COPD with Eosinophilic Inflammation is Susceptible to Particulate Air Pollution Exposure

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) has been linked to air pollution exposure. Air pollution has been associated with eosinophilic inflammation of respiratory disease. The objective of this study was to determine associations between air pollution and eosinophilic inflammation in COPD. A cross-sectional study was conducted on 291 COPD patients recruited from hospitals in Taipei between January 2014 and 2021, including 147 patients with eosinophil blood count ≥2% and 144 patients < 2%. Land use regression (LUR) model was used to estimate exposure levels to particulate matter with an aerodynamic diameter of < 10 µm (PM10), PM2.5 (< 10 µm), nitrogen oxides (NOx) and nitrogen dioxides (NO2). We investigated associations of air pollution with COPD outcomes by performing a linear regression approach. A two-pollutant approach was applied to examine the associations of PM10 or PM2.5 with NOx or NO2 in COPD with eosinophilic inflammation. An increase of 1 µg m⁻³ in PM10 was associated with a 0.62% (95% CI: – 1.10%, –0.13%) decrease in the forced vital capacity (FVC) in COPD. An increase of 1 µg m⁻³ in PM2.5 was associated with a 0.38% (95% CI: – 0.71%, –0.05%) decrease in the FVC. A 1 µg m⁻³ increase in PM10 was associated with a 0.92% (95% CI: –1.68%, –0.16%) decrease in the FVC in COPD patients with eosinophilic inflammation. A 1 µg m⁻³ increase in PM2.5 was associated with an increase of
0.26 points (95% CI: −1.68%, −0.16%) in the COPD Assessment Test (CAT) and a 0.03-times year⁻¹ (95% CI: 0.01, 0.05) increase in the acute exacerbation (AE) of COPD eosinophilic inflammation. Associations of PM₁₀ and PM₂.₅ with lung function decline in COPD eosinophilic inflammation were confirmed by the two-pollutant model. Exposure to particulate air pollution increased the risk of deleterious health outcomes in COPD with eosinophilic inflammation. COPD with eosinophilic inflammation may represent a susceptible group to particulate air pollution exposure.

**Keywords:** Acute exacerbation, Air pollution, Lung function, PM₁₀, PM₂.₅

### 1 INTRODUCTION

While the pattern of inflammation in chronic obstructive pulmonary disease (COPD) is varied and is predominantly characterized by accumulation of macrophages, clusters of differentiation 8⁺ (CD8⁺) T cells, and neutrophils (Kim *et al.*, 2008), eosinophils can often be present in COPD patients (Saha and Brightling, 2006). The prevalence of COPD occurring with eosinophilic inflammation has been reported range from 20%–40% of the COPD populations with various threshold used of blood eosinophil count ≥ 300 cell µL⁻¹ and sputum eosinophil count of ≥ 3% (Kolsum *et al.*, 2017). A meta-analysis of 19 studies with a cutoff level of 2% blood eosinophil found that the overall prevalence of eosinophilic COPD was 54.95% (Wu *et al.*, 2019). A previous study showed that 37% of 1483 COPD patients with no history of asthma had persistent blood eosinophil ≥ 2% (Singh *et al.*, 2014). Increased eosinophils have been associated with reduced lung function and elevated risk of exacerbations in COPD (Tashkin and Wechsler, 2018). Importantly, blood eosinophilia is considered a biomarker that predicts all-cause mortality and a better response to inhaled corticosteroid (ICS) treatment in COPD patients with exacerbation (Bafadhel *et al.*, 2011; Zhang *et al.*, 2020). Eosinophilic inflammation had more exacerbations than non-eosinophilic inflammation in COPD patients (Kerkhof *et al.*, 2017; Pavord *et al.*, 2017).

Eosinophilic inflammation has been linked to air pollution exposure. For example, exposure to traffic-related air pollution was associated with eosinophilic inflammation of the airways in older adult asthmatics patients (Epstein *et al.*, 2013; Fang *et al.*, 2019). Using a distributed lag non-linear model, human eosinophils were found to be significantly affected by exposure to particulate matter of < 10 µm in aerodynamic diameter (PM₁₀) in both women and men (Ding *et al.*, 2020). In addition, the chemometric analysis methods showed that exposure to particulate matter with an aerodynamic diameter of < 2.5 µm (PM₂.₅) and nitrogen dioxide (NO₂) was linked to eosinophilic degranulation, which triggers the processes that cause inflammatory reactions (Mohd Isa *et al.*, 2020). An animal study showed that PM₂.₅ might exacerbate allergic inflammation and lung eosinophil exacerbations in the murine lung via a TLR2/TLR4/MyD88-signaling pathway (He *et al.*, 2017). Neutrophils are commonly known to contribute to the inflammatory changes in COPD. Increase neutrophils counts indicate systemic inflammation which associated with COPD severity and morbidity (Cockayne *et al.*, 2012). However, a recently published study also highlighted the significance of eosinophil levels in determining susceptibility to air pollution (Nurhussien *et al.*, 2022). Therefore, the objective of our study was to investigate the effects of air pollution on eosinophilic inflammation in COPD.

### 2 MATERIALS AND METHODS

#### 2.1 Study Population

We conducted a cross-sectional study on 291 COPD patients recruited from the clinic of the thoracic department of two hospitals in Taipei City between January 2014 and 2021. Patients were included if they had been diagnosed with COPD based on a forced expiratory volume in the first second (FEV₁)/forced vital capacity (FVC) ratio of < 70% following post-bronchodilator treatment as assessed by spirometry (Vestbo *et al.*, 2013), and were aged 40 to 90 years (Fig. 1). Meanwhile, patients who had experienced an exacerbation manifestation 3 months prior to the study or who had been confirmed to have asthma, bronchiectasis, a malignancy, or any chronic inflammatory condition unrelated to COPD were excluded from the study. All the COPD patients in this study was treated based on GOLD guidelines (GOLD, 2022).
Fig. 1. Flowchart of COPD patient inclusion and exclusion criteria.

2.2 Eosinophilic Inflammation in COPD and Health Outcome Measurements

Eosinophilic inflammation was defined as COPD patients who had ≥ 2% eosinophils at the recruitment of a clinic visit (Bafadhel et al., 2011). All study participants underwent blood differential tests, including neutrophils, lymphocytes, and eosinophils. The COPD Assessment Test (CAT) was conducted to assess and quantify the health-related quality of life and symptom burden of COPD patients and was measured based on the CAT users’ guide (Gil et al., 2021). The modified Medical Research Council (mMRC) scale was used to determine the severity of dyspnea in COPD patients (Launois et al., 2012). The BODE (Body-mass index, airflow Obstruction, Dyspnea, and Exercise capacity) index was measured during the admission to the hospital, and AE (acute exacerbation) events were assessed according to the number of times the patients presented to emergency department in one year due to exacerbation. Baseline information was obtained on age, sex, Body Mass Index (BMI), and smoking status.

2.3 Exposure Assessment

Land use regression (LUR) models for air pollutants were utilized to estimate individual level exposure concentrations at the baseline residential addresses of each subject. The European Study of Cohorts for Air Pollution Effects (ESCAPE) criteria (http://www.escapeproject.eu/manuals/) was used as a reference to calculate actual PM10 and PM2.5 concentrations from 20 measurement locations in Taipei (Lee et al., 2014). Meanwhile, NOx and NO2 concentrations were calculated from 40 measurement sites in Taipei Metropolis (Lee et al., 2015). The measurement sites were selected considering the spatial distribution of air pollution at the home addresses of participants (Eeftens et al., 2012). The residential addresses of each subject were collected from two hospital in Taipei city and transformed into geocoded information using Taiwan Geospatial One Stop (www.igos.tw). The geocoded information was then used in buffer analyses to calculate the value of land use types for different buffer sizes. Geographic Information System (GIS) analyses were conducted using ESRI ArcGIS v. 10.8 to calculate the area of each land use type, including roads, industry, commerce, and construction, inverse distance to the nearest major road, residential area, and river area, major road length, urban green areas, natural areas, and low-density residential areas. The area of land use types was incorporated into the LUR model developed for PM10 and PM2.5, and for NOx and NO2 to calculate exposure concentrations (Lee et al., 2014, 2015). Individual exposure concentrations to 1-year air pollutants were estimated from the time of recruitment using R software (R version 3.6.3).

2.4 Statistical Analyses

The Shapiro-Wilk test was conducted to determine the normal distribution of data variables. The winsorization model was implemented to minimize the influence of extreme outliers by
substituting low and high values outside the 1st and 99th percentiles (Tsai et al., 2012). The independent sample t-test was used for normally distributed continuous variables. The Mann-Whitney U-test was utilized for non-normally distributed continuous variables. We investigated associations of air pollution with COPD outcomes by performing a multiple linear regression model. A single-pollutant and two-pollutants models were created to investigate association of PM_{10}, PM_{2.5}, NOx, and NO2 with FEV1, FVC, FEV1/FVC, CAT scale, mMRC score, BODE index, AE, neutrophils, eosinophils, lymphocytes, the eosinophil/lymphocyte ratio (ELR) and neutrophil/lymphocyte ratio (NLR). Co-variables of age, sex, BMI, and smoking status were adjusted for in both pollutant models. A subgroup analysis by gender, smoking status, COPD severity, and eosinophilic inflammation was conducted exploring the associations of PM_{10}, PM_{2.5}, NOx, and NO2 with FEV1, FVC, FEV1/FVC, CAT scale, mMRC score, BODE index, AE events, neutrophils, eosinophils, lymphocytes, the ELR and NLR. Co-variables of age, sex, BMI, and smoking status were adjusted for in the models. SPSS for Windows vers. 20.0 was utilized for statistical analyses (SPSS, Chicago, IL, USA). p values of < 0.05 was set as statistical significance.

3 RESULTS AND DISCUSSION

3.1 Characteristics of Study Subjects

Table 1 summarizes characteristics of the 291 patients recruited in the study; 144 were non-eosinophilic inflammation patients and 147 were eosinophilic inflammation patients. The majority of patients were male (89%) and the average age was 71.9 ± 10.30 years. The average BMI was 23.2 ± 3.94 kg m^{-2}, 55.6% of participants were ex-smokers, and 32.5% were current smokers. The mean of FEV1, FVC, and FEV1/FVC were 59.57 ± 19.33%, 81.95 ± 20.31%, and 73 ± 0.17%, respectively. The CAT, mMRC, BODE index, and AE were 10.72 ± 1.90 points, 1.35 ± 1.00 points, 2.96 ± 1.90 points, and 0.02 ± 0.76 times year^{-3}, respectively. Neutrophils, eosinophils, lymphocytes, the ELR, and NLR were 66.2 ± 12.13%, 2.94 ± 2.74%, 21.7 ± 9.63%, 0.14 ± 0.13%, and 2.95 ± 1.58%, respectively. One-year mean PM_{10}, PM_{2.5}, NOx, and NO2 concentrations of subjects were 23.2 ± 10.46 ppb, and 15.68 ± 3.15 ppb, respectively. Compared to the non-eosinophilic inflammation group, eosinophilic inflammation patients had a higher proportion of non-smoker (p < 0.05), lower neutrophils (p < 0.05), higher lymphocytes (p < 0.05), a higher ELR (p < 0.05), and a lower NLR (p < 0.05).

COPD patients were exposed to a number of PM_{10}, PM_{2.5}, and NO2 levels that were greater than World Health Organization (WHO) recommended parameters (of 5 μg m^{-3}, 15 μg m^{-3}, and 10 ppb, respectively) (WHO, 2021). A previous study in Taiwan showed similar results with our findings regarding concentrations of PM_{10} and PM_{2.5}, but with a lower concentration of NO2 than our findings (Liu et al., 2018). Meanwhile, the mean concentration of NOx levels in our study was found to be lower than the acceptable maximum limit of the United States Environmental Protection Agency (U.S. EPA) (annual NOx of 53 ppb) (U.S. EPA, 2022).

3.2 Associations of Air Pollution with Health Outcomes in COPD Patients

Associations of air pollution with health outcomes in COPD are shown in Fig. 2. We observed that a 1 μg m^{-3} increase in PM_{10} was associated with a 0.62% decrease in FVC (95% confidence interval (CI): –1.10%, –0.13%, p < 0.05). An increase of 1 μg m^{-3} in PM_{2.5} was associated with a 0.38% decrease in FVC (95% CI: –0.71%, –0.05%, p < 0.05). A 1 ppb increase in NOx was associated with decreases of 0.01 times year^{-3} in AE events (95% CI: –0.03, –0.02, p < 0.05) and 0.16% of neutrophils and (95% CI: –0.30%, –0.01%, p < 0.05). A 1 ppb increase in NO2 was associated with decreases of 0.03 times year^{-3} in AE events (95% CI: –0.06, –0.01, p < 0.05) and of 0.60% neutrophils (95% CI: –1.06%, –0.13%, p < 0.05). In the two-pollutant model with NOx, a 1 μg m^{-3} increase in PM_{10} was associated with a 0.68% decrease in FVC (95% CI: –1.18%, –0.18%, p < 0.05). A 1 μg m^{-3} increase in PM_{2.5} with NOx was associated with a 0.67% decrease in the FVC (95% CI: –1.17%, –0.17%, p < 0.05). A 1 μg m^{-3} increase in PM_{2.5} with NOx was associated with a 0.40% decrease in the FVC (95% CI: –0.73%, –0.06%, p < 0.05). A 1 μg m^{-3} increase in PM_{2.5} with NOx was associated with a 0.38% decrease in the FVC (95% CI: –0.72%, –0.05%, p < 0.05).

Our findings were consistent with an earlier investigation that found a significant association between air pollution and a decrease in FEV1 and FVC. The previous study reported that every
Table 1. Characteristics of chronic obstructive pulmonary disease (COPD) study subjects.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total COPD patients ($n = 291$)</th>
<th>Eosinophil inflammation $\geq 2%$ ($n = 147$)</th>
<th>Eosinophil inflammation $&lt; 2%$ ($n = 144$)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean ± SD</td>
<td>71.99 ± 10.30</td>
<td>71.15 ± 9.75</td>
<td>72.85 ± 10.78</td>
<td>0.160</td>
</tr>
<tr>
<td>Male, $n$</td>
<td>89 (260)</td>
<td>91.2 (134)</td>
<td>87.5 (126)</td>
<td>0.312</td>
</tr>
<tr>
<td>Smoking status, $n$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>32.3 (94)</td>
<td>29.3 (43)</td>
<td>35.4 (51)</td>
<td>0.05</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>55.3 (161)</td>
<td>53.7 (79)</td>
<td>56.9 (82)</td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>12.4 (36)</td>
<td>17.0 (25)</td>
<td>7.6 (11)</td>
<td></td>
</tr>
<tr>
<td>BMI, kg m$^{-2}$</td>
<td>23.20 ± 3.94</td>
<td>22.38 ± 4.20</td>
<td>22.98 ± 3.69</td>
<td>0.892</td>
</tr>
<tr>
<td>Lung function, mean ± SD</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>FEV1, %</td>
<td>59.57 ± 19.33</td>
<td>59.29 ± 18.68</td>
<td>59.87 ± 20.07</td>
<td>0.807</td>
</tr>
<tr>
<td>FVC, %</td>
<td>81.95 ± 20.31</td>
<td>83.16 ± 20.86</td>
<td>80.62 ± 19.68</td>
<td>0.308</td>
</tr>
<tr>
<td>FEV1/FVC, %</td>
<td>0.73 ± 0.17</td>
<td>0.71 ± 0.16</td>
<td>0.74 ± 0.16</td>
<td>0.308</td>
</tr>
<tr>
<td>mMRC (points), mean ± SD</td>
<td>1.35 ± 1.00</td>
<td>1.30 ± 1.08</td>
<td>1.46 ± 0.94</td>
<td>0.233</td>
</tr>
<tr>
<td>CAT (points), mean ± SD</td>
<td>10.72 ± 7.23</td>
<td>11.06 ± 7.42</td>
<td>10.10 ± 7.01</td>
<td>0.204</td>
</tr>
<tr>
<td>BODE index (points), mean ± SD</td>
<td>2.96 ± 1.90</td>
<td>3.05 ± 1.88</td>
<td>3.01 ± 1.93</td>
<td>0.902</td>
</tr>
<tr>
<td>AE (times year$^{-1}$), mean ± SD</td>
<td>0.31 ± 0.76</td>
<td>0.28 ± 0.71</td>
<td>0.29 ± 0.69</td>
<td>0.792</td>
</tr>
<tr>
<td>Biochemistry, mean ± SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils, %</td>
<td>66.25 ± 12.13</td>
<td>61.13 ± 8.88</td>
<td>71.98 ± 12.73</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Eosinophils, %</td>
<td>2.94 ± 2.74</td>
<td>4.77 ± 2.62</td>
<td>0.87 ± 0.62</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Lymphocytes, %</td>
<td>21.70 ± 9.63</td>
<td>24.49 ± 7.57</td>
<td>18.52 ± 10.70</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>ELR, %</td>
<td>0.14 ± 0.13</td>
<td>0.21 ± 0.14</td>
<td>0.05 ± 0.05</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>NLR, %</td>
<td>2.95 ± 1.58</td>
<td>2.37 ± 1.36</td>
<td>3.56 ± 1.62</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Air pollutants, mean ± SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PM$_{2.5}$, µg m$^{-3}$</td>
<td>43.15 ± 5.00</td>
<td>42.69 ± 4.30</td>
<td>43.04 ± 5.35</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>PM$_{10}$, µg m$^{-3}$</td>
<td>25.16 ± 7.28</td>
<td>24.92 ± 5.42</td>
<td>26.48 ± 8.72</td>
<td>0.937</td>
</tr>
<tr>
<td>NO$_x$, ppb</td>
<td>40.38 ± 10.46</td>
<td>40.88 ± 10.01</td>
<td>39.30 ± 10.17</td>
<td>0.302</td>
</tr>
<tr>
<td>NO$_2$, ppb</td>
<td>15.68 ± 3.15</td>
<td>15.67 ± 3.17</td>
<td>15.39 ± 2.94</td>
<td>0.117</td>
</tr>
</tbody>
</table>

Abbreviations: SD, standard deviation; BMI, body-mass index; FEV$_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; mMRC, modified medical research council; CAT, COPD Assessment Test; BODE, body-mass index, airflow obstruction, dyspnea, and exercise; AE, acute exacerbation; ELR, eosinophil/lymphocyte ratio; NLR, neutrophil/lymphocyte ratio; PM$_{10}$, particulate matter with an aerodynamic diameter of < 10 µm; PM$_{2.5}$, particulate matter with an aerodynamic diameter of < 2.5 µm; NO$_x$, nitrogen oxides; NO$_2$, nitrogen dioxide.

10 µg m$^{-3}$ increase in daily mean concentration of PM$_{2.5}$ was associated with decreases in the FEV$_1$, FVC, and FEV$_1$/FVC ratio by 26 mL, 28 mL, and 0.09%, respectively (Liu et al., 2017). A pooled analysis of 50 studies reported that short-term exposure to air pollutants (PM$_{10}$, PM$_{2.5}$, NO$_x$, O$_3$, CO, and SO$_2$) led to significant increases in the burden of risk of AE events in COPD patients (Li et al., 2016a). A study from China reported that increases of 10 µg m$^{-3}$ in PM$_{10}$ and NO$_x$ were associated with cumulative 1.58% and 2.35% increases in COPD mortality, respectively (Li et al., 2016b). We observed that increases in PM$_{10}$ and PM$_{2.5}$ were associated with increased CAT score and AE events. These findings are in line with previous reports indicating that PM$_{10}$ exposure had negative effects on the CAT which was also associated with the severity of airflow inflammation in COPD patients (Ghobadi et al., 2012; Pothisrat et al., 2019). In COPD, a total score on the CAT ranging from 10 to 20 can induce one or two exacerbation events per year (GOLD, 2022), which is consistent with our findings regarding the CAT score and AE events of 11.06 ± 7.42 points and 0.28 ± 0.71 times year$^{-1}$, respectively. Together, air pollution exposure is associated with COPD outcomes; however, the phenotypes of air pollution-associated COPD remain unclear.

### 3.3 Associations of Air Pollution on Health Outcomes in COPD by Gender, Smoking Status, and Severity

Fig. 3 shows the associations of air pollution with health outcomes in COPD patients in terms of gender, smoking status, and severity. A 1 µg m$^{-3}$ increase in PM$_{10}$ was associated with
Fig. 2. Associations of air pollutants with health outcomes in chronic obstructive pulmonary disease (COPD) patients. Single-pollutant and two-pollutant models were used to examine associations of particulate matter with an aerodynamic diameter of $< 10 \mu m$ ($PM_{10}$), $PM_{2.5}$, nitrogen oxides ($NO_x$), and $NO_2$ with health outcomes of COPD. Data are provided as beta coefficient ($\beta$) change of health outcomes by a unit increase in $PM_{10}$, $PM_{2.5}$, $NO_x$, and $NO_2$ with a 95% confidence interval (CI). Models were adjusted for age, sex, body-mass index, and smoking status. Statistically significant. *$p < 0.05$
Fig. 3. Associations of air pollutants with health outcomes in chronic obstructive pulmonary disease (COPD) patients stratified by gender, smoking status, and Global Initiative for COPD (GOLD) severity. Linear regression models were used to investigate associations of particulate matter with an aerodynamic diameter of < 10 µM (PM$_{10}$), PM$_{2.5}$, nitrogen oxides (NO$_x$), and NO$_2$ with health outcomes. Data are provided as beta coefficient ($\beta$) change of health outcomes by a unit increase in PM$_{10}$, PM$_{2.5}$, NO$_x$, and NO$_2$ with a 95% confidence interval (CI). Models were adjusted for age, sex, body-mass index, and smoking status. Statistically significant. *$p < 0.05$
decreases of 0.01% in the ELR in females (95% CI: –0.01%, 0.01%, p < 0.05) and 0.68% in the FVC in males (95% CI: –1.16%, 0.11%, p < 0.05). A 1 µg m⁻³ increase in PM₂.₅ was associated with a decrease of 0.40% in the FVC in males (95% CI: –0.03%, –0.78%, p < 0.05). An increase of 1 ppb in NOₓ was associated with a decrease of 0.56% in neutrophils (95% CI: –1.08%, –0.33%, p < 0.05) and a 0.47% increase in lymphocytes in females (95% CI: 0.04%, 0.91%, p < 0.05). A 1 ppb increase in NOₓ was associated with decreases of 0.01% in AE events (95% CI: –0.02%, –0.01%, p < 0.05) and 0.14% in neutrophils in males (95% CI: –0.29%, –0.01%, p < 0.05). A 1 ppb increase in NO₂ was associated with decreases in neutrophils of 1.65% in females (95% CI: –3.30%, –0.01%, p < 0.05) and of 0.59% in males (95% CI: –1.08%, –0.09%, p < 0.05). A 1 ppb increase in NO₂ was associated with a 1.47% increase in lymphocytes in females (95% CI: 0.15%, 2.78%, p < 0.05) and a decrease of 0.03 times year⁻¹ in AE events in males (95% CI: –0.06, –0.01, p < 0.05). We observed that a 1 µg m⁻³ increase in PM₁₀ was associated with a 0.28% decrease in eosinophils in never-smokers (95% CI: –0.45%, 0.07%, p < 0.05) and decreases of 0.68% in the FEV₁ (95% CI: –1.33%, –0.02%, p < 0.05) and 0.73% in the FVC in ex-smokers (95% CI: –1.43%, 0.02%, p < 0.05). A 1 µg m⁻³ increase in PM₂.₅ was associated with decreases of 0.51% in the FEV₁ (95% CI: –0.97%, –0.05%, p < 0.05) and of 0.55% in the FVC (95% CI: –1.05%, 0.05%, p < 0.05) in ex-smokers. A 1 µg m⁻³ increase in PM₂.₅ was associated with a 0.01% increase in the FEV₁/FVC ratio in current smokers (95% CI: 0.01%, 0.02%, p < 0.05). A 1 ppb increases in both NOₓ and NO₂ were associated with decreases of 0.27% (95% CI: –0.48%, 0.05%, p < 0.05) and 0.79% in neutrophils (95% CI: –1.47%, –0.11%, p < 0.05) in ex-smokers. A 1 µg m⁻³ increase in PM₁₀ was associated with a decrease of 0.78% in the FVC 95% CI: –1.59%, 0.04%, p < 0.05) and an increase of 0.05 times year⁻¹ in AE events in severe COPD patients (95% CI: 0.10, 0.01, p < 0.05). A 1 µg m⁻³ increase in PM₂.₅ was associated with decreases of 0.25% in the FEV₁ (95% CI: –0.50%, 0.01%, p < 0.05) and of 0.57% in the FVC (95% CI: –1.10%, –0.04%, p < 0.05) in severe COPD patients. A 1 µg m⁻³ increase in PM₂.₅ was associated with an increase of 0.01% in the FEV₁/FVC ratio in mild COPD cases (95% CI: 0.01%, 0.02%, p < 0.05). A 1 ppb increases in both NOₓ and NO₂ were associated with decreases of 0.19% (95% CI: –0.37%, –0.02%, p < 0.05) and of 0.69% (95% CI: –1.27%, –0.11%, p < 0.05) of neutrophils in mild COPD cases, respectively.

We identified that PM₁₀ and PM₂.₅ were associated with decreased lung function in male COPD patients. Earlier studies showed that increases in PM₂.₅ concentrations were associated with decreased lung function and an increased prevalence of males with COPD (Doiran et al., 2019). Our results showed that exposure to increased concentrations of NOₓ and NO₂ were associated with increased lymphocytes in females. A previous study reported that acute exposure (3 h) to 1.5 ppm of NO₂ decreased lymphocytes in among healthy male and female participants (Frampton et al., 2002). However, majority of the COPD patients in our study were male could affect the significant association between air pollution and lung function decline. A gender difference in response to air pollution exposure in COPD need further investigation.

We studied how air pollution has distinct effects on COPD outcomes stratified by smoking behavior. We observed that exposure to increasing PM₁₀ and PM₂.₅ levels was associated with declines in the FEV₁ and FVC among ex-smokers with COPD. A prior study suggested that ex-smokers with COPD might still retain the probability of adverse effects of PM₁₀ on the FVC (Lamichhane et al., 2018). We observed that increases in NOₓ and NO₂ were associated with neutrophil decreases in ex-smokers. A previous study reported that exposure to diesel exhaust (including PM and NOₓ) led to a decrease in airway neutrophils among ex-smokers with COPD (Wooding et al., 2020). Furthermore, exposure to NO₂ was associated with lower FEV₁ and FVC values in ex-smokers with COPD (Nurhussien et al., 2022). Different pattern of associations was observed in never-smoker showed that exposure to PM₁₀ was associated with a decrease in eosinophils in never-smokers. Notably, our study did not observe significant effects on COPD outcomes in current smokers regarding air pollution exposure, except for the FEV₁/FVC ratio by PM₂.₅. Taken together, ex-smokers COPD patients are more vulnerable to air pollution exposure in terms of health outcomes. However, the association of air pollution and COPD health outcome in never-smoker warrants further investigation.

### 3.4 Associations of Air Pollution with Health Outcomes in Patients with Eosinophilic Inflammation

Fig. 4 presents associations of air pollution with health outcomes in patients with eosinophilic
Fig. 4. Associations of air pollutants with health outcomes in chronic obstructive pulmonary disease (COPD) with eosinophilic inflammation. Single-pollutant and two-pollutant models were used to examine associations of particulate matter with an aerodynamic diameter of <10 µm (PM$_{10}$) or PM$_{2.5}$ and nitrogen oxides (NO$_x$) or NO$_2$ with health outcomes. Data are provided as beta coefficient (β) change of health outcomes by a unit increase in PM$_{10}$, PM$_{2.5}$, NO$_x$, and NO$_2$ with a 95% confidence interval (CI). Models were adjusted for age, sex, body mass index, and smoking status. Statistically significant: *p < 0.05.
A 1 μg m⁻³ increase in PM₁₀ was associated with a 0.92% decrease in the FVC (95% CI: −1.68%, −0.16%, p < 0.05), a 0.36-point increase in the CAT score (95% CI: 0.10, 0.62, p < 0.05), and a 0.04 times year⁻¹ increase in AE events (95% CI: 0.02, 0.07, p < 0.05). A 1 μg m⁻³ increase in PM₂.₅ was associated with an increase of 0.26 points in the CAT score (95% CI: 0.06, 0.46, p < 0.05) and an increase of 0.03 times year⁻¹ in AE events (95% CI: 0.01, 0.05, p < 0.05). In the two-pollutant models, a 1 μg m⁻³ increase in PM₁₀ with NOₓ was associated with a 1.02% decrease in the FVC (95% CI: −1.78%, 0.25%, p < 0.05). A 1 μg m⁻³ increase in PM₁₀ with NO₂ was associated with increases of 0.37 points in the CAT score (95% CI: 0.10, 0.63, p < 0.05) and 0.05 times year⁻¹ in AE events (95% CI: 0.02, 0.07, p < 0.05). A 1 μg m⁻³ increase in PM₁₀ with NOₓ was associated with a decrease of 0.94% in the FVC (95% CI: −1.70%, −0.18%, p < 0.05) and increases in 0.36 points in the CAT score (95% CI: 0.09, 0.62, p < 0.05) and 0.05 times/year in AE events (95% CI: 0.02, 0.07, p < 0.05). A 1 μg m⁻³ increase in PM₂.₅ with NOₓ and in PM₂.₅ with NO₂ was associated with increases of 0.26 points in the CAT score (95% CI: 0.06, 0.46, p < 0.05) and of 0.03 times year⁻¹ in AE events (95% CI: 0.01, 0.05, p < 0.05), respectively.

Notably, we observed that COPD with eosinophilic inflammation was more susceptible to deleterious health outcomes due to air pollution exposure. Increases in PM₁₀ were associated with a decrease in the FVC among eosinophilic inflammation patients in our study. Exposure to PM₁₀ was associated with increased eosinophilic inflammation (Yıldız Gülahn et al., 2020). Reduced exposure to PM₁₀ was associated with slower declines in lung function and a relative improvement in lung function in the elderly (Downs et al., 2007; Hüls et al., 2019). We further observed that an increase in PM₂.₅ was associated with increases in CAT scores and AE events among eosinophilic inflammation patients. Previous work reported that exposure to PM₂.₅ was associated with higher AE events and a worsened health status characterized by higher CAT scores (Huh et al., 2021). It was also reported that interleukin (IL)-33 was shown to induce IL-13 expression in airway eosinophils, which can stimulate alveolar macrophages to produce matrix-metalloproteinase-1 that causes destruction of alveolar septa and consequently leads to emphysema (Zheng et al., 2000; Jacobsen et al., 2015; Doyle et al., 2019). In addition, decreased macrophage performance in clearing apoptotic eosinophils produced intracellular proinflammatory cytokines and was associated with increased severity and exacerbation (Eltboli et al., 2014). Notably, the information of COPD medication (i.e., inhaled corticosteroid, long-acting beta (2)-agonists, and long-acting muscarinic antagonists) should be considered in future works. Together, COPD patients with eosinophilic inflammation could be a population-at-risk for air pollution exposure.

4 CONCLUSIONS

In conclusion, exposure to particulate air pollution increased the risk of deleterious health outcomes in COPD with eosinophilic inflammation. Our findings suggest that exposure to PM₁₀ is significantly associated with a decrease in lung function in COPD patients with eosinophilic inflammation. Reducing exposure to air pollution may slow lung function declines and increase stability in COPD patients, particularly in those with eosinophilic inflammation. The study did not investigate indoor air pollution, which could have contributed to the observed health outcomes. Therefore, future studies should consider indoor air pollution exposure.

ADDITIONAL INFORMATION AND DECLARATIONS

Conflict of Interest
The authors declare that they have no conflicts of interest.

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Authors’ Contributions
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