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RESEARCH ARTICLE

Lung function and air pollution exposure in adults with asthma in Beijing: a 2-year longitudinal panel study

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Abstract **The effect of air pollution on the lung function of adults with asthma remains unclear to date. This study followed 112 patients with asthma at 3-month intervals for 2 years. The pollutant exposure of the participants was estimated using the inverse distance weight method. The participants were divided into three groups according to their lung function level at every visit. A linear mixed-effect model was applied to predict the change in lung function with each unit change in pollution concentration. Exposure to carbon monoxide (CO) and particles less than 2.5 micrometers in diameter ($PM_{2.5}$) was negatively associated with large airway function in participants. In the severe group, exposure to chronic sulfur dioxide (SO_2) was negatively associated with post-bronchodilator forced expiratory flow at 50%, between 25% and 75% of vital capacity % predicted (change of 95% CI per unit: –0.34 (–0.55, –0.12), –0.24 (–0.44, –0.03), respectively). In the mild group, the effect of SO_2 on the small airways was similar to that in the severe group, and it was negatively associated with large airway function. Exposure to CO and $PM_{2.5}$ was negatively associated with the large airway function of adults with asthma. The negative effects of SO_2 were more evident and widely observed in adults with severe and mild asthma than in adults with moderate asthma. Patients with asthma react differently to air pollutants as evidenced by their lung function levels.**

Keywords lung function; asthma; air pollution; adult

Introduction

Asthma is a common chronic respiratory disease worldwide. In 2015, 0.40 million people died from asthma, and the number of patients with asthma increased by 12.6% [1]. Ambient particulate matter pollution is the fourth risk factor contributing to deaths and disability-adjusted life years in China [2]. Asthma and ambient pollution constitute a substantial disease burden.

Many studies demonstrated the influence of ambient air pollution on asthma [3], especially in children. Air pollution can increase the risk of asthma [4–7] and affect the disease stability and healthy quality of life of children with asthma [8]. Air pollution also negatively affects the lung function of children with asthma [6,7,9–12] and similarly impacts the lung function of adolescents [13,14]. In adults with asthma, air pollution exposure increase the use of asthma medication [15], the frequency of acute exacerbation, the number of emergency visits, the frequency of hospital admissions [16–18], and mortality [19].

However, few studies [20–22] have illustrated the relationship between air pollution exposure and lung function in adults with asthma. Current evidence focuses on childhood asthma. Meanwhile, the children and adult studies mentioned above focused on the effects of air pollution on large airway function; data on small airway function are limited, even though dysfunction of the small airways is common in patients with asthma [23–27] and healthy people [28]. Thus, prospective longitudinal cohort studies in adults with asthma are necessary to reveal the relationship between air pollution exposure and lung function, including the large and small airways, in severely polluted developing areas.

In this prospective cohort study, adults with asthma were recruited at Peking Union Medical College Hospital between December 2015 and September 2017 in China. The participants were followed at 3-month intervals during

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the next 2 years to investigate whether or not long-term exposure to high-level air pollution (particles less than 2.5, 10 μm in diameter ($PM_{2.5}$, PM_{10}), nitrogen dioxide (NO_2), ozone (O_3), sulfur dioxide (SO_2), and carbon monoxide (CO)) is associated with large airway function (forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), FEV_1/FVC, small airway lung function (forced expiratory flow at 50% and 75% of vital capacity % predicted (FEF_{50}, FEF_{75}) and forced expiratory flow between 25% and 75% of vital capacity % predicted ($FEF_{25–75}$)) decline. The effect of different lung function levels was also analyzed to explore the disparity of different severity grades.

Methods

Study design

In this prospective study, participants with asthma were evaluated every 3 months for 2 years. Lung functions were measured at each visit, and air pollution data were collected. All participants were residents of Beijing, China. The inclusion criterion was confirmed asthma in accordance with the diagnostic criteria in the 2015 Global Initiative for Asthma (GINA) [29]. House address and demographic characteristics were collected at baseline.

The protocol was approved by the Institutional Review Board of Peking Union Medical College Hospital (JS-914). All participants signed an informed consent prior to this study.

Lung functions

Spirometry (pre- and post-bronchodilator (pre-/post-BD) administration) was conducted at each visit in accordance with the 2005 American Thoracic Society and European Respiratory Society standards [30]. Up to eight tracings were obtained every day. Participants inhaled 500 μg of salbutamol after finishing the pre-BD administration, and post-BD administration was conducted 20 min later. We used pre- and post-BD lung function % predicted as predictive variables in accordance with Global Lung Initiative reference equations to avoid confounding factors, such as sex, height, weight, and age, and we defined these variables as pre-/post-FEV_1, pre-/post-FVC, pre-/post-FEV_1/FVC, pre-/post-FEF_{50}, pre-/post-FEF_{75}, and pre-/post-$FEF_{25–75}$. Spirometry was performed on the FlowScreen spirometer. The FolwScreen spirometer is a pneumotach, and it was calibrated by the 3L calibrator daily at low, moderate, high rates, respectively.

At baseline, some lung function tests were performed on the JAEGER spirometer; those tests were not included in this paper to ensure consistency.

Pollution exposure

The daily average exposure captured by 35 monitors in Beijing was collected from the data issued by the China National Environmental Monitoring Centre hourly. CO, NO_2, SO_2, $PM_{2.5}$, and PM_{10} were 24 h averages, and O_3 was an 8 h largest moving average. For long-term exposure, the past 90 days of chronic exposure (lag90) were evaluated by the air pollutant weighted average of the 90 days before the visit. The individual exposure of the participants was estimated on the basis of pollution concentration data from 35 monitors by using the inverse distance weight (IDW) method [19] with a power parameter of 2, according to the home address of the participants. The daily air pollutant exposure of each participant was estimated by calculating the inverse distance ($1/d^2$) weighted average of each day concentration at the nearest four monitoring stations. The unit of all pollutants was $\mu g/m^3$, except that of CO, which was mg/m^3.

Statistics analysis

The effects of pollution were determined in all participants and also by three lung function levels based on the lung function level of a single visit: severe, post bronchodilator forced expiratory volume in 1 s/forced vital capacity (post-FEV_1/FVC) $< 50\%$; moderate, $50\% \leqslant$ post-FEV_1/FVC $< 70\%$; and mild, post-FEV_1/FVC $\geqslant 70\%$. The lung function at different visits and severity grade were compared using single-factor ANOVA. A linear mixed-effect model was applied to predict changes in lung function with each unit change in exposure concentration, and each subject had a unique intercept to adjust for individual disparities. The effect was explored in univariate analysis, and then the univariate results were used in a multivariate model. Age, sex, cooking, smoking, inhaled corticosteroids (ICS) and long-acting β-agonist (LABA), temperature, humidity, day of week, education, chronic obstructive pulmonary disease (COPD) complications, and season were included in the multivariate model to adjust for confounding factors. The multiple pollution model failed to converge because of the collinearity of the pollutants. The model with the best R2 was the final predictive model, and pollution was the best predictive factor. Interaction terms of pollution exposure and severity were included in the model, and the significance of the model was tested through ANOVA. All data were managed using IBM SPSS statistics version 20. Statistical analysis was performed in R programming language version 3.6.3 through the lmerTest package.

Results

Basic characteristics

Two of 117 patients with asthma withdrew after receiving diagnoses of Churg–Strauss syndrome and allergic bronchopulmonary aspergillosis. Three participants who left Beijing frequently during the 2 years of observation were not included in the analysis. Visits of participants who left Beijing 10 days or more in the past 90 days were also excluded. Finally, during the two years, 112 participants in our study finished 827 visits. Table 1 shows the main characteristics of the participants. The mean age of the participants was 49.8 years; 53.1% were male and 26.1% had complications of COPD. The severe group had the highest regular ICS availability (93.6%), whereas the mild group had the lowest.

The lung function and air pollution concentration for the last 90 days are shown in Table 2. The FVC of all participants was normal, ensuring the accuracy of small airway function. In patients with severe and moderate asthma, the large and small airway functions had a wide decline. In patients with mild asthma, even with optimal lung function and normal FEV_1/FVC, the small airway function failed to eliminate this decline. During the 2 years of observation, the variation in lung function was not significant (all $P > 0.1$) (Table S1). All pollutant concentrations positively correlated with each other (except O_3, which negatively correlated with other pollutants) (Table 3). $PM_{2.5}$ displayed a stronger correlation with CO and PM_{10} (coefficients were 0.85 and 0.83, respectively), which may explain the collinearity of the pollutants.

Associations between air pollution and lung function

$PM_{2.5}$ and CO exposure are negatively associated with the large airway function of patients with asthma

In all participants, $PM_{2.5}$ and CO were negatively associated with pre-FEV_1 and pre-FVC, and CO was also negatively associated with post-FEV_1 and post-FVC (Fig. 1). Other chronic effects were nearly all insignificant (Table S2).

Table 1 Demographic data

	Total	Severe	Moderate	Mild	ANOVA *P* value
Number of participants	112	12	63	83	
Number of visits	827	47	280	500	
Age (year)	49.8±13.2	60.5±9.6	53.0±12.5	47.0±12.9	<0.001
Male	439 (53.1)	33 (70.2)	152 (54.3)	254 (50.8)	0.034
COPD complications	216 (26.1)	47 (100)	169 (60.4)	0 (0)	<0.001
Current smokers	59 (7.1)	8 (17.0)	13 (4.6)	38 (7.6)	0.008
Ever smokers	164 (19.8)	11 (23.4)	43 (15.4)	110 (22.0)	0.187
Pet	223 (27)	17 (36.2)	55 (68.8)	151 (30.2)	0.043
Cooking frequency (times/day)	1.7±0.9	2.0±0.8	1.6±1.0	1.7±0. 9	0.054
Education					<0.001
Primary school	8 (1)	1 (2.1)	7 (2.5)	0 (0)	
Junior middle school	73 (8.8)	20 (42.6)	34 (12.1)	19 (3.8)	
Senior high school	156 (18.9)	9 (19.1)	65 (23.2)	82 (16.4)	
University	590 (71.3)	17 (36.2)	174 (62.2)	399 (79.8)	
ICS + LABA					<0.001
None	176 (21.3)	2 (4.3)	51 (18.2)	123 (24.6)	
Irregular use	137 (16.6)	1 (2.1)	39 (13.9)	97 (19.4)	
Regular use	514 (62.1)	44 (93.6)	190 (67.9)	280 (56.0)	
Season of visit					>0.05
Summer	239 (29.6)	15 (31.9)	80 (28.6)	144 (28.8)	
Spring	206 (24.7)	12 (25.5)	67 (23.9)	127 (25.4)	
Autumn	195 (23.8)	11 (23.4)	71 (25.4)	113 (22.6)	
Winter	187 (21.9)	9 (19.2)	62 (22.1)	116 (23.2)	
Temperature	14.2±10.5	14.7±10.6	14.6±10.4	13.9±10.6	>0.05
Humidity	50.1±11.6	49.7±11.6	50.3±11.8	49.9±11.6	>0.05
Day of week	4.1±1.1	4.3±1.0	4.1±1.1	4.1±1.1	>0.05

Abbreviations: COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids; LABA, long-acting β-agonist; SD, standard deviation.
The values are presented as mean ± SD or number (%).

Table 2 Lung function and air pollution during the observation period in different groups of asthma

	Total	Severe	Moderate	Mild	ANOVA *P* value
Number of visits	827	47	280	500	
Pre-FEV_1	78.39±16.50	48.44±12.70	70.10±15.19	85.36±11.96	<0.001
Post-FEV_1	84.81±15.31	54.79±11.94	78.57±13.62	91.16±11.08	<0.001
Pre-FVC	97.48±14.10	89.57±22.10	98.71±15.32	97.53±12.08	<0.001
Post-FVC	99.90±13.48	98.17±19.56	103.41±14.27	98.09±11.87	<0.001
Pre-FEV_1/FVC	66.71±10.69	44.04±4.96	59.10±7.00	73.10±6.13	<0.001
Post-FEV_1/FVC	70.71±10.83	45.36±4.50	62.57±5.53	77.70±5.28	<0.001
Pre-$FEF_{25–75}$	43.94±20.93	14.43±4.79	29.79±11.41	54.67±18.46	<0.001
Post-$FEF_{25–75}$	54.08±24.49	16.50±4.93	35.40±11.38	68.15±19.75	<0.001
Pre-FEF_{50}	46.65±21.80	14.07±5.38	32.13±12.79	57.86±18.66	<0.001
Post-FEF_{50}	56.45±24.71	16.37±5.56	38.23±12.62	70.48±19.58	<0.001
Pre-FEF_{75}	33.94±18.57	11.82±3.40	22.10±9.01	42.65±17.99	<0.001
Post-FEF_{75}	43.33±23.80	13.35±3.57	26.32±9.90	55.75±21.91	<0.001
Pollution					
O_3 (μg/m^3)	93.55±43.51	94.74±45.61	94.75±43.83	92.76±43.20	>0.05
CO (mg/m^3)	0.93±0.31	0.88±0.23	0.91±0.29	0.94±0.33	>0.05
NO_2 (μg/m^3)	50.72±10.90	48.35±10.99	49.88±11.26	51.41±10.64	>0.05
SO_2 (μg/m^3)	7.65±4.35	7.13±3.80	7.35±4.27	7.87±4.44	>0.05
$PM_{2.5}$ (μg/m^3)	58.25±17.98	54.46±14.47	57.26±16.44	59.17±19.03	>0.05
PM_{10} (μg/m^3)	92.24±24.09	88.81±22.40	90.65±22.79	93.46±24.90	>0.05

Abbreviations: pre-/post-FEV_1, pre-/post-bronchodilator forced expiratory volume in 1 s % predicted; pre-/post-FVC, pre-/post-bronchodilator forced vital capacity % predicted; pre-/post-FEV_1/FVC, pre-/post-bronchodilator forced expiratory volume in 1 s/forced vital capacity; pre-/post-FEF_{50}, pre-/post-bronchodilator forced expiratory flow at 50% of vital capacity % predicted; pre-/post-FEF_{75}, pre-/post-bronchodilator forced expiratory flow at 75% of vital capacity % predicted; pre-/post-$FEF_{25–75}$, pre-/post-bronchodilator forced expiratory flow between 25% and 75% of vital capacity % predicted; O_3, ozone; CO, carbon monoxide; NO_2, nitrogen dioxide; SO_2, sulfur dioxide; $PM_{2.5}$, particles less than 2.5 μm in diameter; PM_{10}, particles less than 10 μm in diameter; SD, standard deviation.
Notes: total, all visits; severe group, low post-FEV_1/FVC visits; moderate group, middle post-FEV_1/FVC visits; mild group, high post-FEV_1/FVC visits. The values are presented as mean±SD (%).

Table 3 Correlation of pollutants, temperature, and humidity

	Humidity	Temperature	CO	NO_2	O_3	PM_{10}	$PM_{2.5}$	SO_2
Humidity	1							
Temperature	0.74	1						
CO	–0.04*	–0.48	1					
NO_2	–0.19	–0.49	0.64	1				
O_3	0.45	0.87	–0.47	–0.60	1			
PM_{10}	–0.25	–0.23	0.55	0.57	–0.10	1		
$PM_{2.5}$	–0.09	–0.36	0.85	0.68	–0.31	0.83	1	
SO_2	–0.53	–0.61	0.70	0.57	–0.43	0.61	0.73	1

Abbreviations: see Table 2.
*P>0.05. All other correlations were significant (P<0.05).

$PM_{2.5}$, CO, and SO_2 are negatively associated with the large and small airway functions of the severe group

In the severe asthma group, $PM_{2.5}$, SO_2, and CO were negatively associated with nearly all $FEF_{25–75}$, FEF_{50}, and FEF_{75}; the effect was weakened after bronchodilator administration, except SO_2 (Fig. 2). $PM_{2.5}$, CO, and SO_2 exposure were negatively associated with pre-FEV_1 and pre-FVC, but the association was not maintained after bronchodilator administration (Fig. 3). Other pollutants, such as NO_2, had a slight reversible effect on small airway function (Table S3).

Air pollution has slight associations with the lung function of the moderate group

In the moderate group, only O_3 was negatively associated with post-FEV_1/FVC and post-FEF_{50} (Table S4).

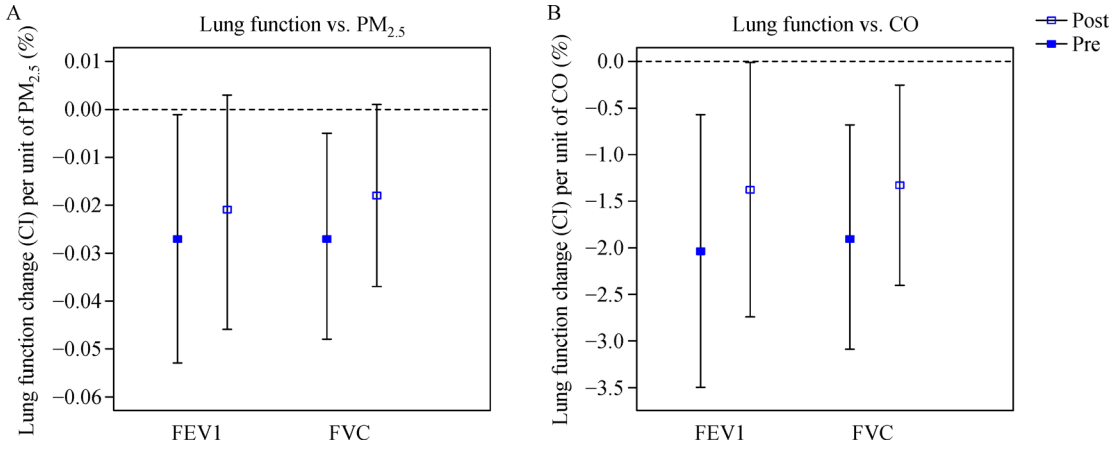

Fig. 1 Associations of $PM_{2.5}$ and CO exposure with large airway function in all participants. (A and B) Large airway function change (CI) per unit of $PM_{2.5}$ and CO, respectively. CI, confidence interval. Other abbreviations, see Table 2.

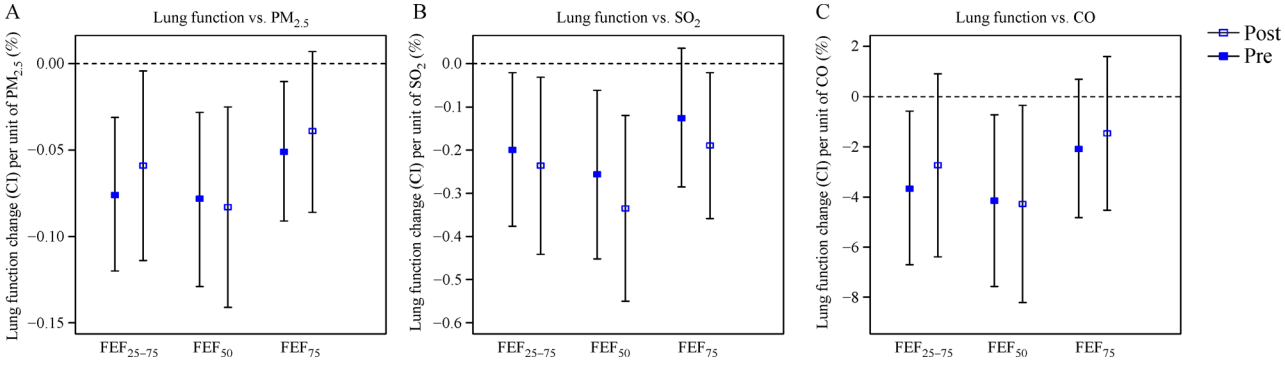

Fig. 2 Association between SO_2, CO, and $PM_{2.5}$ exposure and small airway function in the severe group. (A–C) Small airway function change (CI) per unit of $PM_{2.5}$, SO_2, and CO, respectively. CI, confidence interval. Other abbreviations, see Table 2.

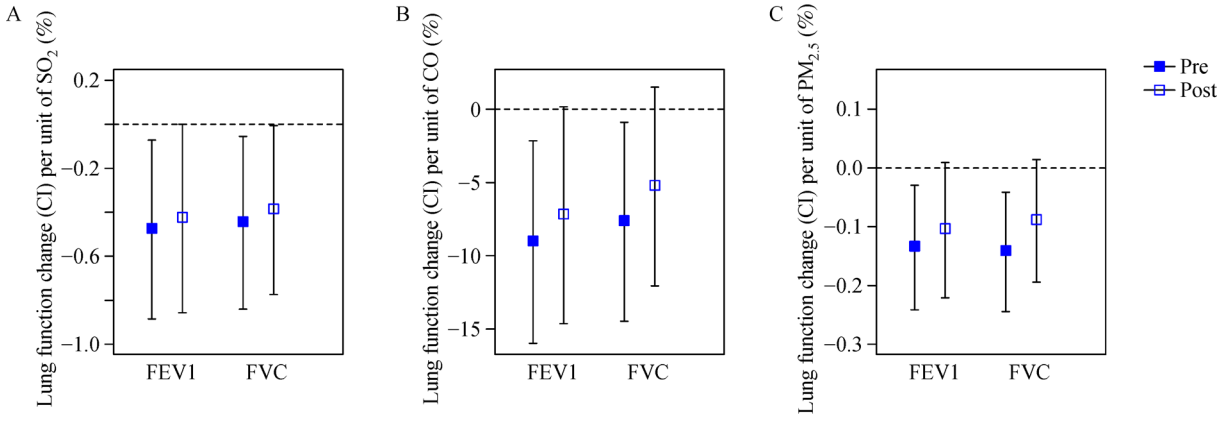

Fig. 3 Association between SO_2, CO, and $PM_{2.5}$ exposure and large airway function in the severe group. (A–C) Large airway function change (CI) per unit of SO_2, CO, and $PM_{2.5}$, respectively. CI, confidence interval. Other abbreviations, see Table 2.

Air pollution shows wide negative associations with the lung function of the mild group

In the mild group, CO, NO_2, $PM_{2.5}$, and PM_{10} were negatively associated with both pre- and post-bronchodilator large airway functions. All the effects slightly alleviated after bronchodilator administration (Fig. 4). SO_2 presented negative impacts on large and small airway functions, and the effect on large airway function alleviated after bronchodilator administration, but that on small airway function was enhanced (Fig. 5). Other pollutants, such as O_3, also presented some impacts (Table S5).

Asthma patients react differently to air pollution based on lung function levels, and the effects of SO_2 are more serious

Fig. 6 presents all effects of air pollution exposure on lung function. CO and $PM_{2.5}$ negatively affected the large airway function of all participants. SO_2, CO, and $PM_{2.5}$ presented more significant effects than the other pollutants. CO and $PM_{2.5}$ presented more effects on large airway function, and effects on small airway function were more prominent in the severe group than in the other groups. SO_2 affected the large and small airway functions more evenly and widely in the severe and mild groups than in the moderate group. This result suggests that the effect of SO_2 may be more prominent in adults with asthma and that the small airways are more sensitive to SO_2 than the large airways. The small airways were the main vulnerable region in the severe group. However, in the mild group, the large airways were considerably more vulnerable to air pollution than the small airways. The moderate group experienced the slightest impact. ANOVA test results of interaction terms for air pollution and group were significant, but some effects of air pollution on lung function were not significant. Table S6 shows the best predictive air pollution factor of each lung function change and its adjusted association of lung function and chronic exposure in all visits and each group.

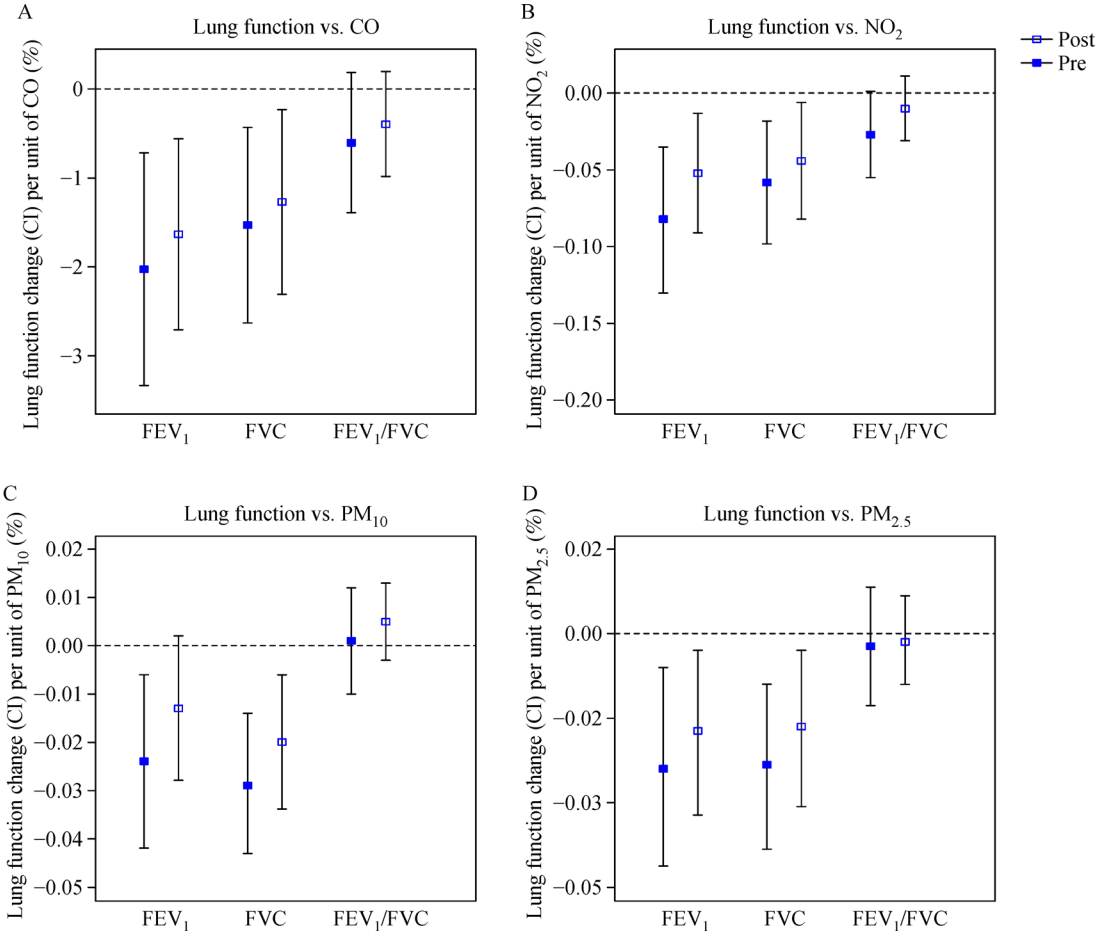

Fig. 4 Associations between CO, NO_2, PM_{10}, and $PM_{2.5}$ exposure and large airway function in the mild group. (A–D) Large airway function change (CI) per unit of CO, NO_2, PM_{10}, and $PM_{2.5}$, respectively. CI, confidence interval. Other abbreviations, see Table 2.

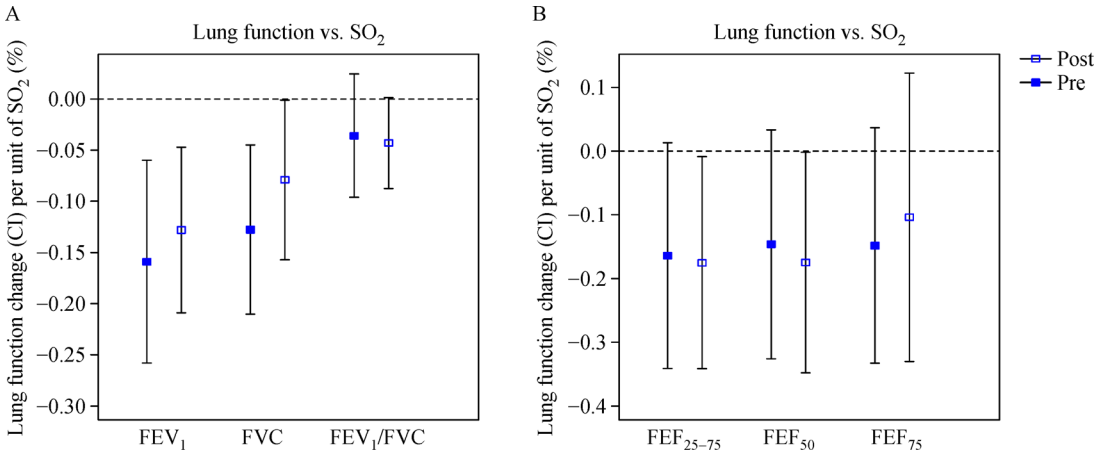

Fig. 5 Associations between SO_2 exposure and lung function in the mild group. (A and B) Large and small airway function change (CI) per unit of SO_2, respectively. CI, confidence interval. Other abbreviations, see Table 2.

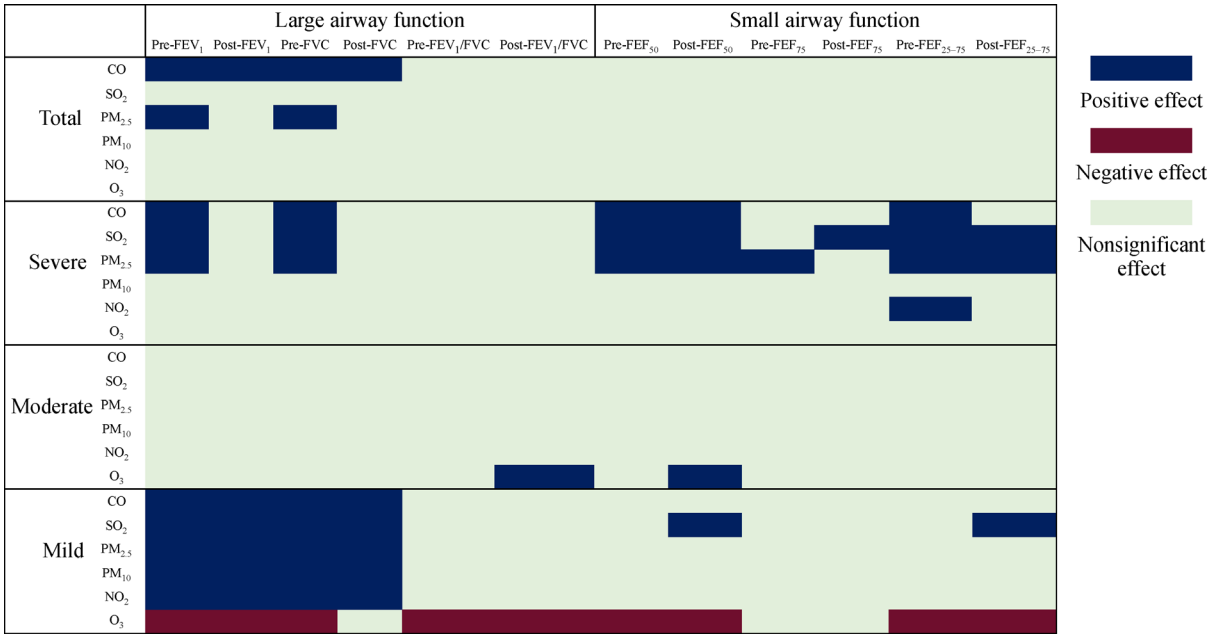

Fig. 6 Summary of all effects of air pollution exposure on lung function. Abbreviations, see Table 2. Blue and red areas represent significant positive and negative air pollution effects, respectively; green areas represent nonsignificant effects.

Discussion

Results showed that the inverse association of CO and $PM_{2.5}$ with large airway function in adults with asthma and the effect of SO_2 were more prominent compared with other pollutants in adults with asthma. Moreover, patients with asthma react differently to air pollutants based on their lung function levels. The small airway functions of patients with asthma were widely impaired, even for those with a relatively normal central airway function.

This prospective longitudinal panel study systematically elaborated the negative associations of chronic air pollution exposure with lung function, including large and small airway functions, in adults with asthma in China for 2 years. In our study, CO and $PM_{2.5}$ presented an overall negative effect on large airway function. Previous studies shared a similar outcome with ours regarding CO [12] and $PM_{2.5}$ [11,21,31–33] exposure on large airway function, but our research added knowledge of the long-term impact of $PM_{2.5}$ and CO on small airway function in asthmatic adults with poor lung function. The effects seemed reversible partly after bronchodilators. Previous trials

showed that annual long-term and 3-day short-term SO_2 exposure is negatively associated with FEV_1/FVC and $FEF_{25–75}$, respectively, in children with asthma [6,9], and single-day SO_2 exposure is associated with FEV_1/FVC in adults with asthma [20]. In our research, SO_2 negatively affected the large and small airway functions of the severe and mild groups, and the small airways seemed more sensitive to SO_2 than the large airways in adults with asthma. Reduction of SO_2 pollution may be a critical strategy in the management of asthma.

The effects of NO_2 and PM_{10} in our study failed to provide new evidence regarding NO_2 [31] and PM_{10} [21] compared with other related studies; these other studies were limited to studies of large airway effects. In participants with moderate asthma, only chronic O_3 exposure was inversely associated with lung function, and the association was consistent with previous evidence [12]. In participants with mild asthma, O_3 exposure was positively associated with lung function. This association was not in accordance with previous results. However, negative correlations were found between O_3 and other pollutants, which prompted that inverse collinearity may lead to the positive effect of O_3 and that the negative effects of other pollutants were significant.

The different asthma subgroups were distinctively affected. The small airways were the main vulnerable region in the severe group, and the lung function in the mild group was affected more widely. In the participants with mild lung function, the large airways were more vulnerable to air pollution than the small airways. By contrast, the adults with moderate asthma experienced the slightest impact. With the deterioration of lung function, the effect on the large airways was attenuated and that on the small airways was enhanced. The severe asthma group had the highest regular ICS availability (93.6%), whereas the mild group had the lowest ICS availability. This result suggests that ICS can lighten the effect of air pollution on the large airways but not on the small airways. Asthma patients with different lung function levels react differently to air pollution exposure, indicating that post-FEV_1/FVC is a reasonable objective marker to distinguish the special subgroups of patients with asthma vulnerable to air pollution. The effect of air pollution presented a U-type effect in our study, and the moderate group presented the weakest effect, whereas obvious and wide effects were found in the severe and mild groups.

The small airways play a key role in the prevalence of asthma [23], and small airway dysfunction leads to asthma persistence and terrible control [26]. A multinational prospective cohort study showed that small airway dysfunction is present in all severities of asthma, particularly in the severe type [27]. In our panel, the small airway functions of the patients with asthma were impaired widely, even in individuals with a relatively normal large airway function, emphasizing the high prevalence of small airway dysfunction in adults with asthma in China.

Our 2-year prospective longitudinal panel showed that chronic air pollution exposure exerted a significantly negative impact on the large and small airway functions of adults with asthma in China. However, this study has some limitations. First, few associations were found in the moderate asthma subgroup, which violated the hypothesis that the air pollution effect coincides with the severity of asthma. Both asthmatic participants with and without complicated COPD were included in the study even though complicated COPD did not show significant effects. This result should be clarified in future studies without including patients with complicated COPD. Second, as in the same city with severe air pollution, the levels of the six air pollutants in Beijing were tightly correlated. Therefore, the single effects of each pollutant were difficult to distinguish definitively because of the inevitable multicollinearity. However, the collinearity of the pollutants could not influence the prediction of lung function variation. We determined the optimal predictive factors based on the R2 of the model. A wearable air quality monitor may better distinguish the single effect of each pollutant, eliminating the collinearity and ambient environmental influence [34].

Conclusions

CO and $PM_{2.5}$ exposure were negatively associated with the large airway function of adults with asthma. Reaction modes of air pollutants varied based on different lung function levels. The negative effects of SO_2 were widely observed in patients with severe and mild asthma but not in patients with moderate asthma.

Acknowledgements

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Compliance with ethics guidelines

Jun Wang, Wenshuai Xu, Xinlun Tian, Yanli Yang, Shao-Ting Wang, and Kai-Feng Xu declare that they have no conflict of interest. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the *Helsinki Declaration* of 1975, as revised in 2000(5). Informed consent was obtained from all patients for being included in the study.

Electronic Supplementary Material Supplementary material is available in the online version of this article at https://doi.org/10.1007/s11684-021-0882-1 and is accessible for authorized users.

The Supplementary material contains the validation exposure assessment in IDW and Tables S1–S5.

References

1. GBD 2015 Chronic Respiratory Disease Collaborators. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Respir Med 2017; 5(9): 691–706
2. Zhou M, Wang H, Zeng X, Yin P, Zhu J, Chen W, Li X, Wang L, Wang L, Liu Y, Liu J, Zhang M, Qi J, Yu S, Afshin A, Gakidou E, Glenn S, Krish VS, Miller-Petrie MK, Mountjoy-Venning WC, Mullany EC, Redford SB, Liu H, Naghavi M, Hay SI, Wang L, Murray CJL, Liang X. Mortality, morbidity, and risk factors in China and its provinces, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2019; 394(10204): 1145–1158
3. Guarnieri M, Balmes JR. Outdoor air pollution and asthma. Lancet 2014; 383(9928): 1581–1592
4. Khreis H, Cirach M, Mueller N, de Hoogh K, Hoek G, Nieuwenhuijsen MJ, Rojas-Rueda D. Outdoor air pollution and the burden of childhood asthma across Europe. Eur Respir J 2019; 54(4): 1802194
5. Norbäck D, Lu C, Zhang Y, Li B, Zhao Z, Huang C, Zhang X, Qian H, Sun Y, Wang J, Liu W, Sundell J, Deng Q. Sources of indoor particulate matter (PM) and outdoor air pollution in China in relation to asthma, wheeze, rhinitis and eczema among pre-school children: Synergistic effects between antibiotics use and PM_{10} and second hand smoke. Environ Int 2019; 125: 252–260
6. Rosser F, Forno E, Kurland KS, Han YY, Mair C, Acosta-Pérez E, Canino G, Celedón JC. Annual SO_2 exposure, asthma, atopy, and lung function in Puerto Rican children. Pediatr Pulmonol 2020; 55 (2): 330–337
7. Knibbs LD, Cortés de Waterman AM, Toelle BG, Guo Y, Denison L, Jalaludin B, Marks GB, Williams GM. 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
8. Hansel NN, Romero KM, Pollard SL, Bose S, Psoter KJ, J Underhill L, Johnson C, Williams D, Curriero FC, Breysse P, Koehler K, Checkley W; GASP Study Investigators. Ambient air pollution and variation in multiple domains of asthma morbidity among Peruvian children. Ann Am Thorac Soc 2019; 16(3): 348–355
9. Liu L, Poon R, Chen L, Frescura AM, Montuschi P, Ciabattoni G, Wheeler A, Dales R. Acute effects of air pollution on pulmonary function, airway inflammation, and oxidative stress in asthmatic children. Environ Health Perspect 2009; 117(4): 668–674
10. Gaffin JM, Hauptman M, Petty CR, Sheehan WJ, Lai PS, Wolfson JM, Gold DR, Coull BA, Koutrakis P, Phipatanakul W. Nitrogen dioxide exposure in school classrooms of inner-city children with asthma. J Allergy Clin Immunol 2018; 141(6): 2249–2255.e2
11. Neophytou AM, White MJ, Oh SS, Thakur N, Galanter JM, Nishimura KK, Pino-Yanes M, Torgerson DG, Gignoux CR, Eng C, Nguyen EA, Hu D, Mak AC, Kumar R, Seibold MA, Davis A, Farber HJ, Meade K, Avila PC, Serebrisky D, Lenoir MA, Brigino-Buenaventura E, Rodriguez-Cintron W, Bibbins-Domingo K, Thyne SM, Williams LK, Sen S, Gilliland FD, Gauderman WJ, Rodriguez-Santana JR, Lurmann F, Balmes JR, Eisen EA, Burchard EG. Air pollution and lung function in minority youth with asthma in the GALA II (Genes-Environments and Admixture in Latino Americans) and SAGE II (Study of African Americans, Asthma, Genes, and Environments) Studies. Am J Respir Crit Care Med 2016; 193(11): 1271–1280
12. Ierodiakonou D, Zanobetti A, Coull BA, Melly S, Postma DS, Boezen HM, Vonk JM, Williams PV, Shapiro GG, McKone EF, Hallstrand TS, Koenig JQ, Schildcrout JS, Lumley T, Fuhlbrigge AN, Koutrakis P, Schwartz J, Weiss ST, Gold DR; Childhood Asthma Management Program Research Group. Ambient air pollution, lung function, and airway responsiveness in asthmatic children. J Allergy Clin Immunol 2016; 137(2): 390–399
13. Fuertes E, Bracher J, Flexeder C, Markevych I, Klümper C, Hoffmann B, Krämer U, von Berg A, Bauer CP, Koletzko S, Berdel D, Heinrich J, Schulz H. 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
14. Gauderman WJ, Urman R, Avol E, Berhane K, McConnell R, Rappaport E, Chang R, Lurmann F, Gilliland F. Association of improved air quality with lung development in children. N Engl J Med 2015; 372(10): 905–913
15. Arnetz BB, Arnetz J, Harkema JR, Morishita M, Slonager K, Sudan S, Jamil H. Neighborhood air pollution and household environmental health as it relates to respiratory health and healthcare utilization among elderly persons with asthma. J Asthma 2020; 57 (1): 28–39
16. Martínez-Rivera C, Garcia-Olivé I, Stojanovic Z, Radua J, Ruiz Manzano J, Abad-Capa J. Association between air pollution and asthma exacerbations in Badalona, Barcelona (Spain), 2008–2016. Med Clin (Barc) 2019; 152(9): 333–338
17. Shin SW, Bae DJ, Park CS, Lee JU, Kim RH, Kim SR, Chang HS, Park JS. Effects of air pollution on moderate and severe asthma exacerbations. J Asthma 2020; 57(8): 875–885
18. Chan CL, Phan DV, Yang NP, Pan RH, Wu CY, Chen CL, Kuo CY. A survey of ambulatory-treated asthma and correlation with weather and air pollution conditions within Taiwan during 2001–2010. J Asthma 2019; 56(8): 799–807
19. Liu Y, Pan J, Zhang H, Shi C, Li G, Peng Z, Ma J, Zhou Y, Zhang L. Short-term exposure to ambient air pollution and asthma mortality. Am J Respir Crit Care Med 2019; 200(1): 24–32
20. Yu S, Park S, Park CS, Kim S. Association between the ratio of FEV_1 to FVC and the exposure level to air pollution in neversmoking adult refractory asthmatics using data clustered by patient in the Soonchunhyang Asthma Cohort Database. Int J Environ Res Public Health 2018; 15(11): 2349
21. Chen CH, Wu CD, Chiang HC, Chu D, Lee KY, Lin WY, Yeh JI, Tsai KW, Guo YLL. The effects of fine and coarse particulate matter on lung function among the elderly. Sci Rep 2019; 9(1): 14790
22. Chambers L, Finch J, Edwards K, Jeanjean A, Leigh R, Gonem S. Effects of personal air pollution exposure on asthma symptoms, lung function and airway inflammation. Clin Exp Allergy 2018; 48(7): 798–805

23. Kraft M. The distal airways: are they important in asthma? Eur Respir J 1999; 14(6): 1403–1417
24. Bjermer L. The role of small airway disease in asthma. Curr Opin Pulm Med 2014; 20(1): 23–30
25. Hamid Q, Song Y, Kotsimbos TC, Minshall E, Bai TR, Hegele RG, Hogg JC. Inflammation of small airways in asthma. J Allergy Clin Immunol 1997; 100(1): 44–51
26. Siroux V, Boudier A, Dolgopoloff M, Chanoine S, Bousquet J, Gormand F, Just J, Le Moual N, Nadif R, Pison C, Varraso R, Matran R, Pin I. Forced midexpiratory flow between 25% and 75% of forced vital capacity is associated with long-term persistence of asthma and poor asthma outcomes. J Allergy Clin Immunol 2016;137(6): 1709–1716.e6
27. Postma DS, Brightling C, Baldi S, Van den Berge M, Fabbri LM, Gagnatelli A, Papi A, Van der Molen T, Rabe KF, Siddiqui S, Singh D, Nicolini G, Kraft M; ATLANTIS study group. Exploring the relevance and extent of small airways dysfunction in asthma (ATLANTIS): baseline data from a prospective cohort study. Lancet Respir Med 2019; 7(5): 402–416
28. Xiao D, Chen Z, Wu S, Huang K, Xu J, Yang L, Xu Y, Zhang X, Bai C, Kang J, Ran P, Shen H, Wen F, Yao W, Sun T, Shan G, Yang T, Lin Y, Zhu J, Wang R, Shi Z, Zhao J, Ye X, Song Y, Wang Q, Hou G, Zhou Y, Li W, Ding L, Wang H, Chen Y, Guo Y, Xiao F, Lu Y, Peng X, Zhang B, Wang Z, Zhang H, Bu X, Zhang X, An L, Zhang S, Cao Z, Zhan Q, Yang Y, Liang L, Liu Z, Zhang X, Cheng A, Cao B, Dai H, Chung KF, He J, Wang C; China Pulmonary Health Study Group. Prevalence and risk factors of small airway dysfunction, and association with smoking, in China: findings from a national cross-sectional study. Lancet Respir Med 2020; 8(11): 1081–1093
29. Reddel HK, Bateman ED, Becker A, Boulet LP, Cruz AA, Drazen JM, Haahtela T, Hurd SS, Inoue H, de Jongste JC, Lemanske RF Jr, Levy ML, O'Byrne PM, Paggiaro P, Pedersen SE, Pizzichini E, Soto-Quiroz M, Szefler SJ, Wong GW, FitzGerald JM. A summary of the new GINA strategy: a roadmap to asthma control. Eur Respir J 2015; 46(3): 622–639
30. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J; ATS/ERS Task Force. Standardisation of spirometry. Eur Respir J 2005; 26(2): 319–338
31. McCreanor J, Cullinan P, Nieuwenhuijsen MJ, Stewart-Evans J, Malliarou E, Jarup L, Harrington R, Svartengren M, Han IK, Ohman-Strickland P, Chung KF, Zhang J. Respiratory effects of exposure to diesel traffic in persons with asthma. N Engl J Med 2007; 357(23): 2348–2358
32. Balmes JR, Cisternas M, Quinlan PJ, Trupin L, Lurmann FW, Katz PP, Blanc PD. Annual average ambient particulate matter exposure estimates, measured home particulate matter, and hair nicotine are associated with respiratory outcomes in adults with asthma. Environ Res 2014; 129: 1–10
33. Penttinen P, Timonen KL, Tiittanen P, Mirme A, Ruuskanen J, Pekkanen J. Number concentration and size of particles in urban air: effects on spirometric lung function in adult asthmatic subjects. Environ Health Perspect 2001; 109(4): 319–323
34. Delfino RJ, Staimer N, Tjoa T, Gillen D, Kleinman MT, Sioutas C, Cooper D. Personal and ambient air pollution exposures and lung function decrements in children with asthma. Environ Health Perspect 2008; 116(4): 550–558