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ORIGINAL RESEARCH

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

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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_{10}, $PM_{2.5}$, NO_2, and O_3 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_{10} was associated with younger age of onset, increased asthma duration, and decreased lung function in EOA patients ($p<0.05$). An increase in PM_{10} 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 $PM_{2.5}$ 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 $PM_{2.5}$ was associated with decreased lung function and ACT score in LOA patients. An increase in NO_2 was associated with increased eosinophil count and decreased lung function in EOA patients ($p<0.05$). An increase in O_3 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.[1–3] 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.[4–7] LOA differs pathologically from EOA and is associated with different disease outcomes in clinic-based and epidemiological studies.[6,8] For decades, researchers have been studying the relationship between the diversity of asthma endpoints and air pollutants.[9] 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.[10] Moreover, epidemiological and mechanistic studies have provided robust evidence of a causal relationship between traffic-related air pollution (TRAP) and the onset of EOA.[11–14] This demonstrates that TRAP exposure is an important risk factor for asthma.

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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.[15] Previous studies using animal and in vitro experimental models showed that TRAP could enhance allergic reactions.[15–17] In addition, exposure to nitrogen dioxide (NO_2) is linked with an increased risk of allergic sensitization, current wheeze, and lower forced expiratory volume in the first second (FEV_1) in asthma patients.[18] Exposure to particulate matter (PM) may lead to reduced lung function, allergic sensitization, lower airways inflammation, and upper airways irritation.[19] 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.[10] 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.[20–22]

Assessment of Exposure to Ambient Air Pollution

Exposure to air pollutants (particles with an aerodynamic diameter ≤10 μm [PM_{10}], particles with an aerodynamic diameter ≤2.5 μm [$PM_{2.5}$], nitrogen dioxide [NO_2], and ozone [O_3]) was estimated at an individual level using a hybrid kriging–land-use regression (LUR) model at the baseline residential address.[23,24] 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). 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.[25] Linear regression analysis was used to examine correlations between PM_{10}, $PM_{2.5}$, NO_2, and O_3 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 (β) 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^2, 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^2)	24.64±6.09	24.09±7.10	24.99±5.33	0.061
Smoking status				
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)	
Age of onset (years)	44.8±22.9	20.3±12.1	60.2±12.2	<0.05
Asthma duration (years)	11.7±16.7	22.5±21.3	4.9±7.2	<0.05
Parental asthma history				
Yes	196 (29.0)	95 (36.5)	101 (24.3)	<0.05
No	479 (71.0)	165 (63.5)	314 (75.7)	
Inflammatory biomarkers				
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
Allergic sensitization status				
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
History of exacerbation in previous year				
Yes	85 (12.6)	38 (14.6)	47 (11.3)	0.506
No	590 (87.4)	222 (85.4)	368 (88.7)	
ACT	21.06±4.04	20.52±4.18	21.38±3.93	<0.05
Lung function				
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_1 (L/s)	1.85±1.01	2.21±1.25	1.62±0.74	<0.05
FEV_1 (%)	70.67±27.20	72.12±29.97	69.76±25.31	0.273
FEV_1/FVC (%)	70.40±23.25	70.45±26.56	70.37±20.95	0.965
Post-BD FEV_1 (% change)	5.95±11.84	5.65±12.64	6.13±11.32	0.608
Mean exposure to PM_{10} (μg/m^3)				
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
Mean exposure to $PM_{2.5}$ (μg/m^3)				
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
Mean exposure to NO_2 (ppb)				
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
Mean exposure to O_3 (ppb)				
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_1, forced expiratory volume in 1 s; BD, bronchodilator; PM_{10}, particles with an aerodynamic diameter of 10 μm or less; $PM_{2.5}$, particles with an aerodynamic diameter of 2.5 μm or less; NO_2, nitrogen dioxide; O_3, ozone.

The mean FEV_1, FVC, and FEV_1/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_{10} Exposure is Associated with Asthma Features in EOA and LOA Patients

Figure 1A and Table S1 illustrate the association between PM_{10} and asthma features in EOA and LOA patients. We observed that a 1 μg/m^3 increase in PM_{10} was associated with decreased age of onset, by 0.316 and 0.258 years, in 6-month and 1-year PM_{10} 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^3 in 6-month and 1-year PM_{10} 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^3 in 1-month and 6-month PM_{10} was associated with 0.672% and 0.534% decreases in FEV_1 (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^3 in PM_{10} was associated with a 0.581% decrease in FEV_1/FVC (%) in 1-month PM_{10} (95% CI: −1.014, −0.149, p<0.05).

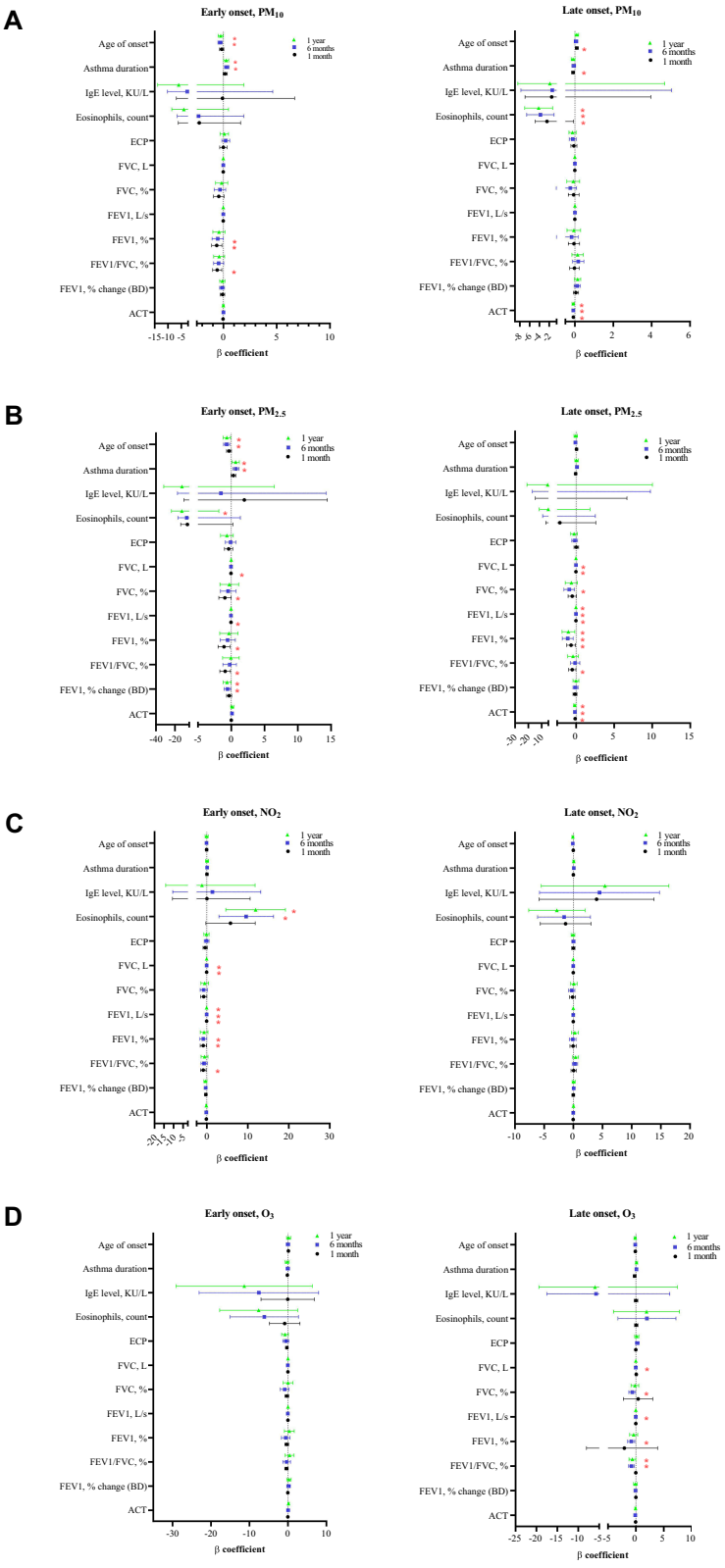

Figure 1 Associations of (**A**) PM_{10}, (**B**) $PM_{2.5}$, (**C**) NO_2, and (**D**) O_3 with asthma features in patients with EOA and LOA. *p<0.05.
Abbreviations: PM, particulate matter; NO_2, nitrogen dioxide; O_3, ozone; EOA, early-onset asthma; LOA, late-onset asthma.

We observed that an increase of 1 μg/m^3 in 1-month 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 μg/m^3 in 1-month 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 μg/m^3 in 1-month, 6-month, and 1-year 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 μg/m^3 in 1-month, 6-month, and 1-year PM_{10} was associated with 0.082, 0.086, and 0.089 decreases in ACT in LOA patients, respectively.

$PM_{2.5}$ Exposure is Associated with Asthma Features in EOA and LOA Patients

Figure 1B and Table S2 illustrate the association between $PM_{2.5}$ and asthma features in EOA and LOA patients. We observed that a 1 μg/m^3 increase in 6-month and 1-year $PM_{2.5}$ 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 μg/m^3 in 1-month and 6-month $PM_{2.5}$ 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 μg/m^3 in 1-year $PM_{2.5}$ 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 μg/m^3 in 1-month $PM_{2.5}$ was associated with 0.042L, 0.955%, 0.038L, 1.091%, and 0.919% decreases in FVC (L), FVC (%), FEV_1 (L), FEV_1 (%), and FEV_1/FVC (%) in EOA patients, respectively.

We observed that an increase of 1 μg/m^3 in 1-month and 6-month $PM_{2.5}$ 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 μg/m^3 in 6-month $PM_{2.5}$ 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 μg/m^3 in 1-month, 6-month, and 1-year $PM_{2.5}$ was associated with 0.022, 0.023, and 0.023 L decreases in FEV_1 in LOA patients, respectively. An increase of 1 μg/m^3 in 1-month, 6-month, and 1-year $PM_{2.5}$ was associated with 0.663%, 1.098%, and 1.020% decreases in FEV_1 in LOA patients, respectively. An increase of 1 μg/m^3 in 1-month $PM_{2.5}$ was associated with a 0.505% decrease in FEV_1/FVC (%) in LOA patients (95% CI: −0.71, −0.05, p<0.05). An increase of 1 μg/m^3 in 1-month, 6-month, and 1-year PM_{10} was associated with 0.130, 0.155, and 0.183 decreases in ACT in LOA patients, respectively.

NO_2 Exposure is Associated with Asthma Features in EOA and LOA Patients

Figure 1C and Table S3 illustrate the association between NO_2 and asthma features in EOA and LOA patients. An increase of 1 ppb in 1-year 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 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 NO_2 was associated with a 0.043, 0.040, 0.039 L decrease in FEV_1 in EOA patients, respectively. An increase of 1 ppb in 1-month and 6-month NO_2 was associated with a 0.862 and 0.845 L decrease in FEV_1 in EOA patients, respectively. An increase of 1 ppb in 1-month NO_2 was associated with a 0.863% decrease in FEV_1/FVC (%) in EOA patients (95% CI: −1.539, −0.118, p<0.05). We did not observe an association between NO_2 and asthma features in LOA.

O_3 Exposure is Associated with Asthma Features in EOA and LOA Patients

Figure 1D and Table S4 illustrate the association between O_3 and asthma features in EOA and LOA patients. An increase of 1 ppb in 1-month 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 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 O_3 was associated with a 0.023 L decrease in FEV_1 in LOA patients (95% CI: −0.039, −0.007, p<0.05). An increase of 1 ppb in 6-month O_3 was associated with a 0.830% decrease in 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 O_3 was associated with 0.762% and 0.623% decreases in FEV_1/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 O_3 and asthma features in EOA.

Associations Between PM_{10} and Asthma Features in EOA and LOA Patients Stratified by Allergic Sensitization Status

Figure 2 and Table S5 illustrate the association between 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 μg/m^3 increase in

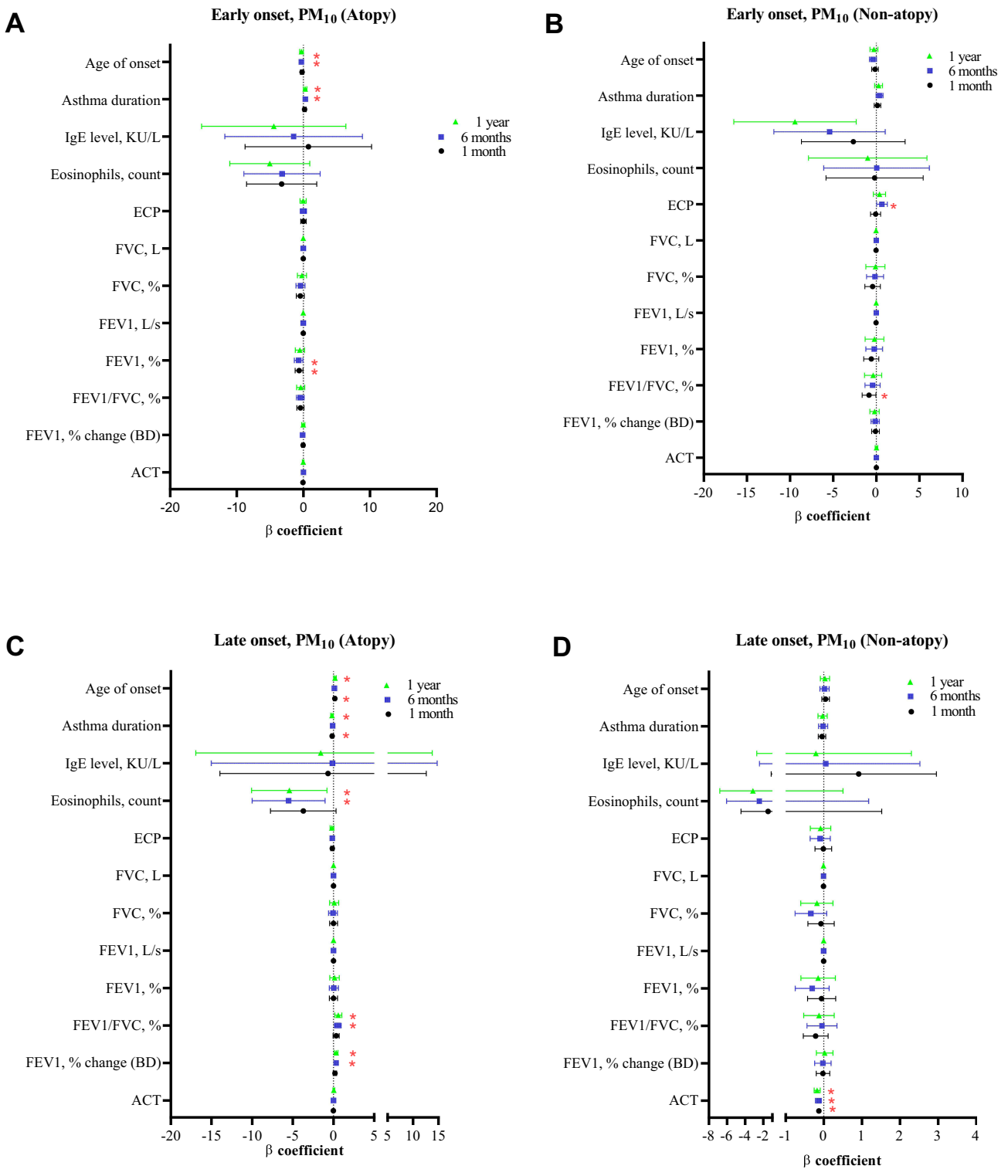

Figure 2 Associations of PM_{10} with asthma features in patients with (**A**) EOA and atopy, (**B**) EOA and non-atopy, (**C**) LOA and atopy, and (**D**) LOA and non-atopy. *$p<0.05$.
Abbreviations: PM, particulate matter; EOA, early-onset asthma; LOA, late-onset asthma.

6-month and 1-year PM_{10} 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 μg/m^3 in 6-month and 1-year PM_{10} 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 μg/m^3 in 1-month and 6-month PM_{10} was associated with decreases of

0.641% and 0.693% in FEV_1, 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 μg/m^3 increase in 1-month and 1-year PM_{10} 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 μg/m^3 in 1-month and 1-year PM_{10} 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 μg/m^3 in 6-month and 1-year PM_{10} 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 μg/m^3 in 6-month and 1-year PM_{10} was associated with increases of 0.531% and 0.588% in FEV_1/FVC (%) and increases of 0.325% and 0.323% in FEV_1 change.

Associations Between $PM_{2.5}$ and Asthma Features in EOA and LOA Patients Stratified by Allergic Sensitization Status

Figure 3 and Table S6 illustrate the association between $PM_{2.5}$ 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 μg/m^3 increase in 1-month, 6-month, and 1-year $PM_{2.5}$ was associated with a decreased age of onset, by 0.519, 0.910, and 1.030 years, respectively. An increase of 1 μg/m^3 in 1-month, 6-month, and 1-year $PM_{2.5}$ was associated with increased asthma duration of 0.519, 0.910, and 1.031, respectively. An increase of 1 μg/m^3 in 1-month $PM_{2.5}$ was associated with a 10.164 decrease in the eosinophil count (95% CI: −20.286, −0.040, $p<0.05$). An increase of 1 μg/m^3 in 1-month $PM_{2.5}$ was associated with decreases of 1.250% and 1.336% in FVC and FEV_1, 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 μg/m^3 increase in 1-month $PM_{2.5}$ was associated with 1.250% and 1.336% decreases in FEV_1 and FEV_1/FVC (%), respectively.

Associations Between NO_2 and Asthma Features in EOA and LOA Patients Stratified by Allergic Sensitization Status

Figure 4 and Table S7 illustrate the association between NO_2 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_2 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_2 was associated with decreases in FVC, FEV_1 (L), and FEV_1 (%). In addition, an increase of 1 ppb in 1-month NO_2 was associated with a 1.032% decrease in FEV_1/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_2 was associated with increases of 0.389% and 0.411% in FEV_1 change, respectively (95% CI: 0.040, 0.738, $p<0.05$, and 95% CI: 0.027, 0.795, $p<0.05$).

Associations Between O_3 and Asthma Features in EOA and LOA Patients Stratified by Allergic Sensitization Status

Figure 5 and Table S8 illustrate the association between O_3 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_3 was associated with decreases of 1.500% and 1.543% in FVC and FEV_1/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.

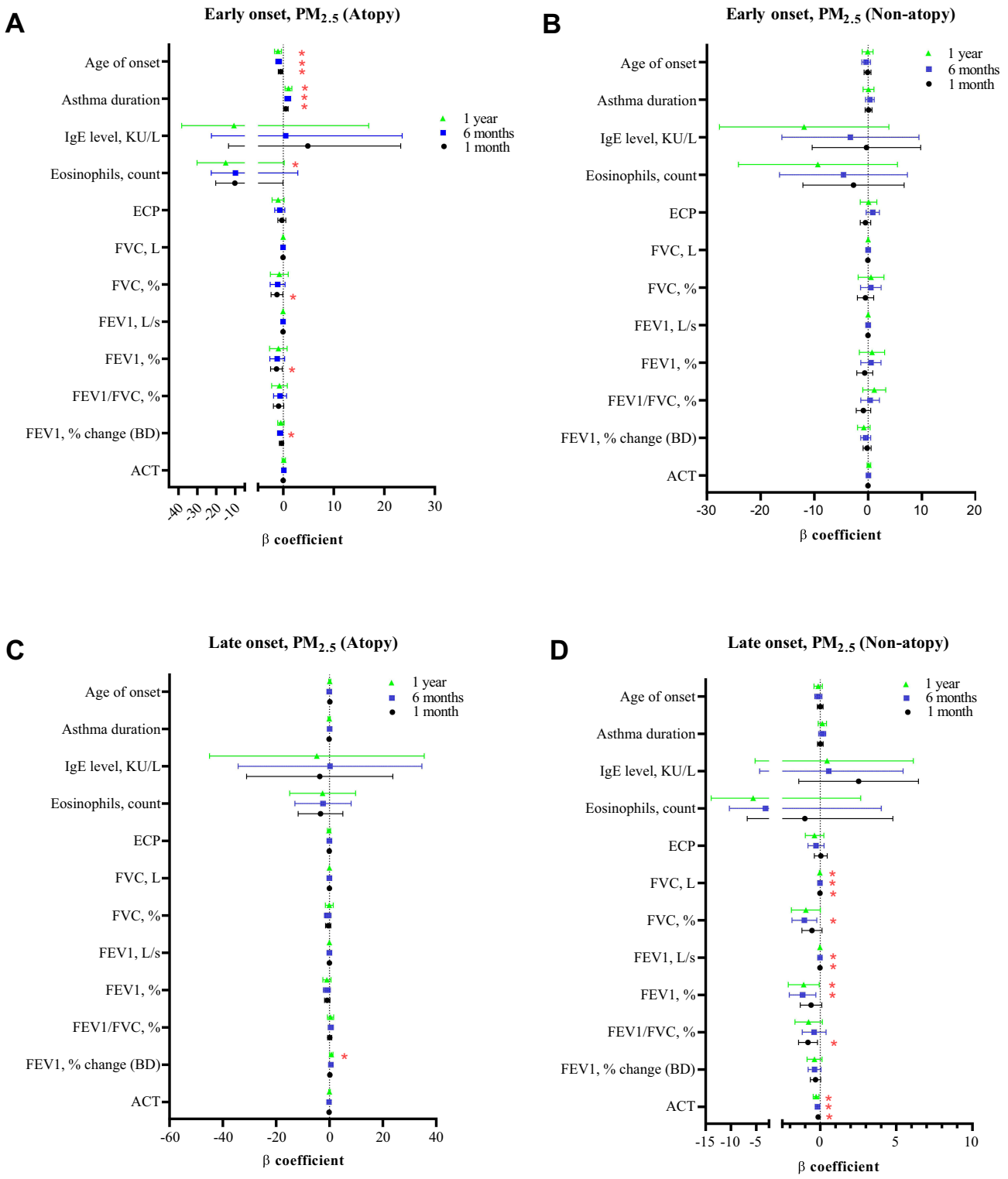

Figure 3 Associations of $PM_{2.5}$ with asthma features in patients with (**A**) EOA and atopy, (**B**) EOA and non-atopy, (**C**) LOA and atopy, and (**D**) LOA and non-atopy. *$p<0.05$.
Abbreviations: PM, particulate matter; EOA, early-onset asthma; LOA, late-onset asthma.

We observed that increased exposure to PM_{10} and $PM_{2.5}$ 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.[26–29] We demonstrated that an increase in PM_{10} and $PM_{2.5}$ 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

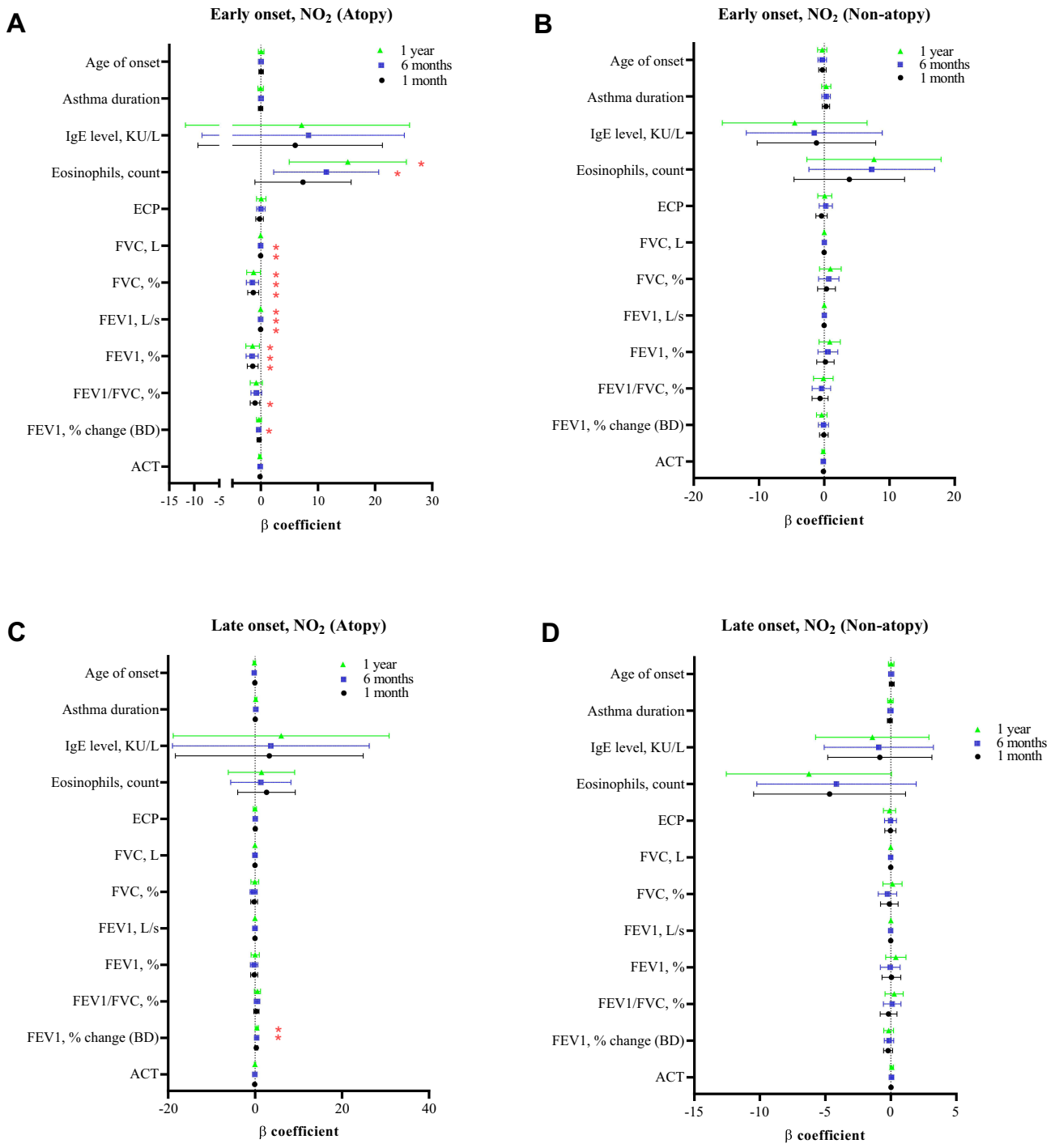

Figure 4 Associations of NO_2 with asthma features in patients with (**A**) EOA and atopy, (**B**) EOA and non-atopy, (**C**) LOA and atopy, and (**D**) LOA and non-atopy. *p<0.05.
Abbreviations: NO_2, nitrogen dioxide; EOA, early-onset asthma; LOA, late-onset asthma.

asthma attacks.[30] Next, we observed that exposure to PM_{10} and $PM_{2.5}$ was a risk factor for reduced lung function in EOA patients. A previous study reported that each 5 μg/m^3/year improvement in PM increased the FEV_1, FVC, and FEV_1/FVC.[31] We also observed that increasing NO_2 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_2 (p=0.003), while the ECP increased significantly after exposure to 600 ppb of NO_2 (p=0.001).[32] NO_2 exposure increased eosinophilic inflammation in the distal lower airways, in response to inhaled allergen, as assessed by bronchial wash and

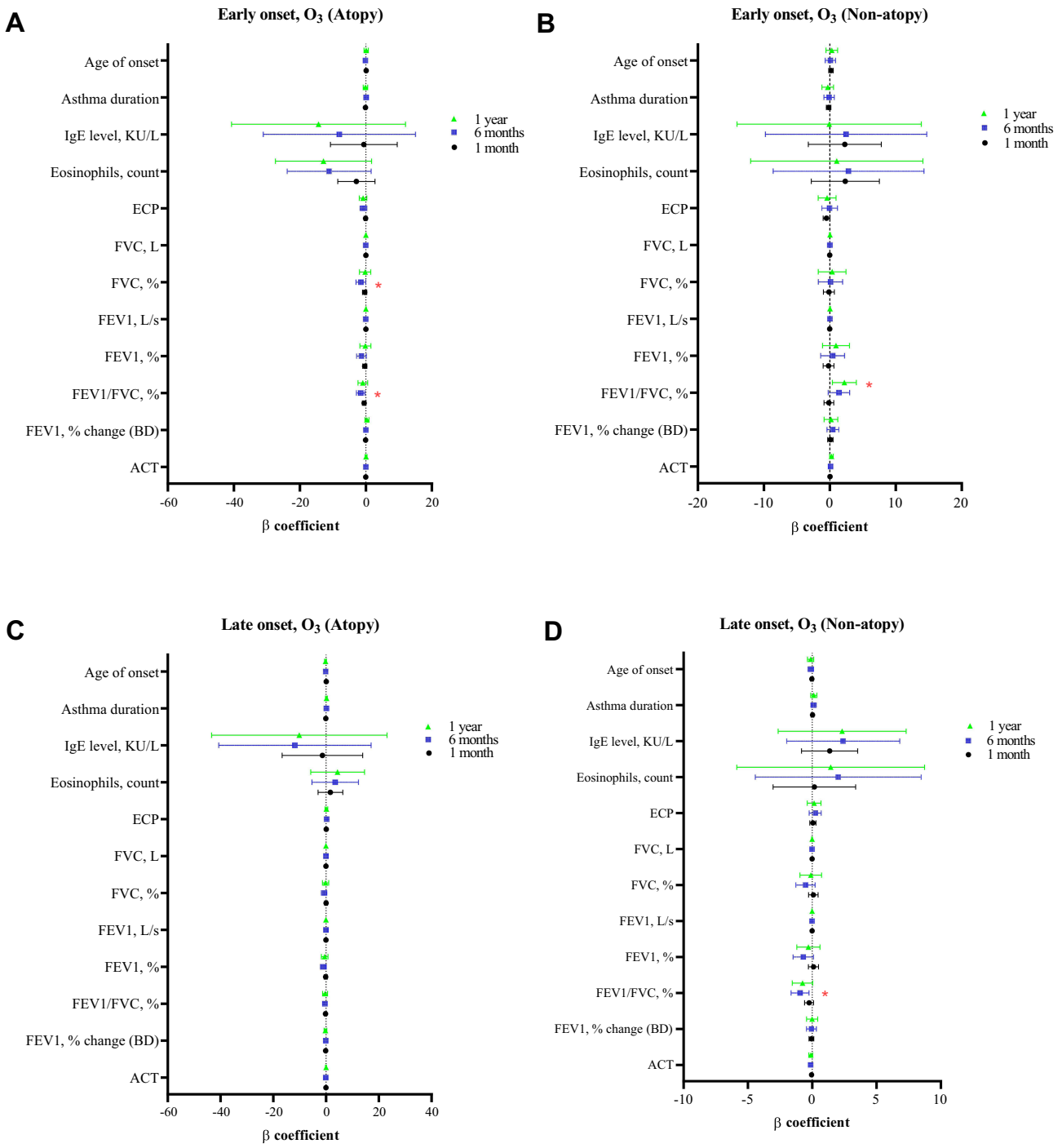

Figure 5 Associations of O_3 with asthma features in patients with (**A**) EOA and atopy, (**B**) EOA and non-atopy, (**C**) LOA and atopy, and (**D**) LOA and non-atopy. *$p<0.05$.
Abbreviations: O_3, ozone; EOA, early-onset asthma; LOA, late-onset asthma.

bronchoalveolar lavage.[33] We observed that NO_2 and O_3 were risk factors for decreased lung function in EOA patients. A case-crossover study in China also reported that exposure to higher than 80 μg/m^3 O_3 increased the risk of reduced lung function.[34] 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 $PM_{2.5}$ decreased the FVC, FEV_1, and FEV_1/FVC.[35] Mechanistic studies have shown that PM can exacerbate allergies by inducing inflammation in the airway epithelium.[36] In animal studies, coexposure to diesel

and house dust mites was shown to contribute to the persistence of T-helper $(Th)_2/Th_{17}$ effector cells or innate lymphoid cells in the lungs. It was also shown to enhance hyperresponsivity in the airways.[13,37,38] The size of PM determines the degree to which it penetrates the human respiratory system.[39] We observed that exposure to PM_{10} is a risk for poorer asthma outcomes in EOA with allergic sensitization. Coarse PM_{10} is deposited primarily in the nasopharynx or primary bronchi, whereas fine $PM_{2.5}$ is deposited in the alveoli and terminal bronchioles.[40] 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_2 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_2 can induce eosinophilic inflammation in the airways.[32,41] We observed that exposure to NO_2 was associated with a decrease in lung function in EOA patients with allergic sensitization. A previous study showed that NO_2 exposure was associated with decreases of 1.35% in predicted FEV_1 (95% CI: −2.21, −0.49) and 1.19% in FVC (95% CI: −2.04, −0.35).[42] The main mechanisms by which NO_2 could adversely affect both lung function and asthma have been proposed as oxidative stress and inflammation.[43] Therefore, our findings indicate that NO_2 increases the blood eosinophil counts and decreases lung function in asthmatic patients.

We found that O_3 had distinct effects on asthma outcomes according to allergic sensitization. We observed that increasing O_3 exposure was associated with decreased FVC and FEV_1/FVC in the EOA patients with allergic sensitization. A systematic review reported that long-term O_3 exposure decreased both lung function and lung function growth.[44] Another study demonstrated that O_3 exposure was associated with a decrease in FEV_1 of 35 mL (95% CI: −69, −6 mL).[45] Taking these findings together, EOA patients with allergic sensitization could be the population at risk upon exposure to O_3.

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_2 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_3 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_1, forced expiratory volume in 1 s; FVC, forced vital capacity; IgE, immunoglobulin E; LOA, late-onset asthma; NO_2, nitrogen dioxide; O_3, ozone; PM, particulate matter; $PM_{2.5}$, particles with an aerodynamic diameter of 2.5 μm or less; PM_{10}, 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).

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Disclosure

The authors declare that they have no competing interests.

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