



Associations of personal exposure to air pollutants with airway mechanics in children with asthma



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ABSTRACT

Background: The importance of airway mechanics has been increasingly recognized in pediatric asthma. However, no studies have examined responses of airway mechanics to air pollution exposure in asthmatic children.

Methods: In this panel study involving indoor air filtration manipulation that created a large gradient of personal exposure to PM_{2.5}, the airway mechanics and lung function of 43 asthmatic children 5–13 years old in a suburb of Shanghai were measured four times within 3 consecutive months. Concentrations of indoor and outdoor PM_{2.5} and ozone were coupled with individual time-activity data to calculate personal exposures. Linear mixed effects models were used to examine the relationships of personal exposure with indicators of airway mechanics and lung function, respectively.

Results: An interquartile range (IQR) increase in 24-hour average PM_{2.5} personal exposure (30.3 μg/m³) in the prior day was associated with significant increases in small airway resistance (R_s-R₂₀) of 15.8%, total airway resistance (R_t) of 6.3%, and airway inflammation (FeNO) of 9.6%. These associations were stronger in children with lower blood eosinophil counts (< 450/μL). No significant associations were found between personal PM_{2.5} exposure and lung function. Low-level ozone exposure (daily maximum 8-hour exposure range 1.1–56.4 ppb) was not significantly associated with any of the outcomes.

Conclusion: Changes in personal PM_{2.5} exposure, partly enhanced by air filtration, were associated with significant changes in airway resistance and inflammation in children with asthma. These findings suggest the importance of reducing PM_{2.5} exposure, via personal air quality management, in improving airflow limitation in the airways, especially the small airways.

Abbreviations: PM_{2.5}, particles with an aerodynamic diameter ≤ 2.5 μm; O₃, ozone; IOS, impulse oscillometry; HEPA, high-efficiency particulate air; I/O ratio, indoor/outdoor; IgE, immunoglobulin E; Z₅, airway impedance measured at 5 Hz; R₅, airway resistance measured at 5 Hz; R₂₀, airway resistance measured at 20 Hz; R₅-R₂₀, difference between airway resistance measured at 5 Hz and 20 Hz; X₅, airway reactance measured at 5 Hz; F_{res}, resonant frequency; FEV₁, forced expiratory volume in first second; FEV₁/FEV₁ predicted, the ratio between FEV₁ and predicted FEV₁; FVC, forced vital capacity; FVC/FVC, predicted: the ratio between FVC and predicted FVC; PEF, peak expiratory flow; FEF₂₅₋₇₅, the average forced expiratory flow during 25% to 75% of FVC; FEV₁/FVC, the ratio between FEV₁ and FVC; FeNO, fractional exhaled nitric oxide; LMER, linear mixed-effects regression; VOCs, volatile organic compounds; SVOCs, semi-volatile organic compounds

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1. Introduction

Airborne fine particles with an aerodynamic diameter $\leq 2.5 \mu\text{m}$ ($\text{PM}_{2.5}$) and ozone (O_3) are well-established risk factors for asthma exacerbation (Guarnieri and Balmes, 2014). Elevated $\text{PM}_{2.5}$ and O_3 levels are found in polluted urban atmospheres worldwide (Lelieveld et al., 2015). Indoor $\text{PM}_{2.5}$ concentrations are substantially elevated in the presence of smoking, cooking, and floor vacuuming. Indoor concentrations are also elevated by the infiltration of outdoor $\text{PM}_{2.5}$ and O_3 in poorly sealed building (Fabian et al., 2012; Stephens et al., 2011). Hence, it is important to understand how personal exposure to these pollutants can affect the physiology and function of the asthmatic lung.

Spirometric lung function, widely used in asthma diagnosis and prognosis, has been associated with personal air pollutant exposure. For example, a previous study reported that the increase in $\text{PM}_{2.5}$ exposure measured 24-hour prior was associated with decreased forced expiratory volume in the first second (FEV_1) in children with asthma (Delfino et al., 2004). Another study reported that the increase in 24-hour average personal $\text{PM}_{2.5}$ exposure measured one day prior was associated with a decrease in peak expiratory flow (PEF) in asthmatic children (Trenka et al., 2006). In contrast, a different study, also in asthmatic children, did not find significant associations between FEV_1 and $\text{PM}_{2.5}$ exposure measured 24-hour prior (Delfino et al., 2007). The inconsistency has been attributed to differences in a variety of factors such as $\text{PM}_{2.5}$ exposure level and/or range, demographic characteristics, air pollution composition, and other unmeasured potential confounders. In addition, lung function changes require a relatively strong acute stimulus or persistent stress to the lung.

Compared to lung function, airway mechanics are a more sensitive metric used to monitor airway obstruction and airflow limitation. Although clinical bench mark values are yet to be established, airway mechanics have been increasingly used as a supplement to spirometry for diagnosing asthma and to monitor disease prognosis (Guan et al., 2015; Saadeh et al., 2015). In addition, while spirometry requires a subject to blow as hard as possible, impulse oscillometry (IOS) is conducted with normal breathing to measure airway mechanics. This minimizes the data loss due to technical noncompliance from certain subjects, especially children, who cannot perform an accurate spirometry test (Komarow et al., 2011). However, to the best of our knowledge, no studies have investigated the relationships of airway mechanics with personal air pollutant exposure in children with asthma.

We hypothesized that increasing personal air pollutant exposure is associated with worsening airway mechanics. To test this hypothesis, we used the data collected from a cohort of children with asthma. We aim to perform exposure-response analyses in examining the associations of airway mechanics (and lung function) with 24-hour average personal pollutant exposure measured zero to six days prior to outcome measurements in asthmatic children. As asthma is a heterogeneous disease, we further explored whether baseline airway eosinophilic inflammation would affect the exposure-response relationships (Berry et al., 2007).

2. Methods

2.1. Study participants

We recruited 43 children (26 boys and 17 girls) 5 to 13 years old from a pool of children who had been diagnosed with mild or moderate asthma at the outpatient clinic of the Shanghai General Hospital, located in Songjiang, a suburb of Shanghai, China. In order to be eligible, participants should have physician-diagnosed asthma and at least one asthma attack during the past year. All the individuals with chronic diseases other than asthma were excluded. Oral assent and written consent were obtained from all participants and their guardians, respectively. The Ethics Committee of Shanghai General Hospital and Duke University Campus IRB approved the study protocol.

2.2. Study design

The present study used data that had been collected in an indoor air filtration intervention in which indoor $\text{PM}_{2.5}$ and O_3 concentrations were manipulated through operation of a portable air purifier (Atmosphere[®], Amway, USA) in participants' bedrooms (Barkjohn et al., 2019; Zhan et al., 2018). Briefly, each air purifier was equipped with a coarse filter, a high-efficiency particulate air (HEPA) filter, and an activated carbon filter to remove particulate matter and O_3 . The operation schedule of the indoor air purifier is shown in Fig. 1. Prior to visits 1 and 3 the air purifier was absent, and prior to visits 2 and 4 the air purifier was present either with all three filters intact or only with the coarse filter (the HEPA and activated carbon filters removed). During the intervention period, the participants were suggested to close their home windows as much as possible whenever they were home. The effects of the intervention on indoor air quality have been reported previously (Brehmer et al., 2019a; Brehmer et al., 2019b; Fang et al., 2019; Norris et al., 2019). In the present analysis, we aim to examine relationships of airway mechanics and lung function with personal pollutant exposure in asthmatic children. The analysis is based on a panel study design as respiratory measurements were taken for each participant four times (at Visits 1–4), with two weeks in between the visits. All the visits occurred between February 14 and April 14, 2017. Efforts were made to conduct all measurements at the same time of day for all four visits.

2.3. Exposure assessment

$\text{PM}_{2.5}$ and O_3 were simultaneously measured both in children's bedrooms and outside a window of their homes. These pollutants were continuously measured using an integrated sensor box equipped with a Plantower PMS3003 sensor for $\text{PM}_{2.5}$ and an Alphasense sensor (OX-A4) for O_3 . The sensors generated the hourly averages of pollutant concentration. These sensors, validated in Beijing, Shanghai, and other cities previously (Barkjohn et al., 2019; Liu et al., 2020; Zhang et al., 2019; Zheng et al., 2018), were field calibrated in Shanghai before the

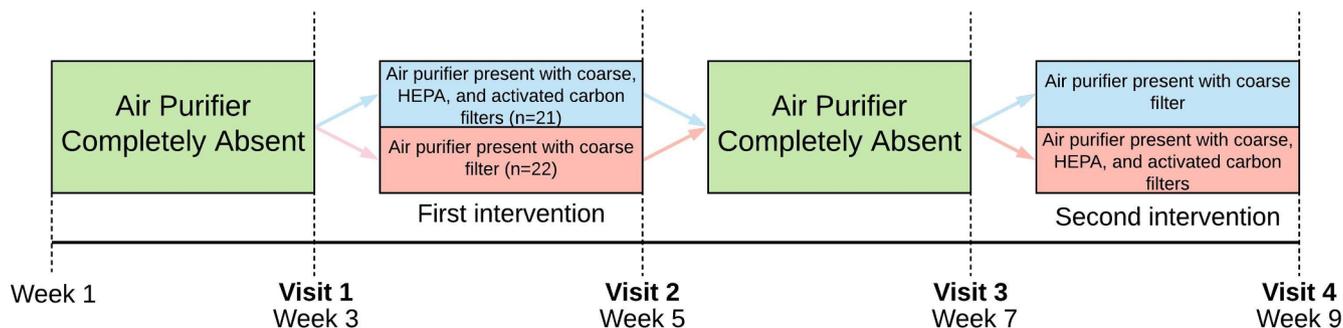


Fig. 1. Air purifier operation schedule in relation to the clinic visits for physiological measurements.

start of the study and at the end of the study to account for any drift in sensor function over the duration of the study. We also obtained the ambient hourly averages of PM_{2.5}, O₃, temperature, and relative humidity during the entire study period from the government monitoring station closest to the research clinic (~9 km away), and they were summarized in Table S1. In this study, the ambient air pollutant concentrations were calculated by averaging the pollutant concentrations measured by all the outdoor sensors and the governmental monitoring station. An indoor/outdoor (I/O) ratio of 0.8 and 0.35 were used to calculate the hourly average for PM_{2.5} and O₃ concentrations (Day et al., 2017), respectively, in other indoor environments (e.g., classroom) based on the measurements of the ambient air pollutant concentration. In addition, pollutant concentrations in cars or subways were calculated using I/O ratios based on the literature. Different I/O ratios were applied when the participants' home windows were recorded to be open (see Table S2 in the Supplement). Combining these measured or estimated pollutant concentrations for each encountered microenvironment with detailed time-activity data (see Table S3 in the Supplement), we calculated 24-hour time-weighted personal PM_{2.5} exposures and maximum 8-hour averages of personal O₃ exposure zero to six days (lag day 0–6) prior to each clinic visit. The lag analysis is based on the consideration that air pollutants have delayed or cumulative respiratory effects on asthma morbidity (Delfino et al., 2004; Von Klot et al., 2002). We also calculated personal PM_{2.5} and O₃ exposure averaged over the two weeks prior to each clinic visit. The detailed exposure assessment is reported in the Supplement.

2.4. Health outcomes

Upon enrollment, each participant was measured for baseline weight, height, airway mechanics, and lung function. Each also received an immunoglobulin E (IgE)-mediated allergy test (Allergy Screen®, Mediwiss Analytic GmbH Germany). Allergens including dust mite, room dust, mold, cat dander, dog dander, roach egg, milk, and shrimp were tested. The blood IgE level of 0.35 kU/L was set as the point of positive for allergic sensitization. We measured airway mechanics by impulse oscillometry (MasterScreen™ IOS, Becton, Dickinson and Company, Germany), lung function by spirometry (MasterScreen™ PFT system, Becton, Dickinson and Company, Germany), and fractional exhaled nitric oxide (FeNO) using a NIOX VERO with the adult mode (Circassia Pharmaceuticals Inc., USA). Indicators of airway mechanics included impedance at 5 Hz (Z₅, increased Z₅ means higher airway impedance), resistance at 5 Hz (R₅, increased R₅ means higher total airway resistance), resistance at 20 Hz (R₂₀, increased R₂₀ means higher large airway resistance), reactance at 5 Hz (X₅, increased X₅ negative values means worse airway resilience), and resonant frequency (Fres, increased Fres means worse airway resilience). Main spirometric lung function indicators included forced expiratory volume in the first second (FEV₁), forced vital capacity (FVC), peak expiratory flow (PEF), forced expiratory flow at 25–75% of the FVC (FEF₂₅₋₇₅), and the ratio between FEV₁ and FVC (FEV₁/FVC). Each participant attempted the impulse oscillometry and spirometry measurements until the variation among the three most recent measurements was smaller than 5%, and the highest value among these three measurements was used for data analysis.

2.5. Statistical analysis

We report means with standard deviation (SD) and medians with interquartile range (IQR) and range for participants' baseline characteristics. The Spearman correlations among personal air pollutant exposures were calculated.

The main objective of this paper is to assess the exposure-response relationships for PM_{2.5} and O₃. As personal exposure was manipulated by air filtration in the bedrooms, we first wanted to evaluate any potential impact of “air filtration status alone”, which was to assess

potential confounding from changes other than PM_{2.5} and O₃ brought by air filtration. We used linear mixed-effects regression (LMER) models in which a health outcome was the dependent variable, filtration status (no filtration versus coarse + HEPA + activated carbon filters versus coarse filters) was the independent variable; the fixed-effects covariates included 2-week average personal PM_{2.5} and O₃ exposure, 2-week average ambient temperature and relative humidity, sex, age, baseline eosinophil count, upper respiratory tract infection status, opioid cough suppressant usage, dust mite allergy status, sleep duration, asthma exacerbation status, inhaled corticosteroids usage, and travel status (whether or not traveled during the two weeks prior to each of the clinical visits). We controlled for random-effect variables including subject ID and the day of the week for clinical visit as random intercepts. From the model output, we calculated percent change (and 95% confidence interval) in the outcome following the use of the three filters together or the use of only coarse filter in reference to following the absence of any filters. The results represent the effect of filtration status alone, not the overall effect of air filtration that would integrate the effect of filtration status alone and the effect of PM_{2.5} and O₃ change resulting from the filtration.

Secondly, we used LMER models to assess the associations between personal air pollutant exposure and a health outcome. In these models, each of the health outcomes was the dependent variable, and the personal pollutant exposure was the independent variable. We adjusted for the same covariates as described in the first model, except that the 2-week average PM_{2.5} and O₃ exposure were not included. From the model output, we calculated percent change (and 95% confidence interval) of the outcome associated with an IQR increase in personal pollutant exposure. Based on the results from the first set of models described above, we deemed it not appropriate to include the data measured following the use of only the coarse filter due to concerns on additional confounding associated with this condition. Hence, the data from three visits per person were used in the analysis of exposure-response relationships.

Thirdly, we conducted stratified analyses to assess the pollutant exposure-response relationship for pulmonary health outcomes based on low (≤ 450 / μ L) versus high (> 450 / μ L) blood eosinophils number, which is a suggested cutoff point for the presence of eosinophilic asthma (Fulkerson and Rothenberg, 2013). In these models, each health outcome was the dependent variable and personal pollutant exposure was the independent variable along with the same covariate structure described in the second set of models. From each model output, we generated estimates in percent change (and 95% confidence interval) in the outcome associated with an IQR increase in pollutant exposure.

Finally, we conducted several sensitivity analyses. (1) We examined the exposure-response relationship in the data collected only in the two no-filtration visits. (2) We used co-pollutant models to examine whether the exposure-response relationships obtained in the single-pollutant models can be retained after controlling for a co-pollutant. (3) We conducted separate analyses by excluding participants who traveled or used an inhaled corticosteroids during the two weeks prior to each of the clinical visits. (4) We conducted separate analyses by including measurement from all the clinical visits. All statistical analyses were conducted using *lme4* and *lmeTest* in R software (version 3.6.1). A P-value of 0.05 was set as the cut point for statistical significance. Based on data distributions, air pollutant exposures and some of health outcomes were natural logarithm-transformed. A detailed description of equations and codes used for the statistical models is provided in the Supplement.

3. Results

3.1. Participant characteristics

We measured 43 children with stable, mild or modest asthma (see Table 1). Among the children, 13 (30.2%) had baseline eosinophil

Table 1
Baseline characteristics of participants.

Subject Characteristics	Value
Age, mean \pm SD [range] (year)	7.8 \pm 2.3[5–13]
Female, No. (%)	17 (40%)
Weight, mean \pm SD [range] (Kg)	31.2 \pm 10.3 [19.0–59.0]
Height, mean \pm SD [range] (cm)	132.3 \pm 13.3 [110.0–166.0]
Blood eosinophil count, mean \pm SD [range] (/ μ L)	378.8 \pm 264.6 [80.0–1260.0]
FEV ₁ /FEV ₁ predicted, mean \pm SD [range] (%)	103.0 \pm 16.5 [65.5–143.0]
FVC/FVC predicted, mean \pm SD [range] (%)	104.8 \pm 12.0 [81.1–140.3]
Baseline FeNO > 20 ppb, No. (%)	13 (30.2%)
Atopic, No. (%)	35 (81.3%)
Dust mite allergy, No. (%)	27 (62.7%)
Opioid cough suppressant usage, No. (%)	3 (7.0%)
Inhaled corticosteroids usage, No. (%)	12 (27.8%)

Definition of abbreviations: FEV₁/FEV₁ predicted = the ratio between FEV₁ and predicted FEV₁; FVC/FVC predicted: the ratio between FVC and predicted FVC

count > 450/ μ L, three (7.0%) had FEV₁/Predicted FEV₁ < 80%, 13 (30.2%) had FeNO > 20 ppb, and 35 (81.3%) were atopic and were mostly allergic to dust mite. During the study period, 9 children (20.9%) had a fever, 7 (16.3%) had asthma exacerbation, 3 (7.0%) used opioid cough suppressant, and 12 (27.8) used inhaled corticosteroids.

3.2. Air pollutant exposure in relation to filtration status

Participants spent 12.3 \pm 2.8 h per day in their bedrooms, which provided an opportunity to generate a wide range of personal pollutant exposures by manipulating the bedroom air pollutant concentration through air filtration. In Table 2, 24-hour average personal PM_{2.5} and O₃ exposure 0–6 days prior to each clinic visit are compared. When the clinic visits occurred following no filtration, the mean personal PM_{2.5} exposures were the highest. When the clinic visits occurred following the use of the three filters, the mean PM_{2.5} exposures were the lowest. When the clinic visits occurred following the use of the coarse filter only, the mean exposures were in the middle. The maximum daily 8-hour average personal O₃ exposure 0–6 days prior to a clinic visit did not differ substantially by filtration status. The results indicate that by operating bedroom air purification, a wider range in personal PM_{2.5} exposure was obtained, while not for O₃ exposure. As shown in Fig. S1, there were no strong correlations between PM_{2.5} exposure and O₃ exposure.

3.3. Health outcomes in relation to filtration status

As shown in Table 2, the participants' airway mechanics were the worst after the 2-week use of only the coarse filter even though concentrations of PM_{2.5} were lower during this period than they were in the absence of any filtration. The effects of "filtration status alone", independent of the effect of PM_{2.5} and O₃ changes resulting from the filtration, are shown in Fig. 2. We found that using only the coarse filter was associated with increases in Z₅, R₅, and R₅-R₂₀ by 8.4% (95%CI: -0.2%–16.9%), 9.7% (-0.9% - 20.3%), and 27.6% (0.5% - 54.7%), respectively, compared with using no filtration at all. However, none of the outcomes changed significantly when comparing the visits following the use of all the three filters to the visits following the absence of any filtration. The filtration status did not show a significant effect on the spirometric lung function measures and FeNO, although it appears that the use of coarse filter was associated with a 12.5% (-4.9% to 33.0%) increase in FeNO (Fig. 2). Please note that these "filtration status alone" effects, excluding the effect of PM_{2.5} reduction caused by the filtration, do not reflect the overall (net) effect of filtration.

3.4. Exposure-response relationship

Concerning the effects of potential co-pollutants exposure as shown above, we excluded the visits following the use of coarse filter in the exposure-response analysis. Using the data from the other three visits, as shown in Fig. 3, we found that an IQR (30.3 μ g/m³) increase in 24-hour personal PM_{2.5} exposure one day prior to the clinic visits was significantly associated with increases in total airway resistance (R₅) of 6.3% (0.1–12.5%), small airway resistance (R₅-R₂₀) of 15.8% (95%CI: 0.4–31.1%), and fractional exhaled nitric oxide (FeNO) of 9.6% (0.7–19.3%). In addition, IQR increases in 24-hour PM_{2.5} exposure measured zero days (27.1 μ g/m³), three days (22.8 μ g/m³), four days (29.2 μ g/m³), and five days (38.9 μ g/m³) prior to the clinic visits were associated with increases in FeNO of 12.1% (1.3% to 24.2%), 20.6% (8.9% to 33.5%), 18.2% (8.4% to 28.9%), and 25.3% (9.5% to 43.4%), respectively. We did not observe a significant association between any prior-day PM_{2.5} exposure and any of the lung function measures. We did not find a significant or a clear trend in association between O₃ exposure and any of the health outcomes (Fig. 3).

3.5. Effect modification

We considered baseline blood eosinophil count as a potential effect modifier. In stratified analyses, we found that the increase in personal PM_{2.5} exposure was associated with significant increases in Z₅, R₅, R₅-R₂₀, and FeNO only in children with lower blood eosinophil counts (\leq 450/ μ L) (Fig. 4). In children with higher blood eosinophil counts, the exposure-response associations were non-significant and unclear, except that an increase in PM_{2.5} exposure five days prior to the clinic visits was associated with significant decreases in Z₅ and R₅, and a significant increase in FEV₁.

4. Discussion

The principal finding of this study is that day-to-day increases in personal PM_{2.5} exposure were associated with worsening airflow limitation in asthmatic children due to increased airway resistance and pulmonary inflammation. As improving airflow is a key challenge in asthma management, these associations point to the importance of reducing personal PM_{2.5} as a practical means of asthma control especially for those living in places with higher concentrations of ambient and/or indoor PM_{2.5}.

In the present study, we found that increased PM_{2.5} exposures measured several days prior were associated with significantly increased FeNO, confirming that FeNO is a sensitive biomarker of air pollutant induced airway inflammation (Ferrante et al., 2013). However, the associations of spirometric lung function and PM_{2.5} exposure were non-significant and unclear (see Fig. 3). The results were supported by previous studies. For example, one study reported that an IQR (24.0 μ g/m³) increase in personal PM_{2.5} exposure averaged over 48-hours prior to the health outcome measurement (mean \pm SD: 36.2 \pm 25.5 μ g/m³) was associated with a significant increase in FeNO of 4.2% in asthmatic children (Delfino et al., 2006). Another study reported that increased PM_{2.5} exposure 24-hour prior to the clinical visit (mean \pm SD: 31.2 \pm 21.8 μ g/m³) was not associated with a change in FEV₁ in asthmatic children (Delfino et al., 2007). In contrast, Delfino et al., 2004 found that an IQR (30.3 μ g/m³) increase in personal PM_{2.5} exposure during the preceding 24-hour (mean \pm SD: 37.9 \pm 19.9 μ g/m³) was associated with a decrease in FEV₁ of 5.9% in children with asthma (Delfino et al., 2004). Although the PM_{2.5} exposure concentrations reported in Delfino et al. (2004) are similar to those of the current study (lag 0 mean \pm SD: 39.5 \pm 17.1 μ g/m³), other factors including differences in demographic characteristics, study design, changes or ranges in exposure concentrations in different association analyses, and potential confounders might contribute to the inconsistency.

Table 2
Mean ± SD of personal air pollutant exposure and health outcomes for different filtration status.

	No Filtration	Filtration (Coarse + HEPA + Activated Carbon Filters)	Filtration (Coarse Filter)
<i>PM_{2.5} (µg/m³, 24-hour average)</i>			
Lag 0	49.0 ± 13.6	23.2 ± 11.7	36.8 ± 14.8
Lag 1	48.1 ± 16.1	21.2 ± 11.6	34.7 ± 19.3
Lag 2	43.0 ± 16.7	19.6 ± 10.4	32.5 ± 15.7
Lag 3	39.8 ± 12.2	21.1 ± 9.8	36.4 ± 16.7
Lag 4	44.0 ± 17.8	20.4 ± 9.5	35.7 ± 14.7
Lag 5	51.2 ± 23.8	20.5 ± 10.5	41.1 ± 26.8
Lag 6	50.3 ± 24.3	20.6 ± 9.2	43.9 ± 24.3
<i>O₃ (ppb, maximum 8-hour average)</i>			
Lag 0	22.2 ± 8.5	22.8 ± 9.0	20.2 ± 8.2
Lag 1	19.7 ± 7.6	19.3 ± 6.8	16.7 ± 6.1
Lag 2	20.8 ± 7.7	18.3 ± 4.9	18.5 ± 4.8
Lag 3	22.7 ± 7.4	18.6 ± 6.0	19.9 ± 6.4
Lag 4	22.8 ± 8.9	19.9 ± 6.5	20.4 ± 8.0
Lag 5	25.8 ± 10.4	22.0 ± 8.6	24.2 ± 10.8
Lag 6	28.0 ± 10.9	24.3 ± 10.6	26.1 ± 11.6
<i>Airway Mechanics</i>			
Z ₅ (cm H ₂ O/L/s)	8.8 ± 2.4	8.6 ± 2.7	9.5 ± 2.6
R ₅ (cm H ₂ O/L/s)	8.3 ± 2.3	7.8 ± 2.5	8.9 ± 2.6
R ₂₀ (cm H ₂ O/L/s)	5.6 ± 1.6	5.2 ± 1.6	5.5 ± 1.2
R ₅ -R ₂₀ (cm H ₂ O/L/s)	2.7 ± 1.7	2.7 ± 1.8	3.4 ± 2.0
X ₅ (cm H ₂ O/L/s)	-1.8 ± 2.5	-1.9 ± 2.6	-2.3 ± 2.1
Fres (Hz)	18.8 ± 6.4	18.7 ± 5.9	20.1 ± 6.5
<i>Lung Function</i>			
FEV ₁ (L)	1.7 ± 0.5	1.7 ± 0.5	1.7 ± 0.5
FVC (L)	2.1 ± 0.6	2.1 ± 0.6	2.1 ± 0.7
PEF (L/s)	3.8 ± 1.2	3.8 ± 1.1	3.9 ± 1.1
FEF ₂₅₋₇₅ (L/s)	1.7 ± 0.6	1.7 ± 0.6	1.7 ± 0.6
FEV ₁ /FVC	83.1 ± 8.6	83.1 ± 7.3	83.1 ± 8.1
<i>Airway Inflammation</i>			
FeNO (ppb)	22.7 ± 20.4	21.9 ± 18.9	25.7 ± 19.3

Definition of abbreviations: Z₅ = airway impedance measured at 5 Hz; R₅ = airway resistance measured at 5 Hz; R₂₀ = airway resistance measured at 20 Hz; R₅-R₂₀ = difference between airway resistance measured at 5 Hz and 20 Hz; X₅ = airway reactance measured at 5 Hz; Fres = resonant frequency; FEV₁ = forced expiratory volume in first second; FEV₁/FEV₁ predicted = the ratio between FEV₁ and predicted FEV₁; FVC = forced vital capacity; FVC/FVC predicted: the ratio between FVC and predicted FVC; PEF: peak expiratory flow; FEF₂₅₋₇₅ = the average forced expiratory flow during 25% to 75% of FVC; FEV₁/FVC = the ratio between FEV₁ and FVC; FeNO = fractional exhaled nitric oxide.

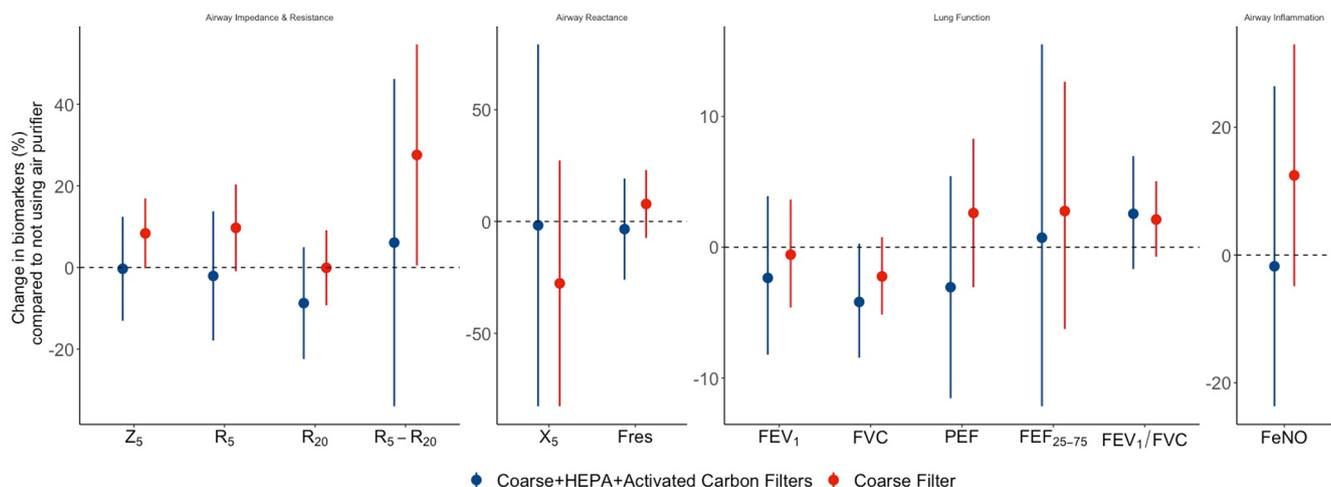


Fig. 2. Estimated means and 95% confident intervals for change in biomarkers (%) measured from after using no air purifier to using either air purifier with all the three filters or with only the coarse filter. Detailed model results were shown in Table S4 in the Supplement. Definition of abbreviations: Z₅ = airway impedance measured at 5 Hz; R₅ = airway resistance measured at 5 Hz; R₂₀ = airway resistance measured at 20 Hz; R₅-R₂₀ = difference between airway resistance measured at 5 Hz and 20 Hz; X₅ = airway reactance measured at 5 Hz; Fres = resonant frequency; FEV₁ = forced expiratory volume in first second; FVC = forced vital capacity; PEF: peak expiratory flow; FEF₂₅₋₇₅ = the average forced expiratory flow during 25% to 75% of FVC; FEV₁/FVC = the ratio of FEV₁ and FVC; FeNO = fractional exhaled nitric oxide.

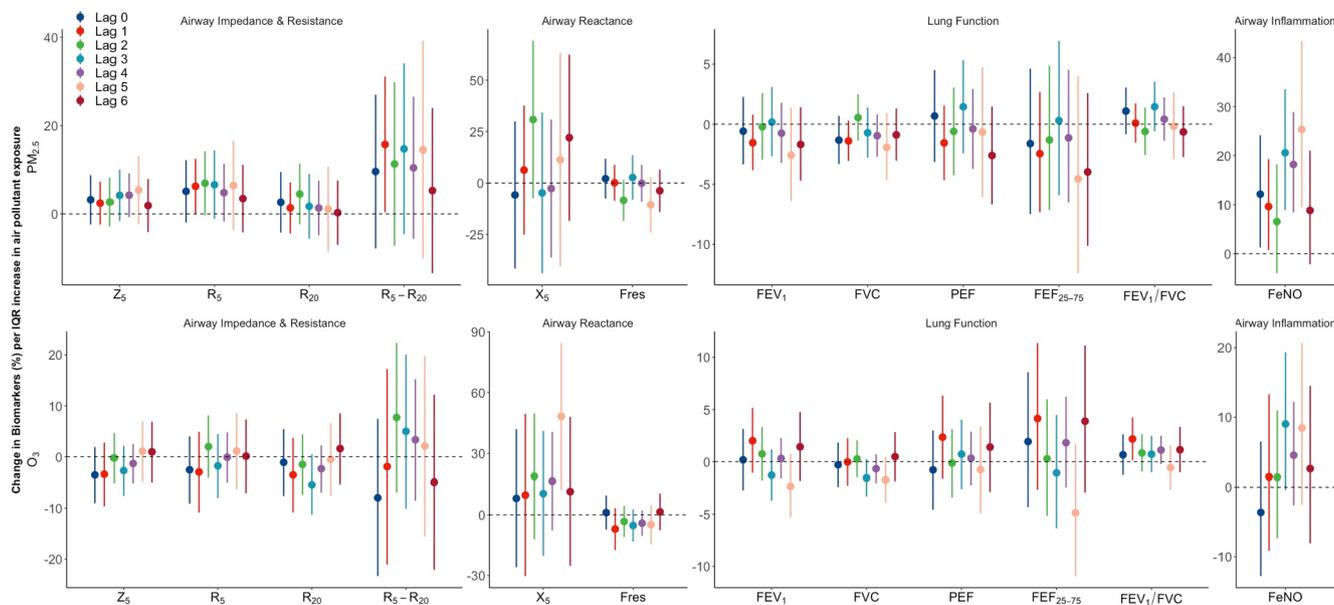


Fig. 3. Estimated means and 95% confident intervals for change in biomarkers (%) with one IQR increase in 24-hour average $PM_{2.5}$ and O_3 personal exposure in zero to six days prior to health outcome measurement (lag 0–6). Detailed model results were shown in Table S5 in the Supplement. Definition of abbreviations: Z_5 = airway impedance measured at 5 Hz; R_5 = airway resistance measured at 5 Hz; R_{20} = airway resistance measured at 20 Hz; R_5-R_{20} = difference between airway resistance measured at 5 Hz and 20 Hz; X_5 = airway reactance measured at 5 Hz; F_{res} = resonant frequency; FEV_1 = forced expiratory volume in first second; FVC = forced vital capacity; PEF : peak expiratory flow; FEF_{25-75} = the average forced expiratory flow during 25% to 75% of FVC ; FEV_1/FVC = the ratio of FEV_1 and FVC ; $FeNO$ = fractional exhaled nitric oxide.

To the best of our knowledge, this is the first study to examine the relationships of personal O_3 exposure, when ambient ozone concentrations were relatively low during a non-ozone season (daily maximum 8-hour ambient O_3 concentration range: 12.6–93.4 ppb), with lung function and $FeNO$ in asthmatic children. As expected at these low concentrations, ozone exposure was not clearly or significantly associated with lung function and $FeNO$ in the present study. In contrast, at relatively higher exposure levels, with daily maximum 8-

hour ambient O_3 concentration ranging from 63.3 to 99.6 ppb, a previous study conducted during an ozone season of Southern New England reported that an increase in maximum 8-hour ambient ozone concentration measured in 24-hour and one day prior to the clinical visit were associated with worsening lung function in asthmatic children (Gent et al., 2003).

The non-significant associations of spirometric lung function with $PM_{2.5}$ and O_3 exposure in the present study suggest that the

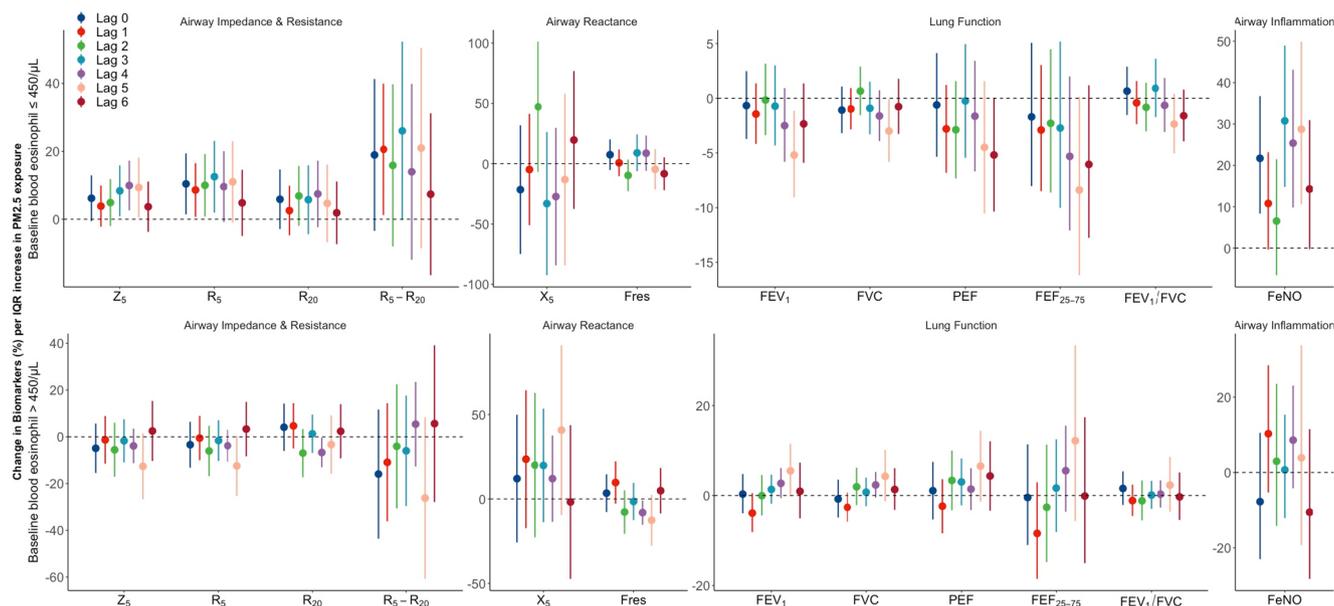


Fig. 4. Estimated means and 95% confident intervals for change in biomarkers (%) with one IQR increase in 24-hour average $PM_{2.5}$ personal exposure in zero to six days prior to health outcome measurement (lag 0–6). Stratified by blood eosinophil number (cutoff point $450/\mu L$). Detailed model results were shown in Table S6 in the Supplement. Definition of abbreviations: Z_5 = airway impedance measured at 5 Hz; R_5 = airway resistance measured at 5 Hz; R_{20} = airway resistance measured at 20 Hz; R_5-R_{20} = difference between airway resistance measured at 5 Hz and 20 Hz; X_5 = airway reactance measured at 5 Hz; F_{res} = resonant frequency; FEV_1 = forced expiratory volume in first second; FVC = forced vital capacity; PEF : peak expiratory flow; FEF_{25-75} = the average forced expiratory flow during 25% to 75% of FVC ; FEV_1/FVC = the ratio of FEV_1 and FVC ; $FeNO$ = fractional exhaled nitric oxide.

concentration and/or duration of pollution exposure in this study might not be adequate to induce functional changes in an asthmatic lung. However, we found that, as the indicators of the early-stage and subtle changes in lung function (Guan et al., 2015), total (R_5) and small airway resistance (R_{5-20}) were associated with personal $PM_{2.5}$ exposure measured several days prior to the outcome measurements. The adverse effects of air pollutant exposure on airway mechanics of healthy children and adults have been previously reported. For example, one study compared the airway mechanics of children from two cities in India, finding that children who lived in the city with higher ambient air pollutant concentrations had worse airway resistance (R_5) and airway reactance (X_5) (De 2019). Another study reported that overnight filtration of bedroom air was associated with significant decreases in airway resistance (R_5) and impedance (Z_5) in healthy adults (Cui et al., 2018). In addition to the previous findings, the present study provides the first evidence to support a significant exposure-response relationship of personal $PM_{2.5}$ exposure with total and small airway resistance.

As total airway resistance is the sum of small and large airway resistance, the results of this study led us to hypothesize that the increases in $PM_{2.5}$ -induced total airway resistance might be largely driven by the increased small airway resistance. The small airways, anatomically defined as airways with inner diameters less than two millimeters, cumulate greater cross-sectional area than the large airways (Macklem, 1998). The small airways are the major sites of airflow obstruction and contribute substantially to airway inflammation in asthma (Tulic et al., 2001; Yanai et al., 1992). $PM_{2.5}$ in inhaled air can penetrate and be retained in the walls of the small airways (Churg et al., 2003), resulting in higher oxidative stress levels and inflammation in the respiratory tract (Zhang et al., 2016). Therefore, decreasing personal exposure to $PM_{2.5}$, which would lead to less $PM_{2.5}$ entering the small airways, would be important in asthma management (Lahzami and King, 2008).

Air purifiers with HEPA and activated carbon filters have been reported to be efficient at removing $PM_{2.5}$ and O_3 , respectively (Batterman et al., 2012; Lee and Davidson, 1999). In the present study, personal exposures to $PM_{2.5}$ were noticeably manipulated by the operation of an indoor air purifier, although O_3 did not vary substantially by filtration status, potentially due to the low ambient O_3 concentration during the study period (see Table 2). On the other hand, we found that, independent of the effect of $PM_{2.5}$ and O_3 changes resulting from the filtration, using an air purifier with only the coarse filter was associated with worsened airway mechanics compared to using no filtration. This might reflect confounding from indoor-generated pollutants such as volatile organic compounds (VOCs) and semi-volatile organic compounds (SVOCs), some of which (e.g., formaldehyde) are known respiratory toxicants (Pappas et al., 2000). During each air filtration period, the participants were asked to close their home windows as much as possible, while it is not required during the no-filtration periods. Indoor VOC and SVOC concentration were expected to be higher when the windows were closed more often, as window closure would reduce indoor-outdoor air exchange and consequently enhanced the accumulation of indoor-generated pollutants (Noguchi et al., 2016). However, VOCs and SVOCs can be captured, at least partly, by the activated carbon filter and the HEPA filter. Hence, we speculate that the window closure influence on indoor levels of VOCs and SVOCs was smaller for the three-filter condition than for the coarse-filter only condition.

Asthma is a phenotypically heterogeneous disease which can be characterized by eosinophilic, neutrophilic, or mixed eosinophilic/neutrophilic inflammatory patterns (Pelaia et al., 2015). Previous studies have reported that patients with eosinophilic asthma are more responsive to allergic sensitization (Walford and Doherty, 2014), while non-eosinophilic (or neutrophilic) asthma is mainly triggered by environmental exposures including bacterial endotoxin and air pollutants (Douwes et al., 2002). In line with previous findings, in this study, we observed that day-to-day increases in personal $PM_{2.5}$ exposure were

associated with significant increases in airway impedance, resistance, reactance, and inflammation mainly in children with non-eosinophilic asthma (i.e., those with baseline blood eosinophils number less than $450/\mu L$). These results suggest that phenotype-targeted therapies based on eosinophilic or non-eosinophilic inflammatory patterns would be important for asthma management.

4.1. Limitations and sensitivity analyses

Our assessment of the coarse-filter only data suggests a potential role of co-pollutant exposures, such as VOCs and SVOCs, in affecting airway mechanics and FeNO. However, we were not able to measure these co-pollutants in the bedrooms. Our findings on $PM_{2.5}$ effect may be subject to confounding of co-pollutants other than ozone that was measured and accounted for. To address this issue, we assumed that the combined use of the activated carbon filter and the HEPA filter would have offset increases in indoor VOCs and SVOCs resulting from increased window closure during filtration period. However, if concentrations of these co-pollutants were different between the three-filter filtration period and the no-filtration period, this could have confounded the $PM_{2.5}$ exposure-response relationship. With this in mind, we analyzed the data collected only in the two no-filtration visits and found that increased $PM_{2.5}$ exposure measured during the 24-hours prior to the clinical visit was associated with significant decreases in FEV₁ and FVC and statistically non-significant increases in airway impedance (Z_5) and inflammation (FeNO) (Fig. S2). This analysis, albeit with reduced statistical power, supports the robustness of the main findings from the three-visits analysis.

Another limitation of this study is that the personal air pollutant exposure was calculated by coupling pollutant concentrations in microenvironments and participants' time activity patterns. Although this calculation might introduce systematic or random error into the statistical analyses of this study, this is a more logistically feasible exposure assessment method than personal monitoring in this study design and for these study participants.

We further evaluated the robustness of the results through three sensitivity analyses. Firstly, there were not remarkable changes in the relationships shown in the co-pollutant models in terms of either statistical significance or effect size (Figs. S3-S4). Similarly, after excluding measurement of participants who traveled or used inhaled corticosteroids during the two weeks prior to each of the clinical visits, the analysis showed similar results (Fig. S5-S6), supporting the robustness of the findings from the main analyses. Thirdly, the $PM_{2.5}$ exposure-response relationships were examined including all the clinical visits. As shown in Fig. S7, we found that day-to-day changes in personal $PM_{2.5}$ exposure was associated with decreased lung function and increased airway resistance and airway inflammation, supporting the findings of the main analyses.

5. Conclusion

Although insufficient to be significantly associated with changes in lung function, day-to-day changes in personal exposure to $PM_{2.5}$, resulting partly from the use of a bedroom air purifier, were significantly and adversely associated with changes in small airway and total airway resistance as well as pulmonary inflammation in children with asthma. These associations were not affected by the co-presence of ozone at low levels when ozone itself was not associated with any of the measured outcomes. Our findings suggest the importance of reducing personal exposure to $PM_{2.5}$ as part of the asthma management plan to improve airflow limitation.

Author contributions

Study conceptualization: JZ, ZL, JS, MB, and MHB. Funding acquisition: JZ, MHB, JS, ZL, and YZ. Investigation: LH, ZL, YT, XC, KB, CN,

LF, LL, QW, XZ, JH, FL, YZ, JS, MHB, and JZ. Methodology: JZ, MHB, ZL, JS, MB, and XC. Resources: ZL, YT, LL, QW, XZ, JH, and FL. Supervision: ZL, JS, MHB, YZ, and JZ. Validation: LH, ZL, YT, XC, KB, CN, LF, MHB, and JZ. Visualization: LH and JZ. Writing-original draft: LH and JZ. Writing-review & editing: LH, JZ, CN, KB, and MHB. JZ takes responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2020.105647>.

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