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ORIGINAL RESEARCH

A Bidirectional Mendelian Randomization Study Investigating the Causal Relationship Between Ankylosing Spondylitis and Chronic Obstructive Pulmonary Disease

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Background: Previous studies have found an association between ankylosing spondylitis (AS) and chronic obstructive pulmonary disease (COPD); however, no research has investigated this relationship using Mendelian randomization (MR).

Methods: This study employed a bidirectional two-sample MR approach to assess the causal connection between AS and COPD. The analysis utilized publicly available statistics on AS and COPD from the Genome-wide Association Study (GWAS). The primary MR method employed was Inverse-Variance Weighting (IVW), supplemented by additional MR methods such as weighted median, MR-Egger, simple mode, and weighted mode. Sensitivity analyses were also performed to evaluate the impact of heterogeneity and pleiotropy on the MR results.

Results: The study included two datasets related to AS (ebi-a-GCST005529 and ukb-a-88) and two datasets related to COPD (ebi-a-GCST90018807 and finn-b-J10_COPD). In our forward MR, the analysis of ebi-a-GCST005529 dataset against ebi-a-GCST90018807 dataset showed that AS was associated with an increased risk of COPD (*OR* = 1.1326, *95% CI* = 1.0181–1.2600, *P* = 0.0221). However, there was no causal relationship between AS and COPD in the rest of the dataset analyses. In reverse MR analysis, no causal effect between COPD and AS was found among the datasets.

Conclusion: Our research provided partial evidence to support the viewpoint that AS may increase the prevalence of COPD. AS may be a risk factor for COPD, however, further studies are needed to validate these results and elucidate the underlying mechanisms.

Keywords: ankylosing spondylitis, chronic obstructive pulmonary disease, Mendelian randomization, causal relationship

Introduction

Ankylosing spondylitis (AS), alternatively referred to as spondylitis or seronegative spondylitis, is an autoimmune condition distinguished by persistent inflammation of the sacroiliac joints and spine.[1] The possibility of men being affected is two to three times that of women.[2] The current prevalence of the disease in Europe ranges from about 0.10% to 1.60%.[3] Typically manifesting in individuals in their twenties and thirties, the clinical presentation of AS includes inflammatory back pain, gradual joint rigidity, and potential progression to spinal ankylosis, deformity, or lasting disability, resulting in significant discomfort and impairment for affected individuals.[4] The pathogenesis of AS is multifaceted and thought to arise from a combination of genetic, microbial, environmental, and immune influences.[5] The strong correlation between HLA-B27 haplotypes and the onset of AS provides substantial evidence in favor of the genetic susceptibility hypothesis,[6] while the impact of environmental factors, such as infections, on the pathogenesis of the disease has also been established.[7,8] However, for pulmonary manifestations of AS, the most common include apical

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fibrosis, mycetoma formation, and pleural thickening.[9] And a study showed that diaphragm ultrasonography is correlated with spirometric findings in radiographic SpA patients.[10]

Chronic obstructive pulmonary disease (COPD) ranks among the top three causes of mortality globally, causing a huge burden in the world.[11] This heterogeneous pulmonary condition is characterized by persistent abnormalities in airway or alveolar function and airflow obstruction,[12] with an estimated prevalence approaching 5% in the general population.[13] Smoking, environmental pollution, and occupational pollutants are considered risk factors for COPD.[14] Moreover, COPD is linked to an aberrant inflammatory response within the pulmonary system, resulting in the destruction of lung parenchyma (emphysema) and/or the development of chronic bronchitis.[15] Currently, there are no efficacious interventions available to impede or decelerate the progression of COPD. However, basic theories of autoimmunity are emerging for the pathogenesis of COPD, which explore the occurrence and development of the disease from the perspective of autoimmunity.[16] Chronic airway inflammation in COPD patients is characterized by activation of the innate immune system, that is, an increased number of innate immune cells, such as natural killer cells (NK) and mature dendritic cells (mDCs). In comparison to individuals without COPD, patients with COPD exhibited a higher presence of macrophages, dendritic cells (DC), neutrophils and lymphocytes in lung tissue.[17,18] Furthermore, in the context of COPD, there is activation of the adaptive immune system characterized by the presence of B-cell infiltration in the lungs and a reduction in airway regulatory T cells.[19,20] Habener et al have shown a notable correlation between elevated levels of IgA+ memory B cells and compromised small airway function.[21] Additionally, the centrilobular phenotype of emphysema in COPD has been reported to be triggered by Th1 responses initiated by infiltrating innate lymphoid cells type 1 (ILC1), NK, and lymphatic tissue inducers (LTi) cells.[22] Infection and inflammation are facilitated by cytokines, which serve as crucial mediators between the lungs and immune system.[23] A previous cohort study in Taiwan showed an increased incidence of asthma in patients with AS, while COPD was included AS part of the participants' baseline description, and COPD was significantly higher in patients with AS compared to healthy controls.[24] A cross-sectional study further indicated a higher prevalence of COPD in individuals with AS compared to controls, with a strong independent association between AS and COPD (*OR*=1.225, *p*=0.031).[25] However, to our knowledge, while a relationship between AS and COPD has been reported in the literature, no studies have explored a possible causal relationship between AS and COPD using the Mendelian randomization (MR) Approach.

MR is an approach commonly employed in academic research to investigate causal relationships between potential risk factors and disease.[26] This method uses genetic variation as an instrumental variables (IVs), thus avoiding the influence of confounding factors such as external environment in the past. In addition, genotype distribution precedes acquired exposure in time, and the association between genotype and disease is not affected by reverse causality. These are the advantages of MR method compared to observational study, and bioinformatics method is more cost-effective than other research methods.[27] Consequently, a bidirectional two-sample MR analysis was conducted to investigate the causal relationship between AS and COPD.

Methods

Study Design

The bidirectional MR study method was used to measure the causal effect in both directions. In order to interpret MR analysis accurately, adherence to three key assumptions is essential.[28] Hypothesis 1 posits a significant relationship between the IV and exposure factors, Hypothesis 2 suggests no association between the IV and any confounding factor impacting the outcome and exposure, and Hypothesis 3 proposes that exposure is the sole mechanism through which the IV influences the outcome. In other words, forward MR studies analyze the impact of AS on the incidence of COPD, and reverse MR studies analyze the impact of COPD on the incidence or development of AS. To investigate the causal relationship between AS and COPD, single nucleotide polymorphisms (SNPs) were utilized as the IV in bidirectional two-sample MR.

Data Source

The summary-level data for the genome-wide association study (GWAS) utilized in this research was obtained from the Integrative Epidemiology Unit (IEU) open GWAS project. To enhance the reliability of our findings, we incorporated two datasets related to AS (ebi-a-GCST005529 and ukb-a-88) and two datasets related to COPD (ebi-a-GCST90018807 and finn-b-J10_COPD). All datasets included individuals of European descent. The ebi-a-GCST005529 dataset was obtained from the International Genetics of Ankylosing Spondylitis (IGAS) Consortium for AS. It has a total of 22,647 people (including 9069 AS cases and 13,578 controls).[29] The ukb-a-88 dataset of 337,159 patients with AS (including 968 cases and 336,191 controls) from the United Kingdom was provided by the Neale Lab Consortium. The ebi-a-GCST90018807 dataset of 468,475 patients with COPD was present in the GWAS data(including 13,530 cases and 454,945 controls).[30] The finn-b-J10_COPD dataset of 193,638 patients with COPD (including 6915 cases and 186,723 controls) from publicly available GWAS in the FinnGen database. Table 1 provides the information regarding GWAS datasets.

Instrumental Variable Selection

IVs are commonly understood as genetic variations, with SNPs being the most frequently utilized. From IEU's open GWAS project, relevant data was extracted to identify single SNP associated with exposure factors. Our screening process involved intense scrutiny of SNPs that exhibited a strong correlation with exposures, as determined by the genome-wide significance level of $p < 5\times10^{-8}$, clumping window greater than 10,000 kb, and the linkage disequilibrium level of $r^2 < 0.001$. The strength of each SNP was evaluated through the calculation of the F-statistic ($F=\beta^2/SE^2$),[31] where a higher value suggests a decreased probability of weak instrument bias, typically observed when the F-statistic surpasses 10.[32]

Statistical Analysis

Inverse-Variance Weighted (IVW) was the primary approach used for estimating the causal effect. This method is considered to possess the highest capability in detecting causation within the two-sample MR analysis.[33] Heterogeneity tests were conducted to determine the appropriate model for the IVW method, with the fixed effects model being utilized in cases of non-significant heterogeneity (P-value > 0.05) and the random effects model being employed in instances of significant heterogeneity (P-value < 0.05). The random effects model was used by default in our analyses. In all two-sample MR analyses, a P-value below 0.05 signified statistical significance of the exposure factors and outcome variables. Supplementary analysis methods including the weighted median, MR-Egger, simple mode, and weighted mode were utilized. The consistency across these five models would bolster the credibility of the results. By using Cochran's Q test, we evaluated the heterogeneity of the IVW model based on IVs. The presence of heterogeneity, as indicated by the p-value of less than 0.05 in Cochran's Q-test, does not necessarily imply the invalidity of the IVW model. Directed pleiotropy was detected using the MR-Egger method, which allows for the presence of a non-zero intercept because the intercept represents the average estimate of pleiotropy for all instrumental variables, indicating the presence of gene pleiotropy only when the intercept is non-zero and P for intercept <0.05. Using leave-one-out analysis, we evaluated the impact of removing one SNP from the analysis. The Radial MR method was utilized to identify outliers, which were subsequently eliminated.[34] Following outlier removal, the MR analysis was repeated. The "TwoSampleMR" and "RadialMR" packages within the R software (version 4.2.0) were utilized for all analyses.[35]

Table 1 Details of GWAS Datasets in Mendelian Randomization Analysis

Phenotype	GWAS ID	Simple size	Population	Link
AS	ebi-a-GCST005529	22,647	European	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST005529/
AS	ukb-a-88	337,159	European	https://gwas.mrcieu.ac.uk/datasets/ukb-a-88/
COPD	ebi-a-GCST90018807	468,475	European	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90018807/
COPD	finn-b-J10_COPD	193,638	European	https://gwas.mrcieu.ac.uk/datasets/finn-b-J10_COPD/

Abbreviations: GWAS, Genome-Wide Association Studies; AS, ankylosing spondylitis; COPD, chronic obstructive pulmonary disease.

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Results

Effects of AS on COPD

Obviously, because we have two data sets for each of the exposure and outcome factors in our study, we have a total of four forward MR analyses. For all IVs in the MR analysis, F-statistics are greater than 10, indicating that there is no bias in the weak instrumental variables (more information about the F-statistics is presented in Supplementary material). In the MR analysis of AS(ebi-a-GCST005529) on COPD(ebi-a-GCST90018807), 25 SNPs were finally included. In the preliminary analysis, weighted median and weighted mode methods suggested that there was a causal relationship between AS and COPD (weighted median *OR* = 1.1748, *95% CI* = 1.0174–1.3564, *P* = 0.0281; weighted mode *OR* = 1.2095, *95% CI* = 1.0510–1.3919, *P* = 0.0139). After using Radial MR to remove outliers, except simple mode method (simple mode *OR* = 1.3203, *95% CI* = 0.9684–1.7999, *P* = 0.0935), the rest of the four methods suggests that AS was associated with an increased risk of COPD (IVW *OR* = 1.1326, *95% CI* = 1.0181–1.2600, *P* = 0.0221; weighted median *OR* = 1.1924, *95% CI* = 1.0381–1.3698, *P* = 0.0128; MR-Egger *OR* = 1.2220, *95% CI* = 1.0244–1.4576, *P* = 0.0375; weighted median *OR* = 1.2097, *95% CI* = 1.0544–1.3879, *P* = 0.0130). However, IVW was the primary method for estimating causal effects and was considered to have the highest causal detection power in two-sample MR analyses. Therefore, AS may serve as a risk factor for COPD. Furthermore, in the examination of pleiotropy and heterogeneity, all P values were greater than 0.05, indicating the absence of pleiotropy and heterogeneity. The results of heterogeneity tests are crucial for evaluating the reliability of IVW method. If heterogeneity exists, it indicates that different IVs have inconsistent effects on the outcome variables, which may indicate that there are uncontrolled confounding factors or that the hypothesis is not valid. Heterogeneity tests can help identify these problems and thus assess the reliability of IVW method. Both Figures 1 and 2 suggest a positive correlation between AS and COPD. The "leave-one-out" sensitivity analysis shown in Figure 3 indicates that the causality of positive results is stable and reliable.

However, in the MR analysis of the other three groups of AS on COPD, we did not find a causal relationship between AS and COPD (detailed information can be seen in Tables 2 and 3). Therefore, the interpretation of the causal relationship between AS and COPD needs to be cautious. After all, we only have evidence of causality in one set of databases, and more rigorous studies are needed for further validation in the future.

Effects of COPD on AS

In the reverse MR analysis, two of the four analyses could not complete the final MR analysis because the outcome data of SNPs related to exposure factors were not extracted from the target dataset. Among the IVs that can be analyzed by MR, the F-statistics are greater than 10 (more information about the F-statistics is presented in Supplementary material). The results of COPD(ebi-a-GCST90018807) on AS(ukb-a-88) suggested that no causal relationship between COPD and AS (IVW *OR* = 1.0000, *95% CI* = 0.9989–1.0011, *P* = 0.9794; no outliers). Meanwhile, the results of COPD(finn-b-J10_COPD) on AS(ukb-a-88) also suggested that no causal relationship between COPD and AS (IVW *OR* = 0.9996, *95% CI* = 0.9985–1.0007, *P* = 0.4810; no outliers). Both the MR-Egger intercept test and Cochran's Q test did not provide evidence of pleiotropy and heterogeneity. More information about the results of the reverse MR analysis can be found in Table 2.

Discussion

Our research provided partial evidence to support the viewpoint that AS may increase the prevalence of COPD. However, the results from the reverse MR analysis indicated that COPD did not have a causal relationship with AS. To the best of our knowledge, this study represents the first bidirectional MR investigation into the association between AS and COPD. As previously noted, there is a limited number of studies in the literature that have examined the relationship between AS and COPD, with no studies utilizing MR for this purpose. AS has a clear autoimmune basis, and COPD is associated with immune dysregulation. Consequently, this study has certain significance for further understanding of the complex relationship between AS and COPD.

A previous cohort study in Taiwan showed an increased incidence of asthma in patients with AS, while COPD was included AS part of the participants' baseline description, and COPD was significantly higher in patients with AS

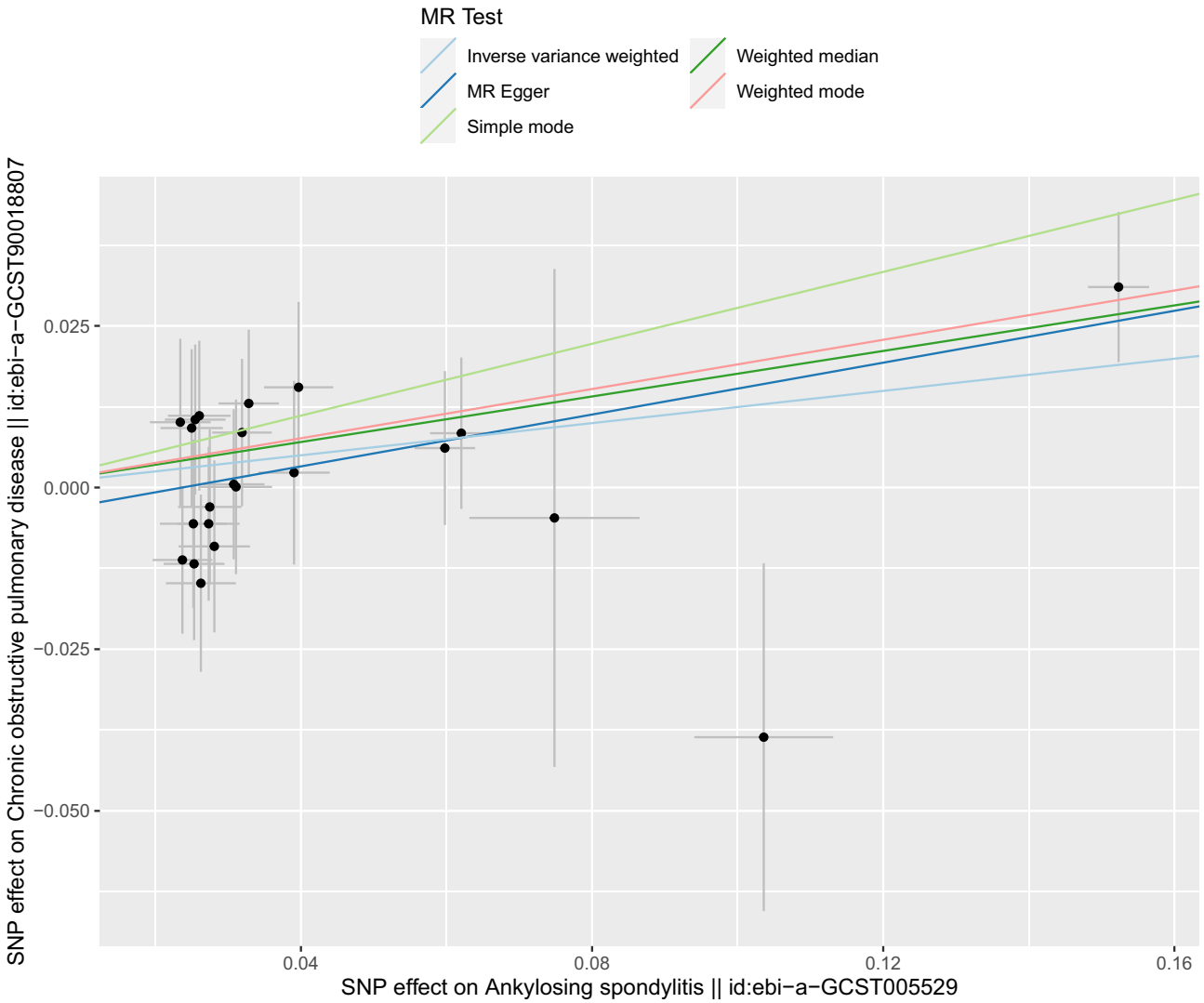

Figure 1 Scatter plot about the causal effect of ankylosing spondylitis (ebi-a-GCST005529) on chronic obstructive pulmonary disease (ebi-a-GCST90018807).

compared to healthy control.[24] A Swiss study showed that 18 of the 26 autoimmune diseases studied had a higher risk of COPD development.[36] The standardized incidence of COPD in patients with AS was 1.72(confidence interval 1.23–2.33).[36] A cross-sectional study further indicated a higher prevalence of COPD in individuals with AS compared to controls, with a strong independent association between AS and COPD (*OR*=1.225, *p*=0.031).[25] SpA can lead to spinal ankylosis and consequently, restrictive pulmonary dysfunction. A study showed that diaphragm ultrasonography is correlated with spirometric findings in radiographic SpA patients.[10] Our forward MR results confirmed the results of the early observational studies: AS may increase the prevalence of COPD. This is consistent with observational findings, which were validated using MR studies to enhance the robustness of causality. The underlying mechanism of the association between AS and COPD is still being investigated.

COPD is distinguished by an aberrant immune response in the lower airway, with disease advancement linked to the infiltration of innate and adaptive inflammatory immune cells that give rise to lymphoid follicles (LF).[37] These LF found in the small airways of COPD patients are substantial collections of B-cells, accompanied by interspersed $CD21^+$ and $CD35^+$ follicular dendritic cells, surrounded by lower quantities of $CD4^+$ (80%-90%) and minimal $CD8^+$ T-cells.[38,39] B-cell activating factor (BAFF) belongs to the tumor necrosis factor (TNF) family and is responsible for the survival and maturation of B-cells, and its over expression is associated with autoimmune diseases.[40] The excessive expression of

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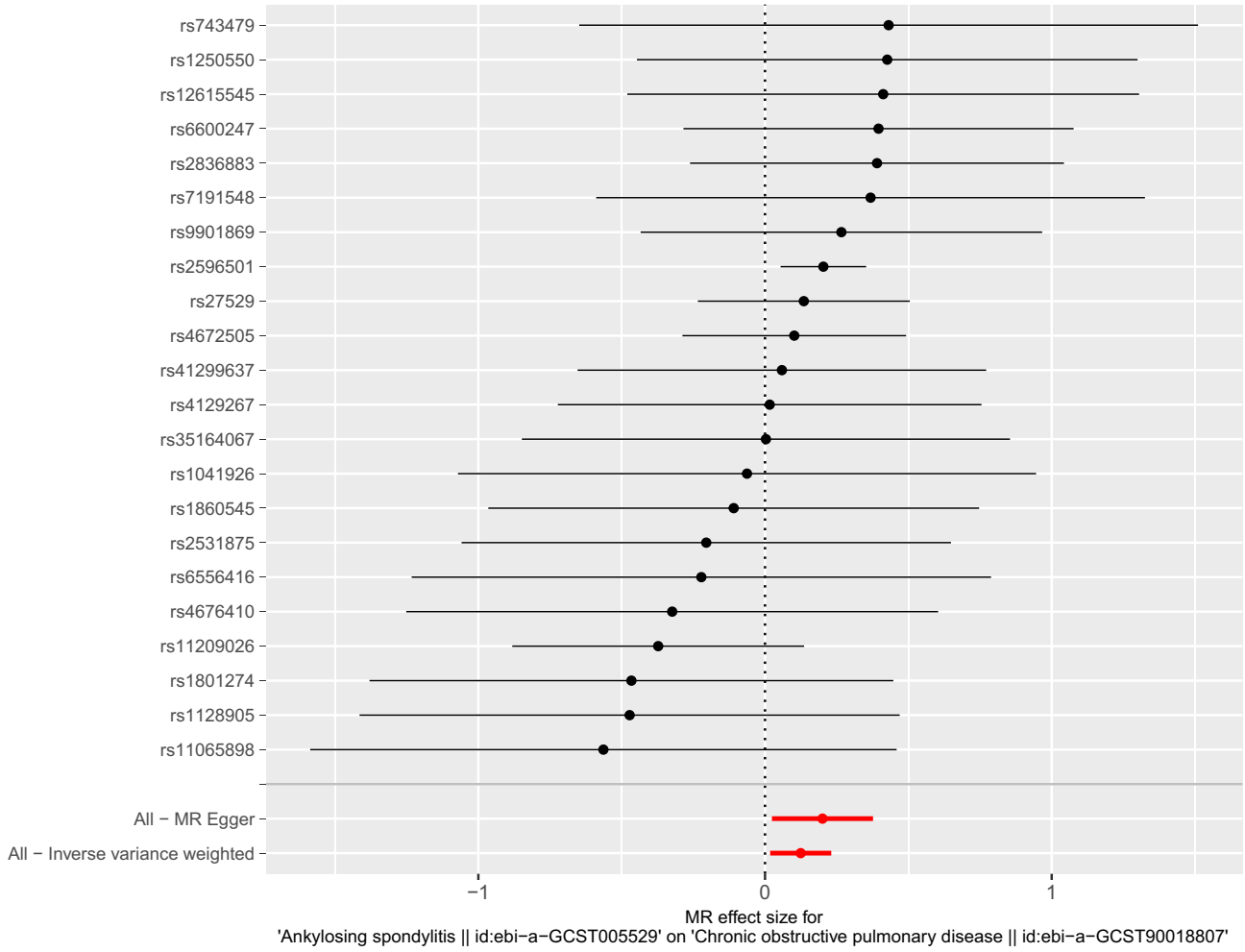

Figure 2 Forest plot for the causal effect of ankylosing spondylitis (ebi-a-GCST005529) on chronic obstructive pulmonary disease (ebi-a-GCST90018807).

BAFF contributes to the progression of COPD by fostering the survival of lung B-cells and the expansion of LF, establishing a self-sustaining cycle.[41] IL-6, initially recognized as B-cell differentiation factor, is a versatile cytokine that potentially plays a role in the development of pulmonary autoimmune reactions in individuals with severe stable COPD.[38,42] Through activation of CXCL12, IL-17A in the peripheral lungs of patients with advanced COPD may contribute to the progression of the disease and to the development of LF.[43] Stable COPD may be attributed to T cell inflammation and autoimmune responses activated in bronchial biopsies and bronchoalveolar lavage (BAL), characterized by elevated levels of signal transducer and activator of transcription (STAT)-4 and interferon (IFN)-γ $CD4^+$ T cells, which are correlated with reduced pulmonary function.[44] For AS, immune cells and innate cytokines have been proposed to be pivotal in the pathogenesis of AS.[45] IL-17 and IL-23 are major cytokines in axial spondyloarthritis and psoriatic arthritis.[46] Research has indicated elevated serum levels of IL-23 and IL-17 and the presence of $IL\text{-}17^+$ cells in the facet joints in AS patients, implying a potential heightened significance of the innate immune system in this condition.[47,48] Additionally, evidence suggests that targeting the IL-23/IL-17 pathway can substantially improve AS symptoms, underscoring its substantial involvement in the pathogenesis of AS.[49] Zhang et al discovered that mononuclear cells in peripheral circulation in individuals with AS and those who are human leucocyte antigen (HLA)-B27-positive exhibited a heightened presence of $IL4^+CD8^+$T cells in comparison to individuals in HLA-B27-negative control groups.[50] This was accompanied by an increased ratio of $IL\text{-}4^+$ to $IFN\text{-}\gamma^+$ cells.[49] $CD8^+$ T cells have the capability to induce the direct lysis of target cells by cytotoxic T lymphocytes through the secretion of perforin/granzyme or Fas/FasL signaling. Additionally, these cells have the capacity to produce inflammatory mediators, such as TNF-α, IFN-γ, and IL-17,

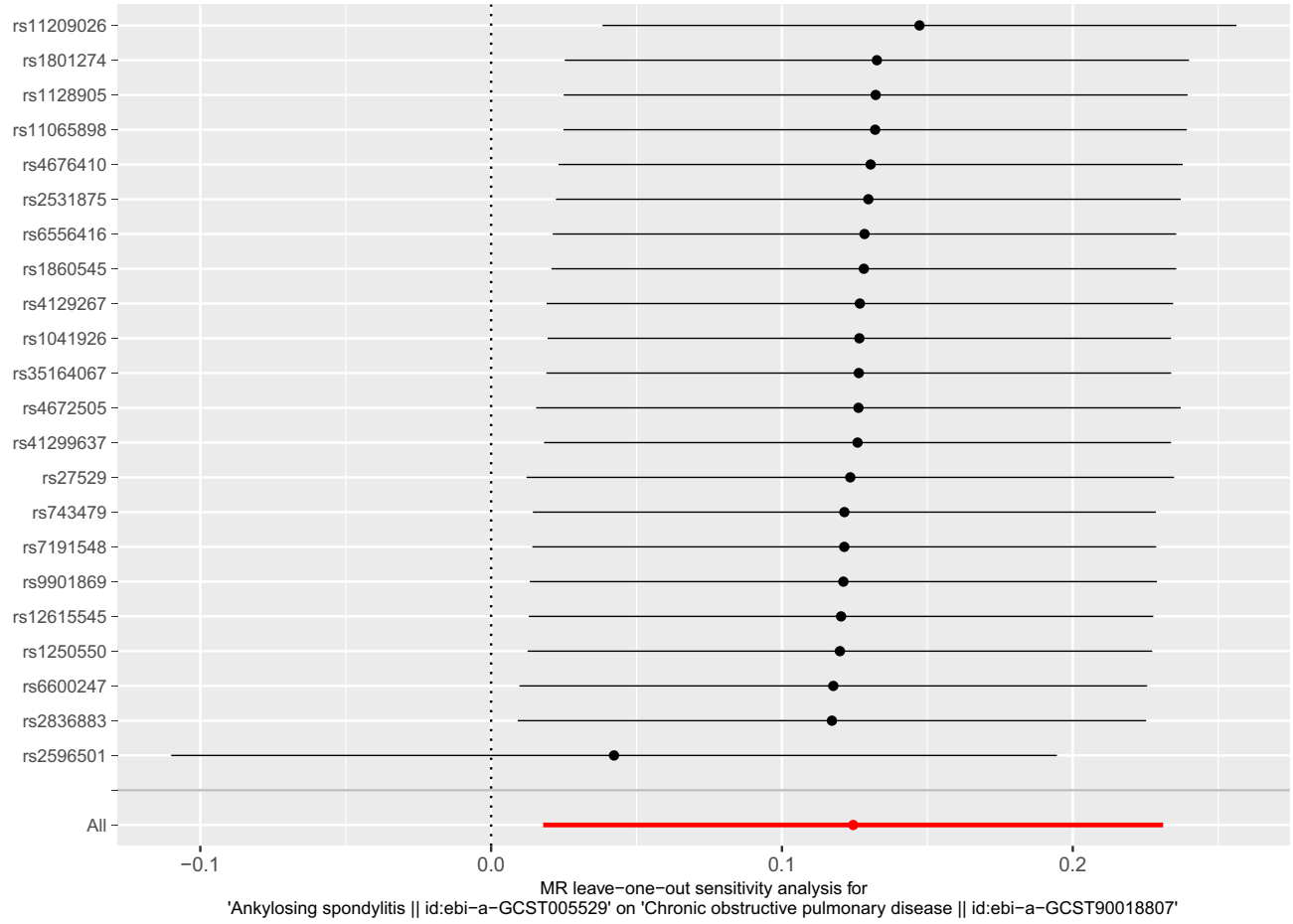

Figure 3 Leave-one-out analysis for the causal effect of ankylosing spondylitis (ebi-a-GCST005529) on chronic obstructive pulmonary disease (ebi-a-GCST90018807).

which contribute to the maintenance of chronic immune responses in individuals with AS.[51,52] B cells act as effectors that may play a role in the pathogenesis of AS through multiple mechanisms. These include differentiation into plasma cells that produce antibodies, potentially impacting immune responses and inducing osteoclast formation. Additionally, B cells secrete cytokines like IL-6 and receptor activator of nuclear factor kappa-B ligand (RANKL), which promote plasma cell and osteoclast generation independently. Furthermore, B cells have the ability to present antigens, serving as co-stimulators during appropriate activation of T cells. Finally, B lymphocytes are essential in the development of ectopic lymphoid tissue germinal centers, which is crucial for promoting the generation of plasma cells.[53] Therefore, the mechanism of AS affecting COPD may be caused by some common immune mechanisms mentioned above. However, it is important to note that the results of the cross-sectional study in Israel suggested that the AS group had a higher percentage of smokers than the control group, but multifactor analysis showed that AS was independently associated with COPD.[25] While smoking is established as a risk factor for COPD,[14] its potential association with AS remains unclear.[54] However, smoking has been correlated with unfavorable disease outcomes in individuals with AS,[55,56] and existing literature suggests a connection between smoking and the development of autoimmune diseases. Potential mechanisms may involve the enhancement of particular pathways that result in the synthesis of pro-inflammatory cytokines like TNF-α, IL-1, and IL-6, along with the genomic harm induced by endogenous free radicals that could potentially trigger autoimmune dysregulation.[57,58] Therefore, prudence is advised in the interpretation of the findings from this MR analysis. The univariate MR analyses solely provide an assessment of the overall effects between exposures and outcomes, lacking the ability to establish direct effects between them. Exposures and outcomes may be linked by extremely complex mechanisms. In the future, we can conduct MR analysis with smoking as a mediating factor.

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Table 2 The Results of the Mendelian Randomization Analyses

Exposure	Outcome	nSNPs	IVW		Weighted median		MR-Egger		Simple mode		Weighted mode		Cochrane's Q test		Pleiotropy		Radial MR
			OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	Q	P	Intercept	P	Outliers
AS(ebi-a-GCST005529)	COPD(ebi-a-GCST90018807)	25	1.0632 (0.9415–1.2006)	0.3233	1.1748 (1.0174–1.3564)	0.0281	1.1238 (0.9115–1.3854)	0.2859	1.1959 (0.8185–1.7474)	0.3642	1.2095 (1.0510–1.3919)	0.0139	36.3808	0.0504	−0.0035	0.5275	rs11190133; rs11624293; rs2517655
AS(ukb-a-88)	COPD(ebi-a-GCST90018807)	7	0.4551 (1.828518e-02-11.3292)	0.6313	0.3209 (1.689191e-02-6.0978)	0.4493	0.0607 (1.915913e-03-1.9257)	0.1731	0.0285 (3.988242e-06-203.5280)	0.4618	0.3163 (1.444979e-02-6.9215)	0.4922	7.1240	0.3095	0.0240	0.0799	rs9275569
AS(ebi-a-GCST005529)	COPD(finn-b-J10_COPD)	24	0.9959 (0.8440–1.1751)	0.9615	1.1016 (0.8714–1.3926)	0.4186	1.0931 (0.8212–1.4549)	0.5481	0.9902 (0.6575–1.4911)	0.9627	1.0628 (0.8603–1.3130)	0.5776	20.7821	0.5944	−0.0058	0.4424	NA
AS(ukb-a-88)	COPD(finn-b-J10_COPD)	6	0.1988 (4.644463e-04-8.507768e+01)	0.6013	0.1040 (2.352073e-03-4.595717e+00)	0.2416	0.0022 (2.721964e-05-1.757612e-01)	0.0521	0.2676 (5.268928e-08-1.358938e+06)	0.8737	0.1176 (3.238750e-03-4.269717e+00)	0.2955	14.0781	0.0151	0.0613	0.0238	rs154980; rs9275569
COPD(ebi-a-GCST90018807)	AS(ebi-a-GCST005529)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
COPD(finn-b-J10_COPD)	AS(ebi-a-GCST005529)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
COPD(ebi-a-GCST90018807)	AS(ukb-a-88)	9	1.0000 (0.9989–1.0011)	0.9794	0.9998 (0.9984–1.0013)	0.8371	1.0004 (0.9972–1.0037)	0.8083	1.0000 (0.9981–1.0020)	0.9679	0.9999 (0.9982–1.0015)	0.8724	3.9260	0.8637	−4.699662e-05	0.8031	NA
COPD(finn-b-J10_COPD)	AS(ukb-a-88)	3	0.9996 (0.9985–1.0007)	0.4810	0.9994 (0.9982–1.0005)	0.2788	0.9973 (0.9929–1.0018)	0.4484	0.9991 (0.9976–1.0005)	0.3323	0.9993 (0.9981–1.0005)	0.3464	2.7950	0.2472	0.0005	0.4901	NA

Abbreviations: nSNPs, number of single nucleotide polymorphisms; IVW, inverse-variance weighted; MR-Egger, Mendelian randomization Egger; OR, odds ratio; 95% CI, 95% confidence interval; AS, ankylosing spondylitis; COPD, chronic obstructive pulmonary disease; NA, not applicable.

Table 3 The Results of Mendelian Randomization Analyses After Removing Outliers

Exposure	Outcome	nSNPs	IVW		Weighted median		MR-Egger		Simple mode		Weighted mode		Cochrane's Q test		Pleiotropy	
			OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	Q	P	Intercept	P
AS(ebi-a-GCST005529)	COPD(ebi-a-GCST90018807)	22	1.1326 (1.0181–1.2600)	0.0221	1.1924 (1.0381–1.3698)	0.0128	1.2220 (1.0244–1.4576)	0.0375	1.3203 (0.9684–1.7999)	0.0935	1.2097 (1.0544–1.3879)	0.0130	15.0028	0.8228	−0.0048	0.3018
AS(ukb-a-88)	COPD(ebi-a-GCST90018807)	6	0.3151 (1.624654e-02-6.1103)	0.4452	0.3115 (1.513595e-02-6.4121)	0.4498	0.2056 (3.436848e-03-12.2939)	0.4907	0.0156 (3.161471e-06-77.1550)	0.3818	0.3420 (1.607276e-02-7.2780)	0.5222	1.2173	0.9432	0.0059	0.7813
AS(ukb-a-88)	COPD(finn-b-J10_COPD)	5	0.1419 (4.599991e-04-4.379995e+01)	0.5044	0.1009 (2.690203e-03-3.782434e+00)	0.2148	0.0023 (2.401007e-05-2.201153e-01)	0.0797	1.6577 (5.408822e-06-5.080453e+05)	0.9413	0.0936 (2.464806e-03-3.554133e+00)	0.2708	9.9972	0.0405	0.0605	0.0615

Abbreviations: nSNPs, number of single nucleotide polymorphisms; IVW, inverse-variance weighted; MR-Egger, Mendelian randomization Egger; OR, odds ratio; 95% CI, 95% confidence interval; AS, ankylosing spondylitis; COPD, chronic obstructive pulmonary disease.

The results of the reverse MR study suggest that COPD may not be associated with the occurrence or development of AS. Such results have suggestive clinical significance because there are no observational studies on the effect of COPD on AS, and such results are also worth exploring. There are several possible reasons for this. First of all, COPD is a chronic disease that is most common in people over 40 years old, while AS is generally most common in young adults, generally not more than 40 years old. Second, although both COPD and AS have immunological pathogenesis at present, the sequence of the onset is different, and the upstream and downstream relationship of the mechanism may cause the occurrence and development of COPD and AS to be unrelated. Finally, it cannot be ruled out that COPD may be related to the occurrence and development of AS. It is possible that the release of more authoritative GWAS data sets in the future may change this conclusion.

This study possesses both strengths and limitations. The MR methodology employed in this study utilizes genetic variation as IVs to causal relationship, effectively reducing the biases that may result from reverse causality and confounding factors.[27] In order to improve the accuracy of MR analysis, we selected multiple data sets for validation, and conducted sensitivity and pleiotropy analysis. Additionally, European populations from diverse countries were utilized for exposures and outcomes to minimize unwarranted biases. Nevertheless, it is crucial to acknowledge the constraints inherent in this study. First, not all MR analyses are completed successfully. Further investigation is warranted to determine if MR results can be achieved by loosening SNP screening criteria. On the other hand, the potential limitation could be mitigated by awaiting the publication of a more authoritative GWAS dataset, thereby potentially bolstering the strength of the IV. Secondly, the unavailability of summary-level GWAS data for separate genders impeded our capacity to conduct a sex-stratified analysis. Thirdly, as with all MR studies, our conclusions are contingent upon adherence to the assumptions of the method, which may introduce inherent limitations. Despite conducting various sensitivity analyses to evaluate the reliability of our outcomes, the potential influence of unmeasured confounders on our results cannot be definitively excluded.[59,60]

Conclusion

This study provided partial evidence to support the viewpoint that AS may increase the prevalence of COPD, while COPD had no causal relationship for AS. Further studies are needed to confirm these findings and elucidate their potential mechanisms of action.

Data Sharing Statement

This study involved the analysis of publicly accessible datasets, which can be accessed through the IEU open GWAS project. The supporting figures and tables can be found in the article.

Ethics Approval and Consent to Participate

This study has been reviewed and approved by the Institutional Review Board of Shanghai General Hospital and the ethics approval document has been obtained. Meanwhile, the Ethics Committee has exempted the informed consent form considering that the data of this study came from an open repository. (File number: 2024KS453).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that there are no conflicts of interest in this article.

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