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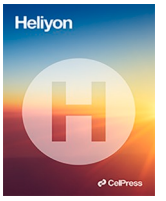

Research article

A bidirectional Mendelian randomization study investigating the relationship between genetically predicted systemic inflammatory regulators and chronic obstructive pulmonary disease

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ABSTRACT

Research has shown a connection between inflammation and chronic obstructive pulmonary disease (COPD), however the relationship between inflammation mediators and COPD causation remains unknown. To investigate the causal relationship of mediators of inflammation and COPD, we conducted a two-sample Mendelian randomization (MR) study. In our study, we incorporated 41 regulators of inflammation from 8293 Finnish individuals from genome-wide association studies (GWASs) of COPD corresponding to GWAS summary data for 2115 cases and 454,233 healthy individuals in Europe. Our research validated that higher levels of interleukin 8 (IL-8) are related with a decrease occurrence of COPD (OR = 0.795, 95 % CI = 0.642–0.984, p = 0.035) but that elevated levels of interleukin 18(IL-18) and interleukin 2 (IL-2) may be connected to an amplified risk of COPD (OR = 1.247, 95 % CI = 1.011–1.538; p = 0.039; OR = 1.257, 95 % CI = 1.037–1.523, p = 0.020, respectively). According to our research, cytokines play a crucial role in the development of COPD, and further investigation is necessary to explore the potential of utilizing these cytokines as targets for treatment and prevention of COPD.

1. Introduction

The long-term respiratory condition known as COPD is marked by restricted airflow due to inflammatory responses and airway remodeling [1]. The global incidence of COPD is estimated at 384 billion cases, with up to 3 million deaths each year [2]. Overall, the present diagnosis and treatment options for COPD are insufficient to meet worldwide healthcare demands. Thus, it is necessary to investigate potential strategies for preventing and managing COPD.

It has been reported that adverse clinical outcomes of COPD may be related to persistent inflammatory states [3]. A meta-analysis of 39,337 subjects revealed significantly increased CRP, leukocyte, fibrinogen, IL-8, and IL-6 levels among individuals with COPD [4]. Some researchers have suggested that the severity of COPD might be related to IL-4- and IL-5-mediated type 2 inflammatory responses

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[5]. Although the connection between cytokines and COPD has been investigated, the majority of these studies were observational and thus susceptible to the impact of reverse causation and confounding factors. Consequently, it's still unknown how cytokines and COPD are related causally.

Mendelian randomization (MR) is a powerful tool for assessing causality between exposure and clinical effect according to genetic differences [6]. Before the disease begins, the genes are distributed randomly during gamete formation, allowing the prevention reverse causality [7]. In this study, we investigated the causal connection between cytokines and COPD incidence using MR analysis and the outcomes of our study revealed a significant association between the levels of IL-8, IL-2, IL-18 and the probability of developing this ailment.

2. Methods

2.1. Study design

There were prerequisites for our analysis [8]: (i) genetic instrument variants are strongly associated with cytokine levels; (ii) genetic instrument variants do not affect outcomes through confounders; and (iii) genetic instrument variants strongly affect the risk of COPD through cytokine levels rather than directly. Fig. 1 illustrates the underlying principle of the research.

2.2. Genetic instruments

Table 1 presents the collective cytokine data from genome-wide association studies (GWASs). Genetic instrument variants were derived from a study of 8293 European individuals utilizing single-nucleotide polymorphisms (SNPs) linked to 41 cytokines and growth factors [9]. The COPD GWAS dataset was obtained from 2115 COPD patients and 454,233 healthy control individuals of European ancestry [9]. We chose SNPs that were highly linked with exposure at the genome-wide significance level. In order to guarantee the independence of the instruments and the precision of causal effects, we eliminated SNPs with linkage disequilibrium (r2>0.001 in the European 1000G reference panel); additionally, palindromic variants were also excluded [10]. When we set the threshold $p < 5 \times 10\text{-}8$, only 16 cytokines were selected based on our criteria described above **(Supplementary Table S1)**. We also set the threshold $p < 5 \times 10\text{-}6$ [11], and 41 systemic inflammatory regulators were chosen as instrumental variables **(Supplementary Table S2)**. In order to investigate additional potential causal factors, we conducted two Mendelian randomization analyses at different P values, and we validated that there was a strong association between the SNPs and exposure. To eliminate weak instruments, we averaged the SNP F-statistics, and those SNPs with F-statistics exceeding 10 were deemed strong [12].

2.3. Statistical analysis

Inverse-variance weighted (IVW) regression analysis was performed under the assumption that there were no genetic instruments that were invalid, including the absence of directional pleiotropy [13]. To account for potential directional pleiotropy, we employed MR−Egger and weighted median methods, which are known to be robust, to estimate the effect size [14]. The MR−Egger approach additionally also estimates directional pleiotropy through its intercept ($p < 0.05$ was considered significant). The heterogeneity was accessed by employing Cochran's Q statistic with significance set at $p < 0.05$ [10]. Moreover, MR-PRESSO was utilized for identifying and eliminating outliers. We also assessed the effect of individual SNPs on the robustness of causal effects [15].

3. Results

The results described below demonstrate the association between systemic inflammatory regulators and COPD. SNPs strongly associated with 16 cytokines were screened at a threshold of $p < 5 \times 10\text{-}8$. The MR analysis of the 16 cytokines indicated that interleukin-18 (IL-18) may contributed to be a risk factor for COPD (OR = 1.247, 95 % CI = 1.011–1.538; p = 0.039). The leave-one-

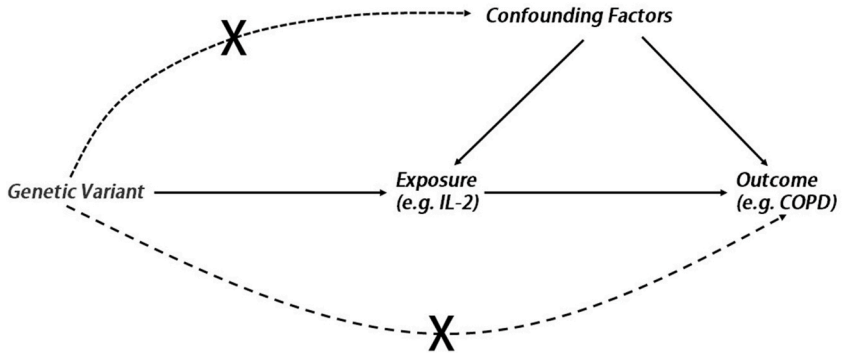

Fig. 1. Flowchart of the MR analysis.

Table 1
The sample size for systemic inflammatory regulators analyzed in this study was acquired from the GWAS.

Systemic Inflammatory Regulators	Abbreviation	Sample size	Number
Eotaxin 1	CCL11	8153	GCST004460
Basic fibroblast growth factor	bFGF	7565	GCST004459
Colony stimulating factor 3	CSF3	7904	GCST004458
C-X-C motif chemokine ligand 1	CXCL 1	3505	GCST004457
Interferon-gamma	IFN-γ	7701	GCST004456
Interleukin-2	IL-2	3475	GCST004455
Interleukin-2 receptor alpha	IL-2 RA	3677	GCST004454
Interleukin-4	IL-4	8124	GCST004453
Interleukin-5	IL-5	3364	GCST004452
Interleukin-7	IL-7	3409	GCST004451
Interleukin-9	IL-9	3634	GCST004450
Hepatocyte growth factor	HGF	8292	GCST004449
Interleukin-1 beta	IL-1β	3309	GCST004448
Interleukin-1 receptor antagonist	IL-RA	3638	GCST004447
Interleukin-6	IL-6	8189	GCST004446
C-X-C motif chemokine ligand 8	CXCL 8	3526	GCST004445
Cytokine synthesis inhibitory factor	CSIF	7681	GCST004444
Interleukin-13	IL-13	3557	GCST004443
Interleukin-17	IL-17	7760	GCST004442
Interferon gamma inducing factor	IGIF	3636	GCST004441
Interferon gamma induced protein 10	IP10	3685	GCST004440
Interleukin-12 p70	IL-12 p70	8270	GCST004439
C–C motif chemokine ligand 2	CCL2	8293	GCST004438
C–C motif chemokine ligand 7	CCL7	843	GCST004437
Colony stimulating factor 1	CSF1	840	GCST004436
C-X-C motif chemokine ligand 9	CXCL9	3685	GCST004435
C–C motif chemokine ligand 3	CCL3	3522	GCST004434
C–C motif chemokine ligand 4	CCL4	8243	GCST004433
Platelet derived growth factor BB	PDGF-BB	8293	GCST004432
C–C motif chemokine ligand 5	CCL5	3421	GCST004431
Interleukin-16	IL-16	3483	GCST004430
Stem cell factor	SCF	8290	GCST004429
Stem cell growth factor beta	SCGFβ	3682	GCST004428
C-X-C motif chemokine ligand 12	CXCL12	5998	GCST004427
Tumor necrosis factor-alpha	TNFα	3454	GCST004426
Tumor necrosis factor-beta	TNFβ	1559	GCST004425
Tumor necrosis factor ligand superfamily member 10	TNFSF10	8186	GCST004424
Macrophage migration inhibitory factor	MIF	3492	GCST004423
Vascular permeability factor	VPF	7118	GCST004422
Beta nerve growth factor	β-NGF	3531	GCST004421
C–C motif chemokine ligand 27	CCL27	3631	GCST004420

out plots in Fig. S1 illustrate the stability of the above MR analysis results. The MR−Egger intercept did not provide any indication of horizontal pleiotropy for IL-18 ($p = 0.958$). Fig. S1 includes funnels plots for visualizing the heterogeneity analysis; however, the effect size of Cochran's Q statistic ultimately determined the heterogeneity. There was no significant heterogeneity detected for IL-18 (all p

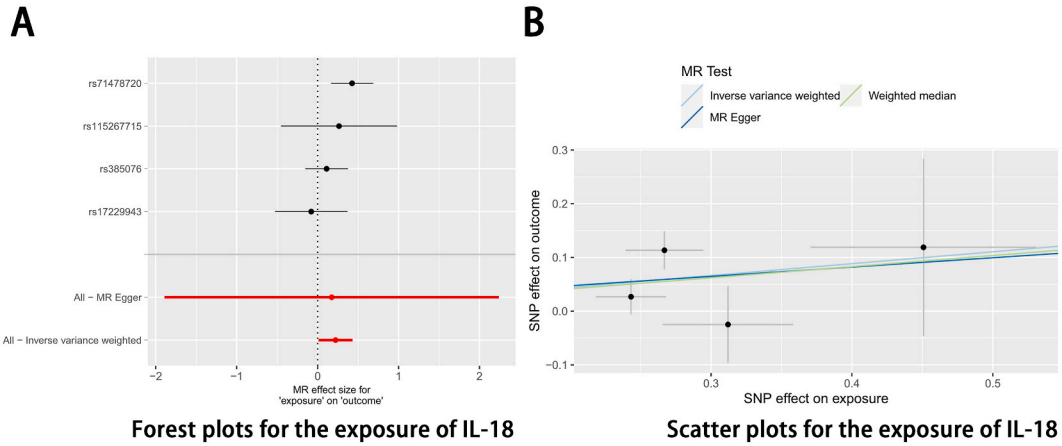

Fig. 2. Forest plots and scatter plots for IL-18.

values > 0.05). The forest plots in Fig. 2 (A) indicate the impact magnitude on results for every SNP demonstrating a robust association between IL-18 and all SNPs. According to the scatter plot in Fig. 2 (B), there is a correlation between higher IL-18 exposure and an elevated risk of COPD.

In addition, SNPs strongly associated with 41 cytokines were screened at a threshold of $p < 5 \times 10\text{-}6$. The MR analysis of the 41 cytokines revealed a positive correlation between elevated levels of interleukin-8 (IL-8) levels were and a reduced risk of COPD when employing the IVW technique (OR = 0.795, 95 % CI = 0.642–0.984; p = 0.035). There was no evidence of potential horizontal pleiotropy of IL-8 as indicated by the MR−Egger intercept (p = 0.942). Moreover, there was no notable heterogeneity in the Q values for IL-8, with all p values exceeding 0.05. The IVW method indicated that a higher circulating level of interleukin-2 (IL-2) was shown to be associated with an increased risk of COPD (OR = 1.257, 95 % CI = 1.037–1.523, p = 0.020) according to the IVW approach, and the MR−Egger intercept did not reveal any evidence of horizontal pleiotropy (p = 0.161). In general, there was no notable heterogeneity observed for IL-2 (all p values > 0.05). Sensitivity analysis of the leave-one-out studies showed that individual studies had no influence on the results. The forest plots in Fig. 3 (A) suggest individual and overall effects of SNPs related to IL-8 on COPD, as was the case for IL-2 in Fig. 3 (B). The scatter plots in Fig. 3 (C, D) suggest that IL-8 may be a protective factor against COPD but that IL-2 may be a risk factor. Fig. S2 presents a visualization of the heterogeneity test for IL-8 and IL-2 is provided in Fig. S2, but heterogeneity was determined based on the p value. The leave-one-out plots in Fig. S3 indicate that neither SNP removed had any effect on the final results, indicating that our analysis results for IL-8 and IL-2 are robust. Furthermore, we showcased through the MR−Egger method that the levels of IL-7 and IL-1β may be associated with the risk of COPD (OR = 1.794, 95 % CI = 1.279–2.527, p = 0.012; OR = 2.890, 95 % CI = 1.665–5.019, p = 0.033, respectively). Nevertheless, the MR-PRESSO global test indicated the existence of horizontal pleiotropy. Hence, we assert that, based on the findings of this study, there is no evident cause-and-effect connection between IL-17 or IL-1β and COPD.

Summary data for the above MR analysis are presented in Table 2. We used the same method to analyze whether the effect sizes of the 41 cytokines were statistically significant when COPD was used as an exposure factor, but genetically predicted COPD was not associated with any inflammatory regulators according to the MR data (Supplementary Tables S3–S4).

4. Discussion

In this study, we employed a 2-sample MR analysis to assess the connection between inflammatory biomarkers and the occurrence of COPD. Our research revealed that prolonged exposure to elevated levels of IL-18 and IL-2 could potentially heighten the likelihood of developing COPD, whereas that extended exposure to heightened levels of IL-8 might potentially mitigate this risk.

IL-18 is an active cytokine of the IL-1 class processed by caspase-1 and is produced mainly by macrophages and dendritic cells; this cytokine modulates innate and adaptive immunity. Abnormal regulation of IL-18 can lead to autoimmune disease or inflammation. IL-18Rα and IL-18β form the components of the IL-18 receptor. In order to establish a high-affinity complex, IL-18 binds to IL-18Rα and causes the recruitment of IL-18β. This complex activates the transcription factors NF-κB and AP-1 through signaling molecules, including MyD88, IPAK, and TRAF6, ultimately activating the proinflammatory program. The combination of IL-18 and IL-12 can

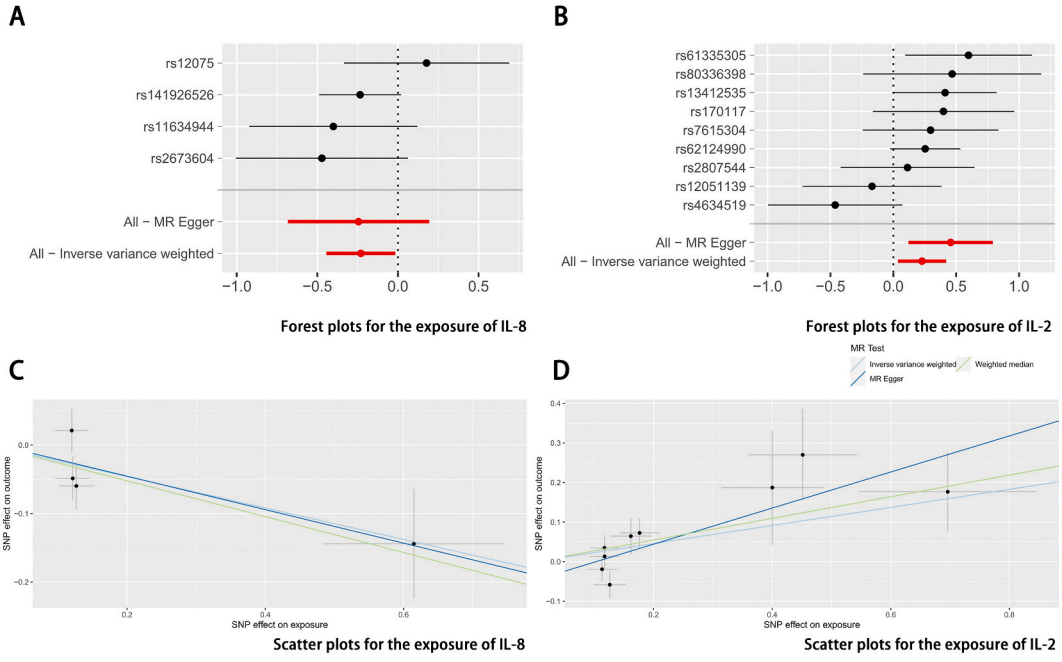

Fig. 3. Forest plots and scatter plots for IL-8 and IL-2.

Table 2
Results of MR analysis evaluating causal associations between systemic inflammatory regulators and risk of COPD.

Systemic Inflammatory Regulators	Analytical method	Numbers of SNPs	Beta	OR (95 % CI)	p	p for the heterogeneity test	p for the MR–Egger intercept	p for MR-PRESSO (0 outliers)
IL-18	Inverse variance weighted	4	0.221	1.247 (1.011–1.538)	0.039	0.091	0.958	0.131
	MR–Egger	4	0.173	1.189 (0.151–9.382)	0.884	0.188		
	Weighted median	4	0.207	1.230 (0.987–1.532)	0.065			
IL-8	Inverse variance weighted	4	−0.230	0.795 (0.642–0.984)	0.035	0.303	0.942	0.125
	MR–Egger	4	−0.244	0.783 (0.505–1.21)	0.389	0.163		
	Weighted median	4	−0.261	0.770 (0.600–0.988)	0.040			
IL-2	Inverse variance weighted	9	0.228	1.257 (1.037–1.523)	0.020	0.137	0.243	0.076
	MR–Egger	9	0.455	1.578 (1.129–2.205)	0.032	0.243		
	Weighted median	9	0.273	1.314 (1.050–1.645)	0.017			
IL-7	Inverse variance weighted	9	0.076	1.073 (0.295–1.245)	0.350	0.166	0.016	0.501
	MR–Egger	9	0.584	1.794 (1.274–2.527)	0.012	0.971		
	Weighted median	9	0.070	1.073 (0.911–1.263)	0.401			
IL-1β	Inverse variance weighted	5	0.212	1.237 (0.789–1.939)	0.355	0.011	0.043	0.407
	MR–Egger	5	1.061	2.890 (1.665–5.019)	0.033	0.652		
	Weighted median	5	0.296	1.344 (0.953–1.897)	0.092			

enhance the activation of NK cells, leading to the production of IFN-γ. In the absence of IL-12, IL-18 induces the synthesis of IL-4 by mast cells and eosinophils [16]. Researchers have also been interested in the connection between IL-18 and respiratory disorders. Our study indicated that elevated levels of IL-18 could potentially heighten the susceptibility to COPD. Luca Giordano et al. reported elevated lung tissue IL-18 levels in patients with COPD, and in addition, serum from a mouse model of emphysema induced by cigarette smoke exposure showed elevated levels of IL-18 [17]. Nikoletta Rovina et al. reported that the levels of IL-18 in the sputum supernatants of individuals with COPD were greater compared to those in the sputum supernatants of both healthy smokers and nonsmokers. Additionally, a negative association was found between IL-18 levels and both FEV1 (percent predicted) and FEV1/FVC in COPD smokers [18]. Nailya Kubysheva et al. also demonstrated that heightened levels of serum IL-18 were linked to a reduction in FEV1 in individuals with asthma-COPD overlap [19]. IL-18 is strongly associated with COPD, but the underlying mechanisms have not been fully elucidated, although inflammation may play an important role in this process. In the study conducted by Min-Jong Kang and colleagues, it was found that IL-18 causes damage to the lung tissue, leading to pulmonary fibrosis, airway damage and vascularization in IL-18-overexpressing mice, a complex mixed inflammatory response similar to the one observed in individuals with COPD [20], and Adelheid Kratzerden et al. reported reduced chemokine production and apoptosis, lung inflammation and emphysema in IL-18-knockout (KO) mice [21]. Many scholars have also focused on the mechanism by which IL-8 causes this inflammatory response in the lungs. Min-Jong Kang et al. proposed that IL-18 boosts the cytotoxicity of NK cells and $CD8^+$ T cells through an IFN-γ-dependent pathway, leading to emphysema development and apoptosis of epithelial cells. In addition, IL-18 stimulates vascular and airway remodeling and lung fibrosis through the IL-17/IL-13 axis [20]. Lu Liu et al. reported that MUC1, which may be an upstream regulator of TLR4/MyD88/NF-κB, was downregulated in asthma patients and further downregulated the expression of IL-18 by collecting sputum specimens from 64 individuals diagnosed with asthma. In addition, activation of TLR4/MyD88/NF-κB resulting from downregulation of MUC1 in asthma patients increased NLRP3 inflammasome-mediated focal death and inflammation in vitro [22]. Meng-Yu Zhang et al. indicated that extracts from cigarette smoke stimulate NLRP3 inflammatory vesicles to recruit caspase-1 through ASC proteins, which cleave and activate IL-18 and IL-1β and ultimately lead to the death of bronchial epithelial cell [23]. These findings indicated that the inflammatory pathway mediated by IL-18 contributes to the progression of COPD. Currently, there are few clinical applications of IL-18 in respiratory diseases. Moore et al. reported that elevated IL-18 levels (>800 pg/mL) were linked to higher 60-day mortality in patients with sepsis-induced ARDS in a cohort of 1285 patients with sepsis [24], and Shizuka Watanabe

et al. reported significantly lower serum interleukin-18 levels in responders than in non-responders among patients with severe asthma who were treated with dupilumab [25]. IL-18 may be utilized as both a biomarker and a therapeutic target for COPD in the future, but further study is required.

IL-8 is a member of the C-X-C subfamily (α-subfamily) and is also known as the chemokine CXCL8. This cytokine is produced not only by monocyte macrophages but also by fibroblasts, epithelial cells, and endothelial cells, among others. The regulation of IL-8 expression has been demonstrated to be influenced by various stimuli, including cytokines (TNFα, IL-1β, etc.), hypoxia, and reactive oxygen species and IL-8 is nearly undetectable in unstimulated cells. The IL-8 receptors are CXCR1 and CXCR2, and IL-8 stimulation of CXCR1 and/or CXCR2 promotes Akt, PKC, calcium mobilization, and MAPK signaling and ultimately leads to changes in cellular function [26]. IL-8 can have chemotactic effects on neutrophils and T cells and mediate the inflammatory response to clear pathogens [27,28]. Our study showed that high levels of IL-8 may reduce the risk of developing COPD. We hypothesized that recruitment of neutrophils by IL-8 via the CXCR1/2 pathway and the elimination of lung infections could potentially be the mechanisms by which IL-8 decrease the risk of COPD. Mark S. Gresnigt et al. reported that CXCR2-deficient mice had impaired neutrophil recruitment to the lungs after infection with Aspergillus and developed severe hypoxia and inflammation, which exacerbated infection and lung injury [29]. Overall, relatively few studies have evaluated the relationship between IL-8 and COPD. Nonetheless, Maria Ferraro et al. reported that individuals suffering from AECOPD exhibited elevated levels of plasma IL-8 levels compared to those with stable COPD [30]. Xiaojun Zhang et al. reported that sputum IL-8 levels were elevated in patients with severe COPD, in addition to elevated alveolar lavage fluid IL-8 levels in cigarette smoke-induced rat COPD models [31]. Bartolome R Celli et al. included 1843 patients in a cohort study and found that elevated levels of IL-8 were linked to death in an independent and significant manner [32]. These studies demonstrate that IL-8 promotes the development of COPD. Our study proposed that high levels of IL-8 reduce the risk of developing COPD. We believe the possible reasons are as follows. First, observational studies frequently fail to entirely eliminate the influence of confounding factors. The secretion of IL-8 can be influenced by smoking, glucocorticoids, and infections, and further studies may be necessary to ascertain the impact of these confounding factors on disease development. Second, IL-8 has a chemotactic effect on immune cells, i.e., through the directed movement of immune cells along a concentration gradient. Hence, the biological function of IL-8 is associated with the concentration gradient of IL-8 rather than its absolute concentration. Higher levels of plasma IL-8 decrease neutrophil and T-cell recruitment to sites of inflammation [33]. Furthermore, immunosuppressive T cells in COPD patients may effectively block IL-8 function. Richard T. McKendry et al. showed that the expression of programmed cell death protein-1 (PD-1) was upregulated in T cells of individuals with COPD leading to impaired T-cell toxic degranulation. In addition, infection led to decreased expression of the macrophage ligand PD-L1 and increased release of IFN-γ and IL-8. That is, the complex relationship between immune cell loss of function and aberrant cytokine regulation in the context of COPD may explain the eventual occurrence of hyperinflammation [34]. Therefore, we hypothesize that this protective effect may only occur within a specific window of time (e.g., early). Although the impact of inhibiting IL-8 in COPD has been studied, there was no notable enhancement in clinical outcomes [35,36]. To sum up, our research demonstrated that the impact of IL-8 on COPD is still controversial. However, additional cohort studies and clinical interventional studies are needed to determine whether IL-8 can act as a marker or therapeutic target in COPD.

IL-2, which is a cytokine generated by activated $CD4^+$ helper T cells, belongs to the class of lymphoid growth factors that regulate both adaptive immunity and maintenance of immune tolerance. IL-2 acts by binding to the IL-2 receptor (IL-2R) on the cell surface. IL-2R attaches to IL-2 mainly via two distinct conformations, namely, IL-2Rαβγ and IL-2Rγ. IL-2Rαβγ is composed mainly of an α-chain (CD25), a β-chain (CD122), and a γ-chain (CD132); IL-2Rβγ is composed mainly of CD122 and CD132. IL-2 binding to IL-2R activates the PI3K, STAT5, and MAPK signaling pathways [37]. Due to variations in receptor subunits' affinities for IL-2 and their distinct distributions on cells, IL-2 exhibits diverse primary roles at different concentrations. IL-2Rαβγ is expressed mainly on regulatory T cells (Tregs), which have a higher affinity for IL-2; therefore, IL-2 mainly plays a role in maintaining immune tolerance at low concentrations [38,39]. IL-2Rβγ is expressed mainly on resting effector T cells (Teffs) and NK cells and has a decreased affinity for IL-2; thus, high concentrations of IL-2 can stimulate T-cell growth and differentiation, enhance T-cell activity, promote NK-cell activation, and enhance the killing activity of NK cells [40,37]. According to our research, elevated levels of IL-2 may increase the risk of COPD, potentially due to the stimulation of T cells and NK cells at high doses. R Finkelstein et al. reported that the degree of lung destruction in emphysema patients is primarily related to T-lymphocyte aggregation rather than to neutrophil aggregation [41]. Juliana Souza Uzeloto et al. reported that COPD patients with more severe airway obstruction had higher peripheral blood IL-2 levels [42]. K Kai McKinstry's study of uninfected mice revealed that IL-2 was linked to decreased lung function and that the dose of IL-2 used to target CD122 was proportional to lung inflammation [43]. Rui He reported that high levels of IL-2 promote the development of lung inflammation in mice but that low doses prevent the development of transfusion-related acute lung injury [44]. Fahmida Alam demonstrated improved lung immunopathology in influenza virus-infected mice via the targeting of CD25 by IL-2 [45]. Camelia Frantz ameliorated pulmonary fibrosis in Treg-deficient mice via low-dose application of IL-2 [46]. In conclusion, our study proposed that elevated IL-2 may increase the risk of COPD development. In conjunction with the results of prior studies, the findings in this study suggest that IL-2 and IL-2R could potentially serve as promising therapeutic agents or targets for COPD treatment in the future.

Only a few observational studies have been undertaken to date to evaluate the association between cytokines and COPD, and no MR analysis has been performed on this topic. MR analysis avoids reverse causality and residual confounding, which are widely used to explain causal relationships [47]. Our study represents the first MR analysis of the association between cytokines and COPD incidence.

The limitations of the current study include the removal of weak instrumental variables, as a weak effect does not necessarily mean that cytokines do not play a role. Second, the data used in this study were from populations of European ancestry, which does not reflect the heterogeneity among different populations. Third, as MR analysis assesses the cumulative effects of genetic variation, we cannot extrapolate the possible effects of clinical treatment [48]. In addition, there may be time-dependent effects and inflammation-environment interactions that could influence the results of our analysis.

In conclusion, we report that cumulative exposure to low levels of IL-8 and high levels of IL-2 and IL-18 are associated with the risk of COPD. Further studies on IL-8, IL-2 and IL-18 will elucidate not only the mechanisms of COPD development but also the application of these cytokines in clinical settings.

Data availability statement

All of these data are accessible via the GWAS Catalog server (https://www.ebi.ac.uk/gwas/) by searching with the accession number. The GWAS accession numbers of 41 cytokines are displayed in Table 1, and the accession number of COPD is GCST90044074.

Ethics approval and consent to participate

All participants/patients (or their proxies/legal guardians) provided informed consent to participate in the study. Since the GWAS Catalog is a public resource, ethical committee review and/or clearance was not required for this work, and ethical approval for the patients involved in the database was already obtained. Users can download relevant data for free and publish relevant articles.

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CRediT authorship contribution statement

Mengyuan Zhang: Writing - original draft. **Shengnan Wang:** Data curation. **Qingtian Guan:** Writing - review & editing, Supervision. **Jianglong Wang:** Writing - review & editing. **Bailing Yan:** Writing - review & editing. **Li Zhang:** Writing - review & editing. **Dan Li:** Writing - review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e24109.

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