# Biomarkers of particulate matter exposure in patients with chronic obstructive pulmonary disease: a systematic review

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**Background:** In recent years, ambient particulate matter (PM) exposure has been strongly linked with health effects. Elevated levels of PM in polluted air have been correlated with the onset and development of chronic obstructive pulmonary disease (COPD). This systematic review was conducted to evaluate biomarkers that could reflect the effects of PM exposure in patients with COPD.

**Methods:** We performed a systematic review of studies published on biomarkers associated with PM exposure in patients with COPD between January 01, 2012 and June 30, 2022 in PubMed/MEDLINE, EMBASE, and Cochrane databases. Studies that included data on biomarkers with COPD exposed PM were eligible for inclusion. Biomarkers were classified into 4 groups according to their mechanisms.

**Results:** Of the 105 studies identified, 22 were included in this study. Nearly 50 biomarkers have been proposed in the studies included in this review, and the most studied in relation to PM are several interleukins. Various mechanisms have been reported by which PM induces and aggravates COPD. Six studies related to oxidative stress, one related to direct effect of innate and adaptive immune systems, 16 associated with genetic regulation of inflammation, and two related to epigenetic regulation of physiology and susceptibility were found. Biomarkers related to these mechanisms were detected in serum, sputum, urine, exhaled breath concentration (EBC), and showed various correlations with PM in COPD.

**Conclusions:** Various biomarkers have shown potential in predicting the extent of PM exposure in COPD patients. Future studies are needed to establish recommendations for regulation to reduce airborne PM, which could be used to develop strategies for prevention and management of environmental respiratory diseases.

**Keywords:** Biomarker; particulate matter (PM); chronic obstructive pulmonary disease (COPD)

## Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable disease associated with chronic pulmonary inflammation and remodeling induced by environmental exposures (1). The global socioeconomic impact of COPD is substantial (2). According to the global health estimates by World Health Organization (WHO) in 2019, COPD was the third leading cause of death worldwide, accounting for 6% of all deaths (3). Although cigarette smoking is an important risk factor for COPD, it has been reported that

approximately 25–45% of patients with COPD have never smoked (4). Risk factors other than smoking currently account for more than 50% of the global burden of COPD (5). Thus, contributory factors linked to COPD other than smoking need to be considered.

In recent decades, air pollution has emerged as a major public health concern (6). Air pollutants include particulate matter (PM) and gaseous components, such as ozone, volatile organic compounds (VOCs), carbon monoxide, and nitrogen oxides. PM is a widespread air pollutant, consisting of a heterogeneous mixture of solid and liquid particles suspended in air (7). Common chemical constituents of PM include sulfate, nitrate, organic and elemental carbon, organic compounds, biological compounds, and heavy metals (8). Numerous scientific studies have shown that PM toxicity is linked to various respiratory diseases, such as asthma, COPD, idiopathic pulmonary fibrosis, and lung cancer (9-12).

Long-term exposure to PM increases the risk of development of COPD in the older population (13). The Global Burden of Disease Study in 2019 (14), reported that the absolute COPD burden attributed to $PM_{2.5}$ (aerodynamic diameter ≤2.5 μm) had greatly increased, and the older population was more vulnerable and bore more burden in line with an aging society. In addition, several epidemiologic studies have revealed that $PM_{2.5}$ aggravates respiratory diseases by decreasing lung function (15), and

has also been associated with increased hospitalization, morbidity, and mortality related to COPD (16-18). PM is considered to play a role in COPD deterioration through a variety of mechanisms, including oxidative stress, inflammatory responses, inhibition of local airway immunity, and epigenetic alterations (19,20). However, there is paucity of evidence to determine biomarkers that would aid in identification of the causal relationship between COPD and PM exposure.

Therefore, we conducted this systematic review to gather data on mechanisms involved in the development and exacerbation of COPD by PM to evaluate putative biomarkers that could reflect the effects of PM exposure in patients with COPD. We present the following article in accordance with the PRISMA reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-78/rc) (21).

## Methods

### Eligibility criteria

The inclusion criteria were as follows: (I) population: patients with COPD; (II) intervention and comparator: PM (2.5, 10) exposure; (III) outcomes: biomarkers of PM exposure and their mechanisms in patients with COPD; (IV) studies published after 2012; and (V) full-text articles in English. The exclusion criteria were as follows: (I) studies that did not target patients with COPD, (II) studies that did not involve exposure to PM, (III) studies that did not report our outcomes of interest, and (IV) duplicated studies.

### Information sources and search strategy

We searched the following electronic international databases (Ovid PubMed/MEDLINE, Ovid EMBASE, the Cochrane Central Register of Controlled Trials) on June 30, 2022 for studies published after January 01, 2012, to identify biomarkers of PM in COPD patients. The search strategy included 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"). Synonyms for PM were included using Medical Subject Heading (MeSH) terms and EMBASE subject headings (Emtree). The search was limited to studies published in English language. The search strategy is presented in Appendix 1.

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**Highlight box**

**Key findings**
- In this study, we searched literatures on relation between biomarkers and particulate matter (PM) exposure in patients with chronic obstructive pulmonary disease (COPD). We found that several biomarkers have various associations with PM exposure and have potential as predictors of development and exacerbation of COPD.

**What is known and what is new?**
- Various biomarkers were classified into four mechanisms in COPD patients exposed to PM. The most studied biological mechanism of biomarkers was related to genetic regulation of inflammation.
- This manuscript added significance of biomarkers to predict extent of PM exposure in patients with COPD.

**What is the implication, and what should change now?**
- This review will help establish preventive strategies for chronic respiratory diseases by identifying mechanism of clinical deterioration caused by PM in COPD patients and verifying available biomarkers.
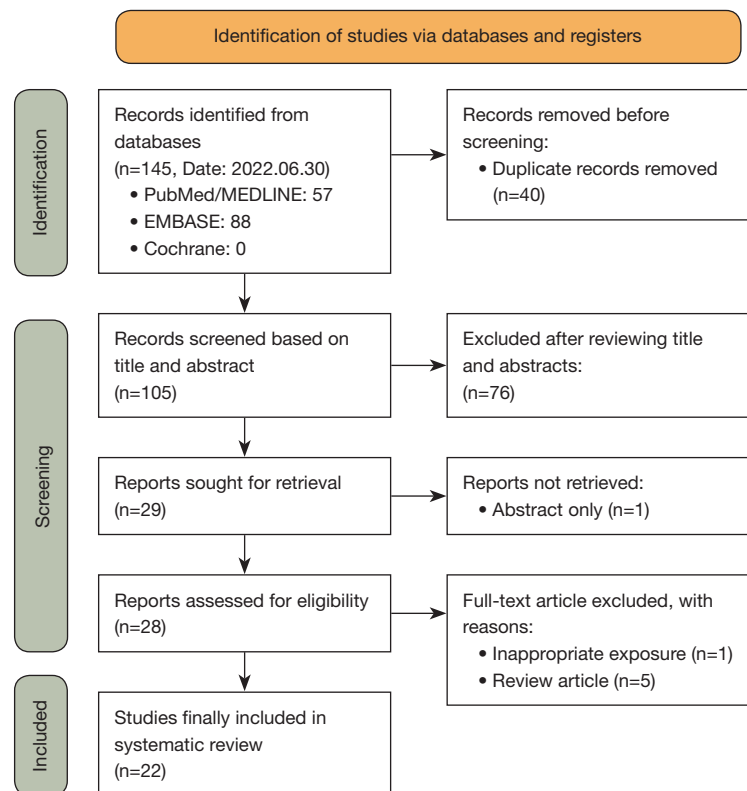
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**Figure 1** PRISMA flow diagram.

### Selection process

Two authors (JK and NYK) screened the titles and abstracts for inclusion of studies. Each author independently assessed the eligibility of the identified studies, and conflicts were resolved by discussion. Full texts were assessed by two authors (JK and NYK) for final decision on inclusion or exclusion. Any disagreement between the two authors was resolved through discussion with a third author (WJK).

### Data items and extraction

The following data were extracted from the eligible studies using an electronic spreadsheet (Microsoft Excel) of a pre-designed data extraction form: author, publication year, study design, study region, study setting, and study outcome. One author (NYK) extracted the data, and two other authors (JK and WJK) independently evaluated the data.

### Study outcomes

The primary outcome was biomarkers of PM exposure and their mechanisms in patients with COPD.

### Statistical analysis

In this study, no other statistical analysis was performed because of the lack of studies summarizing the risk of specific biomarkers. Instead, we fully reviewed the literature that was found through structurally searched results.

### Results

### Study selection and characteristics

A total of 145 studies were identified using the search strategy, and 40 duplicate studies were removed before screening. Of the 105 studies, 76 were excluded after screening the titles and abstracts. Subsequently, the full texts of 29 studies were reviewed. After reviewing the eligibility of the original articles, 22 studies were included (*Figure 1*). The list of excluded studies and reasons for exclusion are presented in Table S1).

   Most studies conducted repeated measures of exposure to ambient pollutants (PM or $PM_{10}$) and biomarkers (22-33), and panel studies (34-36). Other studies were performed by retrospective analysis of cross-sectional (37) or cohort

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designs (38-43). Risk assumption according to primary and secondary outcomes could not be available due to heterogeneity in study outcomes and their reporting of the risk. Instead, in this review, we summarized the possible role of biomarkers linked to COPD according to four representative types of biological plausibility in patients with COPD exposed to PM through a qualitative review. Among 22 studies, six were found to be relevant regarding biomarkers exploring oxidative stress (22-24,37-39); one study investigated the roles of innate and adaptive immune systems (25); and 17 studies investigated genetic regulation (26-32,34-36,38-42) and epigenetic regulation of inflammation (27,43).

### Biological mechanisms of biomarkers

### Oxidative stress

Oxidative stress can be defined as damage resulting from imbalance of oxidation reaction and antioxidant reduction status of the body (44). In total, six original research articles reported an association between PM and oxidative stress biomarkers in patients with COPD (*Table 1*) (22-24,37-39). Human urinary metabolome, including 8-hydroxy-2'-deoxyguanosine (8-OHdG) and malondialdehyde (MDA) were found to positively correlate with PM exposure (22,23). Other $PM_{2.5}$ related metabolic biomarkers such as uric acid, glyceric acid 1,3-biphosphate (GABP) and dopamine 4-sulfate were also found to be associated with COPD (37). In addition, Lee *et al.* (38) reported that elevated ubiquitin and beclin 1 levels were related to oxidative stress in COPD. Tang *et al.* (39) revealed that alteration of prothrombin time (PT) was associated with exacerbated COPD patients exposed to $PM_{2.5}$.

### Direct effect of innate and adaptive immune system

Alveolar macrophages play an important role in clearing the airway by phagocytizing foreign debris, including PM. Exposure to PM stimulates innate and adaptive immune defenses in the respiratory system (45). One research paper related to the role of PM in stimulating innate and adaptive immunities was found through the systematic review (*Table 2*) (25). Belli *et al.* showed that elevated indoor $PM_{2.5}$ was substantially correlated with elevated airway macrophage black carbon in a cohort of former smokers with COPD (Spearman's Rho =0.60, P=0.005). According to a multivariate longitudinal analysis, the total area of airway macrophage black carbon increased by 0.19 $\mu m^2$ for every 10 $\mu g/m^3$ rise in indoor $PM_{2.5}$ (P=0.01). Authors

speculated that increased black carbon content derived from indoor PM exposure may result in dysfunctional macrophages and disruption of immune defense. These findings suggest that the amount of black carbon in alveolar macrophages may serve as an effective non-invasive biomarker of exposure to PM.

### Genetic regulation of inflammation

Airway inflammation is a common pathophysiological mechanism through which air pollutants affect pulmonary diseases (40). A total of 16 articles that presented an association between PM and inflammatory biomarkers in patients with COPD were identified (*Table 3*).

The most frequently reported mechanism was genetic regulation of inflammation, and among them, various interleukins were the most studied entity in relation to PM (26,28-30,33,34,38,41). Eight published studies on several interleukins were included in this review. IL-6 was measured in seven studies and was the most extensively studied biomarker associated with air pollution in this review. Of the seven studies, four showed significant increase in IL-6 levels due to PM exposure (26,29,30,38), while one reported a significant decrease due to PM exposure (33). Two studies showed inconclusive association between IL-6 and PM exposure (28,41). In addition to IL-6, IL-2 (28), IL-12 (28), and IL-17A (28) showed positive correlations with PM, whereas IL-4 (28) and IL-13 (28,33) showed negative correlations. The relationship between PM and IL-8 has yielded inconsistent results in previous studies (28,33,34,41).

Five published studies used plasma C-reactive protein (CRP) as a biomarker, and it was reported that the circulating concentrations of CRP rose in response to inflammation (26,29,30,39,41). It has been generally reported that CRP increased significantly with PM exposure, but Dadvand *et al.* showed an inconclusive result between PM and CRP in COPD patients (41).

Fraction of exhaled nitric oxide (FeNO) is a well-validated noninvasive marker of airway inflammation caused by exposure to air pollution (46). Three published studies which assessed FeNO were included in this review (27,36,40), all of which demonstrated a positive association between PM and FeNO levels.

In addition, various other biomarkers, such as tumor necrosis factor α (TNFα) (28,33,34,41), circulating vascular cell adhesion molecule-1 (sVCAM-1) (26,29,30), fibrinogen (41), hepatocyte growth factor (41), ultrafine particle concentration in exhaled breath (42), and exhaled hydrogen sulfide (36).

**Table 1** Characteristics of the included studies related to oxidative stress

| Author, year | Study design | Location | Follow-up | Age, year[†] | Number | Pollutant | Biomarker | Sample | Outcome | Effect estimate |
|---|---|---|---|---|---|---|---|---|---|---|
| Grady et al., 2018 (22) | Repeated measure (prospectively) | USA | 2012.11–2014.12 | 72.7±8.4 | 82 | $PM_{2.5}$, $NO_2$ | 8-OHdG, MDA | Urine | Biomarkers | ↑8-OHdG; ↑MDA |
| Huang et al., 2018 (37) | Cross-sectional study | China | 2016.3–2016.5 | 71.0±7.8 | 41 | $PM_{2.5}$ | Uric acid, GABP, Dopamine 4-sulfate | Urine | COPD-related metabolic biomarkers (vs. healthy control) | ↓Uric acid; ↓GABP; ↓Dopamine 4-sulfate |
| Huang et al., 2021 (23) | Repeated measure (prospectively) | USA | 2012.11–2014.12 | 72.7±8.4 | 81 | PM-gamma activities | 8-OHdG, MDA | Urine | Biomarkers | ↑8-OHdG; ↑MDA |
| Lee et al., 2016 (38) | Repeated measure (from retrospective cohort) | Taipei | 2013.01–2014.12 | 70.3±9.0 | 43 | $PM_{10}$ | Ubiquitin, Beclin 1 | Blood | Biomarkers, lung function | ↑Ubiquitin; ↑Beclin 1 |
| Tang et al., 2021 (39) | Cross-sectional analysis (from retrospective cohort) | China | 2017.03–2019.09 | <65: 28.7%; >65: 71.3% | 317 | $PM_{2.5}$ | PT | Blood | Markers, acute exacerbation of COPD (hospitalization) | ↓PT |
| Manney et al., 2012 (24) | Repeated measure (prospectively) | Finland, Greece, The Netherlands, UK | 2002.10–2004.03 | 62.3±10.6 | 111 | $PM_{2.5}$, $PM_{10}$, coarse particle, PNC | NOx | EBC | Biomarkers | No association |

Statistically significant increase/decrease (↑/↓). [†], age is presented as mean ± standard deviation or percentage distribution. PM, particulate matter; $NO_2$, nitric dioxide; PNC, particle number concentration; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; MDA, malondialdehyde; GABP, glyceric acid 1,3-biphosphate; PT, prothrombin time; NOx, nitrogen oxides; EBC, exhaled breath concentration; COPD, chronic obstructive pulmonary disease.

**Table 2** Characteristics of the included studies related to direct effect of innate and adaptive immune system

| Author, year | Study design | Location | Follow-up | Age, year[†] | Number | Pollutant | Biomarker | Sample | Outcome | Effect estimate |
|---|---|---|---|---|---|---|---|---|---|---|
| Belli et al., 2016 (25) | Repeated measure (prospectively) | USA | NA | 67±4 | 20 | $PM_{2.5}$ | Airway macrophages black carbon content | Sputum | Biomarker | ↑black carbon content |

Statistically significant increase/decrease (↑/↓). [†], age is presented as mean ± standard deviation. NA, not applicable; PM, particulate matter.

**Epigenetic regulation of physiology and susceptibility**

Epigenetic changes are molecular changes that occur in DNA structure and gene expression due to methylation or acetylation of DNA, and these changes may mediate environmental effects on human health (44,47). We found two studies related to DNA methylation caused by exposure to air pollutants (*Table 4*). Chen *et al.* (27) suggested that some constituents of $PM_{2.5}$ were significantly associated with a decrease in nitric oxide synthase isoform 2A methylation. Lee *et al.* (43) in their epigenome-wide association study identified that DNA methylation signals in blood were associated with long-term ambient air pollution exposure.

## Discussion

In this review, the literature was systematically evaluated to identify biomarkers of COPD patients exposed to PM. This review did not include a meta-analysis because it was difficult to measure risk differences due to the heterogeneous outcomes of the studies. Nearly 50 biomarkers were suggested in the literature included in the review. We classified and organized the biomarkers of COPD patients exposed to PM into four mechanisms.

COPD remains the most common cause of chronic disease-attributable deaths (48), however, there has been no significant progress in its treatment or prevention. To prevent some types of COPD, the Lancet Commission recently classified COPD into five types: genetics, early life events, pulmonary infections, tobacco smoke exposure, and air pollution, and emphasized the possibility of early intervention and prevention (49). The proposed novel classification results from heterogeneity, which contributes to the clinical presentation of COPD (50). The putative pathophysiologic mechanisms implicated in COPD in never-smokers include inflammation, oxidative stress, airway remodeling, and airflow limitation (5).

Several cohort studies have demonstrated that PM is associated with mortality and morbidity in chronic respiratory diseases (20,44,51). Although the toxicological mechanism is still not fully understood, numerous studies in recent years have indicated that oxidative stress is the major mechanism by which toxicity can be exerted (20,52,53). Oxidative stress develops when production of reactive oxygen species (ROS) and antioxidant defense are unbalanced, and redox homeostasis is disrupted (54). Grady *et al.* (22) and Huang *et al.* (23) showed that ambient PM concentration had a significant positive association with urinary surrogate markers of oxidative stress such as 8-OHdG and MDA. Since urinary 8-OHdG is formed due to hydroxyl radical attack on DNA, it is used to evaluate the extent of DNA damage repair caused by ROS (55). In addition, urinary MDA is an end product of fatty acid oxidation, and can be used to estimate the extent of lipid peroxidation (56). A prospective cohort study assessed the relationship between indoor black carbon exposure and urinary oxidative stress biomarkers, 8-OHdG and MDA in participants with COPD. The authors reported a positive association between black carbon exposure and 8-OHdG and MDA, suggesting that exposure to air pollution resulted in lipid peroxidation and oxidative DNA damage in patients with COPD. These positive effects were most prominent on the day before urine collection (6.9% increase per interquartile range) for 8-OHdG and 1–4 days before collection (8.3% increase per interquartile range) for MDA (22). In contrast, uric acid, GABP, and dopamine 4-sulfate are metabolic intermediates in glycolysis and negative metabolites (37).

Chronic airway inflammation is involved in the pathogenesis of COPD, and several studies have been conducted to identify biomarkers to predict COPD changes due to inflammation (57-59). A previous meta-analysis suggested that COPD was associated with systemic inflammation characterized by leukocytosis and increased CRP, IL-6, IL-8, and fibrinogen levels (60). Moreover,

**Table 3** Characteristics of the included studies related to genetic regulation of inflammation

| Author, year | Study design | Location | Follow-up | Age, year[†] | Number | Pollutant | Biomarker | Sample | Outcome | Effect estimate |
|---|---|---|---|---|---|---|---|---|---|---|
| Abramson et al., 2020 (40) | Cross-sectional analysis (from retrospective cohort) | Germany | 1985–1994 | 74.6±2.6 | 236 | $PM_{2.5}$ | FeNO | EBC | Biomarker | ↑FeNO |
| Audi et al., 2017 (33) | Repeated measure (prospectively) | France | 1st phase: 2009–2010; 2nd phase: 2011–2012 | 47.02±10.1 | 72 | $PM_{2.5}$, VOCs | IL4, IL5, IL6, IL8, IL10, IL13, IL17, IFNγ, TNFα | Blood | Biomarkers | ↓IL4, IL6, IL8, IL13, IFNγ, TNFα |
| Busenkell et al., 2022 (26) | Repeated measure (prospectively) | USA | 2012.11–2017.5 | 72.9±8.3 | 144 | $PM_{2.5}$, black carbon | CRP, IL6, sVCAM-1 | Blood | Biomarkers | ↑CRP (non-statin users); ↑IL6 (non-statin users); sVCAM-1: no association |
| Chen et al., 2015 (27) | Repeated measure (prospectively) | China | 2013.9–2013.12 | 64±8 | 30 | $PM_{2.5}$ | FeNO | EBC | Biomarker | ↑FeNO |
| Chen et al., 2021 (34) | Panel study | China | Enrolled from May 2016, 2–4 follow-up visits | 61±8 | 53 | $PM_{2.5}$ | IL8, TNFα | Blood | Biomarkers (vs. healthy control) | ↑time difference of IL8, TNFα (vs. healthy control) |
| Dadvand et al., 2014 (41) | Cross-sectional analysis (from retrospective cohort) | Spain | 2004.1–2006.3 | 67.8±8.6 | 251 | $PM_{2.5}$, $NO_2$ | CRP, TNFα, IL6, IL8, fibrinogen, HGF | Blood | Biomarkers | $PM_{2.5}$: not conclusive; $NO_2$: ↑CRP, IL8, fibrinogen, HGF |
| Gao et al., 2020 (28) | Repeated measure (prospectively) | China | 2015.12–2017.9 | 63.9±6.3 | 84 | $PM_{2.5}$, $PM_{10}$, $NO_2$, $SO_2$, CO, $O_3$ | IL1β, IL2, IL4, IL5, IL6, IL8, IL10, IL12P70, IL13, IL17A, TNFα, IFNγ, VEGF-A, MCP-1, IP10, GM-CSF, sCD40L, MIP, Eotaxin | Blood | Biomarkers, lung function | ↓Eotaxin, IL4, IL13 ↑IL2, IL12, IL17A, IFNγ, MCP-1, sCD40L |
| Garshick et al., 2018 (29) | Repeated measure (prospectively) | USA | 2012.11–2014.12 | 72.7±8.4 | 88 | Indoor black carbon | IL6, CRP, sVCAM-1 | Blood | Biomarkers | ↑CRP; ↑IL6 (non-statin users); sVCAM-1: no association |
| Huang et al., 2020 (30) | Repeated measure (prospectively) | USA | 2012.10–2014.12 | 72.7±8.6 | 85 | PM-gamma activities | CRP, IL6, sVCAM-1 | Blood | Biomarkers | ↑CRP, IL6; sVCAM-1: no association |

**Table 3** (*continued*)

**Table 3** (*continued*)

| Author, year | Study design | Location | Follow-up | Age, year† | Number | Pollutant | Biomarker | Sample | Outcome | Effect estimate |
|---|---|---|---|---|---|---|---|---|---|---|
| Fireman Klein et al., 2020 (42) | Cross-sectional analysis (from prospective design) | Israel | NA | 68.3±8.6 | 58 | $PM_{2.5}$ | Ultrafine particles | EBC | Biomarkers (vs. healthy control) | ↓Ultrafine particles |
| Lee et al., 2016 (38) | Cross-sectional analysis (from retrospective cohort) | Taipei | 2013.01–2014.12 | 70.3±9.0 | 43 | $PM_{10}$ | RAGE, IL6 | Blood | Biomarkers | ↑RAGE; ↑IL6 |
| Lee et al., 2015 (31) | Repeated measure (prospectively) | Taipei | 2013.01–2014.08 | 70.7±8.4 | 50 | $PM_{10}$ | ITIH4, PRG4, APOF | Blood | Biomarkers (vs. healthy control) | ↓ITIH4 |
| Nurhussien et al., 2022 (32) | Repeated measure (prospectively) | USA | 2017.02–2019.01 | 71.1± 8.4 | 30 | $PM_{2.5}$, $NO_2$, $O_3$ | blood eosinophil count | Blood | Biomarker, lung function | $PM_{2.5}$, $NO_2$: ↓$FEV_1$ (BEC >150) |
| Pirozzi et al., 2015 (35) | Panel study | USA | 2012.12–2013.03 | 40–85 | 16 | $PM_{2.5}$ | NOx, 8-isoprostane | EBC | Biomarkers, symptoms | ↑NOx; 8-isoprostane: no association |
| Tang et al., 2021 (39) | Cross-sectional analysis (from retrospective cohort) | China | 2017.03–2019.09 | <65: 28.7%; >65: 71.3% | 317 | $PM_{2.5}$ | CRP | Blood | Biomarker | ↑CRP |
| Wu et al., 2016 (36) | Panel study | China | Period 1: 2014.1–2014.4; Period 2: 2014.8–2014.9 | Period 1: 73.6±4.7; Period 2: 74.8±3.4 | 25 | $PM_{2.5}$, $PM_{10}$, $NO_2$, $SO_2$ | FeNO, Exhaled $H_2S$ | EBC | Biomarker, symptoms | ↑FeNO |

Statistically significant increase/decrease (↑/↓). †, age is presented as mean ± standard deviation, range or percentage distribution. NA, not applicable; PM, particulate matter; VOC, volatile organic compound; $NO_2$, nitric dioxide; FeNO, fractional exhaled nitric oxide; IL, interleukin; IFNγ, interferon gamma; TNFα, tumor necrosis factor α; CRP, C reactive protein; sVCAM-1, circulating vascular cell adhesion molecule–1; HGF, hepatocyte growth factor; VEGF-A, vascular endothelial growth factor A; MCP-1, monocyte displacing protein 1; IP10, interferon gamma-induced protein; GM-CSF, granulocyte-macrophage colony stimulating factor; sCD40L, soluble CD40 ligand; MIP, macrophage inflammatory protein; RAGE, receptor for advanced glycation end-products; ITIH4, inter-alpha-trypsin inhibitor heavy chain 4; PRG4, proteoglycan 4; APOF, apolipoprotein F; NOx, nitrogen oxides; $H_2S$, hydrogen sulfide; EBC, exhaled breath concentration; $FEV_1$, forced expiratory volume in the first second; BEC, blood eosinophil count.

**Table 4** Characteristics of the included studies related to epigenetic regulation of physiology and susceptibility

| Author (year) | Study design | Location | Follow-up | Age, year[†] | Number | Pollutant | Biomarker | Sample | Outcome | Effect estimate |
|---|---|---|---|---|---|---|---|---|---|---|
| Chen et al., 2015 (27) | Repeated measure (prospectively) | China | 2013.9–2013.12 | 64±8 | 30 | $PM_{2.5}$ | NOS2A methylation | Blood | Biomarker | ↓methylation of NOS2A |
| Lee et al., 2019 (43) | Cross-sectional analysis (from prospective design) | Korea | NA | 72.8±6.3 | 100 | $PM_{10}$, $NO_2$ | Methylated CpGs | Blood | Biomarker | Variable effects |

Statistically significant increase/decrease (↑/↓). [†], age is presented as mean ± standard deviation. NA, not applicable; PM, particulate matter; $NO_2$, nitric dioxide; NOS2A, nitric oxide synthase isoform 2A; CpG, C-phosphate-G.

association between systemic inflammatory markers and PM has been widely assessed (61,62). Much of the evidence in this review suggested that interleukins were potential predictors of PM exposure. The seven studies included in this review showed that IL-6 levels exhibited various associations with PM exposure. This might be related to the characteristics of IL-6, which acts as both anti-inflammatory and proinflammatory cytokine (63). Another well-known inflammatory marker, CRP, is a highly sensitive systemic marker of inflammation and tissue damage, which is well-standardized, reproducible, and readily available (64). CRP consistently showed a statistically significant positive association with extent of PM exposure in four CRP-measuring studies which were included in this review (26,29,30,39). Another well-studied systemic marker was FeNO level. Measurement of FeNO is a non-invasive method that rules in asthma, and facilitates the determination of inhaled corticosteroid responsiveness, making it convenient for application in primary care clinics (65). Several epidemiological studies have shown that FeNO is positively linked with PM (66,67). Further research is needed to predict PM exposure using minimally invasive methods to enable early intervention in COPD.

Moreover, air pollutants are known to generate ROS, and oxidative DNA damage can prevent methyltransferases from interacting with DNA, resulting in hypomethylation of cytosine residues at CpG sites (47). Several studies have shown that PM also induces histone modifications that aids in the expression of several inflammatory genes (68,69). One of the studies included in this review by Chen et al. showed that some specific components of PM might be associated with decreased methylation in COPD patients (27). These epigenetic changes are inextricably associated with inflammation and oxidative stress. Thus, oxidative stress,

inflammation, and epigenetic changes are intimately linked (70), and play significant roles in the pathophysiology of COPD.

Although rare, the direct effect of innate and adaptive immune system mechanisms can also be explained as one of the PM-induced mechanisms in patients with COPD. The inhalation of noxious particles is mainly removed by the mucociliary escalator in the tracheobronchial area, but relatively small particles get deposited in the alveolar space (71). Alveolar macrophages play an important role in clearing and processing these fine particles via scavenger and toll-like receptors, and also activate innate and adaptive immune responses (45). Commuting to work by bicycle was found to be related to the inhaled dose of black carbon in a previous study in London. Airway macrophage carbon was detected more frequently in cyclists compared to non-cyclists (72). Consistent with a previous study (72), Belli et al. showed that higher indoor $PM_{2.5}$ was significantly associated with an increase in black carbon of airway macrophages in patients with COPD (0.19 μm² increase per 10 μg/m³ indoor $PM_{2.5}$) (25).

Several airway biomarkers have been proposed to establish strategies for diagnosis and prevention of diseases caused by air pollutants. However, measuring biomarkers related to PM exposure is a challenging task because exposure is usually chronic, with low to moderate exposure levels over long periods of time (73). In addition, it was found that the effect estimates of PM exposure showed various associations with use of single surrogate biomarkers. The ECLIPSE study (74), which defined subtypes of COPD and explored novel biomarkers, used a combined panel of six serum inflammatory markers to compare systemic inflammation between smokers with normal lung function and smokers with COPD. They showed that the mortality

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of participants with persistent systemic inflammation was six times higher than that of participants without inflammation. Certain biomarkers may be more useful in combination with other markers in determining the effects of exposure to air pollution on COPD (62). Further research is needed to predict the disease prognosis of COPD patients exposed to PM using a combination of various biomarkers to validate future therapeutic interventions.

Our study had few limitations. First, this study did not perform a meta-analysis because most of the outcomes were biomarkers, and risk summation could not be performed. Second, most studies analyzed the relationship between a single biomarker and PM, and confounding factors that could affect the biomarker could not be quantified. Third, the available literature lacks longitudinal studies that investigated the temporal relationship between biomarkers and PM.

## Conclusions

This systematic review summarized the available literature on the relationship between PM and biomarkers in patients with COPD. We verified several systemic biomarkers that were significantly associated with PM exposure. It was observed that epigenetic regulation of inflammation was the most studied entity, but the use of biomarker for monitoring COPD patients exposed to PM is still not enough evidence. Future studies are needed to establish recommendations for regulation to reduce airborne PM, which could be used to develop strategies for prevention and management of environmental respiratory diseases.

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## References

1. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. 2023.

2. Safiri S, Carson-Chahhoud K, Noori M, et al. Burden of chronic obstructive pulmonary disease and its attributable risk factors in 204 countries and territories, 1990-2019: results from the Global Burden of Disease Study 2019. BMJ 2022;378:e069679.

3. World Health Organization. The top 10 causes of death. Available online: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death

4. Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. Lancet 2009;374:733-43.

5. Yang IA, Jenkins CR, Salvi SS. Chronic obstructive pulmonary disease in never-smokers: risk factors, pathogenesis, and implications for prevention and treatment. Lancet Respir Med 2022;10:497-511.

6. Shin S, Bai L, Burnett RT, et al. Air Pollution as a Risk Factor for Incident Chronic Obstructive Pulmonary Disease and Asthma. A 15-Year Population-based Cohort Study. Am J Respir Crit Care Med 2021;203:1138-48.

7. World Health Organization. Regional Office for Europe. Health effects of particulate matter: policy implications

for countries in eastern Europe, Caucasus and central Asia. 2013.

8. Kim KH, Kabir E, Kabir S. A review on the human health impact of airborne particulate matter. Environ Int 2015;74:136-43.

9. Peters A, Wichmann HE, Tuch T, et al. Respiratory effects are associated with the number of ultrafine particles. Am J Respir Crit Care Med 1997;155:1376-83.

10. Zhao J, Li M, Wang Z, et al. Role of PM(2.5) in the development and progression of COPD and its mechanisms. Respir Res 2019;20:120.

11. Kim D, Chen Z, Zhou LF, et al. Air pollutants and early origins of respiratory diseases. Chronic Dis Transl Med 2018;4:75-94.

12. Singh K, Tripathi D. Particulate matter and human health. Environ Health 2021. doi: 10.5772/intechopen.100550.

13. Han C, Oh J, Lim YH, et al. Long-term exposure to fine particulate matter and development of chronic obstructive pulmonary disease in the elderly. Environ Int 2020;143:105895.

14. Yang X, Zhang T, Zhang Y, et al. Global burden of COPD attributable to ambient PM2.5 in 204 countries and territories, 1990 to 2019: A systematic analysis for the Global Burden of Disease Study 2019. Sci Total Environ 2021;796:148819.

15. Bloemsma LD, Hoek G, Smit LAM. Panel studies of air pollution in patients with COPD: Systematic review and meta-analysis. Environ Res 2016;151:458-68.

16. Dominici F, Peng RD, Bell ML, et al. Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. JAMA 2006;295:1127-34.

17. Gan WQ, FitzGerald JM, Carlsten C, et al. Associations of ambient air pollution with chronic obstructive pulmonary disease hospitalization and mortality. Am J Respir Crit Care Med 2013;187:721-7.

18. DeVries R, Kriebel D, Sama S. Outdoor Air Pollution and COPD-Related Emergency Department Visits, Hospital Admissions, and Mortality: A Meta-Analysis. COPD 2017;14:113-21.

19. Xu Q, Li X, Wang S, et al. Fine Particulate Air Pollution and Hospital Emergency Room Visits for Respiratory Disease in Urban Areas in Beijing, China, in 2013. PLoS One 2016;11:e0153099.

20. Kaur M, Chandel J, Malik J, et al. Particulate matter in COPD pathogenesis: an overview. Inflamm Res 2022;71:797-815.

21. Page MJ, Moher D, Bossuyt PM, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ 2021;372:n160.

22. Grady ST, Koutrakis P, Hart JE, et al. Indoor black carbon of outdoor origin and oxidative stress biomarkers in patients with chronic obstructive pulmonary disease. Environ Int 2018;115:188-95.

23. Huang S, Koutrakis P, Grady ST, et al. Effects of particulate matter gamma radiation on oxidative stress biomarkers in COPD patients. J Expo Sci Environ Epidemiol 2021;31:727-35.

24. Manney S, Meddings CM, Harrison RM, et al. Association between exhaled breath condensate nitrate + nitrite levels with ambient coarse particle exposure in subjects with airways disease. Occup Environ Med 2012;69:663-9.

25. Belli AJ, Bose S, Aggarwal N, et al. Indoor particulate matter exposure is associated with increased black carbon content in airway macrophages of former smokers with COPD. Environ Res 2016;150:398-402.

26. Busenkell E, Collins CM, Moy ML, et al. Modification of associations between indoor particulate matter and systemic inflammation in individuals with COPD. Environ Res 2022;209:112802.

27. Chen R, Qiao L, Li H, et al. Fine Particulate Matter Constituents, Nitric Oxide Synthase DNA Methylation and Exhaled Nitric Oxide. Environ Sci Technol 2015;49:11859-65.

28. Gao N, Xu W, Ji J, et al. Lung function and systemic inflammation associated with short-term air pollution exposure in chronic obstructive pulmonary disease patients in Beijing, China. Environ Health 2020;19:12.

29. Garshick E, Grady ST, Hart JE, et al. Indoor black carbon and biomarkers of systemic inflammation and endothelial activation in COPD patients. Environ Res 2018;165:358-64.

30. Huang S, Garshick E, Vieira CLZ, et al. Short-term exposures to particulate matter gamma radiation activities and biomarkers of systemic inflammation and endothelial activation in COPD patients. Environ Res 2020;180:108841.

31. Lee KY, Feng PH, Ho SC, et al. Inter-alpha-trypsin inhibitor heavy chain 4: a novel biomarker for environmental exposure to particulate air pollution in patients with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2015;10:831-41.

32. Nurhussien L, Kang CM, Koutrakis P, et al. Air Pollution Exposure and Daily Lung Function in Chronic Obstructive Pulmonary Disease: Effect Modification by Eosinophil Level. Ann Am Thorac Soc 2022;19:728-36.

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33. Audi C, Baïz N, Maesano CN, et al. Serum cytokine levels related to exposure to volatile organic compounds and PM(2.5) in dwellings and workplaces in French farmers - a mechanism to explain nonsmoking COPD. Int J Chron Obstruct Pulmon Dis 2017;12:1363-74.

34. Chen X, Que C, Yao Y, et al. Susceptibility of individuals with lung dysfunction to systemic inflammation associated with ambient fine particle exposure: A panel study in Beijing. Sci Total Environ 2021;788:147760.

35. Pirozzi C, Sturrock A, Carey P, et al. Respiratory effects of particulate air pollution episodes in former smokers with and without chronic obstructive pulmonary disease: A panel study. COPD Res Pract 2015. doi: 10.1186/s40749-015-0004-z

36. Wu S, Ni Y, Li H, et al. Short-term exposure to high ambient air pollution increases airway inflammation and respiratory symptoms in chronic obstructive pulmonary disease patients in Beijing, China. Environ Int 2016;94:76-82.

37. Huang Q, Hu D, Wang X, et al. The modification of indoor PM(2.5) exposure to chronic obstructive pulmonary disease in Chinese elderly people: A meet-in-metabolite analysis. Environ Int 2018;121:1243-52.

38. Lee KY, Chiang LL, Ho SC, et al. Associations of autophagy with lung diffusion capacity and oxygen saturation in severe COPD: effects of particulate air pollution. Int J Chron Obstruct Pulmon Dis 2016;11:1569-78.

39. Tang L, Shi S, Wang B, et al. Effect of urban air pollution on CRP and coagulation: a study on inpatients with acute exacerbation of chronic obstructive pulmonary disease. BMC Pulm Med 2021;21:296.

40. Abramson MJ, Wigmann C, Altug H, et al. Ambient air pollution is associated with airway inflammation in older women: a nested cross-sectional analysis. BMJ Open Respir Res 2020;7:e000549.

41. Dadvand P, Nieuwenhuijsen MJ, Agustí À, et al. Air pollution and biomarkers of systemic inflammation and tissue repair in COPD patients. Eur Respir J 2014;44:603-13.

42. Fireman Klein E, Adir Y, Fireman E, et al. Cigarette-related cadmium and environmental pollution exposure are reflected in airway ultrafine particle content. ERJ Open Res 2020;6:00361-2019.

43. Lee MK, Xu CJ, Carnes MU, et al. Genome-wide DNA methylation and long-term ambient air pollution exposure in Korean adults. Clin Epigenetics 2019;11:37.

44. Kim HJ, Choi MG, Park MK, et al. Predictive and Prognostic Biomarkers of Respiratory Diseases due to Particulate Matter Exposure. J Cancer Prev 2017;22:6-15.

45. Miyata R, van Eeden SF. The innate and adaptive immune response induced by alveolar macrophages exposed to ambient particulate matter. Toxicol Appl Pharmacol 2011;257:209-26.

46. Eckel SP, Zhang Z, Habre R, et al. Traffic-related air pollution and alveolar nitric oxide in southern California children. Eur Respir J 2016;47:1348-56.

47. Baccarelli A, Wright RO, Bollati V, et al. Rapid DNA methylation changes after exposure to traffic particles. Am J Respir Crit Care Med 2009;179:572-8.

48. Prevalence and attributable health burden of chronic respiratory diseases, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Respir Med 2020;8:585-96.

49. Stolz D, Mkorombindo T, Schumann DM, et al. Towards the elimination of chronic obstructive pulmonary disease: a Lancet Commission. Lancet 2022;400:921-72.

50. Celli B, Fabbri L, Criner G, et al. Definition and Nomenclature of Chronic Obstructive Pulmonary Disease: Time for Its Revision. Am J Respir Crit Care Med 2022;206:1317-25.

51. Pope CA 3rd, Dockery DW. Health effects of fine particulate air pollution: lines that connect. J Air Waste Manag Assoc 2006;56:709-42.

52. Ni L, Chuang CC, Zuo L. Fine particulate matter in acute exacerbation of COPD. Front Physiol 2015;6:294.

53. Ling SH, van Eeden SF. Particulate matter air pollution exposure: role in the development and exacerbation of chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2009;4:233-43.

54. Møller P, Jacobsen NR, Folkmann JK, et al. Role of oxidative damage in toxicity of particulates. Free Radic Res 2010;44:1-46.

55. Kim JY, Mukherjee S, Ngo LC, et al. Urinary 8-hydroxy-2'-deoxyguanosine as a biomarker of oxidative DNA damage in workers exposed to fine particulates. Environ Health Perspect 2004;112:666-71.

56. Bae S, Pan XC, Kim SY, et al. Exposures to particulate matter and polycyclic aromatic hydrocarbons and oxidative stress in schoolchildren. Environ Health Perspect 2010;118:579-83.

57. Dahl M, Nordestgaard BG. Markers of early disease and prognosis in COPD. Int J Chron Obstruct Pulmon Dis 2009;4:157-67.

58. Brightling C, Greening N. Airway inflammation in COPD: progress to precision medicine. Eur Respir J

2019;54:1900651.

59. Agustí A, Edwards LD, Rennard SI, et al. Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype. PLoS One 2012;7:e37483.

60. Su B, Liu T, Fan H, et al. Inflammatory Markers and the Risk of Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis. PLoS One 2016;11:e0150586.

61. Corradi M, Goldoni M, Mutti A. A review on airway biomarkers: exposure, effect and susceptibility. Expert Rev Respir Med 2015;9:205-20.

62. Elvidge T, Matthews IP, Gregory C, et al. Feasibility of using biomarkers in blood serum as markers of effect following exposure of the lungs to particulate matter air pollution. J Environ Sci Health C Environ Carcinog Ecotoxicol Rev 2013;31:1-44.

63. Scheller J, Chalaris A, Schmidt-Arras D, et al. The pro- and anti-inflammatory properties of the cytokine interleukin-6. Biochim Biophys Acta 2011;1813:878-88.

64. Pepys MB, Baltz ML. Acute phase proteins with special reference to C-reactive protein and related proteins (pentaxins) and serum amyloid A protein. Adv Immunol 1983;34:141-212.

65. Karrasch S, Linde K, Rücker G, et al. Accuracy of FENO for diagnosing asthma: a systematic review. Thorax 2017;72:109-16.

66. Lin W, Huang W, Zhu T, et al. Acute respiratory inflammation in children and black carbon in ambient air before and during the 2008 Beijing Olympics. Environ Health Perspect 2011;119:1507-12.

67. Jansen KL, Larson TV, Koenig JQ, et al. Associations between health effects and particulate matter and black carbon in subjects with respiratory disease. Environ Health Perspect 2005;113:1741-6.

68. Gilmour PS, Rahman I, Donaldson K, et al. Histone acetylation regulates epithelial IL-8 release mediated by oxidative stress from environmental particles. Am J Physiol Lung Cell Mol Physiol 2003;284:L533-40.

69. Han X, Tian M, Shliaha PV, et al. Real-world particulate matters induce lung toxicity in rats fed with a high-fat diet: Evidence of histone modifications. J Hazard Mater 2021;416:126182.

70. Carmona JJ, Sofer T, Hutchinson J, et al. Short-term airborne particulate matter exposure alters the epigenetic landscape of human genes associated with the mitogen-activated protein kinase network: a cross-sectional study. Environ Health 2014;13:94.

71. Oberdörster G, Oberdörster E, Oberdörster J. Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. Environ Health Perspect 2005;113:823-39.

72. Nwokoro C, Ewin C, Harrison C, et al. Cycling to work in London and inhaled dose of black carbon. Eur Respir J 2012;40:1091-7.

73. Churg A, Brauer M. Ambient atmospheric particles in the airways of human lungs. Ultrastruct Pathol 2000;24:353-61.

74. Faner R, Tal-Singer R, Riley JH, et al. Lessons from ECLIPSE: a review of COPD biomarkers. Thorax 2014;69:666-72.

## Appendix 1 Search strategies

**PubMed/MEDLINE**

| No. | Search strategy |
|-----|-----------------|
| #1 | "("chronic obstructive pulmonary disease" OR COPD OR "Pulmonary Disease, Chronic Obstructive"[Mesh]) |
| #2 | ("Particulate matter" OR "PM2.5" OR "PM(2.5)" OR "PM10" OR "PM(10)") |
| #3 | (biomarker* OR "Biomarkers"[Mesh]) |
| #4 | 2012/01/01:3000/12/31[Date – Publication] |
| #6 | #1 AND #2 AND #3 AND #4 |

**Ovid Embase**

| No. | Search strategy |
|-----|-----------------|
| #1 | ('chronic obstructive pulmonary disease' OR COPD OR 'chronic obstructive lung disease'/exp) |
| #2 | ('Particulate matter' OR 'PM2.5' OR 'PM(2.5)' OR 'PM10' OR 'PM(10)') |
| #3 | (biomarker* OR 'biological marker'/exp) |
| #4 | [2012-2022]/py |
| #5 | [english]/lim |
| #6. | #1 AND #2 AND #3 AND #4 AND #5 |

**Cochrane Library**

| No. | Search strategy |
|-----|-----------------|
| #1 | MeSH descriptor: [Pulmonary Disease, Chronic Obstructive] explode all trees |
| #2 | "chronic obstructive pulmonary disease" OR COPD |
| #3 | #1 OR #2 |
| #4 | "Particulate matter" OR "PM2.5" OR "PM(2.5)" OR "PM10" OR "PM(10)" |
| #5 | MeSH descriptor: [Biomarkers] explode all trees |
| #6 | biomarker*:ti |
| #7 | #5 OR #6 |
| #8 | #3 AND #4 AND #7 |

**Table S1** List of excluded studies after full-text screening

| No | Excluded studies | Reason for exclusion |
|---|---|---|
| 1 | Pirozzi C, Sturrock A, Weng HY, et al. Effect of naturally occurring ozone air pollution episodes on pulmonary oxidative stress and inflammation. Int J Environ Res Public Health 2015;12:5061-75. | Study without biomarkers, inappropriate exposure |
| 2 | Inui T, Nakamoto K, Sada M, et al. Influence of gene polymorphism on biological markers in patients with asthma and COPD associated with air pollutants (2015 APSR congress abstract). | Abstract only |
| 3 | Balasubramanian S, Gunasekaran K, Sasidharan S, et al. MicroRNAs and Xenobiotic Toxicity: An Overview. Toxicol Rep 2020;7:583-95. | Review article |
| 4 | Benedikter BJ, Wouters EFM, Savelkoul PHM, et al. Extracellular vesicles released in response to respiratory exposures: implications for chronic disease. J Toxicol Environ Health B Crit Rev 2018;2:142-60. | Review article |
| 5 | Corradi M, Goldoni M, Mutti A. A review on airway biomarkers: exposure, effect and susceptibility. Expert Rev Respir Med 2015;9:205-20. | Review article |
| 6 | Elvidge T, Matthews IP, Gregory C, et al. Feasibility of using biomarkers in blood serum as markers of effect following exposure of the lungs to particulate matter air pollution. J Environ Sci Health C Environ Carcinog Ecotoxicol Rev 2013;31:1-44. | Review article |
| 7 | Kim HJ, Choi MG, Park MK, Seo YR. Predictive and Prognostic Biomarkers of Respiratory Diseases due to Particulate Matter Exposure. J Cancer Prev 2017;22:6-15. | Review article |