Result of IVW method showed that genetically predicted asthma was not significantly associated with heme oxygenase-1. No significant association was identified in other methods. These results were also showed in the scatter plot (Fig. 4A) and forest plot (Fig. 4B). There was no SNP that was oversensitive and disproportionately responsible for the outcome (Fig. 4C). No evidence of heterogeneity and pleiotropy between SNPs was observed (Table 2, Fig. 4D).

Mendelian randomization of validation group asthma and childhood asthma

The findings were further confirmed in additional asthma datasets and specifically in the context of childhood asthma. Within the validation asthma group, genetically predicted levels of HO-1 were found to be inversely associated with the likelihood of developing asthma (OR 0.924, 95% CI 0.858–0.996). Similarly, within the childhood asthma group, genetically predicted HO-1 levels were also negatively correlated with the risk of childhood asthma (OR 0.770, 95% CI 0.651–0.911). The results of the Mendelian randomization analysis are presented in Fig. 5, with no discernible

exposure	outcome	nsnp	method	pval	OR(95% CI)
Heme oxygenase 1(validation group)	Asthma(validation group)	9	MR Egger	0.238	0.884 (0.733 to 1.066)
		9	Weighted median	**0.043**	0.915 (0.840 to 0.997)
		9	Inverse variance weighted	**0.040**	0.924 (0.858 to 0.996)
		9	Simple mode	0.079	0.885 (0.785 to 0.997)
		9	Weighted mode	0.090	0.911 (0.829 to 1.002)
Asthma(validation group)	Heme oxygenase 1(validation group)	16	MR Egger	0.147	1.394 (0.912 to 2.131)
		16	Weighted median	0.944	1.004 (0.895 to 1.127)
		16	Inverse variance weighted	0.342	0.956 (0.871 to 1.049)
		16	Simple mode	0.840	1.021 (0.837 to 1.246)
		16	Weighted mode	0.569	1.049 (0.893 to 1.233)
Heme oxygenase 1	Childhood asthma (age<16)	8	MR Egger	0.057	0.619 (0.415 to 0.922)
		8	Weighted median	0.072	0.821 (0.662 to 1.018)
		8	Inverse variance weighted	**0.002**	0.770 (0.651 to 0.911)
		8	Simple mode	0.153	0.752 (0.531 to 1.065)
		8	Weighted mode	0.068	0.734 (0.554 to 0.973)
Childhood asthma (age<16)	Heme oxygenase 1	5	MR Egger	0.419	1.109 (0.893 to 1.377)
		5	Weighted median	0.099	1.057 (0.990 to 1.129)
		5	Inverse variance weighted	0.255	1.032 (0.978 to 1.089)
		5	Simple mode	0.881	0.992 (0.898 to 1.095)
		5	Weighted mode	0.194	1.060 (0.985 to 1.141)

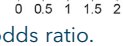

Fig. 5 MR results of validation group asthma and childhood asthma. nsnp, number of snp; OR, odds ratio.

evidence of heterogeneity or pleiotropy among the SNPs examined, as detailed in Table 2.

DISCUSSION

In this study, a bidirectional two-sample Mendelian randomization was conducted to investigate the potential impact of heme oxygenase-1 on asthma. The results of the genetic prediction analysis indicated a significant association between higher levels of heme oxygenase-1 and a reduced risk of asthma. Conversely, the reverse Mendelian randomization analysis using the IVW method suggested a non-significant association between higher asthma risk and lower levels of heme oxygenase-1. These findings align with the majority of experimental and observational studies, and contribute to the understanding of the role of heme oxygenase-1 in the pathogenesis of asthma. The etiology of asthma has been a subject of extensive scholarly investigation, resulting in notable advancements. Multiple mechanisms contribute to the development of asthma, encompassing airway hyperresponsiveness (AHR), airway inflammation, and airway remodeling.[20] Additionally, oxidative stress,[21] Th1/Th2 imbalance[22] and Th17/Treg imbalance[23] are implicated in the pathogenesis of asthma. Furthermore, various experimental and observational studies have identified a protective function of heme oxygenase-1 in the aforementioned pathogenesis of asthma.

Hemoglobin oxygenase-1 is anticipated to exert immunomodulatory effects in the context of asthmatic airway inflammation. Throughout different stages of airway inflammation, heme oxygenase-1 plays a regulatory role in diverse immune cell populations, including dendritic cells, T cells, basophils, mast cells, and macrophages.[24] In eosinophilic asthma, extracellular vesicles generated by dendritic cells expressing HO-1 contribute to the mitigation of allergic airway inflammation by promoting the differentiation of Treg cells and restraining the release of proinflammatory cytokines.[9] Furthermore, it has been observed that heme oxygenase-1 exerts inhibitory effects on the maturation and activation of basophils, leading to the promotion of basophil apoptosis, thereby exhibiting anti-inflammatory properties.[25] Additionally, heme oxygenase-1 demonstrates the capacity to impede eosinophilic inflammation by hindering the phosphorylation of signal transducer and activator of transcription 3 (STAT3) and suppressing the expression of suppressors of cytokine signaling 3 (SOCS3) in naive $CD4^+$ T cells.[26]

Moreover, the role of heme oxygenase-1 in asthmatic airway remodeling is of utmost importance. This process encompasses various factors such as epithelial injury, subepithelial fibrosis, epithelial-mesenchymal transition (EMT), proliferation of airway smooth muscle cells (ASMC), goblet cell proliferation, and angiogenesis.[27] Notably, heme oxygenase-1 has been found to mitigate the airway remodeling process in asthma by inhibiting the proliferation of smooth muscle cells induced by platelet-derived growth factor (PDGF)-BB.[28] In the context of asthma, it is frequently observed that symptoms such as excessive mucus secretion and an increase in the number of goblet cells occur. Mucin 5AC (MUC5AC) is a significant constituent of the mucus found in the airway epithelial cells. The expression of MUC5AC can be enhanced by the presence of IL-13. However, the overexpression of heme oxygenase-1 has the ability to inhibit the IL-13-induced proliferation of goblet cells and the production of MUC5AC.[29]

Oxidative stress is a phenomenon characterized by the detrimental effects resulting from an imbalance between reactive oxygen species (ROS) and the host's antioxidant defense mechanisms. Its significance is evident in the pathogenesis of asthma, neutrophil inflammation, airway remodeling, and resistance to corticosteroids.[30] Additionally, heme oxygenase-1 has been identified as a mitigating factor against oxidative stress in asthma. The involvement of nuclear factor erythroid 2-related factor 2 (Nrf2) in the classical antioxidant pathway is of paramount importance. Dysfunctional Nrf2 gene expression in animal models has been observed to increase susceptibility to asthma induction or exacerbation.[31] Heme oxygenase-1, an antioxidant enzyme, is subject to regulation by Nrf2.[32] In the context of asthma, the activation of the Nrf2/HO-1 pathway by vitamin D3 alleviates oxidative stress.[33]

Th 1/Th 2 imbalance is thought to be the immunopathogenesis of asthma. T cells tilt towards Th2 cells, resulting in an imbalance between Th1 and Th2 cytokines, which promotes the onset and development of asthma.[34] Regulatory T (Treg) cells are

pivotal in maintaining immune homeostasis, and the induction of Treg cells represents a promising therapeutic approach for the treatment of Th2-mediated allergic asthma. Similar to the imbalances between Th1/Th2 cells, imbalances between Treg/Th17 cells are crucial for the development of asthma. Schizandrin B has the ability to activate heme oxygenase-1, which in turn promotes the expansion of Foxp3+ regulatory T cells and plays a role in modulating the immune response in Th2-mediated allergic asthma.[35] The inflammation of allergic airways can be suppressed by $CD4^{+}CD25$ high regulatory T cells, which are mediated by heme oxygenase-1.[36] Additionally, heme oxygenase-1 can provide a protective effect against neutrophilic airway inflammation induced by ovalbumin by inhibiting the immune response mediated by Th17 cells.[37]

In summary, the alleviation of asthma by heme oxygenase-1 is supported by multiple pathways, as indicated by our Mendelian randomization findings. However, a few studies have presented contrasting evidence, focusing on the expression of heme oxygenase-1 in macrophages and monocytes.[10,11,38] The aforementioned studies examined the heightened expression of HO-1 in macrophages and monocytes of individuals with asthma, while our Mendelian randomization study specifically investigated HO-1 expression in blood. It is plausible that the activation of macrophages and monocytes following an asthma attack may result in a localized elevation of HO-1 levels, potentially contributing to an anti-asthmatic effect. Further investigation is required to elucidate the underlying mechanisms in greater detail. The utilization of Mendelian randomization helps to mitigate the influence of unknown or unmeasured confounding factors, thereby reducing the likelihood of spurious associations between exposures and disease outcomes. Despite a slightly lower odds ratio observed in our study, we employed a highly stringent p-value threshold of $<5 \times 10\text{-}8$ during the instrument variable selection stage. Additionally, all F statistic values exceeded 10, indicating no heterogeneity or pleiotropy in the test.

In our Mendelian randomization study, we found positive results as IVW methods with a P value below 0.05, and observed consistent directional alignment across all 5 Mendelian randomization analysis methods. The IVW method is commonly employed as the principal approach for Mendelian randomization due to its high efficacy in detecting causal effects.[39] In cases where multiple genetic tool variables are present, IVW can be utilized by assigning weights based on the effect estimates and standard errors of each single nucleotide polymorphism (SNP) to derive an overall effect estimate. However, it is important to note that IVW may be influenced by biases stemming from horizontal pleiotropy. Alternative methods such as MR-Egger and the weighted median approach, while less statistically powerful than IVW, offer greater robustness against biases caused by horizontal pleiotropy.[40] These methods offer complementary benefits, with the P values of IVW and weighted median in our study both below 0.05, indicating the reliability and robustness of the results. Therefore, it is better to choose the most appropriate method for the given context. Our reverse Mendelian randomization analysis did not reveal a causal relationship between asthma and HO-1 levels. This finding is consistent with our forward Mendelian randomization analysis, which suggests that HO-1 may reduce the risk of asthma, indicating the absence of reverse causality.

There are limitations to our findings, as with many other Mendelian randomization analyses. Our Mendelian randomization analysis utilized GWAS summary statistics, precluding access to raw data and thus precluding stratification by age. However, we identified a dataset of children with asthma for additional validation, enhancing the robustness of our findings. In this investigation, Mendelian randomization was employed to investigate the potential causal association between HO-1 and asthma. To mitigate population heterogeneity, it is generally recommended that exposure and outcome datasets be derived from individuals of the same racial background. Given the absence of HO-1 datasets from non-European populations, our analysis was restricted to European cohorts. The scope of our investigation primarily encompassed individuals of European descent, thus warranting the need for verification of our findings in diverse populations. If possible, future GWAS data or RCT studies involving different populations could be carried out in order to enhance the generalizability of the findings.

To summarize, our Mendelian randomization study genetically predicted heme oxygenase-1 can

reduce asthma. A positive correlation has been established between elevated heme oxygenase-1 levels and a decreased likelihood of asthma. These outcomes necessitate careful consideration in future research endeavors and the formulation of public health interventions pertaining to asthma treatment approaches.

CONCLUSION

The results of MR analysis revealed heme oxygenase-1 as a protective factor for asthma.

Abbreviations

HO-1, heme oxygenase-1; TSMR, two-sample Mendelian randomization; MR, Mendelian randomization; GWAS, genome-wide association studies; IVW, inverse-variance weighted; SNPs, single nucleotide polymorphisms; AHR, airway hyperresponsiveness; CO, carbon monoxide; RCTs, randomized controlled trials; IVs, instrumental variables; LD, linkage disequilibrium; MR-PRESSO, MR pleiotropy residual sum and outlier; STAT3, signal transducer and activator of transcription 3; SOCS3, suppressors of cytokine signaling 3; EMT, epithelial-mesenchymal transition; ASMC, airway smooth muscle cells; PDGF, platelet-derived growth factor; MUC5AC, Mucin 5AC; ROS, reactive oxygen species; Nrf2, nuclear factor erythroid 2-related factor 2.

Declaration of competing interest

The author declares that there is no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2024.100987.

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