

# Different Impacts of Traffic-Related Air Pollution on Early-Onset and Late-Onset Asthma

Ting-Yu Lin<sup>1,2</sup>, Firdian Makrufardi<sup>3,4</sup>, Nguyen Thanh Tung<sup>3,5</sup>, Amja Manullang<sup>3</sup>, Po-Jui Chang<sup>1,2</sup>, Chun-Yu Lo<sup>1,2</sup>, Tzu-Hsuan Chiu<sup>1</sup>, Pi-Hung Tung<sup>1</sup>, Chiung-Hung Lin<sup>1</sup>, Horng-Chyuan Lin<sup>1,2</sup>, Chun-Hua Wang<sup>1,2</sup>, Shu-Min Lin<sup>1,2</sup>

<sup>1</sup>Department of Thoracic Medicine, Chang Gung Memorial Hospital, Taipei, Taiwan; <sup>2</sup>College of Medicine, Chang Gung University, Taoyuan, Taiwan; <sup>3</sup>International Ph.D. Program in Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan; <sup>4</sup>Department of Child Health, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada – Dr. Sardjito Hospital, Yogyakarta, Indonesia; <sup>5</sup>Otorhinolaryngology Department, Cho Ray Hospital, Ho Chi Minh City, Vietnam

Correspondence: Shu-Min Lin, Department of Thoracic Medicine, Chang Gung Memorial Hospital, 199 Tun-Hwa N. Road, Taipei, Taiwan, Fax +886 33272474, Email [smlin100@gmail.com](mailto:smlin100@gmail.com)

**Background:** Early-onset asthma (EOA) and late-onset asthma (LOA) are two distinct phenotypes. Air pollution has been associated with an increase in poorer asthma outcomes. The objective of this study was to examine the effects of traffic-related air pollution (TRAP) on asthma outcomes in EOA and LOA patients.

**Methods:** A cross-sectional study was conducted on 675 asthma patients (LOA: 415) recruited from a major medical center in Taiwan. The land-use regression (LUR) model was used to estimate the level of exposure to PM<sub>10</sub>, PM<sub>2.5</sub>, NO<sub>2</sub>, and O<sub>3</sub> on an individual level. We investigated the association between TRAP and asthma outcomes in EOA and LOA patients, stratified by allergic sensitization status, using a regression approach.

**Results:** An increase in PM<sub>10</sub> was associated with younger age of onset, increased asthma duration, and decreased lung function in EOA patients ( $p < 0.05$ ). An increase in PM<sub>10</sub> was associated with older age of onset, and decreased asthma duration, eosinophil count, and Asthma Control Test (ACT) score in LOA patients. An increase in PM<sub>2.5</sub> was associated with younger age of onset, increased asthma duration, decreased eosinophil count, and lung function in EOA patients ( $p < 0.05$ ). An increase in PM<sub>2.5</sub> was associated with decreased lung function and ACT score in LOA patients. An increase in NO<sub>2</sub> was associated with increased eosinophil count and decreased lung function in EOA patients ( $p < 0.05$ ). An increase in O<sub>3</sub> was associated with decreased lung function in LOA patients ( $p < 0.05$ ). In addition, associations of TRAP with age of onset and eosinophil counts were mainly observed in both EOA and LOA patients with allergic sensitization, and an association with ACT was mainly observed in LOA patients without allergic sensitization.

**Conclusion:** The impact of TRAP on age of onset, eosinophil count, and lung function in EOA patients, and ACT in LOA patients, was affected by the status of allergic sensitization.

**Keywords:** air pollution, allergy, early-onset asthma, late-onset asthma, respiratory disease

## Background

The healthcare burden of asthma is increasing under the effects of urbanization and climate change.<sup>1–3</sup> Early-onset asthma (EOA) and late-onset asthma (LOA) are recognized as two distinct phenotypes in terms of risk factors, comorbidities, inflammatory pathways, and remission rates.<sup>4–7</sup> LOA differs pathologically from EOA and is associated with different disease outcomes in clinic-based and epidemiological studies.<sup>6,8</sup> For decades, researchers have been studying the relationship between the diversity of asthma endpoints and air pollutants.<sup>9</sup> A previous study demonstrated that the proportion of LOA was higher than that of EOA in areas adjacent to a mass of roads with heavy traffic.<sup>10</sup> Moreover, epidemiological and mechanistic studies have provided robust evidence of a causal relationship between traffic-related air pollution (TRAP) and the onset of EOA.<sup>11–14</sup> This demonstrates that TRAP exposure is an important risk factor for asthma.

Allergic sensitization has been linked to TRAP exposure. It has been proposed that TRAP exposure causes oxidative damage to the airways, resulting in inflammation, remodeling, and an increased risk of allergic sensitization.<sup>15</sup> Previous studies using animal and in vitro experimental models showed that TRAP could enhance allergic reactions.<sup>15–17</sup> In addition, exposure to nitrogen dioxide (NO<sub>2</sub>) is linked with an increased risk of allergic sensitization, current wheeze, and lower forced expiratory volume in the first second (FEV<sub>1</sub>) in asthma patients.<sup>18</sup> Exposure to particulate matter (PM) may lead to reduced lung function, allergic sensitization, lower airways inflammation, and upper airways irritation.<sup>19</sup> Taking these factors together, exposure to TRAP results in an increased risk of poorer outcomes in asthma patients with allergic sensitization.

Evidence has emerged in epidemiological and mechanistic studies of a causal relationship between TRAP and asthma endpoints. Also, TRAP has been reported to lead to deleterious health outcomes in patients with asthma with allergic sensitization. This objective of this study was to examine the effects of air pollution on asthma outcomes in EOA and LOA patients, stratified by allergic sensitization status.

## Methods

### Study Design and Subject Recruitment

We conducted a cross-sectional study from a medical center in Taoyuan city, Taiwan, between July 2018 and December 2020, where adult patients diagnosed with asthma by a pulmonologist (based on episodic respiratory symptoms and variable or persistent obstructive pulmonary function) were registered for the Pay-for-Performance Program for Asthma.<sup>10</sup> The Pay-for-Performance Program for Asthma was implemented by the National Health Insurance Administration of Taiwan to strengthen management and health education for asthma patients. This study extracted patients' data from the Pay-for-Performance Program for Asthma, including demographic and clinical characteristics. We recruited consecutive patients who had a primary diagnosis of asthma based on ICD-10 code J45 at least twice within 90 days. We excluded patients who had been confirmed with chronic obstructive pulmonary disease, bronchiectasis, malignancy, or any chronic inflammatory condition unrelated to asthma. The study was performed in accordance with the Declaration of Helsinki and all participants provided written informed consent. All procedures in this study followed the study protocol, which was approved by the Chang Gung Medical Foundation Institutional Review Board (No. 201900211B0).

### Patient Data Collection

At the time of recruitment, we compiled the characteristics of the subjects, including age at the time of asthma diagnosis by a physician, childhood history of dyspnea, frequency of bronchitis, gender, family history of asthma, smoking status, exacerbation history in the previous year, current residence (during the previous 6 months), pulmonary function, and inflammatory biomarkers, including eosinophil count, eosinophil cationic protein (ECP), and total immunoglobulin E (IgE) levels, and specific IgE (ImmunoCAP, Phadia, Sweden). Patients with positive specific IgE to allergens (>0.35 KU/L) of any type were considered allergy sensitive. Allergens were tested based on the physicians' discretion. In general, the common aeroallergens, including mites, cat or dog dander, cockroaches, fungus, and pollen, were tested. We determined gender based on a person's reproductive system and other physical characteristics at birth, as indicated on the patients' birth certificates. We quantified the duration of asthma based on the time from the initial diagnosis of asthma to the recruitment date. Asthma control was assessed using the Asthma Control Test (ACT). Patients who were ≥40 years old at the onset of asthma without a childhood history of dyspnea and frequent bouts of bronchitis were classified as having LOA; otherwise, patients were categorized as having EOA.<sup>20–22</sup>

### Assessment of Exposure to Ambient Air Pollution

Exposure to air pollutants (particles with an aerodynamic diameter ≤10 μm [PM<sub>10</sub>], particles with an aerodynamic diameter ≤2.5 μm [PM<sub>2.5</sub>], nitrogen dioxide [NO<sub>2</sub>], and ozone [O<sub>3</sub>]) was estimated at an individual level using a hybrid kriging–land-use regression (LUR) model at the baseline residential address.<sup>23,24</sup> We obtained 1-, 6-, and 1-year mean air pollutant data from air quality monitoring stations operated by the Taiwan Environmental Protection Administration

(<https://airtw.epa.gov.tw/>). Taiwan Geospatial One Stop was used to collect the subjects' residential addresses and convert them into geocoded data ([www.tgos.tw](http://www.tgos.tw)). Geographic Information System (ESRI ArcGIS version 10.8) analysis was conducted to calculate the concentration of air pollutants for each land-use variable for each individual exposure. The individual exposure concentration was calculated following the LUR models using R software (R version 3.6.3).

## Statistical Analysis

Continuous variables were analyzed using a *t*-test, and categorical variables were analyzed using the chi-squared or Fisher's exact test. Utilizing a winsorization approach, we managed extreme outliers by replacing values exceeding the 1st and 99th percentiles.<sup>25</sup> Linear regression analysis was used to examine correlations between PM<sub>10</sub>, PM<sub>2.5</sub>, NO<sub>2</sub>, and O<sub>3</sub> exposure levels (1-, 6-, and 12-month average levels), the age of onset, the expression of T2 inflammatory biomarkers (total IgE, absolute counts [cells/μL], as well as ECP levels), pulmonary function, and ACT in the EOA and LOA groups as a function of atopy status. We ensured that the assumptions of the linear regression model were fulfilled before conducting the analysis. Adjusted covariates in the models included age, family history of asthma, and smoking history. The effect of pollution on asthma features was expressed as an estimated regression coefficient ( $\beta$ ) for each type of air pollution. Data were analyzed using R version 3.6.3 software. Statistical significance was determined based on a *p*-value <0.05.

## Results

Table 1 summarizes the characteristics of the 675 consecutive asthma patients recruited to the study between July 2019 and April 2021; 415 were LOA patients and 260 were EOA patients. The majority of the patients were female (52.3%) and the average age was 56.5 years. The average BMI was 24.64 kg/m<sup>2</sup>, 22.8% of participants were ex-smokers, and 12.9% were current smokers. The average age at asthma onset was 44.8 years, and 29% had a parental asthma history.

**Table 1** Characteristics of Patients with Early- or Late-Onset Asthma

Characteristics	Number of Patients (N=675)	EOA (N=260)	LOA (N=415)	p-Value
Age (years)	56.5±17.9	42.7±17.1	65.1±12.0	<0.05
Males	322 (47.7)	119 (45.8)	203 (48.9)	0.425
BMI (kg/m <sup>2</sup> )	24.64±6.09	24.09±7.10	24.99±5.33	0.061
<b>Smoking status</b>				
Current smoker	87 (12.9)	39 (15.0)	48 (11.6)	<0.05
Ex-smoker	154 (22.8)	40 (15.4)	114 (27.4)	
Non-smoking	434 (64.3)	181 (69.6)	253 (61)	
<b>Age of onset (years)</b>	44.8±22.9	20.3±12.1	60.2±12.2	<0.05
<b>Asthma duration (years)</b>	11.7±16.7	22.5±21.3	4.9±7.2	<0.05
<b>Parental asthma history</b>				
Yes	196 (29.0)	95 (36.5)	101 (24.3)	<0.05
No	479 (71.0)	165 (63.5)	314 (75.7)	
<b>Inflammatory biomarkers</b>				
IgE level (KU/L)	254.56±443.77	299.86±416.49	226.17±458.25	<0.05
Eosinophils (%)	1.89±2.66	2.01±2.89	1.81±2.51	0.693
Eosinophil count (cells/μL)	164.78±216.70	180.19±237.93	155.12±201.97	0.143
ECP (μg/L)	11.37±16.90	15.86±20.57	8.56±13.39	<0.05
<b>Allergic sensitization status</b>				
Yes	316 (46.8)	157 (60.4)	159 (38.3)	<0.05
No	359 (53.2)	103 (39.6)	256 (61.7)	

(Continued)

Table 1 (Continued).

Characteristics	Number of Patients (N=675)	EOA (N=260)	LOA (N=415)	p-Value
<b>History of exacerbation in previous year</b>				
Yes	85 (12.6)	38 (14.6)	47 (11.3)	0.506
No	590 (87.4)	222 (85.4)	368 (88.7)	
<b>ACT</b>	21.06±4.04	20.52±4.18	21.38±3.93	<0.05
<b>Lung function</b>				
FVC (L)	2.40±1.16	2.78±1.39	2.16±0.91	<0.05
FVC (%)	75.62±26.45	77.09±30.10	74.70±23.87	0.253
FEV <sub>1</sub> (L/s)	1.85±1.01	2.21±1.25	1.62±0.74	<0.05
FEV <sub>1</sub> (%)	70.67±27.20	72.12±29.97	69.76±25.31	0.273
FEV <sub>1</sub> /FVC (%)	70.40±23.25	70.45±26.56	70.37±20.95	0.965
Post-BD FEV <sub>1</sub> (% change)	5.95±11.84	5.65±12.64	6.13±11.32	0.608
<b>Mean exposure to PM<sub>10</sub> (μg/m<sup>3</sup>)</b>				
1-month	27.56±7.90	27.60±7.47	27.54±8.16	0.923
6-month	28.80±7.00	29.38±7.04	28.44±6.96	0.089
12-month	30.36±6.69	30.63±6.48	30.19±6.82	0.406
<b>Mean exposure to PM<sub>2.5</sub> (μg/m<sup>3</sup>)</b>				
1-month	15.14±4.11	15.16±4.06	15.13±4.15	0.926
6-month	16.05±3.35	16.27±3.35	15.90±3.34	0.162
12-month	16.85±2.84	16.88±2.74	16.83±2.90	0.823
<b>Mean exposure to NO<sub>2</sub> (ppb)</b>				
1-month	15.20±4.63	15.61±4.77	14.95±4.54	0.071
6-month	15.84± 4.34	16.37±4.26	15.51±4.36	<0.05
12-month	16.24± 4.01	16.57±3.88	16.04±4.09	0.095
<b>Mean exposure to O<sub>3</sub> (ppb)</b>				
1-month	29.57±7.44	28.93±7.32	29.98±7.50	0.073
6-month	28.91±3.58	28.96±3.26	28.89±3.77	0.804
12-month	29.31±3.14	29.15±2.85	29.42±3.31	0.651

**Note:** Data are presented as mean ± SD or number (percentage).

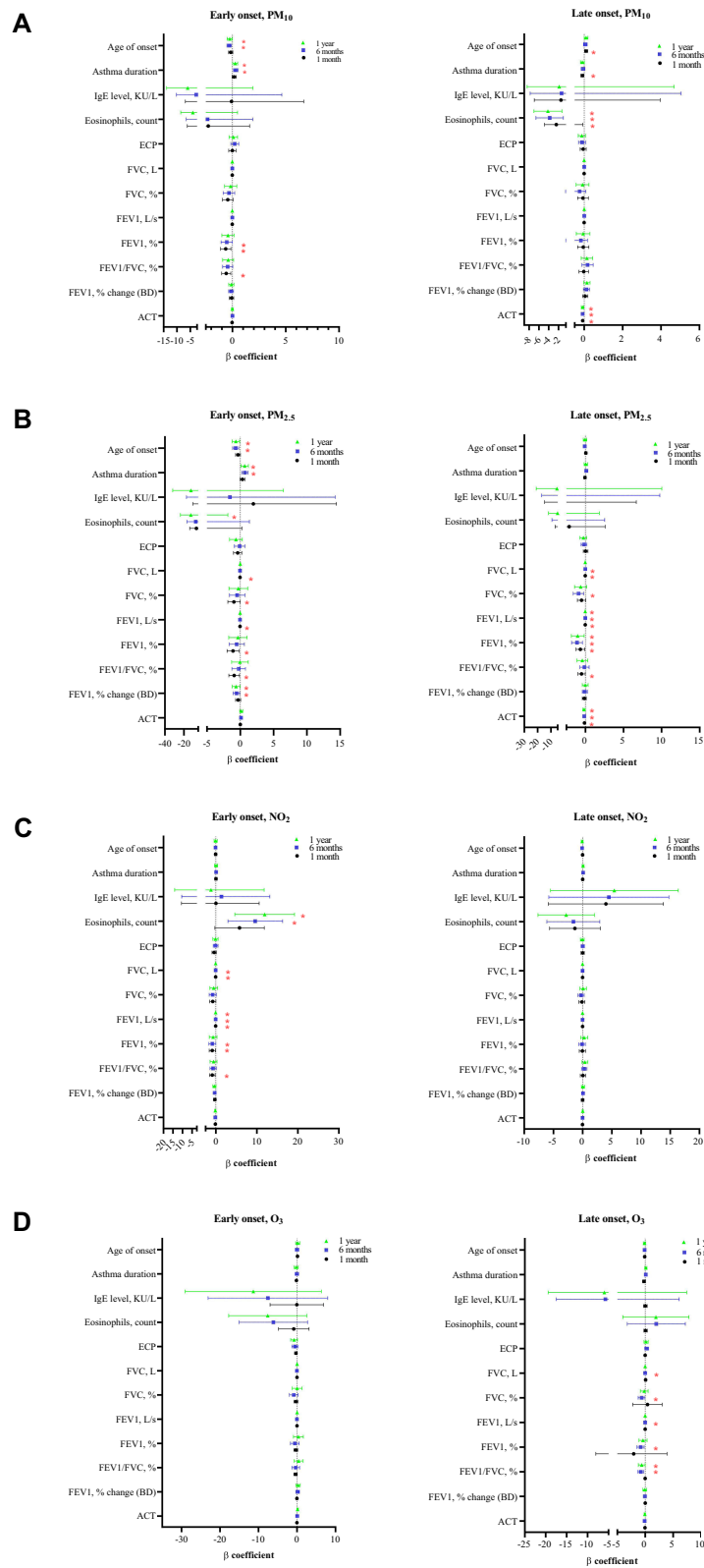
**Abbreviations:** EOA, early-onset asthma; LOA, late-onset asthma; BMI, body mass index; IgE, immunoglobulin E; ECP, eosinophil cationic protein; ACT, Asthma Control Test; FVC, forced vital capacity; FEV<sub>1</sub>, forced expiratory volume in 1 s; BD, bronchodilator; PM<sub>10</sub>, particles with an aerodynamic diameter of 10 μm or less; PM<sub>2.5</sub>, particles with an aerodynamic diameter of 2.5 μm or less; NO<sub>2</sub>, nitrogen dioxide; O<sub>3</sub>, ozone.

The mean FEV<sub>1</sub>, FVC, and FEV<sub>1</sub>/FVC were 70.67%, 75.62%, and 70.40%, respectively. Mean IgE level, absolute eosinophil count, and ECP level were 254.56 KU/L, 1.89%, and 11.37 μg/L, respectively.

## Associations Between TRAP and Asthma Features in EOA and LOA Patients

### PM<sub>10</sub> Exposure is Associated with Asthma Features in EOA and LOA Patients

Figure 1A and Table S1 illustrate the association between PM<sub>10</sub> and asthma features in EOA and LOA patients. We observed that a 1 μg/m<sup>3</sup> increase in PM<sub>10</sub> was associated with decreased age of onset, by 0.316 and 0.258 years, in 6-month and 1-year PM<sub>10</sub> in EOA patients, respectively (95% CI: −0.532, −0.100, *p*<0.05, and 95% CI: −0.490, −0.025, *p*<0.05). An increase of 1 μg/m<sup>3</sup> in 6-month and 1-year PM<sub>10</sub> was associated with increased asthma duration of 0.316 and 0.258 years in EOA patients (95% CI: 0.100, 0.532, *p*<0.05, and 95% CI: 0.020, 0.490, *p*<0.05). An increase of 1 μg/m<sup>3</sup> in 1-month and 6-month PM<sub>10</sub> was associated with 0.672% and 0.534% decreases in FEV<sub>1</sub> (in EOA patients, respectively (95% CI: −1.109, −0.145, *p*<0.05, and 95% CI: −1.065, 0.003, *p*<0.05). An increase of 1 μg/m<sup>3</sup> in PM<sub>10</sub> was associated with a 0.581% decrease in FEV<sub>1</sub>/FVC (%) in 1-month PM<sub>10</sub> (95% CI: −1.014, −0.149, *p*<0.05).



**Figure 1** Associations of (A) PM<sub>10</sub>, (B) PM<sub>2.5</sub>, (C) NO<sub>2</sub>, and (D) O<sub>3</sub> with asthma features in patients with EOA and LOA. \* $p < 0.05$ . **Abbreviations:** PM, particulate matter; NO<sub>2</sub>, nitrogen dioxide; O<sub>3</sub>, ozone; EOA, early-onset asthma; LOA, late-onset asthma.

We observed that an increase of  $1 \mu\text{g}/\text{m}^3$  in 1-month  $\text{PM}_{10}$  was associated with increased age of onset, by 0.098 years, in LOA patients (95% CI: 0.017, 0.180,  $p < 0.05$ ). An increase of  $1 \mu\text{g}/\text{m}^3$  in 1-month  $\text{PM}_{10}$  was associated with a 0.098 year decrease in asthma duration in LOA patients (95% CI:  $-0.180$ ,  $-0.017$ ,  $p < 0.05$ ). An increase of  $1 \mu\text{g}/\text{m}^3$  in 1-month, 6-month, and 1-year  $\text{PM}_{10}$  was associated with decreases of 2.466, 3.801, and 4.160 in the eosinophil count of LOA patients, respectively. An increase of  $1 \mu\text{g}/\text{m}^3$  in 1-month, 6-month, and 1-year  $\text{PM}_{10}$  was associated with 0.082, 0.086, and 0.089 decreases in ACT in LOA patients, respectively.

### **$\text{PM}_{2.5}$ Exposure is Associated with Asthma Features in EOA and LOA Patients**

Figure 1B and Table S2 illustrate the association between  $\text{PM}_{2.5}$  and asthma features in EOA and LOA patients. We observed that a  $1 \mu\text{g}/\text{m}^3$  increase in 6-month and 1-year  $\text{PM}_{2.5}$  was associated with decreased age of onset, by 0.684 and 0.665 years, in EOA patients, respectively (95% CI:  $-1.144$ ,  $-0.224$ ,  $p < 0.05$ , and 95% CI:  $-1.227$ ,  $-0.103$ ,  $p < 0.05$ ). An increase of  $1 \mu\text{g}/\text{m}^3$  in 1-month and 6-month  $\text{PM}_{2.5}$  was associated with increased asthma duration, by 0.684 and 0.665 years, in EOA patients, respectively (95% CI: 0.224, 1.144,  $p < 0.05$ , and 95% CI: 0.103, 1.227,  $p < 0.05$ ). An increase of  $1 \mu\text{g}/\text{m}^3$  in 1-year  $\text{PM}_{2.5}$  was associated with a 12.770 decrease in absolute eosinophil count in EOA patients (95% CI:  $-0.71$ ,  $-0.05$ ,  $p < 0.05$ ). An increase of  $1 \mu\text{g}/\text{m}^3$  in 1-month  $\text{PM}_{2.5}$  was associated with 0.042L, 0.955%, 0.038L, 1.091%, and 0.919% decreases in FVC (L), FVC (%),  $\text{FEV}_1$  (L),  $\text{FEV}_1$  (%), and  $\text{FEV}_1/\text{FVC}$  (%) in EOA patients, respectively.

We observed that an increase of  $1 \mu\text{g}/\text{m}^3$  in 1-month and 6-month  $\text{PM}_{2.5}$  was associated with 0.026 and 0.025 L decreases in FVC in LOA patients (95% CI:  $-0.044$ ,  $-0.008$ ,  $p < 0.05$ , and 95% CI:  $-0.048$ ,  $-0.002$ ,  $p < 0.05$ ). An increase of  $1 \mu\text{g}/\text{m}^3$  in 6-month  $\text{PM}_{2.5}$  was associated with a 0.909% decrease in FVC in LOA patients (95% CI:  $-1.592$ ,  $-0.225$ ,  $p < 0.05$ ). An increase of  $1 \mu\text{g}/\text{m}^3$  in 1-month, 6-month, and 1-year  $\text{PM}_{2.5}$  was associated with 0.022, 0.023, and 0.023 L decreases in  $\text{FEV}_1$  in LOA patients, respectively. An increase of  $1 \mu\text{g}/\text{m}^3$  in 1-month, 6-month, and 1-year  $\text{PM}_{2.5}$  was associated with 0.663%, 1.098%, and 1.020% decreases in  $\text{FEV}_1$  in LOA patients, respectively. An increase of  $1 \mu\text{g}/\text{m}^3$  in 1-month  $\text{PM}_{2.5}$  was associated with a 0.505% decrease in  $\text{FEV}_1/\text{FVC}$  (%) in LOA patients (95% CI:  $-0.71$ ,  $-0.05$ ,  $p < 0.05$ ). An increase of  $1 \mu\text{g}/\text{m}^3$  in 1-month, 6-month, and 1-year  $\text{PM}_{10}$  was associated with 0.130, 0.155, and 0.183 decreases in ACT in LOA patients, respectively.

### **$\text{NO}_2$ Exposure is Associated with Asthma Features in EOA and LOA Patients**

Figure 1C and Table S3 illustrate the association between  $\text{NO}_2$  and asthma features in EOA and LOA patients. An increase of 1 ppb in 1-year  $\text{NO}_2$  was associated with an increase of 11.917 in the eosinophil count of EOA patients (95% CI: 4.622, 19.213,  $p < 0.05$ ). An increase of 1 ppb in 1-month and 6-month  $\text{NO}_2$  was associated with decreases of 0.041 and 0.037 L in FVC of EOA patients (95% CI:  $-0.073$ ,  $-0.009$ ,  $p < 0.05$ , and 95% CI:  $-0.074$ ,  $-0.001$ ,  $p < 0.05$ ). An increase of 1 ppb in 1-month, 6-month, and 1-year  $\text{NO}_2$  was associated with a 0.043, 0.040, 0.039 L decrease in  $\text{FEV}_1$  in EOA patients, respectively. An increase of 1 ppb in 1-month and 6-month  $\text{NO}_2$  was associated with a 0.862 and 0.845 L decrease in  $\text{FEV}_1$  in EOA patients, respectively. An increase of 1 ppb in 1-month  $\text{NO}_2$  was associated with a 0.863% decrease in  $\text{FEV}_1/\text{FVC}$  (%) in EOA patients (95% CI:  $-1.539$ ,  $-0.118$ ,  $p < 0.05$ ). We did not observe an association between  $\text{NO}_2$  and asthma features in LOA.

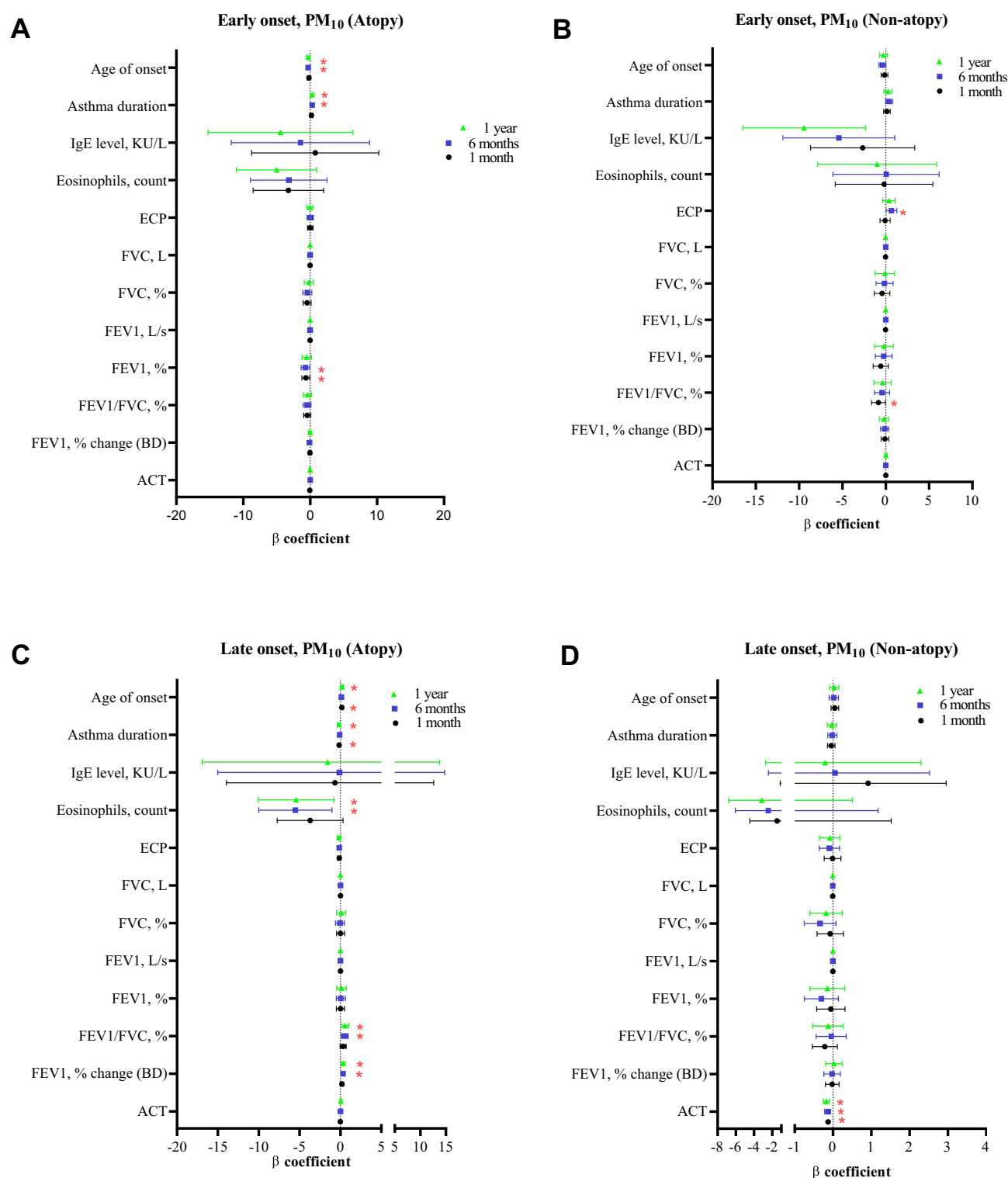
### **$\text{O}_3$ Exposure is Associated with Asthma Features in EOA and LOA Patients**

Figure 1D and Table S4 illustrate the association between  $\text{O}_3$  and asthma features in EOA and LOA patients. An increase of 1 ppb in 1-month  $\text{O}_3$  was associated with a 0.022 L decrease in FVC in LOA patients (95% CI:  $-0.042$ ,  $-0.002$ ,  $p < 0.05$ ). An increase of 1 ppb in 6-month  $\text{O}_3$  was associated with a 0.648% decrease in FVC in LOA patients (95% CI:  $-1.251$ ,  $-0.045$ ,  $p < 0.05$ ). An increase of 1 ppb in 6-month  $\text{O}_3$  was associated with a 0.023 L decrease in  $\text{FEV}_1$  in LOA patients (95% CI:  $-0.039$ ,  $-0.007$ ,  $p < 0.05$ ). An increase of 1 ppb in 6-month  $\text{O}_3$  was associated with a 0.830% decrease in  $\text{FEV}_1$  in LOA patients (95% CI:  $-1.465$ ,  $-0.195$ ,  $p < 0.05$ ). An increase of 1 ppb in 6-month and 1-year  $\text{O}_3$  was associated with 0.762% and 0.623% decreases in  $\text{FEV}_1/\text{FVC}$  (%) in LOA patients (95% CI:  $-1.292$ ,  $-0.232$ ,  $p < 0.05$ , and 95% CI:  $-1.229$ ,  $-0.017$ ,  $p < 0.05$ ). We did not observe an association between  $\text{O}_3$  and asthma features in EOA.

## **Associations Between $\text{PM}_{10}$ and Asthma Features in EOA and LOA Patients Stratified by Allergic Sensitization Status**

Figure 2 and Table S5 illustrate the association between  $\text{PM}_{10}$  and asthma features in EOA and LOA patients stratified by allergic sensitization status. In patients with EOA and allergic sensitization, we observed that a  $1 \mu\text{g}/\text{m}^3$  increase in





**Figure 2** Associations of PM<sub>10</sub> with asthma features in patients with (A) EOA and atopy, (B) EOA and non-atopy, (C) LOA and atopy, and (D) LOA and non-atopy. \* $p < 0.05$ . Abbreviations: PM, particulate matter; EOA, early-onset asthma; LOA, late-onset asthma.

6-month and 1-year PM<sub>10</sub> was associated with a decreased age of onset, by 0.295 and 0.272 years, respectively (95% CI: -0.552, 0.037,  $p < 0.05$ , and 95% CI: -0.543, 0.000,  $p < 0.05$ ). An increase of 1  $\mu\text{g}/\text{m}^3$  in 6-month and 1-year PM<sub>10</sub> was associated with increased asthma duration of 0.295 and 0.272 years, respectively (95% CI: 0.037, 0.552,  $p < 0.05$ , and 95% CI: 0.000, 0.543,  $p < 0.05$ ). An increase of 1  $\mu\text{g}/\text{m}^3$  in 1-month and 6-month PM<sub>10</sub> was associated with decreases of

0.641% and 0.693% in FEV<sub>1</sub>, respectively (95% CI: -1.235, -0.046,  $p < 0.05$ , and 95% CI: -1.339, -0.046,  $p < 0.05$ ). In patients with LOA and allergic sensitization, we observed that a 1  $\mu\text{g}/\text{m}^3$  increase in 1-month and 1-year PM<sub>10</sub> was associated with an increased age of onset, by 0.163 and 0.182 years, respectively (95% CI: 0.022, 0.303,  $p < 0.05$ , and 95% CI: 0.019, 0.344,  $p < 0.05$ ). An increase of 1  $\mu\text{g}/\text{m}^3$  in 1-month and 1-year PM<sub>10</sub> was associated with decreased asthma duration of 0.163 and 0.182, respectively (95% CI: -0.303, -0.022,  $p < 0.05$ , and 95% CI: -0.344, -0.019,  $p < 0.05$ ). An increase of 1  $\mu\text{g}/\text{m}^3$  in 6-month and 1-year PM<sub>10</sub> was associated with 5.521 and 5.431 decreases in the eosinophil count, respectively (95% CI: -10.001, -1.040,  $p < 0.05$ , and 95% CI: -10.064, -0.798,  $p < 0.05$ ). An increase of 1  $\mu\text{g}/\text{m}^3$  in 6-month and 1-year PM<sub>10</sub> was associated with increases of 0.531% and 0.588% in FEV<sub>1</sub>/FVC (%) and increases of 0.325% and 0.323% in FEV<sub>1</sub> change.

## Associations Between PM<sub>2.5</sub> and Asthma Features in EOA and LOA Patients Stratified by Allergic Sensitization Status

Figure 3 and Table S6 illustrate the association between PM<sub>2.5</sub> and asthma features in EOA and LOA patients stratified by allergic sensitization status. In patients with EOA and allergic sensitization, we observed that a 1  $\mu\text{g}/\text{m}^3$  increase in 1-month, 6-month, and 1-year PM<sub>2.5</sub> was associated with a decreased age of onset, by 0.519, 0.910, and 1.030 years, respectively. An increase of 1  $\mu\text{g}/\text{m}^3$  in 1-month, 6-month, and 1-year PM<sub>2.5</sub> was associated with increased asthma duration of 0.519, 0.910, and 1.031, respectively. An increase of 1  $\mu\text{g}/\text{m}^3$  in 1-month PM<sub>2.5</sub> was associated with a 10.164 decrease in the eosinophil count (95% CI: -20.286, -0.040,  $p < 0.05$ ). An increase of 1  $\mu\text{g}/\text{m}^3$  in 1-month PM<sub>2.5</sub> was associated with decreases of 1.250% and 1.336% in FVC and FEV<sub>1</sub>, respectively (95% CI: -2.418, -0.082,  $p < 0.05$  and -2.487, -0.186,  $p < 0.05$ ). In addition, in patients with LOA and allergic sensitization, we observed that a 1  $\mu\text{g}/\text{m}^3$  increase in 1-month PM<sub>2.5</sub> was associated with 1.250% and 1.336% decreases in FEV<sub>1</sub> and FEV<sub>1</sub>/FVC (%), respectively.

## Associations Between NO<sub>2</sub> and Asthma Features in EOA and LOA Patients Stratified by Allergic Sensitization Status

Figure 4 and Table S7 illustrate the association between NO<sub>2</sub> and asthma features in EOA and LOA patients stratified by allergic sensitization status. In patients with EOA and allergic sensitization, we observed that an increase of 1 ppb in 6-month and 1-year NO<sub>2</sub> was associated with increases of 11.458 and 15.224 in the eosinophil count, respectively (95% CI: 2.266, 20.650,  $p < 0.05$ , and 95% CI: 4.973, 25.474,  $p < 0.05$ ). An increase of 1 ppb in 1-month, 6-month, and 1-year NO<sub>2</sub> was associated with decreases in FVC, FEV<sub>1</sub> (L), and FEV<sub>1</sub> (%). In addition, an increase of 1 ppb in 1-month NO<sub>2</sub> was associated with a 1.032% decrease in FEV<sub>1</sub>/FVC (%) (95% CI: -1.877, -0.186,  $p < 0.05$ ). Moreover, in LOA patients with allergic sensitization, an increase of 1 ppb in 6-month and 1-year NO<sub>2</sub> was associated with increases of 0.389% and 0.411% in FEV<sub>1</sub> change, respectively (95% CI: 0.040, 0.738,  $p < 0.05$ , and 95% CI: 0.027, 0.795,  $p < 0.05$ ).

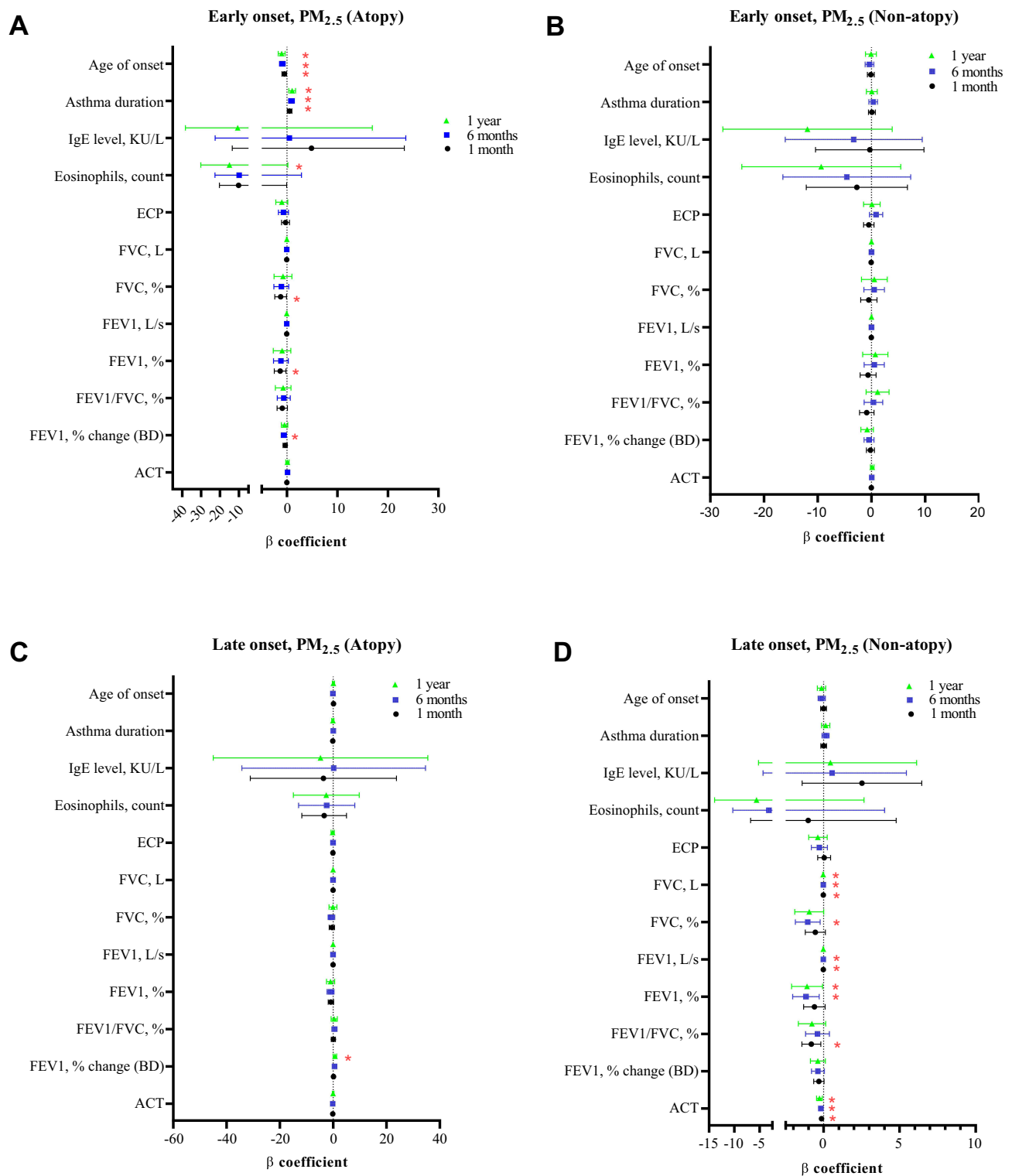
## Associations Between O<sub>3</sub> and Asthma Features in EOA and LOA Patients Stratified by Allergic Sensitization Status

Figure 5 and Table S8 illustrate the association between O<sub>3</sub> and asthma features in EOA and LOA patients stratified by allergic sensitization status. In patients with EOA and allergic sensitization, we observed that a 1 ppb increase in 6-month O<sub>3</sub> was associated with decreases of 1.500% and 1.543% in FVC and FEV<sub>1</sub>/FVC, (%) respectively (95% CI: -2.967, -0.034,  $p < 0.05$ , and 95% CI: -2.821, -0.265,  $p < 0.05$ ).

## Discussion

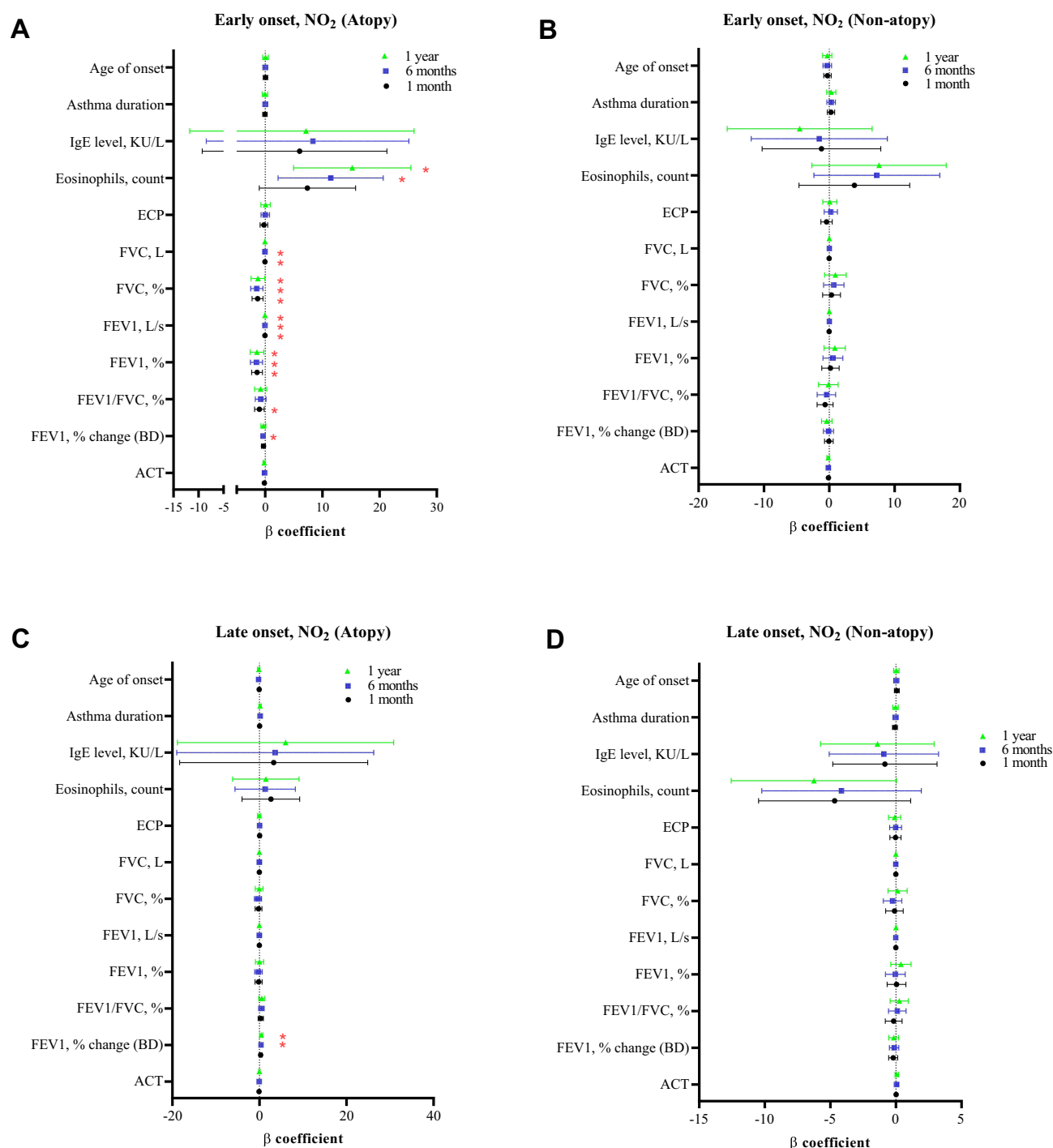
The novelty of this study is that we investigated the association between TRAP and asthma endpoints with stratification by allergic sensitization status. We observed that exposure to particulate air pollution was associated with deleterious asthma outcomes, especially in EOA with allergic sensitization. Importantly, we observed that increases in particulate air pollution were associated with onset at an earlier age, longer asthma duration, lower eosinophil count, and reduced lung function in EOA with allergic sensitization. Our results suggest that EOA patients with allergic sensitization could be susceptible to problems caused by particulate air pollution exposure.





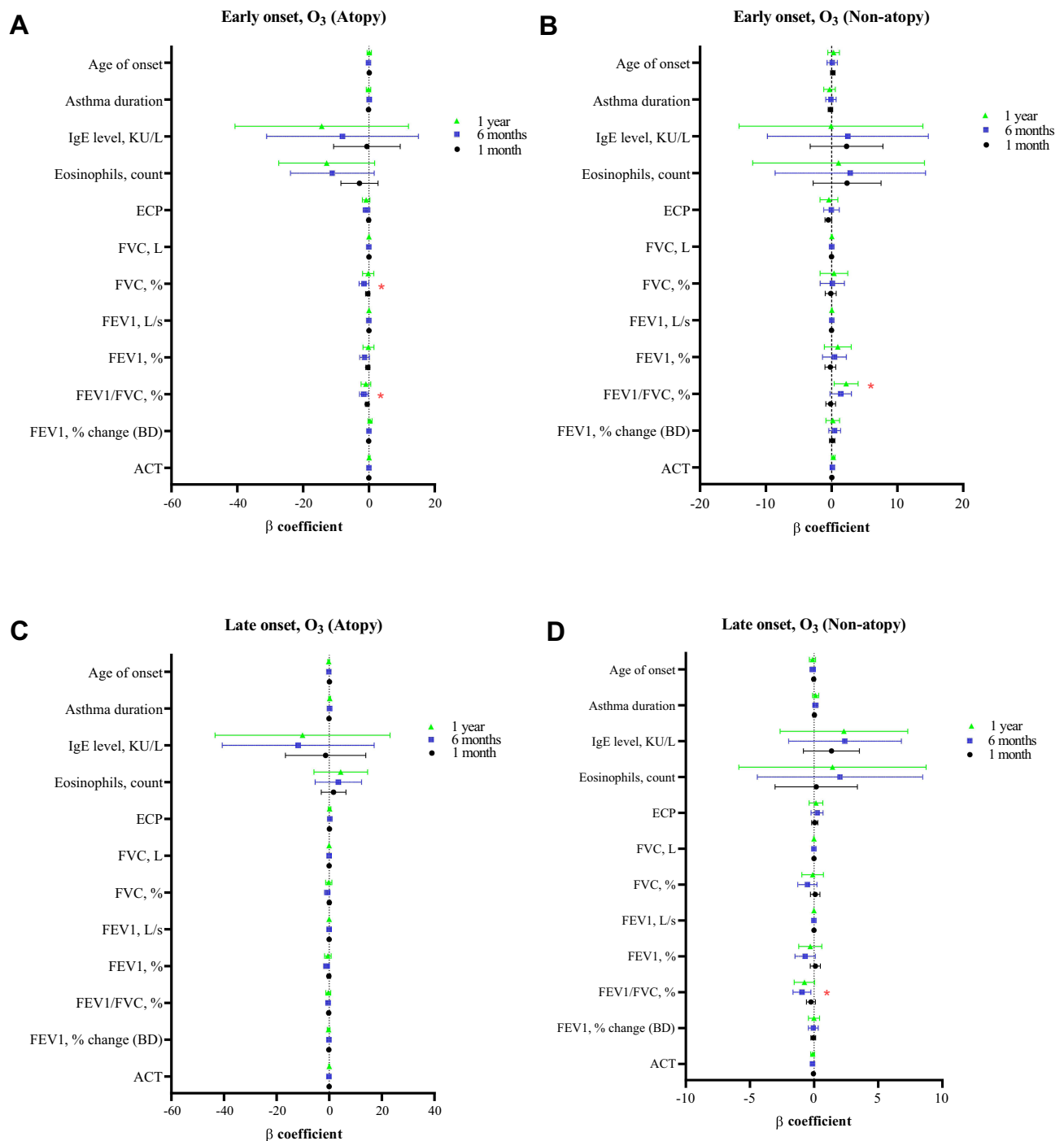
**Figure 3** Associations of PM<sub>2.5</sub> with asthma features in patients with (A) EOA and atopy, (B) EOA and non-atopy, (C) LOA and atopy, and (D) LOA and non-atopy. \* $p < 0.05$ . **Abbreviations:** PM, particulate matter; EOA, early-onset asthma; LOA, late-onset asthma.

We observed that increased exposure to PM<sub>10</sub> and PM<sub>2.5</sub> was associated with decreased age of onset in EOA patients. Previous reports showed an increased risk of onset of childhood asthma associated with early-life exposure to PM.<sup>26–29</sup> We demonstrated that an increase in PM<sub>10</sub> and PM<sub>2.5</sub> exposure increased the duration of asthma in EOA patients. A previous study reported that PM exposure during 1 week and 2 weeks resulted in a significant increase in the risk of



**Figure 4** Associations of NO<sub>2</sub> with asthma features in patients with (A) EOA and atopy, (B) EOA and non-atopy, (C) LOA and atopy, and (D) LOA and non-atopy. \* $p < 0.05$ . **Abbreviations:** NO<sub>2</sub>, nitrogen dioxide; EOA, early-onset asthma; LOA, late-onset asthma.

asthma attacks.<sup>30</sup> Next, we observed that exposure to PM<sub>10</sub> and PM<sub>2.5</sub> was a risk factor for reduced lung function in EOA patients. A previous study reported that each 5  $\mu\text{g}/\text{m}^3/\text{year}$  improvement in PM increased the FEV<sub>1</sub>, FVC, and FEV<sub>1</sub>/FVC.<sup>31</sup> We also observed that increasing NO<sub>2</sub> was associated with an increase in the eosinophil count in EOA patients. Previous research found that the percentage of eosinophils increased by 57% after exposure to 600 ppb of NO<sub>2</sub> ( $p=0.003$ ), while the ECP increased significantly after exposure to 600 ppb of NO<sub>2</sub> ( $p=0.001$ ).<sup>32</sup> NO<sub>2</sub> exposure increased eosinophilic inflammation in the distal lower airways, in response to inhaled allergen, as assessed by bronchial wash and



**Figure 5** Associations of O<sub>3</sub> with asthma features in patients with (A) EOA and atopy, (B) EOA and non-atopy, (C) LOA and atopy, and (D) LOA and non-atopy. \* $p < 0.05$ . **Abbreviations:** O<sub>3</sub>, ozone; EOA, early-onset asthma; LOA, late-onset asthma.

bronchoalveolar lavage.<sup>33</sup> We observed that NO<sub>2</sub> and O<sub>3</sub> were risk factors for decreased lung function in EOA patients. A case-crossover study in China also reported that exposure to higher than 80  $\mu\text{g}/\text{m}^3$  O<sub>3</sub> increased the risk of reduced lung function.<sup>34</sup> Thus, patients with EOA could be the population at risk upon exposure to air pollution.

We found that PM had distinct effects on endpoints in patients with asthma and allergic sensitization. A previous study showed that exposure to PM<sub>2.5</sub> decreased the FVC, FEV<sub>1</sub>, and FEV<sub>1</sub>/FVC.<sup>35</sup> Mechanistic studies have shown that PM can exacerbate allergies by inducing inflammation in the airway epithelium.<sup>36</sup> In animal studies, coexposure to diesel

and house dust mites was shown to contribute to the persistence of T-helper (Th)<sub>2</sub>/Th<sub>17</sub> effector cells or innate lymphoid cells in the lungs. It was also shown to enhance hyperresponsivity in the airways.<sup>13,37,38</sup> The size of PM determines the degree to which it penetrates the human respiratory system.<sup>39</sup> We observed that exposure to PM<sub>10</sub> is a risk for poorer asthma outcomes in EOA with allergic sensitization. Coarse PM<sub>10</sub> is deposited primarily in the nasopharynx or primary bronchi, whereas fine PM<sub>2.5</sub> is deposited in the alveoli and terminal bronchioles.<sup>40</sup> The fact that asthma patients have a more profound effect from PM exposure underlines the importance of particle size in shaping asthma features in susceptible subjects.

Notably, we observed that exposure to NO<sub>2</sub> was associated with an increase in blood eosinophil count in EOA patients with allergic sensitization. Previous studies on allergens in mice and asthmatic patients reported that exposure to NO<sub>2</sub> can induce eosinophilic inflammation in the airways.<sup>32,41</sup> We observed that exposure to NO<sub>2</sub> was associated with a decrease in lung function in EOA patients with allergic sensitization. A previous study showed that NO<sub>2</sub> exposure was associated with decreases of 1.35% in predicted FEV<sub>1</sub> (95% CI: -2.21, -0.49) and 1.19% in FVC (95% CI: -2.04, -0.35).<sup>42</sup> The main mechanisms by which NO<sub>2</sub> could adversely affect both lung function and asthma have been proposed as oxidative stress and inflammation.<sup>43</sup> Therefore, our findings indicate that NO<sub>2</sub> increases the blood eosinophil counts and decreases lung function in asthmatic patients.

We found that O<sub>3</sub> had distinct effects on asthma outcomes according to allergic sensitization. We observed that increasing O<sub>3</sub> exposure was associated with decreased FVC and FEV<sub>1</sub>/FVC in the EOA patients with allergic sensitization. A systematic review reported that long-term O<sub>3</sub> exposure decreased both lung function and lung function growth.<sup>44</sup> Another study demonstrated that O<sub>3</sub> exposure was associated with a decrease in FEV<sub>1</sub> of 35 mL (95% CI: -69, -6 mL).<sup>45</sup> Taking these findings together, EOA patients with allergic sensitization could be the population at risk upon exposure to O<sub>3</sub>.

There are some limitations to this study. First, we were unable to obtain information related to prenatal exposure, occupational exposure, socio-economic status, or indoor pollution, which could be confounding factors in this cross-sectional study. Second, the cross-sectional design of this study is susceptible to recall bias regarding the age of onset. In future studies, it will be important to estimate the effects of traffic-related air pollution in larger samples and to incorporate indoor environmental factors. Furthermore, the study is limited by its cross-sectional design; therefore, the results of this study do not imply causation.

## Conclusions

In conclusion, exposure to particulate air pollution was associated with deleterious asthma outcomes, especially in EOA and allergic sensitization. An increase in particulate air pollution was associated with onset at an earlier age, longer asthma duration, lower eosinophil count, and a decline in lung function in EOA and allergic sensitization. Exposure to NO<sub>2</sub> was associated with increased blood eosinophils and a decline in lung function in EOA and allergic sensitization. Reducing air pollution exposure may slow the decline in lung function and improve the quality of life for asthma patients, particularly those with allergic sensitization. Increases in PM and O<sub>3</sub> were associated with poor asthma control and/or reduced lung function in LOA patients without allergic sensitization.

## Abbreviations

ACT, Asthma Control Test; BD, bronchodilator; ECP, eosinophil cationic protein; EOA, early-onset asthma; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; IgE, immunoglobulin E; LOA, late-onset asthma; NO<sub>2</sub>, nitrogen dioxide; O<sub>3</sub>, ozone; PM, particulate matter; PM<sub>2.5</sub>, particles with an aerodynamic diameter of 2.5 µm or less; PM<sub>10</sub>, particles with an aerodynamic diameter of 10 µm or less; TRAP, traffic-related air pollution.

## Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Ethics Approval and Consent to Participate

The study was performed in accordance with the Declaration of Helsinki and all participants provided written informed consent. The study protocol was approved by the Chang Gung Medical Foundation Institutional Review Board (No. 201900211B0).

## Funding

This research was funded by a Chang Gung Medical research program grant (CMRPG3L1261).

## Disclosure

The authors declare that they have no competing interests.

## References

- Clark NA, Demers PA, Karr CJ, et al. Effect of early life exposure to air pollution on development of childhood asthma. *Environ Health Perspect.* 2010;118(2):284–290. doi:10.1289/ehp.0900916
- Burbank AJ, Sood AK, Kesic MJ, Peden DB, Hernandez ML. Environmental determinants of allergy and asthma in early life. *J Allergy Clin Immunol.* 2017;140(1):1–12. doi:10.1016/j.jaci.2017.05.010
- Pacheco SE, Guidos-Fogelbach G, Annesi-Maesano I, et al., American Academy of Allergy, Asthma & Immunology Environmental Exposures and Respiratory Health Committee. Climate change and global issues in allergy and immunology. *J Allergy Clin Immunol.* 2021;148(6):1366–1377. doi:10.1016/j.jaci.2021.10.011
- de Nijs SB, Venekamp LN, Bel EH. Adult-onset asthma: is it really different? *Eur Respir Rev.* 2013;22(127):44–52. doi:10.1183/09059180.00007112
- Hekking PP, Loza MJ, Pavlidis S, et al. Pathway discovery using transcriptomic profiles in adult-onset severe asthma. *J Allergy Clin Immunol.* 2018;141(4):1280–1290. doi:10.1016/j.jaci.2017.06.037
- Miranda C, Busacker A, Balzar S, Trudeau J, Wenzel SE. Distinguishing severe asthma phenotypes: role of age at onset and eosinophilic inflammation. *J Allergy Clin Immunol.* 2004;113(1):101–108. doi:10.1016/j.jaci.2003.10.041
- Baan EJ, de Roos EW, Engelkes M, et al. Characterization of asthma by age of onset; a multi-database cohort study. *J Allergy Clin Immunol Pract.* 2022;10(7):1825–1834.e8. doi:10.1016/j.jaip.2022.03.019
- Moore WC, Meyers DA, Wenzel SE, et al. Identification of asthma phenotypes using cluster analysis in the severe asthma research program. *Am J Respir Crit Care Med.* 2010;181(4):315–323. doi:10.1164/rccm.200906-0896OC
- Koenig JQ. Air pollution and asthma. *J Allergy Clin Immunol.* 1999;104(4 Pt 1):717–722. doi:10.1016/S0091-6749(99)70280-0
- Lin TY, Lin HC, Liu YS, et al. Proximity to heavy traffic roads and patient characteristics of late of onset asthma in an urban asthma center. *Front Med.* 2021;8:783720. doi:10.3389/fmed.2021.783720
- Pénard-Morand C, Raherison C, Charpin D, et al. Long-term exposure to close-proximity air pollution and asthma and allergies in urban children. *Europ resp J.* 2010;36(1):33–40. doi:10.1183/09031936.00116109
- Patel MM, Quinn JW, Jung KH, et al. Traffic density and stationary sources of air pollution associated with wheeze, asthma, and immunoglobulin E from birth to age 5 years among New York City children. *Environ Res.* 2011;111(8):1222–1229. doi:10.1016/j.envres.2011.08.004
- Brandt EB, Biagini Myers JM, Acciani TH, et al. Exposure to allergen and diesel exhaust particles potentiates secondary allergen-specific memory responses, promoting asthma susceptibility. *J Allergy Clin Immunol.* 2015;136(2):295–303 e297. doi:10.1016/j.jaci.2014.11.043
- Khreis H, Kelly C, Tate J, Parslow R, Lucas K, Nieuwenhuijsen M. Exposure to traffic-related air pollution and risk of development of childhood asthma: a systematic review and meta-analysis. *Environ Int.* 2017;100:1–31. doi:10.1016/j.envint.2016.11.012
- Guarnieri M, Balmes JR. Outdoor air pollution and asthma. *Lancet.* 2014;383(9928):1581–1592. doi:10.1016/S0140-6736(14)60617-6
- Brandt EB, Myers JM, Ryan PH, Hershey GK. Air pollution and allergic diseases. *Curr Opin Pediatr.* 2015;27(6):724–735. doi:10.1097/MOP.0000000000000286
- Lu C, Wang F, Liu Q, Deng M, Yang X, Ma P. Effect of NO<sub>2</sub> exposure on airway inflammation and oxidative stress in asthmatic mice. *J Hazard Mater.* 2023;457:131787. doi:10.1016/j.jhazmat.2023.131787
- Bowatte G, Lodge CJ, Knibbs LD, et al. Traffic-related air pollution exposure is associated with allergic sensitization, asthma, and poor lung function in middle age. *J Allergy Clin Immunol.* 2017;139(1):122–129.e121. doi:10.1016/j.jaci.2016.05.008
- Falcon-Rodriguez CI, Osornio-Vargas AR, Sada-Ovalle I, Segura-Medina P. Aeroparticles, composition lung diseases. *Front Immunol.* 2016;20:7.
- Baptist AP, Ross JA, Clark NM. Older adults with asthma: does age of asthma onset make a difference? *J Asthma.* 2013;50(8):836–841. doi:10.3109/02770903.2013.816967
- Turrin M, Rizzo M, Bonato M, et al. Differences between early- and late-onset asthma: role of comorbidities in symptom control. *J Allergy Clin Immunol Pract.* 2022;10(12):3196–3203. doi:10.1016/j.jaip.2022.08.007
- Brusselle G, Germinar M, Weiss S, Zangrilli J. Reslizumab in patients with inadequately controlled late-onset asthma and elevated blood eosinophils. *Pulm Pharmacol Ther.* 2017;43:39–45. doi:10.1016/j.pupt.2017.01.011
- Chen T-H, Hsu Y-C, Zeng Y-T, et al. A hybrid kriging/land-use regression model with Asian culture-specific sources to assess NO<sub>2</sub> spatial-temporal variations. *Environ Pollut.* 2020;259:113875. doi:10.1016/j.envpol.2019.113875
- C-D W, Zeng Y-T, Lung S-C-C. A hybrid kriging/land-use regression model to assess PM<sub>2.5</sub> spatial-temporal variability. *Sci Total Environ.* 2018;645:1456–1464. doi:10.1016/j.scitotenv.2018.07.073
- Tsai DH, Riediker M, Wuerzner G, et al. Short-term increase in particulate matter blunts nocturnal blood pressure dipping and daytime urinary sodium excretion. *Hypertension.* 2012;60(4):1061–1069. doi:10.1161/HYPERTENSIONAHA.112.195370

26. Zhang Y, Wei J, Shi Y, et al. Early-life exposure to submicron particulate air pollution in relation to asthma development in Chinese preschool children. *J Allergy Clin Immunol.* **2021**;148(3):771–782.e712. doi:10.1016/j.jaci.2021.02.030
27. Lu C, Liu Z, Yang W, et al. Early life exposure to outdoor air pollution and indoor environmental factors on the development of childhood allergy from early symptoms to diseases. *Environ Res.* **2023**;216(Pt 2):114538. doi:10.1016/j.envres.2022.114538
28. Lu C, Wang L, Liao H, et al. Impacts of intrauterine and postnatal exposure to air pollution on preschool children's asthma: a key role in cumulative exposure. *Build Environ.* **2023**;245:110874. doi:10.1016/j.buildenv.2023.110874
29. Norbäck D, Lu C, Zhang Y, et al. Onset and remission of childhood wheeze and rhinitis across China - associations with early life indoor and outdoor air pollution. *Environ Int.* **2019**;123:61–69. doi:10.1016/j.envint.2018.11.033
30. Wu J, Zhong T, Zhu Y, Ge D, Lin X, Li Q. Effects of particulate matter (PM) on childhood asthma exacerbation and control in Xiamen, China. *BMC Pediatric.* **2019**;19(1):194. doi:10.1186/s12887-019-1530-7
31. Bo Y, Chang L-Y, Guo C, et al. Reduced ambient PM<sub>2.5</sub>, better lung function, and decreased risk of chronic obstructive pulmonary disease. *Environ Int.* **2021**;156:106706. doi:10.1016/j.envint.2021.106706
32. Ezratty V, Guillossou G, Neukirch C, et al. Repeated nitrogen dioxide exposures and eosinophilic airway inflammation in asthmatics: a randomized crossover study. *Environ Health Perspect.* **2014**;122(8):850–855. doi:10.1289/ehp.1307240
33. Barck C, Sandström T, Lundahl J, et al. Ambient level of NO<sub>2</sub> augments the inflammatory response to inhaled allergen in asthmatics. *Respir Med.* **2002**;96(11):907–917. doi:10.1053/rmed.2002.1374
34. Huang W, Wu J, Lin X. Ozone exposure and asthma attack in children. *Front Pediatr.* **2022**;10:830897. doi:10.3389/fped.2022.830897
35. Guo C et al. (2018). Effect of long-term exposure to fine particulate matter on lung function decline and risk of chronic obstructive pulmonary disease in Taiwan: a longitudinal, cohort study. *Lancet Planet Health*, 2(3), e114–e125. doi:10.1016/S2542-5196(18)30028-7
36. De Grove KC, Provoost S, Brusselle GG, Joos GF, Maes T. Insights in particulate matter-induced allergic airway inflammation: focus on the epithelium. *Clin Exp Allergy.* **2018**;48(7):773–786. doi:10.1111/cea.13178
37. De Grove KC, Provoost S, Hendriks RW, et al. Dysregulation of type 2 innate lymphoid cells and TH2 cells impairs pollutant-induced allergic airway responses. *J Allergy Clin Immunol.* **2017**;139(1):246–257 e244. doi:10.1016/j.jaci.2016.03.044
38. Brandt EB, Kovacic MB, Lee GB, et al. Diesel exhaust particle induction of IL-17A contributes to severe asthma. *J Allergy Clin Immunol.* **2013**;132(5):1194–1204 e1192. doi:10.1016/j.jaci.2013.06.048
39. Manisalidis I, Stavropoulou E, Stavropoulos A, Bezirtzoglou E. Environmental and health impacts of air pollution: a review. *Front Public Health.* **2020**;8:14.
40. Chen CH, Wu CD, Chiang HC, et al. The effects of fine and coarse particulate matter on lung function among the elderly. *Sci Rep.* **2019**;9(1):14790. doi:10.1038/s41598-019-51307-5
41. Bevelander M, Mayette J, Whittaker LA, et al. Nitrogen dioxide promotes allergic sensitization to inhaled antigen. *J Immunol.* **2007**;179(6):3680–3688. doi:10.4049/jimmunol.179.6.3680
42. Knibbs LD, Cortés de Waterman AM, Toelle BG, et al. The Australian Child Health and Air Pollution Study (ACHAPS): a national population-based cross-sectional study of long-term exposure to outdoor air pollution, asthma, and lung function. *Environ Int.* **2018**;120:394–403. doi:10.1016/j.envint.2018.08.025
43. Fuertes E, Bracher J, Flexeder C, et al. Long-term air pollution exposure and lung function in 15 year-old adolescents living in an urban and rural area in Germany: the GINIplus and LISAplus cohorts. *Int J Hyg Environ Health.* **2015**;218(7):656–665. doi:10.1016/j.ijheh.2015.07.003
44. Holm SM, Balmes JR. Systematic review of ozone effects on human lung function, 2013 through 2020. *Chest.* **2022**;161(1):190–201. doi:10.1016/j.chest.2021.07.2170
45. Jung S-W, Lee K, Cho Y-S, et al. Association by Spatial Interpolation between ozone levels and lung function of residents at an industrial complex in South Korea. *Int J Environ Res Public Health.* **2016**;13(7):728. doi:10.3390/ijerph13070728

## Publish your work in this journal

The Journal of Asthma and Allergy is an international, peer-reviewed open-access journal publishing original research, reports, editorials and commentaries on the following topics: Asthma; Pulmonary physiology; Asthma related clinical health; Clinical immunology and the immunological basis of disease; Pharmacological interventions and new therapies. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/journal-of-asthma-and-allergy-journal>