A Causal Inference Study on the Impact of Asthma on the Onset of Chronic Obstructive Pulmonary Disease: Two-Sample Mendelian Randomization

Keywords
COPD, GWAS, Mendelian Randomization, Asthma, Causal Relationship, Environmental Exposure Factors

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Introduction

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Material and methods

In this study, utilizing a two-sample Mendelian randomization (MR) approach and analyzing publicly available genome-wide association study (GWAS) datasets, we explored the causal impact of asthma on the onset of COPD. Using genetic instrumental variables associated with asthma ($p < 5 \times 10^{-8}$) and applying multiple MR methods (IVW, MR-Egger, and weighted median), we identified a significant causal relationship between asthma and COPD. The inverse variance weighted (IVW) method indicated that asthma increases the risk of developing COPD with an odds ratio (OR) of 1.35 (95% confidence interval [CI]: 1.12–1.58, p = 0.002).

Results

Additionally, multivariable MR analysis was performed to account for potential confounders, such as eosinophil count, smoking, and falls, which demonstrated that the association remains significant even after adjusting for these factors (OR: 1.29, 95% CI: 1.08–1.50, p = 0.004).

Conclusions

This study provides robust evidence supporting the causal link between asthma and COPD, offering a more comprehensive understanding of their relationship.
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Keywords: Asthma, GWAS, Mendelian Randomization, Causal Relationship, COPD, Environmental Exposure Factors

Introduction

Respiratory diseases have long been a focus of research in the field of public health, posing a serious threat to the health of the global population [1]. Among them, asthma and COPD are two highly prevalent diseases, posing significant challenges to patients' quality of life and the consumption of social medical resources. Although asthma and COPD have distinct pathological and physiological differences, with the former mainly characterized by chronic airway inflammation and the latter encompassing pathological changes such as chronic bronchitis and emphysema, their relationship and mutual influence remain a scientific puzzle of great concern[2, 3].

Asthma manifests as a complex chronic inflammatory condition, featuring airway hyperresponsiveness and reversible airway obstruction. Hundreds of millions of people worldwide suffer from asthma, affecting both adults and children[4]. COPD mainly includes chronic bronchitis and emphysema, is a progressive disease commonly found in smokers, and is also influenced by environmental factors such as air pollution. Both diseases are primarily characterized by symptoms such as dyspnea, cough, and chest tightness, causing significant inconvenience to patients' lives and work[5].

Although asthma and COPD differ in presentation and progression, their commonalities cannot be ignored. Studies have shown that in some patients, asthma and COPD might coexist, referred to as "asthma-COPD overlap syndrome" (ACOS)[6]. This situation complicates the management and

treatment of the disease, making it even more necessary to delve into the relationship between asthma and COPD to better understand their shared pathophysiological mechanisms and provide more precise bases for treatment strategies[7].

Previous studies have mainly focused on the pathogenesis and causative factors of asthma and COPD individually. However, the question of whether there is a causal relationship between the two, and whether asthma might be a potential factor in the development of COPD, remains relatively unclear in academia. Some observational studies have provided some clues, but due to the presence of numerous confounding factors, the research findings are contentious. Therefore, we need a more precise method to control for confounding variables.

By adopting a Mendelian randomization approach, which enables exploration of the causal relationship between asthma and COPD without being influenced by confounding factors, this study aims to delve into the possible association between the two conditions. Integrating publicly available genome-wide association study (GWAS) datasets and employing careful selection of genetic instrumental variables, alongside various Mendelian randomization analysis methods, the study seeks to elucidate the genetic mechanisms underlying asthma and COPD, thereby providing a clearer understanding of their interrelation.

Materials and Methods

Guidelines for Reporting and Study Design

This study utilized a two-sample MR approach and publicly available datasets to investigate the impact of asthma on COPD. The study report adheres to the STROBE-MR Statement, which enhances the reporting of observational studies in epidemiology using Mendelian randomization [8],

Figure 1 illustrates the study design schematic.

Data Sources

Genome-wide association study (GWAS) data for preliminary analysis of asthma indicators: GWAS analysis data conducted by Demenais et al. on 127,669 individuals of European ancestry, including 107,715 controls and 19,954 asthma cases [9]. GWAS analysis data conducted by Valette et al. on 408,442 individuals of European ancestry, including 352,255 controls and 56,167 asthma cases [10]. Chronic obstructive pulmonary disease (COPD) GWAS data: COPD GWAS data (ebi-a-GCST90018807) conducted by Sakaue et al. on 468,475 individuals of European ancestry, including 13,530 COPD cases and 454,945 controls [11].

Other GWAS data: Eosinophil cell count (ieu-b-33) from GWAS analysis conducted by Vuckovic et al., including 563,946 samples [12] [13]; Past tobacco smoking (ukb-b-2134) [14]from approximately 500,000 samples from the UK Biobank [15]; Falling risk (ebi-a-GCST90012857) GWAS data analysis including 451,179 samples [16] [17].

Instrumental Variable Selection

Effective genetic instrumental variables must meet three core assumptions: (1) the relevance assumption, i.e., the chosen instrumental variables must exhibit a significant association with the exposure factor; (2) the independence assumption, i.e., instrumental variables must lack statistical significance correlated with potential confounding factors that might affect exposure or outcome; (3) the exclusion restriction assumption, i.e., instrumental variables must exclusively influence the outcome through the pathway "instrumental variable → exposure → outcome".

In this study, the selection criteria for exposure instrumental variables are as follows: SNPs (Single Nucleotide Polymorphisms) with $P < 5 \times 10^{-8}$ in GWAS are used as the primary screening

condition; SNPs in linkage disequilibrium ($r^2 < 0.001$) and with a physical distance > 10,000 kb between every two genes are excluded. Then, outcome data are extracted from GWAS based on the selected SNPs.

MR Causal Effect Estimation

Various two-sample MR methods are used to assess the causal effects between exposure and outcome, including: Inverse-variance weighted (IVW), MR-Egger, Weight Median, Simple Mode, and Weight Mode. Studies have shown [18] that the IVW method is slightly stronger under certain conditions than other methods. Its characteristic is that it does not consider the presence of intercept terms during regression and uses the reciprocal of the outcome variance as weights for fitting. Therefore, in the absence of pleiotropy, regardless of the presence or absence of heterogeneity, the IVW method is used as the main MR analysis method in this study, with the other four methods used as supplements (IVW random effects model is used when heterogeneity exists). When pleiotropy exists, the MR-Egger method is used to calculate the results. The reverse causal effect is assessed using the same methods for the outcome's potential causal effect on exposure.

Sensitivity Analysis

Various methods, including heterogeneity testing, pleiotropy testing, and leave-one-out testing, are used to perform sensitivity analysis on the analysis results, as follows:

(1) Heterogeneity testing: Cochran's Q test is used to assess heterogeneity among estimated values of each SNP. If Cochran's Q test is statistically significant, it indicates significant heterogeneity in the results, and the effect size of the causal effect is evaluated using the IVW random effects model. Since Cochran's Q test could only determine the presence or absence of heterogeneity and cannot determine its distribution, the I^2 statistic is used to reflect the proportion of heterogeneity in the

total variation of instrumental variables: I^2 ≤ 0 indicates no observed heterogeneity; I^2 = 0–25% indicates mild heterogeneity; I^2 = 25–50% indicates moderate heterogeneity; I^2 > 50% indicates high heterogeneity. The specific calculation formula is as follows:

(2) Pleiotropy assessment: The MR-Egger method is employed to examine pleiotropy in instrumental variables. A MR-Egger's intercept p-value <0.05 suggests substantial horizontal pleiotropy in genetic variation.

(3) Leave-one-out testing: The leave-one-out method is used to evaluate whether a single SNP affects the association between asthma and COPD by sequentially removing individual SNPs and calculating the MR results with the remaining instrumental variables. If there is a large difference between the MR effect estimate after removing a particular instrumental variable and the cumulative effect estimate, it indicates sensitivity of the MR effect estimate to that SNP.

Multivariable MR Analysis

MVMR is an extension of MR that uses genetic variations associated with multiple exposures possibly correlated with a single outcome evaluate the impacts of various exposures on a singular outcome.It could assess the direct effects of individual exposure factors on the outcome. We conducted multivariable MR analysis by considering several relevant exposure factors of COPD: Eosinophil cell count (ieu-b-33), Past tobacco smoking (ukb-b-2134), Falling risk (ebi-a-GCST90012857), and the significant exposure asthma to obtain the direct effect of asthma on COPD.

Statistical Analysis

All data processing and statistical analyses were performed using the R programming language (version 4.2.2). Mendelian randomization analysis primarily relied on the TwoSampleMR package

[19]. To ensure the robustness and reliability of the results, Cochran's Q test and leave-one-out analysis were utilized. Additionally, genetic pleiotropy was assessed using MR-Egger's intercept method. Evaluation metrics consisted of odds ratios (OR) and their corresponding 95% confidence intervals (95% CI). All statistical P-values were two-sided, with SNP loci generated from GWAS studies considered statistically significant at $P < 5 \times 10^{-8}$; statistical significance was determined for other tests at a threshold of $P < 0.05$.

Results

Analysis Framework and Flowchart

The flowchart was shown in Figure 1.

Instrumental Variable Selection

Based on the selection criteria for instrumental variables, SNPs with linkage disequilibrium were removed, and SNPs associated with asthma ($P < 5 \times 10^{-8}$, clump=TRUE, $r^2 < 0.001$, kb=10,000) were included as instrumental variables after matching with COPD GWAS data. The information of instrumental variables for each indicator was shown in Table S1.

MR Causal Effect Estimation

Analysis was conducted using five models: MR Egger, Weighted median, IVW (Inverse variance weighted), Simple mode (SM), and Weighted mode. The results of the five models for the causal relationship between asthma and COPD (Figure 2a, Table 1) indicated a significant causal relationship between asthma and COPD, with higher levels of all circulating metabolites associated with an increased risk of COPD occurrence. Different models of MR analysis for asthma (Figure 2b-c) provided consistent directional estimates, with relatively consistent slopes.

Sensitivity Analysis

Heterogeneity testing of significant results was conducted using Cochran's Q test and I^2 statistic, as shown in Table 2. The results indicated high heterogeneity in the Mendelian randomization (MR) results for asthma (Asthma, id: ebi-a-GCST006862) with respect to COPD (I^2=50.65%, Cochran Q p-value < 0.05). However, there was no significant heterogeneity in the MR results for asthma (Asthma, id: ebi-a-GCST90014325) with respect to COPD (Cochran Q p-value > 0.05, I^2 < 50%). The exposure of asthma (Asthma, id: ebi-a-GCST006862) with high heterogeneity was removed, and the exposure of asthma (Asthma, id: ebi-a-GCST90014325) was analyzed further. The funnel plot of instrumental variables for asthma (Asthma, id: ebi-a-GCST90014325) (Figure 3A) showed a symmetrical distribution of scatter points, indicating no potential bias in the causal association effect.

Instrumental variable horizontal pleiotropy testing was conducted using MR-Egger regression. The p-value of the intercept term in the statistical hypothesis test for p-value associated with asthma (Asthma, id: ebi-a-GCST90014325) exceeded 0.05, and the intercept value approached zero. indicating that the causal inference of this study was not affected by horizontal pleiotropy (Table 3). We performed leave-one-out analysis, systematically excluding each instrumental variable locus, to examine the causal impact of asthma on COPD (Figure 3b). It was found that there was no significant deviation from the total effect of the instrumental variable set. The Steiger directional test result was TRUE with a p-value less than 0.05, indicating no reverse causal effect (Table 4).

B. Forest plot showing the sequential effect estimates of asthma and COPD using single SNP locus analysis.

Reverse MR Analysis

To evaluate reverse causal effects, we used COPD s exposure and asthma (id: ebi-a-GCST90014325) as the outcome. Following the selection criteria for instrumental variables in this study and removing SNPs with linkage disequilibrium, the reverse causal MR analysis results (Figure 4) indicated that COPD did not have a significant causal effect on asthma (P value > 0.05), as shown in Table 5.

Multivariable MR Analysis

We conducted multivariable MR analysis by incorporating exposures such as eosinophil cell count (ieu-b-33), past tobacco smoking (ukb-b-2134), falling risk (ebi-a-GCST90012857), etc., to assess the direct effect of asthma (Asthma, ebi-a-GCST90014325) on COPD (Table 6). In Model 1, correcting for the indirect effect of eosinophil cell count, the results indicated that asthma (Asthma, ebi-a-GCST90014325) still significantly affects COPD. In Model 2, correcting for the influence of smoking, the results showed that asthma (Asthma, ebi-a-GCST90014325) still significantly affects COPD. In Model 3, considering the impact of falling risk, the results demonstrated that asthma (Asthma, ebi-a-GCST90014325) still significantly affects COPD.

Discussion

This study delves into the causal impact of asthma on COPD through a two-sample Mendelian randomization design. Firstly, by rigorously screening publicly available GWAS data, we successfully selected a series of SNPs that meet the criteria for instrumental variables for subsequent causal effect estimation. Through various two-sample MR methods, we conclude that asthma serves as a significant risk factor for COPD, providing solid genetic evidence for further elucidating the relationship between these two diseases.

In sensitivity analysis, we validated the robustness of the results through methods such as

heterogeneity testing and pleiotropy testing. Even after excluding SNPs with high heterogeneity, the results remained significant. Through Leave-one-out analysis, we further confirmed the robustness of the instrumental variables, eliminating the significant influence of individual SNPs on the overall outcomes. The results of the MR-Egger intercept method also indicate that the causal inference of this study is not significantly affected by horizontal pleiotropy.

To gain a more comprehensive understanding of the impact of asthma on COPD, we conducted reverse MR analysis and found that COPD does not have a significant causal effect on asthma, thereby ruling out the possibility of reverse causality.

Finally, through multivariable MR analysis, we explored the impact of multiple potential confounding factors on the relationship between asthma and COPD. The results indicate that the causal effect of asthma on COPD still exists after considering factors such as eosinophil cell count, smoking, and falling.

Previous research in the asthma and COPD field had extensively explored their pathogenesis, pathophysiological processes, and their relationship with environmental, genetic, and other factors. However, the relationship between asthma and COPD has always been a contentious issue. Here are some key points and findings from previous studies: 修改为 "Previous research in the asthma and COPD field had extensively explored their pathogenesis, pathophysiological processes, and their relationship with environmental, genetic, and other factors. For instance, recent studies, such as the one by Kurmi et al.[20], have also investigated the genetic links and shared risk factors between these diseases, further supporting the potential overlap in their etiology . However, the relationship between asthma and COPD remains a contentious issue."

Traditionally, asthma and COPD were considered to be two diseases with distinct biological

characteristics[21]. Asthma mainly involves airway inflammation and reversible airway obstruction, while COPD includes chronic bronchitis and emphysema, characterized by irreversible airway narrowing[22]. However, recent studies suggest that some patients might have both asthma and COPD, leading to asthma-COPD overlap syndrome (ACOS), with symptoms and biomarkers showing overlapping features, thereby increasing attention to the relationship between the two[23]. Early observational studies attempted to reveal the relationship between asthma and COPD but faced challenges due to confounding factors. For example, smoking, air pollution, occupational exposure, etc., are factors that affect respiratory health, making it difficult for observational studies to establish whether asthma directly leads to the development of COPD[24]. In recent years, advances in techniques such as genome-wide association studies (GWAS) have enriched our comprehension of the genetic underpinnings of respiratory disorders. Some genes have been confirmed to be associated with asthma and COPD, but their specific mechanisms and their interrelationship remain uncertain.

In clinical practice, distinguishing between asthma and COPD is sometimes not straightforward, especially in some elderly patients or long-term smokers. The presence of this overlapping pathological state increases the difficulty of disease management[25].

Additionally, the understanding of asthma-COPD overlap syndrome (ACOS) remains incomplete, necessitating further research to elucidate the nature of this dual pathological state.

Our study contributes to this discussion by providing evidence that asthma is a risk factor for COPD development. To further understand the mechanisms involved, exploring how asthma-related factors influence COPD onset is crucial. Given the overlap of symptoms in ACOS and the inconclusive findings from previous observational studies, our study stands out by utilizing genetic evidence

from GWAS to establish a causal relationship between asthma and COPD. Additionally, our results emphasize the importance of addressing asthma control to potentially prevent COPD progression. Future research directions may involve studying specific asthma-related genetic markers and their impact on COPD development, as well as implementing personalized therapeutic interventions based on genetic susceptibility analysis. Overall, our study highlights the significance of recognizing asthma as a contributing factor to COPD and underscores the necessity for targeted interventions to alleviate disease burden and improve patient outcomes.

When discussing the mechanisms by which asthma affects COPD and their application in disease prevention or treatment, several mechanisms may be utilized. Firstly, the inflammation regulation mechanism may be one of them. Both asthma and COPD are associated with inflammation response, so studying the mechanism of inflammation regulation, such as reducing airway inflammation through medication or biological treatment, may prevent or treat the progression of COPD[26]. Further research may include the development of novel inflammation-regulating agents and their effectiveness and safety in clinical practice. Secondly, airway remodeling mechanism is also an important research direction. Asthma and COPD patients have abnormal airway structure and function, so studying the mechanism of airway remodeling and attempting to restore normal airway structure and function through medication or other treatment methods may prevent or treat the development of COPD[27]. Further research may include the development of novel treatment methods targeting airway remodeling and the evaluation of their long-term effects on COPD patients. Lastly, the immune regulation mechanism may also be a promising treatment approach. The immune system plays an important role in the development of asthma and COPD, so studying the mechanism of immune response regulation, such as the use of immunomodulators, may prevent or treat the

development of COPD[28]. Further research may include the evaluation of the effectiveness and safety of different types of immunomodulators and the determination of the optimal treatment strategy. These potential mechanisms require further research to promote their application in disease prevention or treatment. Such research may include basic scientific research, such as mechanism studies and drug development, as well as clinical research, such as clinical trials and epidemiological studies, to evaluate the effectiveness and safety of these mechanisms and determine the optimal treatment strategies. Additionally, interdisciplinary cooperation is needed to promote joint efforts from different fields of expertise and accelerate the application of these mechanisms in clinical practice.

增加讨论参考：

"In addition to genetic factors, immune pathways play a significant role in the development of both asthma and COPD. Recent studies have highlighted the importance of Th17 cells and the IL-31/IL-33 axis in modulating chronic inflammation and immune responses, which are pivotal in the pathogenesis of these diseases. Furthermore, factors such as vitamin D and the microbiome have been shown to influence immune regulation, potentially impacting disease progression. For example, recent work by Drożdżal et al. [29] discussed these mechanisms in the context of chronic immune-mediated diseases, offering new insights into their therapeutic potential."

The innovation of this study lies in starting from the perspective of genetics, using Mendelian randomization methods to minimize the interference of confounding factors as much as possible, and exploring whether asthma directly affects the risk of COPD. This will help fill the gaps in existing research and provide new directions for future studies. Additionally, through multivariable MR analysis, we will explore the impact of other exposure factors related to COPD, thereby

achieving a more comprehensive understanding of this complex disease relationship.

In summary, this study provides new genetic evidence and theoretical support for understanding the relationship between asthma and COPD through comprehensive analysis from multiple perspectives and methods. This has positive implications for the formulation of preventive and therapeutic strategies for related diseases and the selection of future genetic research directions.

In this study, there are limitations that need to be considered. Firstly, despite our efforts to screen publicly available GWAS data rigorously, the limited nature of the data prevents us from conducting detailed analyses on more disease pathological types. Particularly, due to the scarcity of patients and the lack of specific SNP data, we cannot confirm the relationship between asthma and certain specific pathological types of COPD. Additionally, due to the diversity of “exposure” sources and the lack of relevant SNP data, we have yet to investigate whether specific sources of "exposure" exert similar biological effects on diseases and whether "exposure" has a consistent impact across different subgroups. It is worth noting that our data primarily consist of samples of European ancestry, and thus, may not adequately differentiate ethnic variations from various regions, potentially limiting the generalizability of these results to a global scale. Although the data from GWAS or large samples used for diseases are continuously increasing, there still exists a problem of data insufficiency. Further exploration of the basic multicenter research mechanisms between “exposure” and “outcome” is needed to better understand how asthma affects the occurrence and development of COPD.

Conclusion

Our research findings suggest that there is a significant causal relationship between asthma and

COPD, indicating that the occurrence of asthma elevates the likelihood of developing COPD in patients. Even when considering potential confounding factors, asthma still exerts a significant causal effect on COPD. These findings deepen our understanding the association between COPD and asthma providing important reference for further research and clinical practice. Future studies should delve deeper into the complex relationship between these two diseases to promote the formulation of prevention and treatment strategies for respiratory system diseases.

Abbreviations

COPD	chronic obstructive pulmonary disease
GWAS	enome-wide association study
MR	Mendelian randomization
ACOS	asthma-COPD overlap syndrome
SNP	Single nucleotide polymorphisms
IVW	Inverse-variance weighted
MVMR	Multivariable mendelian randomization
OR	Odds ratio
CI	Confidence interval

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Data and material are available from (https://www.eqtlgen.org/) and corresponding GWAS consortium.

Competing interests

The authors declared that they have no conflict of interest.

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No.

Authors' Contributions

WS and YH were responsible for study conception and design. ZL and HS were in charge of data collection and analysis and wrote the paper. All authors read and approved the final manuscript.

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Figure legends

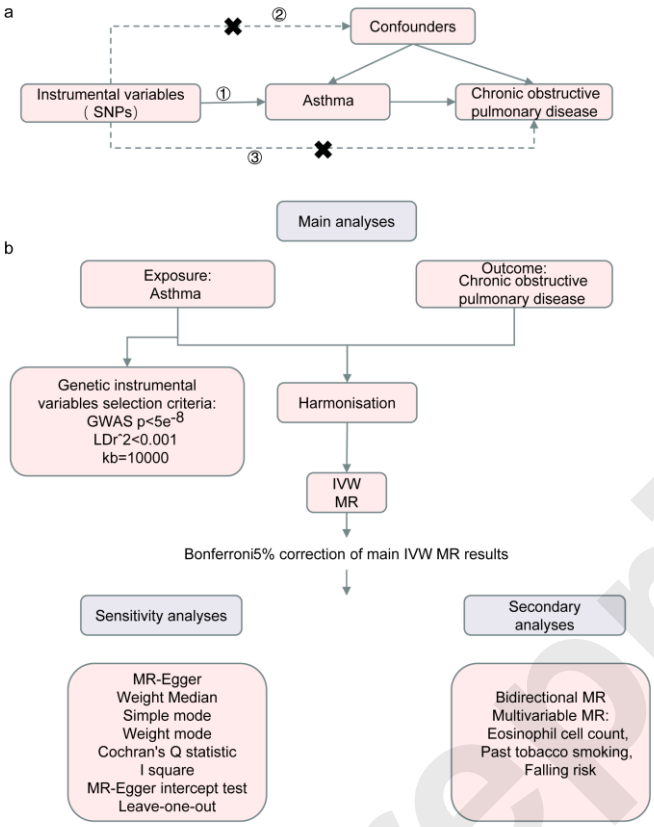

Figure 1. Mendelian randomization analysis flowchart. (a) Basic assumptions of Mendelian randomization analysis, including (1) the relevance assumption, which states that selected instrumental variables must be significantly associated with the exposure factor; (2) the exclusion restriction assumption, which states that instrumental variables could only affect the outcome through the pathway "instrumental variable → exposure → outcome"; (3) the independence assumption, which states that instrumental variables must not be significantly correlated with potential confounding factors that might affect exposure or outcome. (b) Flowchart of the analysis methods used in this study. SNP, single nucleotide polymorphism. IVW, inverse variance weighted. MR-Egger, Mendelian randomization-Egger. GWAS, genome-wide association study.

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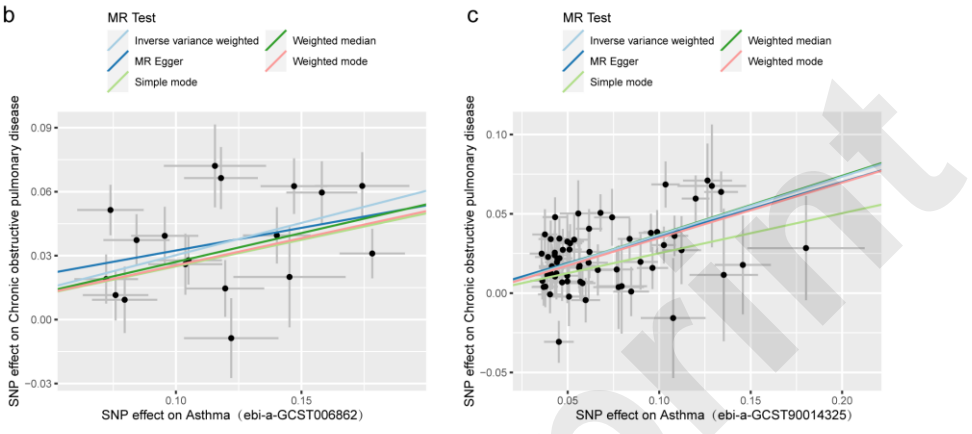
Exposure	method	β	OR95CI	P value
Asthma（ebi-a-GCST90014325）	Inverse variance weighted	0.3671981	1.44 (1.36, 1.53)	9.99e-35
Asthma（ebi-a-GCST90014325）	MR Egger	0.3407018	1.41 (1.21, 1.63)	3.12e-05
Asthma（ebi-a-GCST90014325）	Simple mode	0.2518579	1.29 (1.06, 1.56)	0.0128
Asthma（ebi-a-GCST90014325）	Weighted median	0.3698692	1.45 (1.33, 1.57)	7.18e-18
Asthma（ebi-a-GCST90014325）	Weighted mode	0.3482749	1.42 (1.23, 1.63)	7.78e-06
Asthma（ebi-a-GCST006862）	Inverse variance weighted	0.3022835	1.35 (1.25, 1.46)	4.72e-15
Asthma（ebi-a-GCST006862）	MR Egger	0.2120904	1.24 (0.95, 1.61)	0.134
Asthma（ebi-a-GCST006862）	Simple mode	0.2493573	1.28 (1.09, 1.51)	0.00841
Asthma（ebi-a-GCST006862）	Weighted median	0.2704959	1.31 (1.20, 1.43)	1.97e-09
Asthma（ebi-a-GCST006862）	Weighted mode	0.2546926	1.29 (1.13, 1.47)	0.00149



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446 **Figure 2. Multiple model analysis results of mendelian randomization analysis for asthma and**

447 **chronic obstructive pulmonary disease.** (a) Forest plot showing the causal association analysis

448 results of Mendelian randomization using multiple models for asthma and chronic obstructive

449 COPD. Effect estimates are presented using OR and 95% CI, along with the number of instrumental

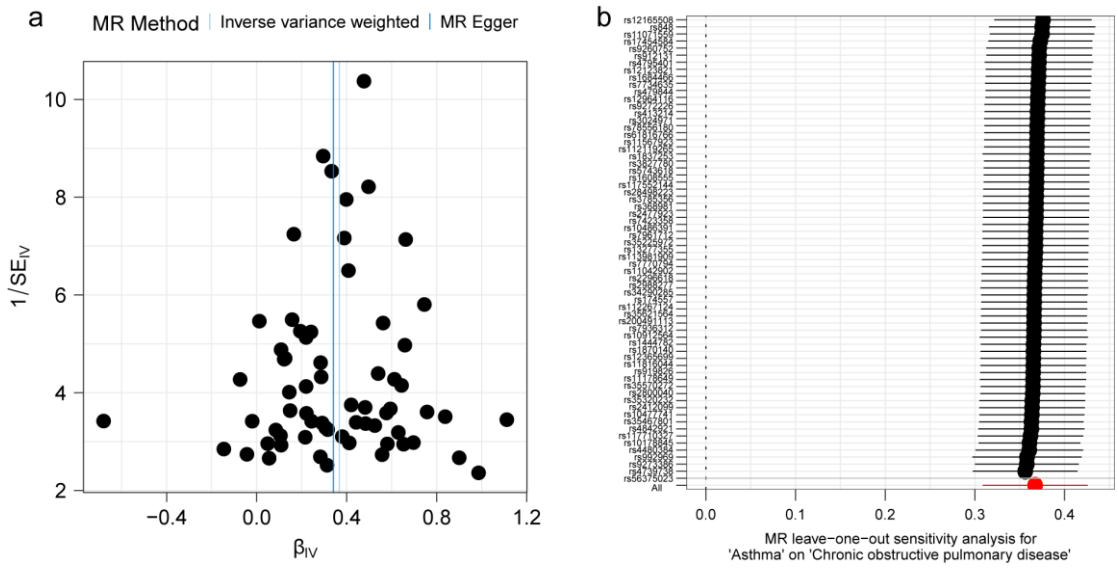
450 variables used in each model, as well as the calculated beta values and standard errors. B-C. Scatter

451 plots showing the causal relationship between Asthma (id: ebi-a-GCST006862) (b), Asthma (id: ebi-

452 a-GCST90014325) (c), and chronic obstructive pulmonary disease. The slope of the line represents

453 the magnitude of the causal relationship predicted by different models. SNPs, Single Nucleotide

454 Polymorphisms; OR, Odds Ratio; CI, Confidence Interval.



455

456 **Figure 3. Funnel plot for heterogeneity testing and effect estimates of IVW random effects**
457 **model in mendelian randomization analysis of asthma and chronic obstructive pulmonary**
458 **disease.** (a) Funnel plot displaying the causal effect estimates of each instrumental variable for
459 asthma and chronic obstructive pulmonary disease. The causal effect estimates of the IVW and MR
460 Egger models are indicated by lines on the plot. (b) Forest plot showing the sequential effect
461 estimates of asthma and COPD using single SNP locus analysis.

Exposure	method	β	OR95CI	P value
Chronic obstructive pulmonary disease	Inverse variance weighted	0.055008497	1.06 (0.96, 1.16)	0.235
Chronic obstructive pulmonary disease	MR Egger	-0.136972222	0.87 (0.73, 1.05)	0.179
Chronic obstructive pulmonary disease	Simple mode	0.017520151	1.02 (0.93, 1.11)	0.698
Chronic obstructive pulmonary disease	Weighted median	0.003900208	1.00 (0.95, 1.06)	0.888
Chronic obstructive pulmonary disease	Weighted mode	0.004347437	1.00 (0.96, 1.05)	0.866

462

463 **Figure 4. Multiple model analysis results of reverse causal mendelian randomization analysis**
464 **for chronic obstructive pulmonary disease and asthma.** The forest plot presents the results of
465 reverse causal association analysis between COPD and asthma using multiple Mendelian
466 randomization models. Effect estimates are displayed using OR and 95% CI, along with the number
467 of instrumental variables used in each model, as well as the calculated beta values and standard

errors. SNPs, Single Nucleotide Polymorphisms; OR, Odds Ratio; CI, Confidence Interval.

Table 1 Estimates of Mendelian randomized causal effects of Asthma and Chronic obstructive pulmonary disease .

Exposure	Methed	Number of SNPs	β	Standard error	P value	OR
Asthma （ ebi-a-GCST90014325）	Inverse variance weighted	65	0.3671 98137	0.02987 265	9.99E -35	1.44 (1.36, 1.53)
Asthma （ ebi-a-GCST90014325）	MR Egger	65	0.3407 01751	0.07590 4004	3.12E -05	1.41 (1.21, 1.63)
Asthma （ ebi-a-GCST90014325）	Simple mode	65	0.2518 57948	0.09838 223	0.012 8	1.29 (1.06, 1.56)
Asthma （ ebi-a-GCST90014325）	Weighted median	65	0.3698 69234	0.04294 8228	7.18E -18	1.45 (1.33, 1.57)
Asthma （ ebi-a-GCST90014325）	Weighted mode	65	0.3482 74863	0.07158 0068	7.78E -06	1.42 (1.23, 1.63)
Asthma （ ebi-a-	Inverse	18	0.3022	0.03858	4.72E	1.35

GCST006862）		variance weighted		83474	5381	-15	(1.25, 1.46)
Asthma （GCST006862）	ebi-a-	MR Egger	18	0.2120 9039	0.13430 7392	0.134	1.24 (0.95, 1.61)
Asthma （GCST006862）	ebi-a-	Simple mode	18	0.2493 573	0.08367 6473	0.008 41	1.28 (1.09, 1.51)
Asthma （GCST006862）	ebi-a-	Weighted median	18	0.2704 95937	0.04507 9563	1.97E -09	1.31 (1.20, 1.43)
Asthma （GCST006862）	ebi-a-	Weighted mode	18	0.2546 92559	0.06737 5612	0.001 49	1.29 (1.13, 1.47)

472 SNP，Single Nucleotide Polymorphism；OR，Odds Ratio; CI，Confidence Interval。

473

474 Table 2 Mendelian randomization analysis heterogeneity test for the association between Asthma

475 and Chronic obstructive pulmonary disease

Exposure	Q	Q df	Cochran Q p-value	I2 (%)
Asthma（ebi-a-GCST006862）	34.45016675	17	0.007340785	50.65
Asthma（ebi-a-GCST90014325）	80.35204633	64	0.081408939	20.35

476

477 Table 3 Mendelian randomization analysis of horizontal pleiotropy for the association between

478 Asthma and Chronic obstructive pulmonary disease

Exposure	MR-Egger intercept	Standard error	P value
Asthma（ebi-a-GCST90014325）	0.001909126	0.005021459	0.705080595

479

480 Table 4 Mendelian randomization analysis of Asthma on Chronic obstructive pulmonary disease

481 Steiger directionality test

Exposure	Outcome	SNP r2 exposure	SNP r2 outcome	Correct causal direction	Steiger P value
Asthma（ebi-a-GCST90014325）	Chronic obstructive pulmonary disease	0.010916669	0.000575918	TRUE	0

482 SNP，Single Nucleotide Polymorphism；r2，方差解释率。

483

484 Table 5 Results of reverse causal Mendelian randomization analysis of Chronic obstructive

485 pulmonary disease and Asthma.

Exposure	Outcome	Method	Number of	β	Standard error	P value

			SNPs			
Chronic obstructive pulmonary disease	Asthma（ebi-a-GCST90014325）	MR Egger	10	-0.136972222	0.092977815	0.178926771
Chronic obstructive pulmonary disease	Asthma（ebi-a-GCST90014325）	Weighted median	10	0.003900208	0.027606237	0.887648 78
Chronic obstructive pulmonary disease	Asthma（ebi-a-GCST90014325）	Inverse variance weighted	10	0.055008497	0.046306146	0.234860669
Chronic obstructive pulmonary disease	Asthma（ebi-a-GCST90014325）	Simple mode	10	0.017520151	0.043791 52	0.698426597
Chronic obstructive pulmonary disease	Asthma（ebi-a-GCST90014325）	Weighted mode	10	0.004347437	0.025058646	0.866105254

SNP，Single Nucleotide Polymorphism。

Table 6 The results of multivariable Mendelian randomization analysis on the impact of Asthma and Chronic obstructive pulmonary disease

Model	Exposure	Outcome	nSNP	Beta	SE	Pvalue	OR (95%CI)
Model 1	Eosinophil cell count	Chronic obstructive pulmonary disease	398	0.037394501	0.03433414	0.276094521	1.038(1.110,0.971)
	Asthma	Chronic obstructive pulmonary disease	34	0.362836557	0.036274363	1.49E-23	1.437(1.339,1.543)
Model 2	Past tobacco smoking	Chronic obstructive pulmonary disease	77	-0.737199808	0.087208236	2.83E-17	0.478(0.403,0.568)
	Asthma	Chronic obstructive pulmonary disease	64	0.37334249	0.029146487	1.46E-37	1.453(1.372,1.538)
Model 3	Falling risk	Chronic obstructive pulmonary disease	2	0.117250627	0.228771877	0.608285706	1.124(0.718,1.761)
	Asthma	Chronic obstructive pulmonary disease	70	0.366839717	0.028134419	7.36E-39	1.443(1.366,1.525)

Model，Multivariable MR analysis of Asthma and Eosinophil cell count on Chronic obstructive pulmonary disease；Model 2，Multivariable MR analysis of Asthma and Past tobacco smoking on Chronic obstructive pulmonary disease；Model 3，Multivariable MR analysis of Asthma and Falling risk on Chronic obstructive pulmonary disease。 MR，Mendelian Randomization；SNPs：Single Nucleotide Polymorphisms。

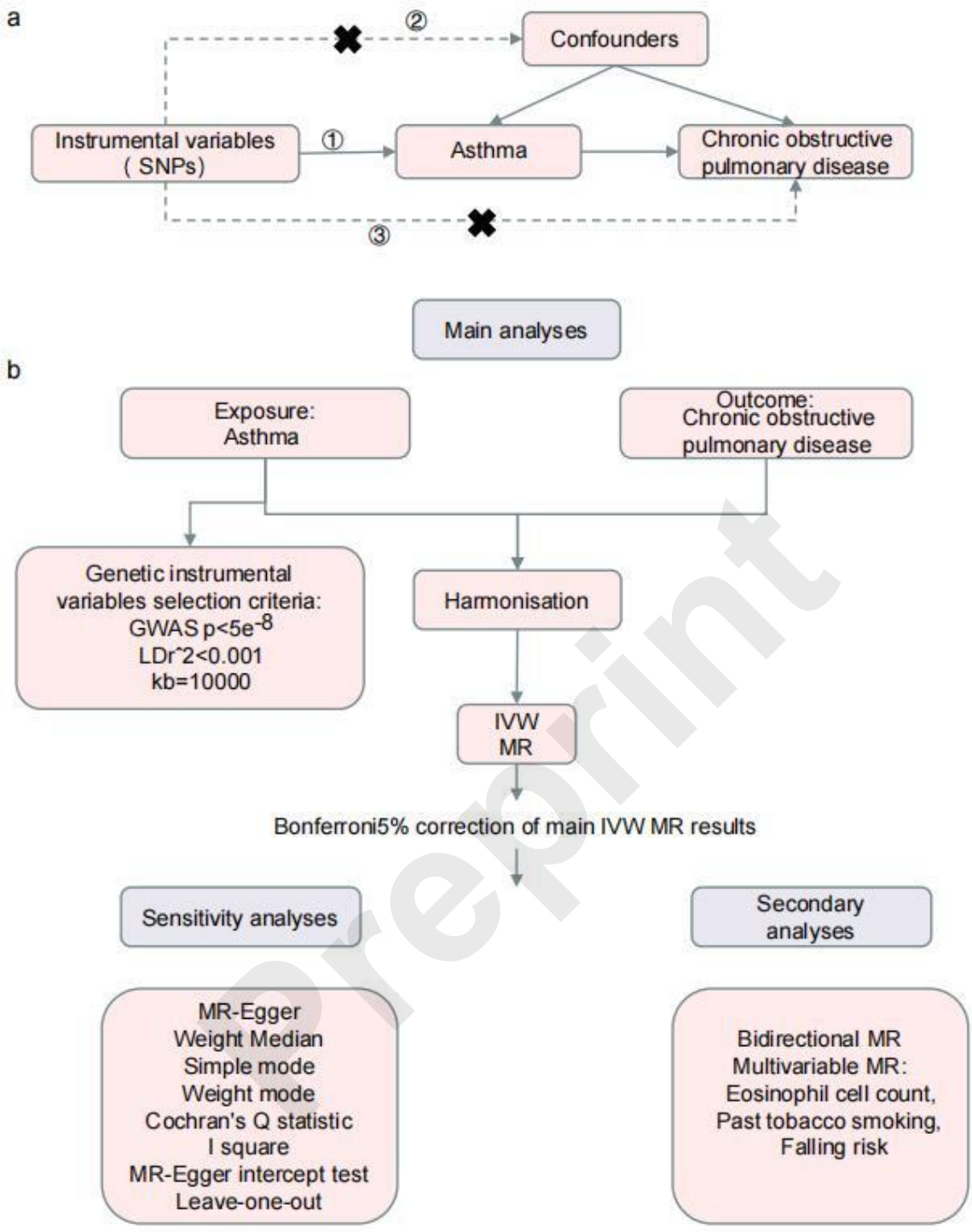

a
②
Confounders
Instrumental variables
(SNPs)
①
Asthma
Chronic obstructive
pulmonary disease
③
b
Main analyses
Exposure:
Asthma
Outcome:
Chronic obstructive
pulmonary disease
Genetic instrumental
variables selection criteria:
GWAS p<5e-8
LDr^2<0.001
kb=10000
Harmonisation
IVW
MR
Bonferroni5% correction of main IVW MR results
Sensitivity analyses
Secondary
analyses
MR-Egger
Weight Median
Simple mode
Weight mode
Cochran's Q statistic
I square
MR-Egger intercept test
Leave-one-out
Bidirectional MR
Multivariable MR:
Eosinophil cell count,
Past tobacco smoking,
Falling risk

Table 1 Estimates of Mendelian randomized causal effects of Asthma and Chronic obstructive pulmonary disease .

Exposure		Methed	Number of SNPs	β	Standard error	P value	OR
Asthma （GCST90014325）	ebi-a-	Inverse variance weighted	65	0.367198137	0.02987265	9.99E-35	1.44 (1.36, 1.53)
Asthma （GCST90014325）	ebi-a-	MR Egger	65	0.340701751	0.075904004	3.12E-05	1.41 (1.21, 1.63)
Asthma （GCST90014325）	ebi-a-	Simple mode	65	0.251857948	0.09838223	0.0128	1.29 (1.06, 1.56)
Asthma （GCST90014325）	ebi-a-	Weighted median	65	0.369869234	0.042948228	7.18E-18	1.45 (1.33, 1.57)
Asthma （GCST90014325）	ebi-a-	Weighted mode	65	0.348274863	0.071580068	7.78E-06	1.42 (1.23, 1.63)
Asthma （GCST006862）	ebi-a-	Inverse variance weighted	18	0.302283474	0.038585381	4.72E-15	1.35 (1.25, 1.46)
Asthma （GCST006862）	ebi-a-	MR Egger	18	0.212009039	0.134307392	0.134	1.24 (0.95, 1.61)
Asthma （GCST006862）	ebi-a-	Simple mode	18	0.2493573	0.083676473	0.00841	1.28 (1.09, 1.51)

Asthma（GCST006862）	ebi-a-	Weighted median	18	0.27049593	0.04507563	1.97E-09	1.31 (1.20, 1.43)
Asthma（GCST006862）	ebi-a-	Weighted mode	18	0.25469255	0.06737612	0.00149	1.29 (1.13, 1.47)

SNP，Single Nucleotide Polymorphism；OR，Odds Ratio; CI，Confidence Interval。

Table 2 Mendelian randomization analysis heterogeneity test for the association between Asthma and Chronic obstructive pulmonary disease

Exposure	Q	Q df	Cochran Q p-value	I^2 (%)
Asthma（ebi-a-GCST006862）	34.45016675	17	0.007340785	50.65
Asthma（ebi-a-GCST90014325）	80.35204633	64	0.081408939	20.35

Table 3 Mendelian randomization analysis of horizontal pleiotropy for the association between Asthma and Chronic obstructive pulmonary disease

Exposure	MR-Egger intercept	Standard error	P value
Asthma（ebi-a-GCST90014325）	0.001909126	0.005021459	0.705080595

Table 4 Mendelian randomization analysis of Asthma on Chronic obstructive pulmonary disease Steiger directionality test

Exposure	Outcome	SNP r^2 exposure	SNP r^2 outcome	Correct causal direction	Steiger P value
Asthma（ebi-a-GCST90014325）	Chronic obstructive pulmonary disease	0.010916669	0.000575918	TRUE	0

SNP，Single Nucleotide Polymorphism；r^2，方差解释率。

Table 5 Results of reverse causal Mendelian randomization analysis of Chronic obstructive pulmonary disease and Asthma.

Exposure	Outcome	Method	Number of SNPs	β	Standard error	P value
Chronic obstructive pulmonary disease	Asthma（ebi-a-GCST90014325）	MR Egger	10	-0.136972222	0.092977815	0.178926771
Chronic obstructive pulmonary disease	Asthma（ebi-a-GCST90014325）	Weighted median	10	0.003900208	0.027606237	0.887648 78
Chronic obstructive pulmonary disease	Asthma（ebi-a-GCST90014325）	Inverse variance weighted	10	0.055008497	0.046306146	0.234860669
Chronic obstructive pulmonary disease	Asthma（ebi-a-GCST90014325）	Simple mode	10	0.017520151	0.043791 52	0.698426597
Chronic obstructive pulmonary disease	Asthma（ebi-a-GCST90014325）	Weighted mode	10	0.004347437	0.025058646	0.866105254

SNP，Single Nucleotide Polymorphism。

Table 6 The results of multivariable Mendelian randomization analysis on the impact of Asthma and Chronic obstructive pulmonary disease

Model	Exposure	Outcome	nSNP	Beta	SE	Pvalue	OR (95%CI)
Model 1	Eosinophil cell count	Chronic obstructive pulmonary disease	398	0.037394501	0.03433414	0.276094521	1.038(1.110,0.971)
	Asthma	Chronic obstructive pulmonary disease	34	0.362836557	0.036274363	1.49E-23	1.437(1.339,1.543)
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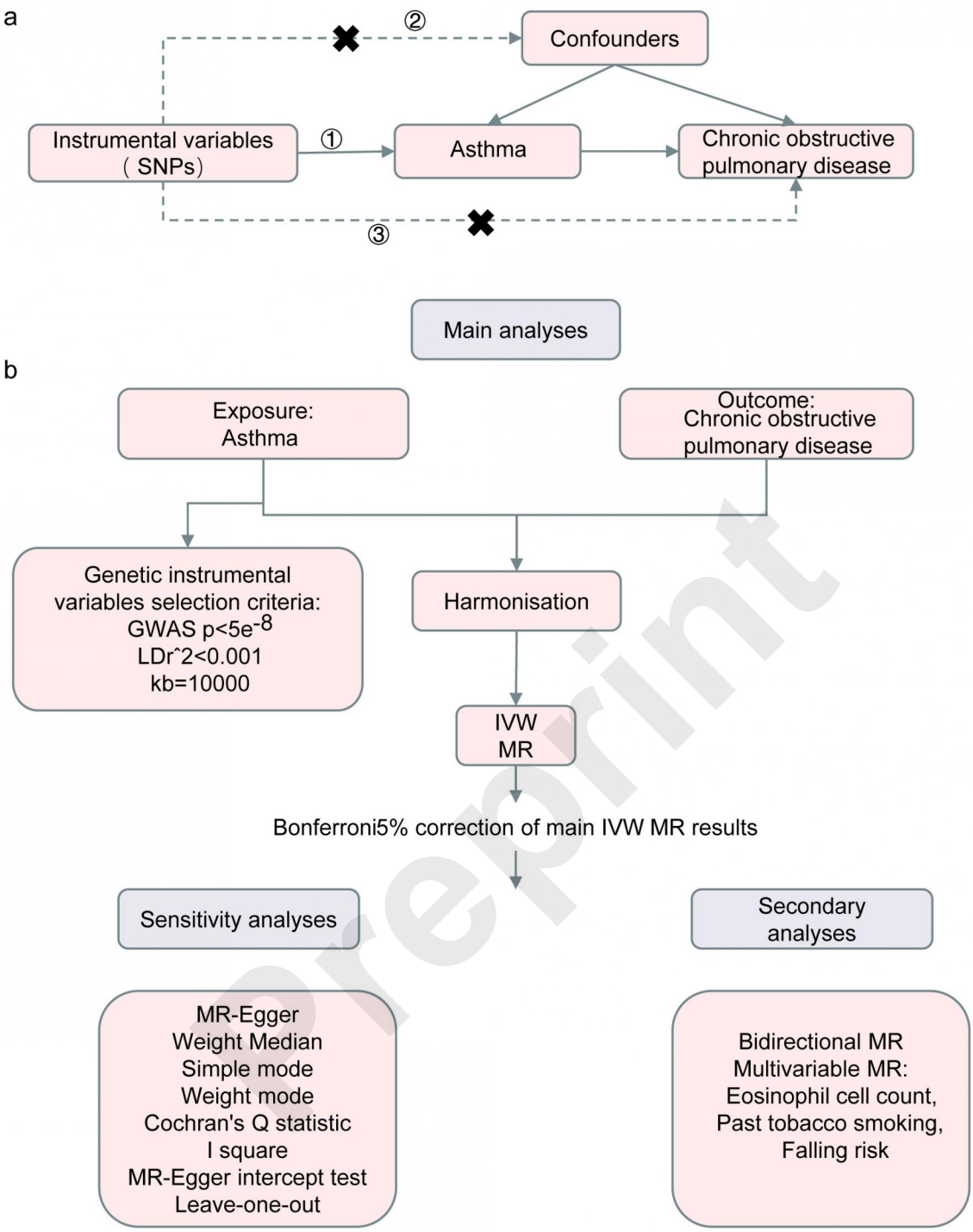
	Asthma	Chronic obstructive pulmonary disease	64	0.37334249	0.029146487	1.46E-37	1.453(1.372,1.538)
Model 3	Falling risk	Chronic obstructive pulmonary disease	2	0.117250627	0.228771877	0.608285706	1.124(0.718,1.761)
	Asthma	Chronic obstructive pulmonary disease	70	0.366839717	0.028134419	7.36E-39	1.443(1.366,1.525)

Model，Multivariable MR analysis of Asthma and Eosinophil cell count on Chronic obstructive pulmonary disease；Model 2，Multivariable MR analysis of Asthma and Past tobacco smoking on Chronic obstructive pulmonary disease；Model 3，Multivariable MR analysis of Asthma and Falling risk on Chronic obstructive pulmonary

disease。 MR，Mendelian Randomization；SNPs：Single Nucleotide Polymorphisms。


a
②
Confounders
Instrumental variables
（SNPs）
①
Asthma
Chronic obstructive
pulmonary disease
③
b
Main analyses
Exposure:
Asthma
Outcome:
Chronic obstructive
pulmonary disease
Genetic instrumental
variables selection criteria:
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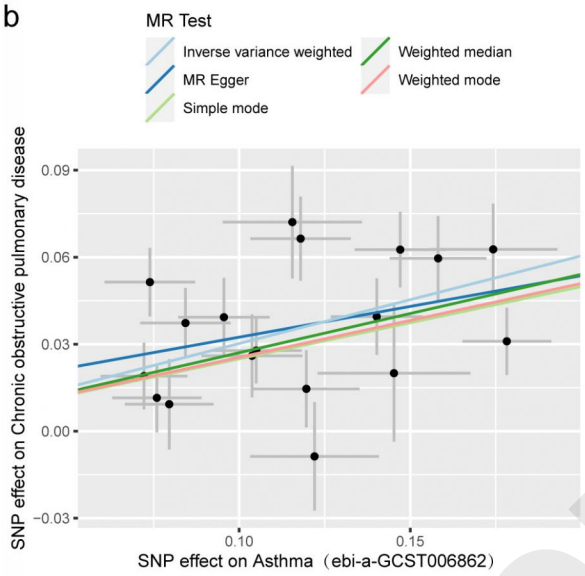
LDr^2<0.001
kb=10000
Harmonisation
IVW
MR
Bonferroni5% correction of main IVW MR results
Sensitivity analyses
Secondary
analyses
MR-Egger
Weight Median
Simple mode
Weight mode
Cochran's Q statistic
I square
MR-Egger intercept test
Leave-one-out
Bidirectional MR
Multivariable MR:
Eosinophil cell count,
Past tobacco smoking,
Falling risk

a

Exposure	method	β	OR95CI	P value
Asthma（ebi-a-GCST90014325）	Inverse variance weighted	0.3671981	1.44 (1.36, 1.53)	9.99e-35
Asthma（ebi-a-GCST90014325）	MR Egger	0.3407018	1.41 (1.21, 1.63)	3.12e-05
Asthma（ebi-a-GCST90014325）	Simple mode	0.2518579	1.29 (1.06, 1.56)	0.0128
Asthma（ebi-a-GCST90014325）	Weighted median	0.3698692	1.45 (1.33, 1.57)	7.18e-18
Asthma（ebi-a-GCST90014325）	Weighted mode	0.3482749	1.42 (1.23, 1.63)	7.78e-06
Asthma（ebi-a-GCST006862）	Inverse variance weighted	0.3022835	1.35 (1.25, 1.46)	4.72e-15
Asthma（ebi-a-GCST006862）	MR Egger	0.2120904	1.24 (0.95, 1.61)	0.134
Asthma（ebi-a-GCST006862）	Simple mode	0.2493573	1.28 (1.09, 1.51)	0.00841
Asthma（ebi-a-GCST006862）	Weighted median	0.2704959	1.31 (1.20, 1.43)	1.97e-09
Asthma（ebi-a-GCST006862）	Weighted mode	0.2546926	1.29 (1.13, 1.47)	0.00149

b



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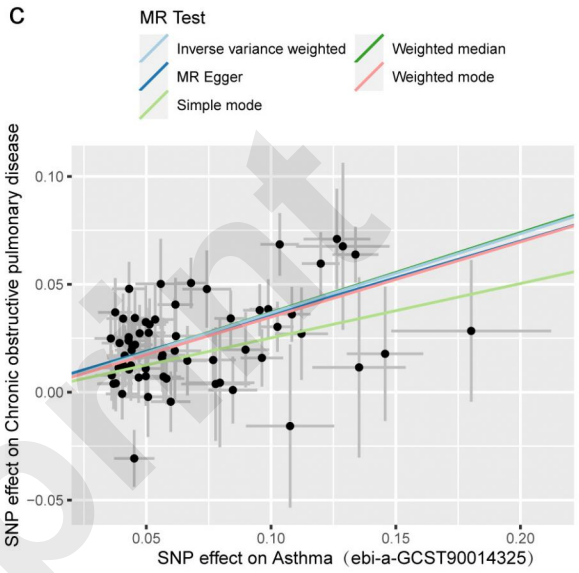

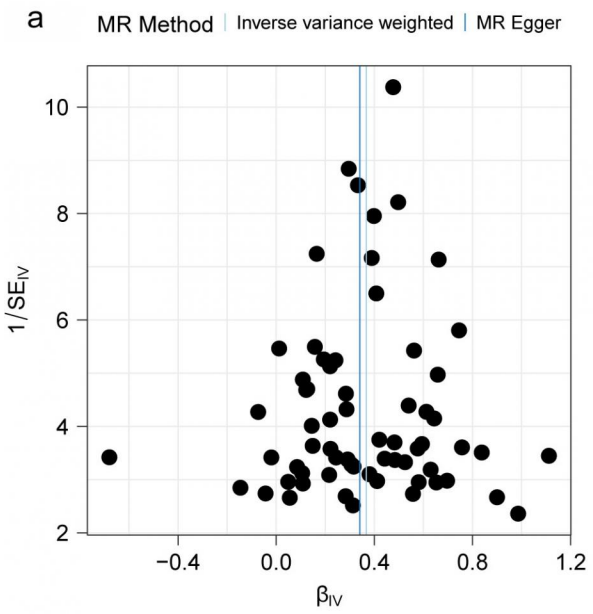
a
MR Method
Inverse variance weighted
MR Egger
10
8
6
4
2
1/SE_IV
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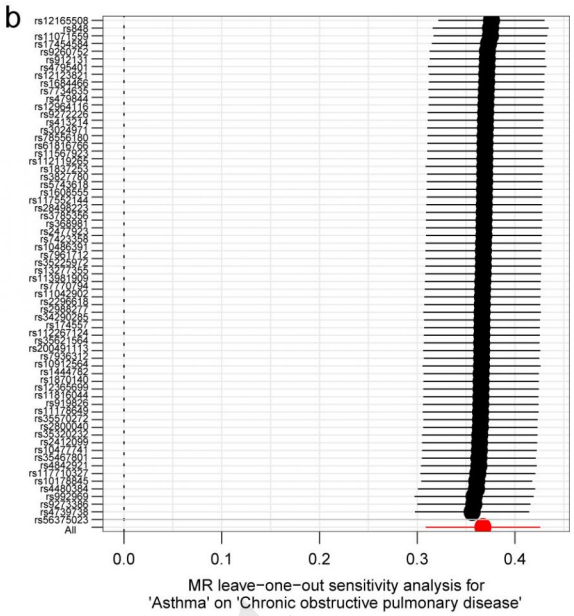
0.0
0.4
0.8
1.2
β_IV


b
All
0.0
0.1
0.2
0.3
0.4
MR leave−one−out sensitivity analysis for
'Asthma' on 'Chronic obstructive pulmonary disease'

Exposure	method	β	OR95CI	P value
Chronic obstructive pulmonary disease	Inverse variance weighted	0.055008497	1.06 (0.96, 1.16)	0.235
Chronic obstructive pulmonary disease	MR Egger	-0.136972222	0.87 (0.73, 1.05)	0.179
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