REVIEW

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Biomarkers of the relationship of particulate matter exposure with the progression of chronic respiratory diseases

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A high level of particulate matter (PM) in air is correlated with the onset and development of chronic respiratory diseases. We conducted a systematic literature review, searching the MEDLINE, EMBASE, and Cochrane databases for studies of biomarkers of the effect of PM exposure on chronic respiratory diseases and the progression thereof. Thirty-eight articles on biomarkers of the progression of chronic respiratory diseases after exposure to PM were identified, four of which were eligible for review. Serum, sputum, urine, and exhaled breath condensate biomarkers of the effect of PM exposure on chronic obstructive pulmonary disease (COPD) and asthma had a variety of underlying mechanisms. We summarized the functions of biomarkers linked to COPD and asthma and their biological plausibility. We identified few biomarkers of PM exposure-related progression of chronic respiratory diseases. The included studies were restricted to those on biomarkers of the relationship of PM exposure with the progression of chronic respiratory diseases. The predictive power of biomarkers of the effect of PM exposure on chronic respiratory diseases varies according to the functions of the biomarkers.

Keywords: Asthma; Biomarkers; Lung diseases; Pulmonary disease, chronic obstructive; Particulate matter

INTRODUCTION

What is a biomarker?

According to the United States National Institutes of Health, a biomarker is a "characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention" [1]. Thus, biomarkers are measurable indicators of molecular, histologic, radiographic, or physiologic characteristics [2].

Particulate matter (PM)

Air pollution is a major public health concern, and PM is a major component of polluted air [3]. PM comprises a combination of solid and liquid particles [4]. The typical chemical components of PM include sulfate, nitrate, and carbon in both elemental and organic forms, as well as organic substances, biological materials, and heavy metals [5]. An increase in PM exposure has been linked to the mortality and morbidity associated with respiratory diseases [3,6-8].

BIOMARKERS OF PM EXPOSURE: CHRONIC RESPIRATORY DISEASES

Chronic obstructive pulmonary disease (COPD)

According to the Global Burden of Disease Study [9], exposure to fine PM ($PM_{2.5}$, aerodynamic diameter ≤ 2.5 μm), which is linked to COPD, has increased, particularly in the elderly population [10]. Exposure to $PM_{2.5}$ decreases lung

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function and aggravates respiratory diseases [11], leading to hospitalization, morbidity, and mortality [12-14]. Biomarkers are categorized as blood, urine, sputum, and fractional exhaled nitric oxide (FeNO) (Table 1).

Exposure to PM alters the levels of blood biomarkers in patients with COPD. Ubiquitin and beclin 1 levels change with increasing PM exposure [15]. The blood levels of some interleukins (ILs) increased, whereas the levels of others decreased, with increasing PM exposure [16,17]. An increased blood C-reactive protein (CRP) level is a marker of inflammation [18-20]. Also, biomarkers related to epigenetic regulation, such as reduced DNA methylation, have been identified [21].

Exposure to PM modulates the levels of urine biomarkers. The levels in urine of the metabolites 8-hydroxy-2′-deoxyguanosine (8-OHdG) and malondialdehyde (MDA) increased with increasing PM exposure [22,23]. Additionally, the levels of uric acid, glyceric acid 1,3-biphosphate (GABP), and dopamine-4-sulfate were elevated with increasing PM exposure [24].

Regarding sputum biomarkers, the black carbon (BC) content of airway macrophages (AMs), which target external environmental substances such as PM in the respiratory tract, increases as the PM level increases, suggesting potential as a biomarker of elevated PM exposure [25]. In addition, the level of FeNO, a marker of airway inflammation, increases after PM exposure in COPD [21,26].

Asthma

The air exhaled by patients with asthma contains biomarkers of PM exposure. The levels of biomarkers of asthma can be measured in exhaled breath condensate (EBC), blood,

Table 1. Biomarkers of PM and COPD

Type of biomarker	Biomarker	Response to increased PM
Blood	Ubiquitin, Beclin 1 [15]	↑ Ubiquitin, ↑ Beclin 1
	Various ILs [16,17]	↓ IL4, IL6, IL8, IL13, ↑ IL2, IL12, IL17A
	CRP [18-20]	↑ CRP
	NOS2A methylation [21]	↓ NOS2A methylation
Urine	Human urinary metabolome (8-OHdG, MDA) [22,23]	↑ 8-OHdG, ↑ MDA
	Uric acid, GABP, dopamine 4-sulfate [24]	↓ Uric acid, ↓ GABP, ↓ Dopamine 4-sulfate
Sputum	Airway macrophages black carbon content [25]	↑ Black carbon content of airway macrophage
FeNO	FeNO [21,26]	↑ FeNO

COPD, chronic obstructive pulmonary disease; CRP, C reactive protein; FeNO, fractional exhaled nitric oxide; GABP, glyceric acid 1,3-biphosphate; IL, interleukin; MDA, malondialdehyde; NOS2A, nitric oxide synthase isoform 2A; PM, particulate matter; 8-OHdG, 8-hydroxy-2′-deoxyguanosine.

Table 2. Biomarkers of PM and asthma

Type of biomarker	Biomarker	Response to increased PM
Exhaled breath condensate	EBC NO [27]	↑ EBC NO
	EBC pH [28]	↓ pH
Blood	IL-6,8,10, MCP-1, TNF-alpha [29]	↑ IL-6, IL-8, IL-10, MCP-1 TNF-a
	IgE, IL-4,13 [30]	↑ IgE, IL-4 IL-13
	Circulating various serum cytokines (TNFα, IL-6, IL-8, IL-10) [31]	↓ TNFα, IL-6, IL-8, and IL-10 (after intervention)
Urine	Leukotriene E4 [32]	↑ Leukotrien E4
	aMT6s, MDA [33]	↑ aMT6s, MDA
Saliva	CD63 [34]	↑ CD63

aMT6s, 6-sulfatoxymelatonin; EBC, exhaled breath condensate; IgE; immunoglobulin E; IL, interleukin; MCP, monocyte chemotacticprotein; MDA, malondialdehyde; PM, particulate matter; TNF-α, tumor necrosis factor-alpha.

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urine, and saliva (Table 2).

Whether exposure to PM is associated with oxidative stress was evaluated in an epidemiological study. The authors assessed exposure to PM by quantifying nitrite plus nitrate (NOx) in the EBC of 133 subjects with asthma or COPD [27]. The pH of EBC has promise as a biomarker of airway inflammation. In a cross-sectional study, asthma was significantly associated with a low EBC pH independent of indoor air quality [28].

Blood biomarkers have been suggested to be associated with PM exposure in patients with asthma. One study evaluated the effect of asthma status on the association between polluted air exposure and systemic effects by measuring blood levels of cytokines. Exposure to NO_2 and PM was associated with higher levels of the proinflammatory cytokines IL-6 and TNF-α [29]. The levels of proinflammatory (IgE, IL-4, and IL-13) biomarkers were elevated following exposure to metals in $PM_{2.5}$ in outdoor air around the homes of patients with asthma [30]. Indeed, air pollution, including PM, reduced the serum levels of TNF-α, IL-6, IL-8, and IL-10 in patients with asthma for 2 months [31].

Urinary leukotriene E4 is a biomarker of exposure to < 2.5 mm ambient polluted air (AMB-$PM_{2.5}$) or secondhand smoke (SHS-$PM_{2.5}$) [32]. In children with asthma, urinary 6-sulfatoxymelatonin (aMT6s), a surrogate marker of the circulating melatonin level, is associated with an increased level of MDA, a biomarker of systemic oxidative stress. Increased daily personal exposure to ozone (O_3) and $PM_{2.5}$ was associated with an increased level of aMT6s in patients with asthma [33].

Sputum markers of lung inflammation have been reported. Chemometric and regression results showed that the sputum CD63 level explained 72% of the variance in asthma incidence among patients exposed to $PM_{2.5}$, and the models had high predictive accuracies. CD63 is associated with the activation and degranulation of eosinophils and neutrophils [34].

BIOMARKERS OF THE EFFECT OF PM EXPOSURE ON THE PROGRESSION OF CHRONIC RESPIRATORY DISEASES

Most biomarkers of the effect of PM exposure on chronic respiratory diseases have been evaluated in a small number of epidemiological cross-sectional studies. This literature review focuses on the mechanisms underlying the progression of chronic respiratory diseases linked to PM, with the aim of identifying biomarkers of the effect of PM exposure in patients with chronic respiratory diseases.

Methods

Eligibility criteria

Disease progression is defined in terms of incidence, progression, or the clinical deterioration of patients with chronic respiratory diseases (e.g., COPD, asthma, or idiopathic pulmonary fibrosis [IPF]). However, none of the studies focused on IPF; therefore, we reviewed studies on COPD and asthma. We performed a literature search based on the following inclusion criteria: population: patients with chronic respiratory diseases (COPD and asthma); intervention and comparator: PM ($PM_{2.5}$, PM_{10}) exposure; outcomes: biomarkers of disease progression according to PM exposure; published after 2013; and full-text articles in English. The exclusion criteria were as follows: studies that did not target patients; studies that did not involve exposure to PM; studies that did not report the outcomes of interest; and duplicate studies.

Information sources and search strategy

We searched the Ovid MEDLINE, Ovid EMBASE, and Cochrane Central Register of Controlled Trials electronic data-

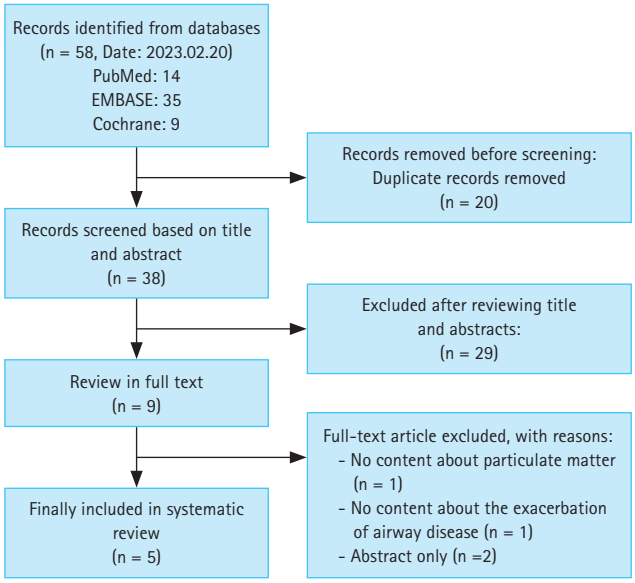

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Table 3. Characteristics of the included studies on the relationships of biomarkers of PM exposure with the progression of chronic respiratory diseases

Author, year	Study design	Country	Diseases	Subjects (n)	Pollutant	PM measurement method	Biomarker	Sample	Effect estimate	Smoking history	Occupational history
Tejwani et al., 2022 [40]	Retrospective cohort	USA	COPD	Patients (324)	$PM_{2.5}$, NO_2, ozone (outdoor), nicotine (indoor)	Using Spatiotemporal modeling according to subjects' address (outdoor) [41,42] Using measurement modeling from previous studies (indoor) [43]	AM-BC content	Sputum	↑AM-BC content	Current smoker (44.4%)	Not mentioned
Tang et al., 2021 [38]	Prospective cohort	China	COPD	Patients (317)	$PM_{2.5}$, PM_{10}	Hourly concentrations of PM2.5 and PM10 were measured at the Chinese environmental monitoring station and then averaged daily	CRP, PT	Blood	↑CRP, ↓PT	Current smoker (13.25%)	Not mentioned
Fireman Klein et al., 2019 [36], 2020 [37]	Prospective cohort	Israel	COPD	Patients (58) vs. controls (40)	$PM_{2.5}$, PM_{10}	The short-term exposure (3 days) and the long-term exposure of 3 months were obtained by estimating according to location information using the Israeli Ministry of Environment's online database	UFP	EBC, blood	↓UFP (urine)	COPD (96%), and controls (57.5%) had smoking history.	Not mentioned
He et al., 2022 [39]	Prospective cohort	China	Asthma	Patients (43)	$PM_{2.5}$, ozone	Using a specific sensor which checked the average of weekly exposure for each individual and also used the analysis technology suggested in previous research [44]	IL-6	Salivary	↑IL-6	Not mentioned	Not mentioned

AM-BC, airway macrophage black carbon; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; EBC, exhaled breath condensate; IL, interleukin; PM, particulate matter; PT, prothrombin time; UFP, ultrafine particle.

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bases on 20 January 2023, for articles describing studies of biomarkers of the effect of PM exposure on chronic respiratory diseases published after 1 January 2013. The search was performed using the following combinations of keywords: ("particulate matter" OR "PM_{10}" OR "$PM_{2.5}$") AND ("chronic obstructive pulmonary disease" OR "COPD") AND ("biomarker" OR "Biomarkers") AND (''Incidence'' OR "Disease progression" OR "Clinical deterioration"). Chronic respiratory disease was considered to encompass diseases such as asthma and IPF. Synonyms for PM, biomarkers, chronic respiratory disease, and disease progression were included among Medical Subject Headings (MeSH) terms, EMBASE subject headings, and text words. The search was limited to studies published in the English language. The search strategy is shown in Supplementary File 1.

Study selection and statistical analysis

Two expert pulmonologists (JK and SJC) screened the titles and abstracts of articles according to the inclusion criteria. Each author independently assessed the eligibility of the studies; conflicts were resolved by discussion. Full texts were assessed by two authors (JK and SJC) to reach a final decision on article inclusion or exclusion. Disagreement was resolved by discussion with a third author (WJK). No other statistical analysis was performed.

Risk of bias assessment

A validated tool was used to evaluate risk of bias based on study design. The Risk of Bias Assessment Tool for Non-randomized Studies (RoBANS) 2.0 was used for nonrandomized studies [35]. This tool comprises eight domains: possibility of target group comparisons, target group selection, confounders, exposure measurement, blinding of assessors, outcome assessment, incomplete outcome data, and selective outcomes. Each domain was classified as low, high, or unclear risk of bias. Quality assessments were conducted by two authors (JK and SJC), and disagreements were resolved by discussion with a third author (WJK).

Results

A total of 58 studies were identified, and 20 duplicate studies were removed before screening. Of the remaining 38 studies, 30 were excluded after screening the titles and abstracts. Subsequently, the full texts of eight studies were reviewed for eligibility. Ultimately, four studies were included (Fig. 1). Two articles contained related contents by same authors. The excluded studies and reasons for their exclusion are provided in Supplementary File 2.

The characteristics of the included studies are listed in Table 3. Three studies [36-38] had a high risk of bias in the possibility of target group comparisons domain, and another [38] in the confounders domain. One study [39] had a high risk of bias in the exposure measurement domain, and another [38] in the outcome domain (Fig. 2).

Few studies have evaluated the relationships of biomarkers of PM exposure with the progression of chronic respiratory diseases. This review focuses on biomarkers of the effect of PM on chronic respiratory diseases (COPD and asthma) and their biological plausibility.

BC in AMs

AMs, which are important immune cells for tissue repair in

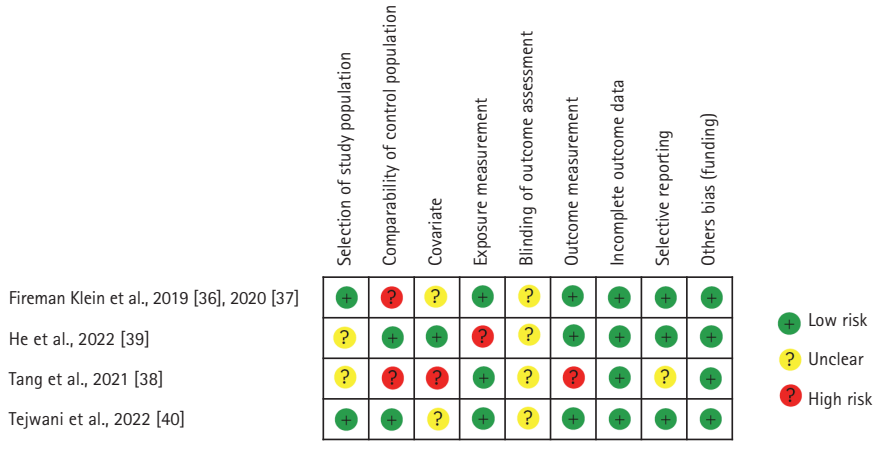

Figure 2. Risk of bias of the included studies according to the judgement of the authors.

COPD, are exposed to airborne pollutants, including PM. AM-BC, measured as the mean BC cross-sectional area (mm^2) per macrophage, is a biomarker of exposure to airborne PM and tobacco smoke. Tejwani et al. [40] investigated the relationships of the AM-BC level and $PM_{2.5}$ exposure with sputum, spirometry, and respiratory outcomes. They used spatiotemoral modeling according to subjects' address for estimating outdoor pollution [41,42] and also used mesurement modeling from previous study for estimating indoor polution [43]. The results showed that the AM-BC level has potential as a biomarker of COPD exacerbation and PM exposure [40]. An increase in the indoor $PM_{2.5}$ concentration was associated with an increase in AM-BC area (β = 9.96%, 95% confidence interval [CI] 0.47–20.4%) and percentage (β = 13.1%, 95% CI 3.49–23.6%). An increase in AM-BC area was not associated with an increase in overall COPD exacerbation frequency over 1 year but was associated with an increased risk of severe exacerbations (odds ratio [OR] = 1.52, 95% CI 1.01–2.28). Similarly, an increase in AM-BC percentage was not correlated with an increase in the overall exacerbation frequency but was associated with an increased risk of severe exacerbations (OR = 2.19, 95% CI 1.0–44.63).

CRP and prothrombin time (PT)

Abnormal inflammatory responses to environmental factors, including PM, have been linked to COPD. CRP, a marker of the systemic inflammatory response, has been proposed as a biomarker of COPD. Tang et al. measured the blood CRP level and PT in 317 patients with acute COPD exacerbation (AECOPD) 1 day before admission; the CRP level was increased during COPD exacerbation and PM elevation [38]. Of the subjects, 13.25% were smokers, and their occupational histories were not evaluated. Patients with AECOPD exposed to > 25 mg/L $PM_{2.5}$ had a significantly shorter PT and a significantly higher CRP level compared to those exposed to ≤ 25 mg/L $PM_{2.5}$.

Ultrafine particles (UFPs)

UFPs are small, toxic materials that reflect the severity of inflammation in patients with COPD. Einat et al. evaluated the UFP levels in the EBC and blood of patients with COPD and 40 healthy controls. A low UFP level in EBC and a high level in serum were indicative of high PM exposure [36]. In addition, a low UFP level in EBC was an independent predictor of frequent exacerbations (OR = 3.6, 95% CI 1.06–7.97; $p = 0.04$). Therefore, a low UFP level in EBC has potential as a biomarker of COPD exacerbation and high PM exposure [37].

Salivary IL-6 level

Exposure to air pollution causes inflammation in the oral cavity, which may exacerbate airway inflammation and asthma symptoms. He et al. [39] reported that asthmatic children had an elevated salivary IL-6 level, a biomarker of an increased $PM_{2.5}$ level, and exacerbation of asthma symptoms. They used a specific sensor which checked the average of weekly exposure for each individual and also used the analysis technology suggested in previous research [44]. Additionally, the asthma control test (ACT) score decreased as the salivary IL-6 level increased, indicating worsening of asthma symptoms.

Epidemiologic perspectives

Environmental factors, including PM exposure, have a marked effect on the development and course of chronic respiratory diseases, including asthma and COPD [7,8]. Therefore, monitoring and reducing PM exposure is important for controlling these diseases [1]. Biomarkers are important considerations when formulating regulations to restrict emissions [45]. Therefore, the identification of biomarkers of PM exposure would improve the management of chronic respiratory diseases.

In this study, we described biomarkers of the effect of PM exposure on asthma and COPD and reviewed studies on biomarkers of PM exposure during exacerbations of those diseases. Only one study evaluated biomarkers associated with PM exposure in patients with COPD [46].

This review had several limitations. Most of the included studies evaluated a single disease-related biomarker in populations distinguished based on age, race, country, and respiratory disease status compared to healthy controls or the effect of PM exposure on the levels of biomarkers. This introduces a risk of selection bias when attempting to generalize the results (Fig. 2). Additionally, although standardized assessment methods facilitate the assessment of PM exposure, uncertainty remains because of rapid technological advancements. Other potential covariates—such as components of outdoor/indoor air pollutants, smoking history, and occupational history—which are risk factors for disease, should also be evaluated. These covariates were not accounted for in some studies, so further research is needed.

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CONCLUSIONS

Few studies have explored the relationships of PM biomarkers with the progression of chronic respiratory diseases. The predictive power of biomarkers of the effect of PM exposure on chronic respiratory diseases varies according to the functions of the biomarkers. Because of the limitations of the included studies, there are few data on biomarkers of the effect of PM exposure on chronic respiratory diseases. Further prospective studies are required to establish regulations to reduce airborne PM and develop public health strategies for the prevention and management of respiratory diseases caused by environmental factors.

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CRedit authorship contributions
Junghyun Kim: conceptualization, methodology, data curation, writing - original draft, writing - review & editing; Soo Jie chung: methodology, writing - original draft; Woo Jin Kim: conceptualization, methodology, writing - review & editing, funding acquisition

Conflicts of interest
The authors disclose no conflicts.

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Supplementary File 1. Search strategies

1) PubMed

1-1. PM-OCPD:5

1-2. PM-IPF:0

1-3. PM-Asthma:2

1-4. PM-bronchiectaiss: 0

	No.	Search strategy
1-1.	#1	"pulmonary disease, chronic obstructive"[mesh]
	#2	"pulmonary disease, chronic obstructive" OR "chronic obstructive lung disease" OR "chronic obstructive pulmonary diseases" OR "coad" OR "copd" OR "chronic obstructive airway disease" OR "chronic obstructive pulmonary disease" OR "airflow obstruction, chronic" OR "airflow obstructions, chronic" OR "chronic airflow obstructions" OR "chronic airflow obstruction" OR "chronic airway obstruction" OR "chronic obstructive bronchopulmonary disease" OR "chronic obstructive lung disorder" OR "chronic obstructive pulmonary disorder" OR "chronic obstructive respiratory disease" OR "chronic pulmonary obstructive disease" OR "chronic pulmonary obstructive disorder" OR "lung chronic obstructive disease" OR "lung disease, chronic obstructive" OR "obstructive chronic lung disease" OR "obstructive chronic pulmonary disease" OR "obstructive lung disease, chronic" OR "pulmonary disorder, chronic obstructive"
1-2.	#3	"idiopathic pulmonary fibrosis"[mesh]
	#4	"idiopathic pulmonary fibrosis" OR "idiopathic pulmonary fibroses" OR "pulmonary fibroses, idiopathic" OR "idiopathic fibrosing alveolitis, chronic form" OR "pulmonary fibrosis, idiopathic" OR "usual interstitial pneumonia" OR "interstitial pneumonia, usual" OR "usual interstitial pneumonias" OR "interstitial pneumonitis, usual" OR "pneumonitides, usual interstitial" OR "pneumonitis, usual interstitial" OR "usual interstitial pneumonitides" OR "usual interstitial pneumonitis" OR "fibrosing alveolitis" OR "alveolitis, fibrosing" OR "chronic diffuse interstitial fibrosis" OR "chronic interstitial pneumonia" OR "diffuse interstitial fibrosis" OR "diffuse interstitial lung fibrosis" OR "diffuse interstitial pulmonary fibrosis" OR "diffuse lung fibrosis" OR "diffuse pulmonary fibrosis" OR "hamman rich disease" OR "hamman rich syndrome" OR "hamman-rich syndrome" OR "idiopathic fibrosing alveolitis" OR "idiopathic interstitial fibrosis" OR "idiopathic interstitial lung fibrosis" OR "idiopathic lung fibrosis"OR "interstitial fibrosis" OR "interstitial lung fibrosis" OR "interstitial pulmonary fibrosis" OR "ipf" OR "lung alveolar fibrosis" OR "lung fibrosing alveolitis" OR "lung fibrosis, interstitial" OR "lung interstitial fibrosis" OR "pulmonary fibrosis, interstitial" OR "pulmonary interstitial fibrosis"
1-3.	#5	"asthma"[mesh]
	#6	"asthmas" OR "bronchial asthma" OR "asthma, bronchial" OR "asthma bronchiale" OR "asthma pulmonale" OR "asthmatic" OR "asthmatic subject" OR "bronchus asthma" OR "childhood asthma" OR "chronic asthma" OR "lung allergy" OR "asthma"
1-4.	#7	"bronchiectasis"[mesh]
	#8	"bronchiectasis" OR "bronchiectases" OR "saccular bronchiectasis" OR "bronchiectasis, saccular" OR "saccular bronchiectases" OR "cystic bronchiectasis" OR "bronchiectasis, cystic" OR "cystic bronchiectases" OR "cylindrical bronchiectasis" OR "bronchiectasis, cylindrical" OR "cylindrical bronchiectases" OR "varicose bronchiectasis" OR "bronchiectasis, varicose" OR "varicose bronchiectases" OR "bronchiectasia" OR "bronchoectasia"
PM	#9	"particulate matter"[mesh]
	#10	"particulate matter" OR "airborne particulate matter" OR "particulate matter, airborne" OR "air pollutants, particulate" OR "particulate air pollutants" OR "ambient particulate matter" OR "particulate matter, ambient" OR "ultrafine particulate matter" OR "particulate matter, ultrafine" OR "ultrafine particles" OR "particles, ultrafine" OR "ultrafine particle" OR "particle, ultrafine"
Biomarkers	#11	"biomarkers"[mesh]

Supplementary File 1. Continued

	No.	Search strategy
	#12	"Biomarkers" OR "marker, biological" OR "biological marker" OR "biologic marker" OR "marker, biologic" OR "biological markers" OR "biologic markers" OR "markers, biologic" OR "biomarker" OR "markers, biological" OR "markers, immunologic" OR "immune markers" OR "markers, immune" OR "marker, immunologic" OR "immunologic markers" OR "immune marker" OR "marker, immune" OR "immunologic marker" OR "serum markers" OR "markers, serum" OR "marker, serum" OR "serum marker" OR "surrogate endpoints" OR "endpoints, surrogate" OR "surrogate end point" OR "end point, surrogate" OR "surrogate end points" OR "end points, surrogate" OR "surrogate endpoint" OR "endpoint, surrogate" OR "markers, clinical" OR "clinical markers" OR "clinical marker" OR "marker, clinical"biochemical marker"markers, biochemical" OR "marker, biochemical" OR "biochemical markers" OR "markers, laboratory" OR "laboratory marker" OR "marker, laboratory" OR "surrogate markers" OR "markers, surrogate" OR "marker, surrogate" OR "surrogate marker" OR "laboratory markers"
	#13	"incidence"[mesh]
	#14	"incidence" OR "incidences" OR "secondary attack rate" OR "attack rate, secondary" OR "rate, secondary attack" OR "secondary attack rates" OR "incidence proportion" OR "incidence proportions" OR "proportion, incidence" OR "attack rate" OR "attack rates" OR "rate, attack" OR "cumulative incidence" OR "cumulative incidences" OR "incidence, cumulative" OR "incidence rate" OR "incidence rates" OR "rate, incidence" OR "person-time rate" OR "person time rate" OR "person-time rates" OR "rate, person-time"
	#15	"Disease Progression"[Mesh]
	#16	"disease progression" OR "progression, disease" OR "clinical course" OR "clinical progression" OR "progression, clinical" OR "disease exacerbation" OR "exacerbation, disease" OR "disease course" OR "disease attributes" OR "disease development" OR "disease evolution" OR "disease progressions" OR "progressions, disease"
	#17	"clinical deterioration"[mesh]
	#18	"clinical deterioration" OR "aggravation, disease" OR "disease aggravation" OR "disease flare" OR "disease progression" OR "exacerbation, disease" OR "disease exacerbation" OR "symptom flare up" OR "exaggeration, symptom" OR "magnification, symptom" OR "symptom worsening" OR "symptom exacerbations" OR "increase, symptom" OR "symptom increase" OR "symptom exaggeration" OR "symptom exaggerations" OR "symptom magnifications" OR "exacerbation, symptom" OR "symptom magnification" OR "symptom exacerbation" OR "worsening, symptom" OR "flare up, symptom" OR "flare ups, symptom" OR"symptom flareup" OR "flaring up, symptom" OR "flareup, symptom" OR "acute symptom flare" OR "symptom flare ups" OR "symptom flareups" OR "flare-up, symptom" OR "flareups, symptom" OR "symptom flare, acute" OR "symptom flare-up" OR "symptom flaring up" OR "acute symptom flares" OR "symptom flare-ups" OR "flare-ups, symptom"
1-1	#19	#1 OR #2
1-2	#20	#3 OR #4
1-3	#21	#5 OR #6
1-4	#22	#7 OR #8
PM	#23	#9 OR #10
Biomarkers	#24	#11 OR #12
	#25	#13 OR #14 OR #15 OR #16 OR #17 OR #18
1-1	#26	#19 AND #23 AND #24 AND #25 AND 2018/01/01:3000/12/31[Date – Publication]
1-2	#27	#20 AND #23 AND #24 AND #25 AND 2018/01/01:3000/12/31[Date – Publication]
1-3	#28	#21 AND #23 AND #24 AND #25 AND 2018/01/01:3000/12/31[Date – Publication]
1-4	#29	#22 AND #23 AND #24 AND #25 AND 2018/01/01:3000/12/31[Date – Publication]

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Supplementary File 1. Continued

2) Ovid Embase
1-1. PM-COPD : 16
1-2. PM-IPF : 1
1-3. PM-Asthma : 16
1-4. PM-Bronchiectasis : 2

	No.	Search strategy
1-1.	#1	'chronic obstructive lung disease'/exp
	#2	'pulmonary disease, chronic obstructive' OR 'chronic obstructive lung disease' OR 'chronic obstructive pulmonary diseases' OR 'coad' OR 'copd' OR 'chronic obstructive airway disease' OR 'chronic obstructive pulmonary disease' OR 'airflow obstruction, chronic' OR 'airflow obstructions, chronic' OR 'chronic airflow obstructions' OR 'chronic airflow obstruction' OR 'chronic airway obstruction' OR 'chronic obstructive bronchopulmonary disease' OR 'chronic obstructive lung disorder' OR 'chronic obstructive pulmonary disorder' OR 'chronic obstructive respiratory disease' OR 'chronic pulmonary obstructive disease' OR 'chronic pulmonary obstructive disorder' OR 'lung chronic obstructive disease' OR 'lung disease, chronic obstructive' OR 'obstructive chronic lung disease' OR 'obstructive chronic pulmonary disease' OR 'obstructive lung disease, chronic' OR 'pulmonary disorder, chronic obstructive'
1-2.	#3	'fibrosing alveolitis'/exp
	#4	'idiopathic pulmonary fibrosis' OR 'idiopathic pulmonary fibroses' OR 'pulmonary fibroses, idiopathic' OR 'idiopathic fibrosing alveolitis, chronic form' OR 'pulmonary fibrosis, idiopathic' OR 'usual interstitial pneumonia' OR 'interstitial pneumonia, usual' OR 'usual interstitial pneumonias' OR 'interstitial pneumonitis, usual' OR 'pneumonitides, usual interstitial' OR 'pneumonitis, usual interstitial' OR 'usual interstitial pneumonitides' OR 'usual interstitial pneumonitis' OR 'fibrosing alveolitis' OR 'alveolitis, fibrosing' OR 'chronic diffuse interstitial fibrosis' OR 'chronic interstitial pneumonia' OR 'diffuse interstitial fibrosis' OR 'diffuse interstitial lung fibrosis' OR 'diffuse interstitial pulmonary fibrosis' OR 'diffuse lung fibrosis' OR 'diffuse pulmonary fibrosis' OR 'hamman rich disease' OR 'hamman rich syndrome' OR 'hamman-rich syndrome' OR 'idiopathic fibrosing alveolitis' OR 'idiopathic interstitial fibrosis' OR 'idiopathic interstitial lung fibrosis' OR 'idiopathic lung fibrosis' OR 'interstitial fibrosis' OR 'interstitial lung fibrosis' OR 'interstitial pulmonary fibrosis' OR 'ipf' OR 'lung alveolar fibrosis' OR 'lung fibrosing alveolitis' OR 'lung fibrosis, interstitial' OR 'lung interstitial fibrosis' OR 'pulmonary fibrosis, interstitial' OR 'pulmonary interstitial fibrosis'
1-3.	#5	'asthma'/exp
	#6	'asthmas' OR 'bronchial asthma' OR 'asthma, bronchial' OR 'asthma bronchiale' OR 'asthma pulmonale' OR 'asthmatic' OR 'asthmatic subject' OR 'bronchus asthma' OR 'childhood asthma' OR 'chronic asthma' OR 'lung allergy' OR 'asthma'
1-4.	#7	bronchiectasis/exp
	#8	'bronchiectasis' OR 'bronchiectases' OR 'saccular bronchiectasis' OR 'bronchiectasis, saccular' OR 'saccular bronchiectases' OR 'cystic bronchiectasis' OR 'bronchiectasis, cystic' OR 'cystic bronchiectases' OR 'cylindrical bronchiectasis' OR 'bronchiectasis, cylindrical' OR 'cylindrical bronchiectases' OR 'varicose bronchiectasis' OR 'bronchiectasis, varicose' OR 'varicose bronchiectases' OR 'bronchiectasia' OR 'bronchoectasia'
PM	#9	'particulate matter'/exp
	#10	'particulate matter' OR 'airborne particulate matter' OR 'particulate matter, airborne' OR 'air pollutants, particulate' OR 'particulate air pollutants' OR 'ambient particulate matter' OR 'particulate matter, ambient' OR 'ultrafine particulate matter' OR 'particulate matter, ultrafine' OR 'ultrafine particles' OR 'particles, ultrafine' OR 'ultrafine particle' OR 'particle, ultrafine'
Biomarkers	#11	'biological marker'/exp

Supplementary File 1. Continued

	No.	Search strategy
	#12	'Biomarkers' OR 'marker, biological' OR 'biological marker' OR 'biologic marker' OR 'marker, biologic' OR 'biological markers' OR 'biologic markers' OR 'markers, biologic' OR 'biomarker' OR 'markers, biological' OR 'markers, immunologic' OR 'immune markers' OR 'markers, immune' OR 'marker, immunologic' OR 'immunologic markers' OR 'immune marker' OR 'marker, immune' OR 'immunologic marker' OR 'serum markers' OR 'markers, serum' OR 'marker, serum' OR 'serum marker' OR 'surrogate endpoints' OR 'endpoints, surrogate' OR 'surrogate end point' OR 'end point, surrogate' OR 'surrogate end points' OR 'end points, surrogate' OR 'surrogate endpoint' OR 'endpoint, surrogate' OR 'markers, clinical' OR 'clinical markers' OR 'clinical marker' OR 'marker, clinical' OR 'biochemical marker' OR 'markers, biochemical' OR 'marker, biochemical' OR 'biochemical markers' OR 'markers, laboratory' OR 'laboratory marker' OR 'marker, laboratory' OR 'surrogate markers' OR 'markers, surrogate' OR 'marker, surrogate' OR 'surrogate marker' OR 'laboratory markers'
	#13	incidence/exp
	#14	'incidence' OR 'incidences' OR 'secondary attack rate' OR 'attack rate, secondary' OR 'rate, secondary attack' OR 'secondary attack rates' OR 'incidence proportion' OR 'incidence proportions' OR 'proportion, incidence' OR 'attack rate' OR 'attack rates' OR 'rate, attack' OR 'cumulative incidence' OR 'cumulative incidences' OR 'incidence, cumulative' OR 'incidence rate' OR 'incidence rates' OR 'rate, incidence' OR 'person-time rate' OR 'person time rate' OR 'person-time rates' OR 'rate, person-time'
	#15	'disease course'/exp
	#16	'disease progression' OR 'progression, disease' OR 'clinical course' OR 'clinical progression' OR 'progression, clinical' OR 'disease exacerbation' OR 'exacerbation, disease' OR 'disease course' OR 'disease attributes' OR 'disease development' OR 'disease evolution' OR 'disease progressions' OR 'progressions, disease'
	#17	'disease exacerbation'/exp
	#18	'clinical deterioration' OR 'aggravation, disease' OR 'disease aggravation' OR 'disease flare' OR 'disease progression' OR 'exacerbation, disease' OR 'disease exacerbation' OR 'symptom flare up' OR 'exaggeration, symptom' OR 'magnification, symptom' OR 'symptom worsening' OR 'symptom exacerbations' OR 'increase, symptom' OR 'symptom increase' OR 'symptom exaggeration' OR 'symptom exaggerations' OR 'symptom magnifications' OR 'exacerbation, symptom' OR 'symptom magnification' OR 'symptom exacerbation' OR 'worsening, symptom' OR 'flare up, symptom' OR 'flare ups, symptom' OR 'symptom flareup' OR 'flaring up, symptom' OR 'flareup, symptom' OR 'acute symptom flare' OR 'symptom flare ups' OR 'symptom flareups' OR 'flare-up, symptom' OR 'flareups, symptom' OR 'symptom flare, acute' OR 'symptom flare-up' OR 'symptom flaring up' OR 'acute symptom flares'
1-1	#19	#1 OR #2
1-2	#20	#3 OR #4
1-3	#21	#5 OR #6
1-4	#22	#7 OR #8
pm	#23	#9 OR #10
Biomarkers	#24	#11 OR #12
	#25	#13 OR #14 OR #15 OR #16 OR #17 OR #18
1-1	#26	#19 AND #23 AND #24 AND #25 AND [2018-2023]/py
1-2	#27	#20 AND #23 AND #24 AND #25 AND [2018-2023]/py
1-3	#28	#21 AND #23 AND #24 AND #25 AND [2018-2023]/py
1-4	#29	#22 AND #23 AND #24 AND #25 AND [2018-2023]/py

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Supplementary File 1. Continued

3) Cochrane Library
1-1. PM-COPD : 6
1-2. PM-IPF : 0
1-3. PM-Asthma : 3
1-4. PM-Bronchiectasis : 0

	No.	Search strategy
1-1.	#1	mesh descriptor: [pulmonary disease, chronic obstructive] explode all trees
	#2	pulmonary disease, chronic obstructive OR chronic obstructive lung disease OR chronic obstructive pulmonary diseases OR coad OR copd OR chronic obstructive airway disease OR chronic obstructive pulmonary disease OR airflow obstruction, chronic OR airflow obstructions, chronic OR chronic airflow obstructions OR chronic airflow obstruction OR chronic airway obstruction OR chronic obstructive bronchopulmonary disease OR chronic obstructive lung disorder OR chronic obstructive pulmonary disorder OR chronic obstructive respiratory disease OR chronic pulmonary obstructive disease OR chronic pulmonary obstructive disorder OR lung chronic obstructive disease OR lung disease, chronic obstructive OR obstructive chronic lung disease OR obstructive chronic pulmonary disease OR obstructive lung disease, chronic OR pulmonary disorder, chronic obstructive
1-2.	#3	MeSH descriptor: [Idiopathic Pulmonary Fibrosis] explode all trees
	#4	('idiopathic pulmonary fibrosis' OR 'idiopathic pulmonary fibroses' OR 'pulmonary fibroses, idiopathic' OR 'idiopathic fibrosing alveolitis, chronic form' OR 'pulmonary fibrosis, idiopathic' OR 'usual interstitial pneumonia' OR 'interstitial pneumonia, usual' OR 'usual interstitial pneumonias' OR 'interstitial pneumonitis, usual' OR 'pneumonitides, usual interstitial' OR 'pneumonitis, usual interstitial' OR 'usual interstitial pneumonitides' OR 'usual interstitial pneumonitis' OR 'fibrosing alveolitis' OR 'alveolitis, fibrosing' OR 'chronic diffuse interstitial fibrosis' OR 'chronic interstitial pneumonia' OR 'diffuse interstitial fibrosis' OR 'diffuse interstitial lung fibrosis' OR 'diffuse interstitial pulmonary fibrosis' OR 'diffuse lung fibrosis' OR 'diffuse pulmonary fibrosis' OR 'hamman rich disease' OR 'hamman rich syndrome' OR 'hamman-rich syndrome' OR 'idiopathic fibrosing alveolitis' OR 'idiopathic interstitial fibrosis' OR 'idiopathic interstitial lung fibrosis' OR 'idiopathic lung fibrosis' OR 'interstitial fibrosis' OR 'interstitial lung fibrosis' OR 'interstitial pulmonary fibrosis' OR 'ipf' OR 'lung alveolar fibrosis' OR 'lung fibrosing alveolitis' OR 'lung fibrosis, interstitial' OR 'lung interstitial fibrosis' OR 'pulmonary fibrosis, interstitial' OR 'pulmonary interstitial fibrosis'
1-3.	#5	mesh descriptor: [asthma] explode all trees
	#6	asthmas OR bronchial asthma OR asthma, bronchial OR asthma bronchiale OR asthma pulmonale OR asthmatic OR asthmatic subject OR bronchus asthma OR childhood asthma OR chronic asthma OR lung allergy OR asthma
1-4.	#7	mesh descriptor: [bronchiectasis] explode all trees
	#8	bronchiectasis OR bronchiectases OR saccular bronchiectasis OR bronchiectasis, saccular OR saccular bronchiectases OR cystic bronchiectasis OR bronchiectasis, cystic OR cystic bronchiectases OR cylindrical bronchiectasis OR bronchiectasis, cylindrical OR cylindrical bronchiectases OR varicose bronchiectasis OR bronchiectasis, varicose OR varicose bronchiectases OR bronchiectasia OR bronchoectasia
PM	#9	mesh descriptor: [particulate matter] explode all trees
	#10	particulate matter OR airborne particulate matter OR particulate matter, airborne OR air pollutants, particulate OR particulate air pollutants OR ambient particulate matter OR particulate matter, ambient OR ultrafine particulate matter OR particulate matter, ultrafine OR ultrafine particles OR particles, ultrafine OR ultrafine particle OR particle, ultrafine
Biomarkers	#11	mesh descriptor: [biomarkers] explode all trees

Supplementary File 1. Continued

	No.	Search strategy
	#12	Biomarkers OR marker, biological OR biological marker OR biologic marker OR marker, biologic OR biological markers OR biologic markers OR markers, biologic OR biomarker OR markers, biological OR markers, immunologic OR immune markers OR markers, immune OR marker, immunologic OR immunologic markers OR immune marker OR marker, immune OR immunologic marker OR serum markers OR markers, serum OR marker, serum OR serum marker OR surrogate endpoints OR surrogate end point OR end point, surrogate OR surrogate end points OR end points, surrogate OR surrogate endpoint OR endpoint, surrogate OR markers, clinical OR clinical markers OR clinical marker OR marker, clinical OR biochemical marker OR markers, biochemical OR marker, biochemical OR biochemical markers OR markers, laboratory OR laboratory marker OR marker, laboratory OR surrogate markers OR markers, surrogate OR surrogate marker OR laboratory markers
	#13	mesh descriptor: [incidence] explode all trees
	#14	incidence OR incidences OR secondary attack rate OR attack rate, secondary OR rate, secondary attack OR secondary attack rates OR incidence proportion OR incidence proportions OR proportion, incidence OR attack rate OR attack rates OR rate, attack OR cumulative incidence OR cumulative incidences OR incidence, cumulative OR incidence rate OR incidence rates OR rate, incidence OR person-time rate OR person time rate OR person-time rates OR rate, person-time
	#15	mesh descriptor: [disease progression] explode all trees
	#16	disease progression OR progression, disease OR clinical course OR clinical progression OR progression, clinical OR disease exacerbation OR exacerbation, disease OR disease course OR disease attributes OR disease development OR disease evolution OR disease progressions OR progressions, disease
	#17	mesh descriptor: [symptom flare up] explode all trees
	#18	clinical deterioration OR aggravation, disease OR disease aggravation OR disease flare OR disease progression OR exacerbation, disease OR disease exacerbation OR symptom flare up OR exaggeration, symptom OR magnification, symptom OR symptom worsening OR symptom exacerbations OR increase, symptom OR symptom increase OR symptom exaggeration OR symptom exaggerations OR symptom magnifications OR exacerbation, symptom OR symptom magnification OR symptom exacerbation OR worsening, symptom OR flare up, symptom OR flare ups, symptom OR flaring up, symptom OR flareup, symptom OR acute symptom flare OR symptom flare ups OR symptom flareups OR flare-up, symptom OR flareups, symptom OR symptom flare, acute OR symptom flare-up OR symptom flaring up OR acute symptom flares OR symptom flare-ups OR flare-ups, symptom
1-1	#19	#1 OR #2
1-2	#20	#3 OR #4
1-3	#21	#5 OR #6
1-4	#22	#7 OR #8
pm	#23	#9 OR #10
마커	#24	#11 OR #12
	#25	#13 OR #14 OR #15 OR #16 OR #17 OR #18
1-1	#26	#19 AND #23 AND #24 AND #25 with Publication Year from 2018 to 2023, in Trials
1-2	#27	#20 AND #23 AND #24 AND #25 with Publication Year from 2018 to 2023, in Trials
1-3	#28	#21 AND #23 AND #24 AND #25 with Publication Year from 2018 to 2023, in Trials
1-4	#29	#22 AND #23 AND #24 AND #25 with Publication Year from 2018 to 2023, in Trials

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Supplementary File 2. List of excluded studies after full-text screening

No	Excluded studies	Reason for exclusion
1	MacLeod, Mairi, et al. Chronic obstructive pulmonary disease exacerbation fundamentals: diagnosis, treatment, prevention, and disease impact. Respirology. 2021; 26(6): 532-551.	No content about particulate matter
2	Long, Erin, and Christopher Carlsten. Controlled human exposure to diesel exhaust: results illuminate health effects of traffic-related air pollution and inform future directions. Particle and Fibre Toxicology 2022;19(1): 1-35.	No content about the exacerbation of airway disease
3	Johns Hopkins University. Motivational Interviewing and Air Cleaners for Smokers with COPD (MOVE COPD). 15 Sep 2018 to 31 May 2024. Clinical trials. Gov.	Abstract only
4	Ryu, M. H., et al. The Thromboxane A2 Pathway, as Assessed by Urinary Eicosanoids, Is Increased After Acute Controlled Exposure to Diesel Exhaust in Participants with COPD. In: B105. MORE CALLS TO ACTION: AIR POLLUTION EXPOSURES AND HEALTH. American Thoracic Society;2022. p. A3579-A3579.	Abstract only