



# Personal exposure to average weekly ultrafine particles, lung function, and respiratory symptoms in asthmatic and non-asthmatic adolescents

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## ABSTRACT

An increasing amount of evidence suggests ultrafine particles (UFPs) are linked to adverse health effects, especially in those with chronic conditions such as asthma, due to their small size and physicochemical characteristics. Toxicological and experimental studies have demonstrated these properties, and the mechanisms by which they deposit and translocate in the body result in increased toxicity in comparison to other air pollutants. However, current epidemiological literature is limited due to exposure misclassification and thus identifying health outcomes associated with UFPs. The objective of this study was to investigate the association between weekly personal UFP exposure with lung function and respiratory symptoms in 117 asthmatic and non-asthmatic adolescents between 13 and 17 years of age in the Cincinnati area. Between 2017 and 2019, participants collected weekly UFP concentrations by sampling for 3 h a day in their home, school, and during transit. In addition, pulmonary function was evaluated at the end of the sampling week, and respiratory symptoms were logged on a mobile phone application. Multivariable linear regression and zero-inflated Poisson (ZIP) models were used to estimate the association between personal UFP and respiratory outcomes. The average median weekly UFP exposure of all participants was 4340 particles/cm<sup>3</sup> (p/cc). Results of fully adjusted regression models revealed a negative association between UFPs and percent predicted forced expiratory volume/forced vital capacity ratio (%FEV<sub>1</sub>/FVC) ( $\beta$ : -0.03, 95% CI [-0.07, 0.02]). Prediction models estimated an association between UFPs and respiratory symptoms, which was greater in asthmatics compared to non-asthmatics. Our results indicate an interaction between asthma status and the likelihood of experiencing respiratory symptoms when exposed to UFPs, indicating an exacerbation of this chronic condition. More research is needed to determine the magnitude of the role UFPs play on respiratory health.

## 1. Introduction

Ultrafine particles (UFPs, particles < 100 nm in diameter) dominate particle number concentrations in ambient air, but epidemiologic studies primarily measure and study the health effects of larger particles, including coarse and fine particulate matter (PM<sub>10</sub> and PM<sub>2.5</sub>, respectively). These studies consistently demonstrate that both short- and long-term PM<sub>10</sub> and PM<sub>2.5</sub> exposure is associated with increased cardiopulmonary mortality and morbidity among adults and children (Babatola, 2018; Cohen et al. 2017; Health Effects Institute, 2019; Lelieveld et al. 2015). However, evidence from toxicological studies suggests that the size, surface area, and deposition of UFPs may result in

increased toxicity compared to larger PM (Geiser and Kreyling 2010; Lee et al. 2010; Oberdörster et al., 2005). Potential mechanisms underlying the increased toxicity of UFPs include their deposition into the alveolar region and alveolar airspace of the lungs through evasion from host defenses and the ability to induce the creation of reactive oxygen species (Li et al., 2008; Moller et al., 2008). Furthermore, their high oxidant potential plays an important role in pro-allergic pathways by enhancing allergic inflammation in the lung (Li et al. 2009), up-regulating pro-inflammatory cytokines (Beck-Speier et al. 2012) and exacerbating inflammation in sensitive individuals (Li et al. 2010).

Despite evidence of increased respiratory toxicity of UFPs, epidemiologic studies of their health effects are lacking. This is due, in part, to

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challenges in UFP exposure assessment, including appropriate exposure metrics (i.e., particle number concentration, surface area, mass) and limited UFP sampling equipment (Baldauf et al. 2016). Advances in technology, however, have resulted in increased availability of stationary and personal UFP monitors with a corresponding increase in studies of the health consequences of UFP exposure. The majority of these have examined daily levels of UFPs at central monitoring sites and population-level health outcomes, including mortality or hospital admissions for cardiopulmonary outcomes in adults. To date, the results of these studies have been inconsistent with limited evidence that UFPs confer increased risk for cardiovascular or respiratory morbidity beyond that of larger particles or other pollutants, though positive associations have been observed for respiratory mortality (Lanzinger et al. 2016), decreased lung function (Strak et al., 2010), acute inflammatory indices of respiratory symptoms (Cole-Hunter et al. 2013), and pulmonary inflammation markers (Gong et al. 2014). Fewer studies have focused on the effects of UFP and respiratory health in children, though a recent review of UFP effects on children's health suggests that exposure to UFPs is significantly associated with decreased peak expiratory flow (PEF), increased inflammatory biomarkers, and elevated respiratory symptoms (da Costa e Oliveira et al., 2019).

A critical challenge to epidemiologic studies of both children and adults is that there are multiple indoor and outdoor sources of UFPs, and their high spatio-temporal variability make exposure classification challenging. Studies of children using model-derived, individual-level estimates of UFP exposure at their homes (based on stationary or mobile monitoring campaigns) have found positive associations between prenatal UFP exposure and the incidence of asthma during childhood (Lavigne et al. 2019) and increased biomarkers of systemic inflammation (Clifford et al. 2018). However, personal monitoring of UFP exposures has identified specific locations and activities (i.e., 'microenvironments') outside the home associated with elevated exposure that result in disproportionately higher exposures than the time spent in these activities or locations (Ryan et al., 2015; Buonanno et al., 2014, 2013). In addition, exposures in similar microenvironments, for example during commute, can contribute peak exposures within individuals and varying exposure between individuals depending on their route of choice (Cole-Hunter et al. 2012). The participant burden and high costs associated with personal sampling have limited the widespread use of personal monitoring in children's health studies. The objectives of this study were to utilize a wearable UFP monitor to characterize typical weekly exposure to UFPs among adolescents with and without asthma and determine if these exposures are associated with respiratory health outcomes, including changes in pulmonary function and asthma symptoms.

## 2. Methods

### 2.1. Study population

Adolescents with and without asthma were recruited to participate in the Ecological Momentary Assessment of Personal Particle Exposure (EcoMAPPE) study. Participants were recruited via advertisements placed throughout Cincinnati Children's Hospital Medical Center (CCHMC) and emails sent to CCHMC employees. In addition, adolescents with asthma enrolled in the Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS), a longitudinal study of traffic-related air pollution and respiratory health, were also invited to participate (Brunst et al., 2015; Ryan et al., 2005). Eligibility criteria for EcoMAPPE included being between the ages of 13 and 17, non-smoking, and not planning to change residence in the next 12 months. We attempted to enroll a target sample size of 100 participants, of which, one-half of the study population to have asthma, defined as caregiver report of physician diagnosed asthma. Caregivers provided written informed consent, and adolescents provided assent prior to the start of any study activity.

### 2.2. Ultrafine particle assessment

Participants completed one sampling session totaling seven days. Personal UFP exposure was measured using the Personal Ultrafine Particle Counter (PUFP C200, Enmont LLC, Cincinnati, OH USA), which has previously been used in the literature (Grabinski et al., 2017; Ryan et al., 2015). Briefly, the PUFP C200 (US patent # US 844965) is a water-based condensation particle counter (CPC) with a flow rate of 0.25 L/min, a weight of 750 g, and approximately 3 h of continuous battery operation ([www.enmont.com](http://www.enmont.com)). The PUFP is comprised of an evaporation–condensation-tube, a miniature diaphragm air pump, an optical detection module, a flow regulator, water tank, global positioning system (GPS), and battery pack in a plastic shell body. Two central processing units convert analog laser particle scattering signature to digital counting data. The PUFP C200 measures a wide range of particle concentrations (up to  $2 \times 10^5$  p/cc) and sizes (6 nm – 3  $\mu$ m) at a one-second resolution, has a good correlation with a reference CPC ( $\pm 10\%$ ) (Asbach et al. 2017), and is easy to wear and use by participants in field tests (Ryan et al. 2015). In a separate study, the PUFP showed positive linearity to a TSI Model 3007 CPC (slope  $\sim 1.16$ ,  $R^2 \sim 0.99$ ) when evaluating the performance of respirators (He et al. 2013).

Participants were instructed to wear the PUFP C200 for 3 h each day of sampling. During the school year, sampling of particles up to 1  $\mu$ m in size was conducted before and after school hours, including transit to minimize disruptions during school attendance. During the weekends and summer sampling period, participants were instructed to begin sampling approximately ½ hour before leaving their home for the first time that day or, if they stayed at home that day, to sample for three hours between 11 AM and 7 PM at their discretion.

### 2.3. Health outcomes

Participants completed study visits at CCHMC before and at the conclusion of each sampling session. During each study visit, caregivers completed questionnaires pertaining to their child's health history and environmental and housing conditions, including current asthma symptoms and exposure to mold and tobacco smoke. Children with asthma completed the Asthma Control Test (ACT) (Nathan et al. 2004), the Asthma Control Questionnaire (Juniper et al., 1999a), and the Miniature Asthma Quality of Life Questionnaire (miniAQLQ) (Juniper et al., 1999b) to ascertain current asthma control.

All participants also completed spirometry at each clinic visit following American Thoracic Society-European Respiratory Society (ATS-ERS) guidelines (Miller et al. 2005) and administered by a technician who completed a NIOSH-approved training course. A hand-held spirometer (KoKo® SX 1000, KoKo LLC, Longmont, CO USA) was used to record the best forced expiratory volume in 1 s (FEV<sub>1</sub>), forced vital capacity (FVC), and average expiratory flow of FVC between 25 and 75% (FEF<sub>25–75%</sub>). Predicted lung function values were calculated based on sex, age, height, and ethnicity using the Global Lung Function Initiative (GLI) Network for reference values of routine lung function testing (Quanjer et al., 2012). Participant lung function measurements were reported as a percentage of their predicted values. In addition, FEV<sub>1</sub> as a percentage of FVC (ratio of FEV<sub>1</sub>/FVC) was determined.

Respiratory symptom questions were adapted from ISAAC questionnaire (Asher et al. 1995) and ACT (Nathan et al. 2004) and recorded by study participants during each personal sampling session using Ecological Momentary Assessment (EMA). EMA is a research method whereby participants are queried multiple times to repeatedly report their behaviors, feelings, symptoms, and other experiences. EMA enables outcome assessment to occur across multiple environments and situations to assess individual-level changes, describe trends over time, analyze contextual situations, and study temporal sequences (Shiffman et al. 2008). EMA data was collected during each sampling session using a survey-based, real-time mobile application on study-provided smartphones (PiLR Health, <https://pilirhealth.com>).

[com/pilr-ema-product-features/](https://www.pilr-ema-product-features/).) The PiLR health platform has been used in several studies to aid in the understanding of substance abuse behaviors (McQuoid et al. 2018) and examine changes in mood and smoking behaviors in postpartum mothers (Allen et al. 2018). In the current study, EMA questionnaires were triggered by time of day, entry and departure from homes and schools, and motion detected by the accelerometer sensor in the phone. EMA questions varied by the time of day and location and queried the participants of observations of their current surroundings, method of transportation, nearby sources of UFP exposures, including smoking and cooking. On all EMA questionnaires, participants reported whether they experienced respiratory symptoms, including wheeze, cough, and/or shortness of breath, in the previous 30 mins. The total count of respiratory symptoms reported during personal sampling for each participant was determined as the sum of all reported symptoms during the week. Because cough is a non-specific symptom of asthma, reported counts of cough were excluded from our analyses.

2.4. Covariates

*A priori*, we used a causal directed acyclic graph (DAG) to identify possible confounding pathways and to identify the covariates to be included in our adjusted models (Fig. 1). These covariates included residential proximity to the nearest major roadway (>400 m or ≤400 m), average number of steps walked per day, and season of sampling session (winter, spring, summer, or fall). Secondhand smoke exposure was not included in our analysis as less than 10% (n = 10) of participants reported living in a household with a smoker.

2.4.1 *Microenvironment*: All UFP concentrations were classified as occurring in one of five microenvironments based on a spatiotemporal algorithm. GPS equipment on each PUFF recorded the location (latitude / longitude) of each UFP measurement at a 1-second resolution. Missing GPS coordinates were imputed based on distance between the last known coordinate and first non-missing coordinate. If the distance between coordinates was less than 100 m, missing coordinates were assigned the value of the last known coordinate and jittered by less than 5 m. Coordinates were jittered in order to simulate noise in the GPS signal. After imputation, the data was aggregated to a resolution of 5-seconds characterized as either stationary or non-stationary (transit) using the *circclust* R package (Wolfe, C. n.d.). The *circclust* algorithm calculates

a circular variance of coordinates within a five-minute moving window and defines points as either belonging to a spatiotemporal cluster or in motion based on departures from a threshold value. A circular variance threshold of 0.7 was used in our analysis. Participant coordinates were classified into one of five microenvironments: transit, home, school, other, and undefined. Stationary coordinates identified by the *circclust* algorithm were classified based on proximity to the participant-defined locations. The centroid of each spatiotemporal cluster or ‘place’ was calculated. Places with a centroid within 100 m of the participant’s home were labeled ‘home’, and those with a centroid within 300 m of the participant’s school were labeled as ‘school’. Because most participants could not sample during class, clusters labeled as ‘school’ were samples collected before or after school hours while still on the school’s premises. Remaining spatiotemporal clusters were classified as ‘other’. Finally, sampling coordinates were labeled ‘undefined’ if GPS coordinates were not recorded during the sampling session. Coordinates may also be characterized as ‘undefined’ if missing coordinates occurred at the beginning of sampling and followed by transit or end of sampling and were preceded by transit.

2.4.2 *Proximity to nearby traffic*: Residential locations of study participants were geocoded using our stand-alone and validated geocoder (Brokamp et al. 2017). Residential distance to the nearest primary (S1100) roadways was calculated using previously developed DeGAUSS software ([degauss-org.github.io](https://degauss-org.github.io), Brokamp et al. 2017) and categorized as either near (≤400 m) or far (>400 m) from major traffic sources.

2.4.3 *Daily activity*: Participants received Fitbit activity monitors (Fitbit, Inc., San Francisco, CA) and were instructed to wear them during the entirety of their sampling session. Heart rate, physical activity, and sleep quality were collected by each device and paired with study-appointed smartphones using the Fitbit mobile application. Data was retrieved from the Fitbit web API. For each participant, the number of steps per minute were aggregated to the average steps per day of the entire sampling session for analysis.

2.5. Statistical analysis

Distributions of UFP concentrations and health outcomes for the entire sample and by asthma status were characterized using summary statistics. Weekly UFP concentrations were summarized by calculating the median for the entire sampling week for each participant. UFP

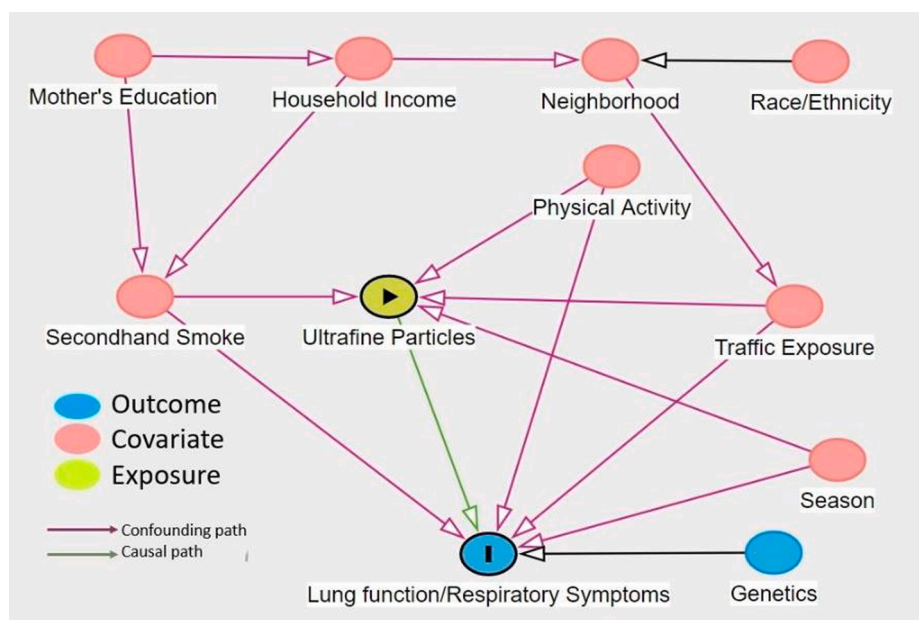


Fig. 1. Directed acyclic graph representation of confounding pathways. Covariates identified in graph were used in fully adjusted models. Genetics: ancestor of outcome.

concentrations recorded by the PUF above 250,000 p/cc were replaced with 250,000 p/cc in order to eliminate readings outside the particle range capacity of the device. This resulted in truncation of 1% of the total dataset. Weekly UFP median concentrations were log-transformed to ensure normality of model residuals. The average percent of sampling time participants spent in each microenvironment (home, school, transit, other, undefined) of their overall sampling duration was calculated from corresponding GPS data as described above.

The association between weekly median UFP exposures and lung function assessed at the completion of the personal sampling week was examined using multivariable linear regression. Individual models were built for each lung function outcome (%FEV<sub>1</sub>, %FVC, %FEF<sub>25-75</sub>, and %FEV<sub>1</sub>/FVC). The association between UFP exposure and respiratory symptoms was estimated using zero-inflated Poisson (ZIP) regression models after performing a Vuong likelihood ratio test to verify their superior fit over Poisson regression models (Vuong 1989). Total respiratory symptom count used in the ZIP models included wheeze and shortness of breath symptoms only. ZIP regression is a two-part model that fits zero-inflated counts as (1) a logistic regression model for group membership in the zero-inflated group and (2) a Poisson regression model that fits the number counts among those not in the zero-inflated group from the first part. The results from this model were characterized using odds ratios (OR) and risk ratios (RR), respectively.

To examine potential effect modification by asthma status, we added an interaction term between asthma diagnosis and UFP exposure to each of the multivariable regression models and ZIP models. We considered effect modification to be present if the interaction term had a corresponding p-value of < 0.05. Only outcomes with significant effect modification of asthma status on UFP were used to generate asthma-specific model coefficients. Though the Poisson portion of the ZIP models produced a significant interaction term between asthma status and UFP exposure, we did not have enough power to estimate the effect within asthmatics and non-asthmatics separately. Therefore, to illustrate this difference, a prediction model was built to predict the outcome of each asthmatic and non-asthmatic using median values for each covariate.

All data analyses were conducted using R version 3.6.1. R packages used: pscl version 1.5.5 for zero-inflation models (Zeileis et al., 2008) and ggplot2 version 3.3.2 for graphics (Wickham, 2016).

### 3. Results

#### 3.1. Study population

Characteristics of the study population are presented in Table 1. In total, 118 children completed at least one sampling session; however, 1 participant was omitted from analysis due to a sensor malfunction leaving a sample size of 117. Of these, 52 (44%) were male and 65 (56%) were female. Among the participants, 21 (18%) were African American, and 42% had been diagnosed with asthma by a physician. Participants' average age was 15.4 years. Participants with and without asthma were similar with respect to age, sex, race, and proximity to major roads (Table 1). However, participants with asthma reported lower household income (p = 0.02) (Table 1). Participants with asthma reported an average Asthma Control Test score of 21.5 (±2.97) with 70% being well-controlled (defined as having a score > 20).

Overall, participants recorded the majority of their personal UFP exposure while at their home (65%), with the remaining sampling being conducted at schools (10%), in transit (9%), other locations (19%), or undefined locations (9%).

#### 3.2. Ultrafine PM exposure

A summary of EcoMAPPE participants' weekly personal UFP exposure is provided in Table 2 for the entire sample as well as by asthma status. Overall, the median weekly personal exposure to UFP among all

**Table 1**  
Characteristics of the EcoMAPPE study population.

Characteristic	All Participants (n = 117)	Asthmatic (n = 49)	Non-asthmatic (n = 68)	p *
Age	15.4 (1.2)	15.6 (1.3)	15.2 (1.2)	0.11
Sex, n (%)				0.22
Male	52 (44.4)	18 (36.7)	34 (50.0)	
Female	65 (55.6)	31 (63.3)	34 (50.0)	
Race, n (%)				0.11
White	87 (74.4)	32 (65.3)	55 (80.9)	
Black	21 (17.9)	13 (26.5)	8 (11.8)	
Mixed	9 (7.7)	4 (8.2)	5 (7.4)	
Household Income, n (%)				0.02
< 10,000	2 (1.9)	2 (4.3)		
10,000–19,999	2 (1.9)	2 (4.3)		
20,000–29,999	4 (3.7)	3 (6.4)	1 (1.6)	
30,000–39,999	7 (6.5)	3 (6.4)	4 (6.6)	
40,000–49,999	7 (6.5)	6 (12.8)	1 (1.6)	
50,000–69,999	13 (12.0)	8 (17.0)	5 (8.2)	
70,000–89,999	8 (7.4)	2 (4.3)	6 (9.8)	
90,000–109,999	12 (11.1)	2 (4.3)	10 (16.4)	
Over 110,000	51 (47.2)	19 (40.4)	32 (52.5)	
Distance to Nearest Major Roadway, n (%)				0.61
< 400 m	9 (7.7)	5 (10.2)	4 (5.9)	
> 400 m	108 (92.3)	44 (89.8)	64 (94.1)	
Percent Predicted Lung Function, mean (SD)				
FEV <sub>1</sub> (%)	102 (13)	102 (12)	103 (14)	0.85
FVC (%)	108 (13)	109 (12)	106 (14)	0.30
FEF <sub>25-75</sub> (%)	96 (24)	91 (23)	99 (25)	0.13
FEV <sub>1</sub> /FVC Ratio (%)	95 (7)	93 (7)	96 (7)	0.08
Respiratory Symptoms, mean (SD)				
Total Symptoms	2.0 (4.0)	3.3 (5.5)	1.1 (2.0)	0.01
Total Symptoms - cough	0.8 (2.3)	1.7 (3.4)	0.2 (0.6)	0.004

FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; FEF<sub>25-75%</sub>, average expiratory flow between 25 and 75% of FVC; FEV<sub>1</sub>/FVC Ratio, FEV<sub>1</sub> as percentage of FVC; Values are mean (SD) or n (%); Age in years; \*p values represent significant differences between asthmatic and non-asthmatic groups determined by two-sample t test

**Table 2**  
Summary of weekly median ultrafine particle exposures.

	Mean (SD)	1st Quartile	Median (range)	3rd Quartile
Entire Sample	6792 (7358)	2720	4340 (351, 58300)	8740
Non-asthmatic	6716 (8524)	2555	4210 (351, 58300)	7423
Asthmatic	6898 (5420)	3130	4660 (584, 26800)	10,400

Values are UFP PNC (particle number concentration) in particles/cm<sup>3</sup>; Non-asthmatic n = 68; Asthmatic n = 49.

participants was 4340 p/cc [range: 351–58,300 p/cc]. Median UFP exposure was not significantly higher among asthmatics (4,660 p/cc [range: 584–26,800 p/cc]) than non-asthmatics (4210 p/cc [range: 351–58,300 p/cc]). On average, sampling sessions in the fall revealed higher median exposure to UFPs (6680p/cc [range: 584–58,300 p/cc]) than other seasons (Winter: 4635 p/cc [range: 1240–18,300 p/cc]; Spring: 5465 p/cc [range: 1010–26,800 p/cc]; Summer: 3375p/cc [range: 351–37,500 p/cc]) and were significantly higher than sampling sessions that occurred during summer months (p = 0.02).

### 3.3. Lung function

Average percent predicted spirometry values as measured at the clinic visit following study participation for all participants are provided in Table 1. Overall, the mean %FEV<sub>1</sub> for EcoMAPPE participants was 102%. The mean %FVC value was 108%, %FEF<sub>25-75%</sub> was 96%, and %FEV<sub>1</sub>/FVC ratio was 95%. Two-sample *t* tests revealed no significant differences between the asthmatic and non-asthmatic group occurred for any of the lung function outcomes (*p* > 0.05). As shown in Fig. 2, unadjusted median weekly UFP exposures were negatively associated with %FEV<sub>1</sub>, %FEV<sub>1</sub>/FVC, and %FEF<sub>25-75%</sub>, while positively associated with %FVC, though no relationships reached statistical significance.

We did not observe an interaction between asthma status and UFP exposure on any lung function. As presented in Table 3, after adjustment for distance to nearest roadway, daily activity, and season, multivariable linear regression models revealed the overall effect of weekly median UFP exposure was negative for %FEV<sub>1</sub> (−0.01, 95% CI [−0.08, 0.06]), %FEV<sub>1</sub>/FVC ratio (−0.03, 95% CI [−0.07, 0.02]), and %FEF<sub>25-75%</sub> (−0.03, 95% CI [−0.18, 0.11]), and positive for %FVC (0.03, 95% CI [−0.05, 0.11]). None of the effects reached statistical significance.

### 3.4. Respiratory symptoms

The proportion of participants who did not experience any symptoms during their sampling week was 55% (64/117). After the number of cough symptoms experienced by participants were eliminated from total number of symptom tallies, we observed 76% (90/117) of participants experienced 0 symptoms throughout the week. The average (±SD)

**Table 3**

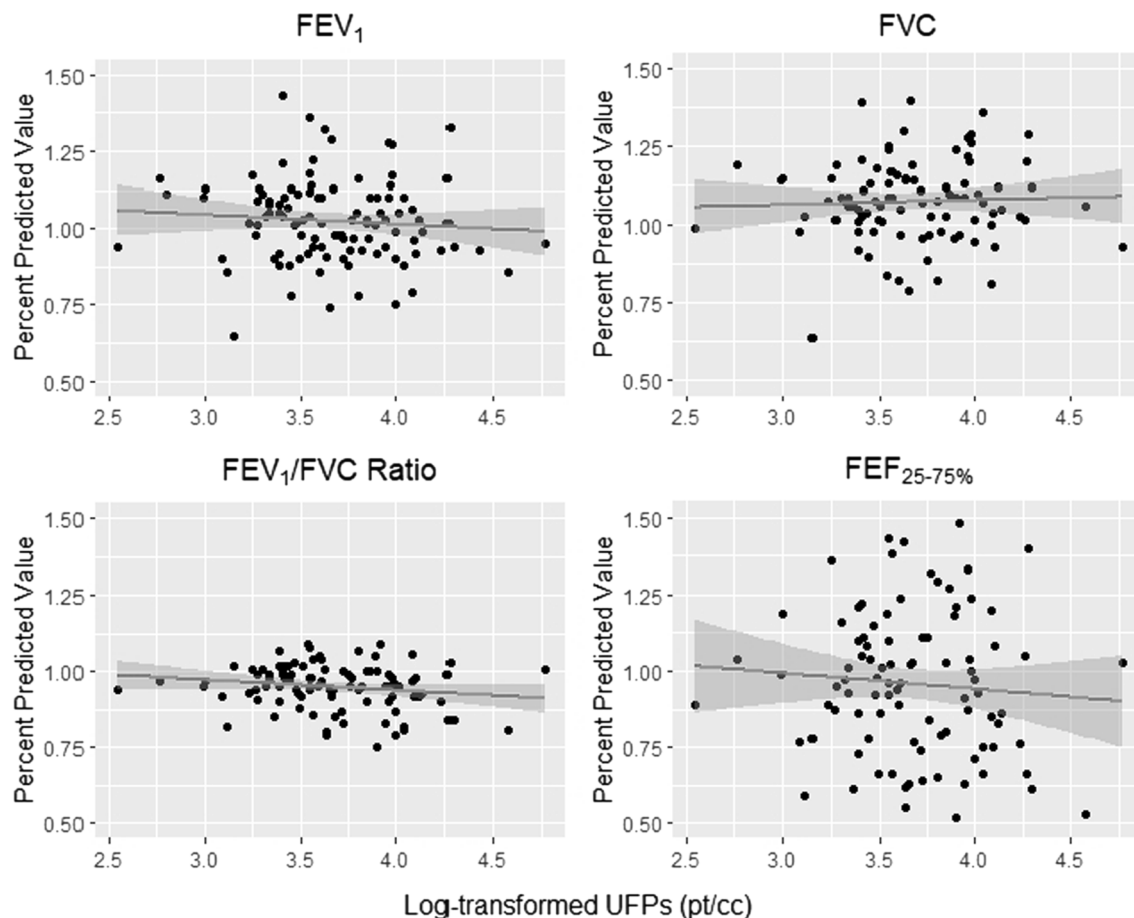
Association between median weekly UFP exposure and lung function.

	Estimate (95% CI) <sup>1</sup>	<i>p</i>	Estimate (95% CI) <sup>2</sup>	<i>p</i>
FEV <sub>1</sub>	−0.01 (−0.08, 0.06)	0.74	−0.03 (−0.10, 0.04)	0.38
FVC	0.03 (−0.05, 0.11)	0.47	0.02 (−0.06, 0.09)	0.68
FEF <sub>25-75%</sub>	−0.03 (−0.18, 0.11)	0.66	−0.08 (−0.21, 0.06)	0.26
FEV <sub>1</sub> /FVC Ratio	−0.03 (−0.07, 0.02)	0.23	−0.03 (−0.08, 0.01)	0.09

β expressed as change in estimate per 10p/cc. FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; FEF<sub>25-75%</sub>, average expiratory flow between 25 and 75% of FVC; FEV<sub>1</sub>/FVC Ratio, FEV<sub>1</sub> as percentage of FVC; PM, particulate matter. <sup>1</sup>Adjusted for distance to nearest roadway, average total steps per day, and season. <sup>2</sup>Unadjusted model.

number of total symptoms experienced by participants throughout sampling was 2 (±4) for any reported symptoms and 0.8 (±2.3) excluding cough as a symptom (Table 1). The asthmatic group reported a significantly higher number of symptoms for both outcomes (total symptoms: *p* = 0.01; total symptoms excluding cough: *p* < 0.01).

After adjustment for model covariates, we did not find any association between having at least 1 respiratory symptom (ZIP OR: 1.31, 95% CI [0.22, 7.69]) or total non-zero symptoms (ZIP RR: 1.09, 95% CI [0.41, 2.83]) and a ten-fold increase in UFP exposure. We detected effect interaction by asthma status in the Poisson portion of the model (*p* < 0.001), resulting in a significant increase in the risk of experiencing any number of symptoms in asthmatics according to ZIP model results (RR = 1.68, 95% CI [1.31, 2.14]). Our prediction model estimated median UFP exposure of 10,000 p/cc was associated with an average of 2.0 symptoms in asthmatics and 0.20 symptoms in non-asthmatics (Fig. 3). It was



**Fig. 2.** Plots of unadjusted association between lung function outcomes (percent predicted values) and median UFPs (particles/cm<sup>3</sup>). Each blue line represents regression coefficient for entire sample. The shadow bars represent 95% confidence intervals. FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; FEF<sub>25-75%</sub>, average expiratory flow between 25 and 75% of FVC; FEV<sub>1</sub>/FVC Ratio, FEV<sub>1</sub> as percentage of FVC.

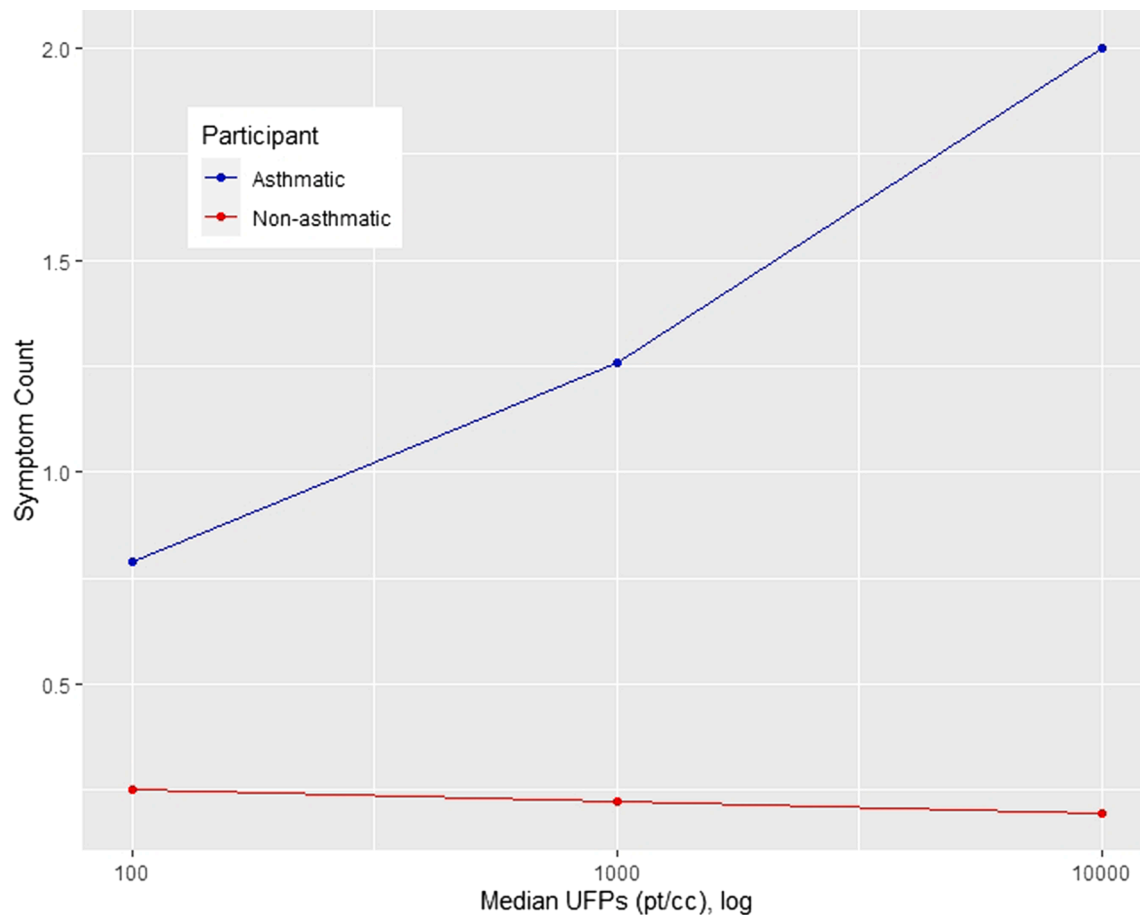


Fig. 3. Prediction plot of the effect of UFPs (particles/cm<sup>3</sup>) on total number of weekly symptoms; Median levels of covariates were used to create an average asthmatic and non-asthmatic adolescent from sample.

determined that asthmatics, on average, experienced more respiratory symptoms in response to UFPs compared to non-asthmatics.

#### 4. Discussion

In our study, we did not observe a significant association between increased personal weekly UFP exposures and lung function. However, participants with greater UFP exposure were 1.3 times more likely to report at least one respiratory symptom and of those who experienced at least 1 symptom, experienced an increase of 9% in total symptoms for the week. ZIP models revealed higher UFP exposure was associated with significant increases in the number of non-zero symptoms in the asthmatic group compared with non-asthmatics. Our analysis suggests an interaction between asthma status and UFP exposure, and perhaps playing a greater role on respiratory effects in asthmatics when compared to non-asthmatics.

While weekly median UFP was negatively associated with %FEV<sub>1</sub>, %FEF<sub>25-75%</sub>, and %FEV<sub>1</sub>/FVC in the fully adjusted model, this effect was not statistically significant. In addition, we did not observe effect modification by asthma status on the association between UFP and lung function. One potential explanation for these findings is that adolescents with asthma in this population are effectively managing their disease, as suggested by the ACT data. Prior studies of UFP exposure among asthmatic children have reported contrasting results. In two separate longitudinal studies, UFPs of two size ranges averaged over the previous four days were associated with deviations of morning PEF measurements from the total mean of each subject's respective PEF measurements ( $\beta = -0.483$  L/min [UFP size: 0.032–0.10  $\mu\text{m}$ ],  $-0.728$  L/min [UFP size: 0.01–0.032  $\mu\text{m}$ ], Pekkanen et al. 1997), ( $\beta = -0.43$  L/min,

Tiittanen et al., 1999) but were not statistically significant. A cross-sectional study on three European birth cohorts found mostly negative associations between UFPs and lung function outcomes in children with persistent respiratory symptoms, however results were not significant and effects were not modified by persistent respiratory symptom status (Paunescu et al., 2019). This study differed from ours such that dependent variables were dichotomized according to ATS 2005 criteria (Miller et al. 2005) and were measured within 1-hour of exposure sampling. Positive associations have also been reported in an asthmatic population (FEV<sub>1</sub>: 0.11 L increase per IQR increase in UFPs [5646p/cc],  $p < 0.05$ ; FEF<sub>25-75%</sub>: 0.36 L/s per IQR increase in UFPs,  $p < 0.05$ ) (Li et al. 2016). These studies did not report on asthma control, therefore it is unknown whether their sample were effectively managing their disease at the time of the study and sampling of UFPs was carried out using a stationary monitor. Personal UFP sampling was used in a recent study in which significantly negative relationships between alveolar deposited surface area UFP dose and both FEV<sub>1</sub> ( $\beta = -0.0025$  %mm<sup>-2</sup>,  $p = 0.02$ ) and FEF<sub>25-75%</sub> ( $\beta = -0.0075$  %mm<sup>-2</sup>,  $p = 0.004$ ) were reported (Buonanno et al. 2013). Previous studies using similar methodologies of weekly black carbon (BC, a proxy to traffic-related air pollution exposure) effects on lung function have been conducted using wearable sensors (Laeremans et al., 2018a, 2018b). Results of these studies found significant decreases in PEF, but not FEV<sub>1</sub>, FVC, or FEV<sub>1</sub>/FVC were associated with increased BC exposure, and the protective effect of physical activity on lung function decreases with increasing BC exposure. These studies highlight the importance of personal sampling for determining individual-based dose–response relationships.

In contrast to lung function, we did find weekly exposure to UFPs among children with an asthma diagnosis to have significantly increased

risk of experiencing respiratory symptoms throughout the week, suggesting they are more susceptible to UFP-induced respiratory health effects. This finding is in agreement with prior studies that have reported on infants. In one such study, they found infants experienced a significant increase in symptoms when exposed to UFPs (Andersen et al. 2008). Logistic regression models revealed IQR increases in UFPs averaged over 3 days prior to exposure was significantly associated with wheezing symptoms in children age 0–1 years living within 5 km of the urban pollutant monitoring stations (OR = 2.46, 95% CI [1.04, 5.84]). Several other studies have reported on the effect of UFPs on respiratory symptoms in children, though relationships were not significant, and results were inconsistent. For example, Tiittanen and colleagues observed increases in UFPs averaged over the previous 4 days resulted in a 24% increase in cough symptoms, though negative associations were observed on the same day of exposure and none of the effects were significant (Tiittanen et al., 1999). In a Korean based study, the association of wheeze and 7-day average UFP exposure in asthmatic and non-asthmatic children was assessed, resulting in a greater positive association for both outdoor UFP sources (OR = 1.46, 95% CI [0.89, 2.41]) and classroom UFPs (OR = 1.36, 95% CI [0.5, 3.68]), though neither reached statistical significance (Kim et al. 2011). Separate associations between coughing and wheezing and UFPs were observed in a study among children in Australia (Clifford et al. 2018), resulting in a similar odds ratio for respiratory symptoms (OR = 1.059, 95% CI [0.91, 1.25]). This result, however, was restricted to wheeze symptoms only. These studies were limited by sample size and exposure measurement errors using central monitoring stations, which limit the strength of their conclusions. In a series of commuter studies, real-time UFPs were measured during high and low traffic routes to determine proximity to emission source as a factor in health risks and acute inflammatory responses. Lower inhaled particle counts, up to 48%, were observed in low traffic routes (Cole-Hunter et al. 2012), along with significantly lower mean PNC exposure levels (Cole-Hunter et al. 2013). Nasopharyngeal irritation frequency was significantly increased during high exposure routes (Cole-Hunter et al. 2012), suggesting changes in microenvironment may predispose individuals to higher cardiorespiratory risks.

Studies in toxicology have revealed there are several pathways in the body that may be responsible for UFP-linked adverse respiratory health effects. For example, UFPs may trigger airway remodeling, lung inflammation, and activation and creation of oxidative stress (Xu et al., 2013; Heidenfelder et al., 2009; Rhoden et al., 2004). Further, inhaled UFPs preferentially deposit into alveoli within the lung (Kreyling et al. 2006) and are retained in the airways longer than larger-sized particles (Moller et al. 2008) creating these effects. Children are at an increased risk to the effects of UFPs and air pollution, in part, due to their developing immune and respiratory symptoms and also differences in personal behaviors and thus exposures when compared to adults. In this study, we attempted to mimic the variations in time-based behaviors through personal sampling. Because UFPs have a high degree of spatio-temporal variability (Zhu et al. 2002), there is a greater need for personal monitoring in epidemiological-based studies. Higher UFP concentrations occur near traffic sources, which may explain why we did not find strong associations in the current study. Most of the children lived more than 400 m from a major roadway (92%) and the majority of their overall sampling time was spent indoors, away from traffic sources, possibly lowering the total amount of UFP exposure they experienced throughout the week. However, for the time spent in transit, we were unable to ascertain participants' proximity to high traffic areas and whether this impacted their exposure levels.

There are some important differences between our study and prior research that should be considered including the age of children, our sampling design, and methods of UFP exposure assessment. One limitation of our study was participants sampled UFPs for a total of 3 h per day of their own choosing, which may result in UFP exposure concentrations that may not be representative of their typical daily exposure. Of the studies measuring UFP exposure, average UFP concentrations were

mostly higher than what was measured in our sample, leading us to believe the participants' daily exposure was underrepresented. However, we did not observe significant differences in UFP exposure or time spent sampling in each microenvironment between asthmatics and non-asthmatics, therefore it is unlikely this limitation confounded our results. In addition, EMA questionnaires were prompted multiple times per day, but not intentionally coordinated with UFP measurements. This is unlikely to significantly affect our results, however, given our focus on overall weekly exposures. Finally, our sample size was too underpowered to determine asthma status-specific coefficients in our ZIP models, which limited our findings. However, based on our prediction model, we observed asthmatics and non-asthmatics experience UFP-linked respiratory effects differently, a finding that supports theories of air pollution risk on asthma exacerbation (Orellano et al. 2017).

There were also several strengths to the study that should be noted. Most impressive was the sampling strategy used to characterize the spatial and temporal variability of UFPs. The use of personal sampling in this study to measure UFP exposure is a more accurate way of determining time-based behaviors that affect exposure compared to stationary monitors used in other studies. In addition to personal samplers, we also included Fitbit data into our final models to assess and control for personal behavior and mobility that could affect exposure patterns. However, the sampling monitor used in the study was only able to capture UFPs. It is possible that other pollutants, including PM<sub>2.5</sub>, may be associated with the health outcomes, and therefore the possibility of unmeasured confounding cannot be excluded. However, UFPs generally do not correlate well with PM<sub>2.5</sub> or other pollutants. For example, in a multi-country study on the relationship between UFP and PM<sub>2.5</sub> concentrations, Pearson's correlation tests revealed poor linear correlation for the cities analyzed ( $r = 0.07$ – $0.53$ ) (de Jesus et al. 2019). Differences between ambient concentrations of PM<sub>2.5</sub> and UFPs, distribution, and seasonal variability are primarily driven by source and climate factors. UFP concentrations are driven by vehicle emissions, and PM<sub>2.5</sub> is dominated by secondary aerosols.

Finally, the use of EMA to capture symptoms and exposures in real-time reduced the possibility of recall bias (Bradburn et al. 1987). EMA sampling schemes used in literature are either event-based or time-based; several studies have observed greater validity above traditional global questionnaires (Kamarck et al. 2007) and recall-based studies (Todd et al., 2005; van den Brink et al., 2001).

## 5. Conclusion

In the present study, we analyzed the adverse effects of weekly exposure to UFPs in adolescents. Results show increased exposure reduces respiratory health that is further influenced by asthma status. Specifically, we found that increased UFP exposure affects asthmatics and non-asthmatics differently with respect to respiratory symptoms. The results of this study highlight the need for future research to better characterize the relationship between UFPs and respiratory health outcomes. Current epidemiological studies on UFP-linked health outcomes rely on stationary outdoor monitors to characterize exposures which are unable to capture exposures from indoor sources or identify individual peaks, thus reducing overall effect sizes. The methodology used in the current study allowed for more precise exposure measurement of the spatiotemporal variability of UFPs, providing a more accurate time-series evaluation of short-term exposure in adolescents. However, a larger sample size and longer sampling times in future studies would enhance results of the current study and identify potentially susceptible individuals requiring interventions. Sources of UFPs are largely attributed to location and microenvironment, therefore it would advantageous to establish source-specific respiratory health risks. Also, findings of this study are a result of exposure across an entire week, which may have masked effects of smaller temporal resolutions. Future analyses on exposure windows immediately preceding the outcomes assessed are suggested to capture short-term effects of UFPs.

## CRedit authorship contribution statement

**Ashley Turner:** Data curation, Formal analysis, Visualization, Writing - original draft, Writing - review & editing. **Cole Brokamp:** Methodology, Resources, Software, Writing - original draft, Writing - review & editing, Supervision. **Chris Wolfe:** Methodology, Resources, Software, Data curation, Writing - review & editing, Investigation, Project administration. **Tiina Reponen:** Resources, Writing - review & editing, Supervision. **Patrick Ryan:** Methodology, Writing - review & editing, Conceptualization, Supervision, Funding acquisition.

## 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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