The Effects of Indoor Air Filtration on Peak Expiratory Flow (PEF) in Children with Stable Asthma:

A Randomized Double-Blind Crossover Trial in Shanghai, China

By

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Executive Summary

Air pollution is a global environmental and public health issue. The World Health Organization estimated that 92% of the world's population live in areas where health-based air pollution limits are exceeded and that 12% of world deaths annually are attributable to air pollution. A pollutant of specific concern is $PM_{2.5}$ (particulate matter with an aerodynamic diameter of 2.5 micrometers or smaller). This class of pollutants can penetrate deep into the lungs and has been shown to have many deleterious health impacts, including decreased lung function, aggravated asthma, arrhythmia, and premature death.

Asthmatic children are a susceptible subpopulation for the health effects of air pollution due to their stage of lung development and existing lung inflammation and/or obstruction. Since upwards of 80% of time is spent indoors, the use of portable filtration devices is a potential environmental control measure to mitigate exposure to air pollutants. However, evidence is limited to support whether indoor air filtration can bring health benefits.

To assess the respiratory health impacts of an indoor filtration intervention in asthmatic children, we conducted a randomized, double-blind, crossover trial in Shanghai, China. Forty-three asthmatic children (40% female) aged 5 to 14 participated in the study. Each participant received true filtration and sham filtration interventions in a randomized sequence, with a two-week washout period separating both.

This study is focused on one particular health outcome, namely peak expiratory flow (PEF). PEF is the maximum speed in which an individual can breathe out or expire, which is used as a measure of lung obstruction. Participants recorded their PEF two times a day throughout the study period, at 7:00am and 9:00pm.

The aims of this study were three fold:

1. Examine the diurnal variability of PEF;
2. Assess the impact of indoor air filtration on PEF; and
3. Examine temporal relationships between length of filtration intervention and PEF.

Diurnal variability was examined by analyzing the differences between morning and evening values of PEF within subjects. Approximately 40% of subjects were found to have significant diurnal variability, with higher PEF values in the evening compared to their morning values.

Pollutant levels within the children's bedrooms were shown to be significantly impacted by the use of a filtration device. Compared to sham filtration, true filtration significantly decreased $PM_{2.5}$ concentrations in the bedrooms by 60%, and also decreased their total daily exposure to $PM_{2.5}$. The true filtration intervention significantly increased PEF by 4.2 [95% CI: 2.4, 6.0] l/min, indicating improvements on lung obstruction. Additionally, no relationship was found between the length of filtration intervention and effect on PEF, reflecting that the effect of the filtration intervention on PEF did not increase over time. These findings indicate that the use of indoor air filtration may provide health benefits in asthmatic children living with moderate levels of ambient air pollution. However, indoor filtration should only be considered as 'the last resort'

for alleviating health impact of air pollution, as the ultimate solution is undoubtfully environmental control measures to improve ambient air quality.

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1. Introduction

Air pollution is an international environmental health issue. Ninety-two percent of the world's population live in areas where air pollution exceeds the World Health Organization's (WHO) standards[1]. The WHO estimates that air pollution is responsible for close to 12% of all deaths worldwide[1]. There are specific subpopulations that are more susceptible to the negative health effects of air pollutant exposures, including asthmatic children.

This study explores changes in lung function associated with the implementation of air filtration devices in the bedrooms of asthmatic children in Shanghai, China. While this study does take place in a single geographic location, the range of pollutant levels seen in Shanghai are comparable to many other cities in developing counties such India, Nigeria, Nepal, and Mexico, as well as cities in developed countries such as Chile, Israel, and Turkey[2]. Therefore, this study is seen to be representative of areas with moderate levels of air pollution.

In children, asthma is the most prevalent non-communicable disease worldwide[3]. Asthmatic children are an at-risk population to the negative health effects of air pollutant exposure. Children's lungs are still developing and thus are more susceptible to long term health effects associated with pollution exposures[4,5]. Asthmatic children are a specific subpopulation of concern due to their already compromised lung function. Asthmatic children living in areas with elevated levels of air pollution are in need of mitigation options to reduce exposure and health effects of air pollution. One of these environmental control options is the use of air filtration devices. However, studies investigating the respiratory health effects of this intervention in asthmatic children residing in areas of moderate levels of outdoor air pollution are lacking. This study will explore the relationship between air filtration device use and changes in peak expiratory flow measurements.

1.1 International Scope of Air Pollution and its Effects

The research for this study was conducted in Shanghai, China. However, the results from this study are meant to be transferable to other cities with moderate levels of air pollution in both developing and developed countries. Different components of air pollution have been related to negative health outcomes and increased mortality. Many countries have set enforceable limits to various air pollutants, and WHO has also established guideline health standards with the goal of protecting public health (Appendix 1). The pollutant of focus within this research is $PM_{2.5}$.

$PM_{2.5}$ is particulate matter with an aerodynamic diameter of 2.5 micrometers or smaller (Figure 1). There are many sources of $PM_{2.5}$ including construction, automobiles, power plants, and industrial activities[6,7]. $PM_{2.5}$ has the potential to cause adverse health effects due to its small size and ability to penetrate deep into the lungs and enter the bloodstream. Additionally, their small size leads to relatively high surface areas which allows for carrying various types of potentially toxic compounds[8]. Health affects associated with $PM_{2.5}$ exposure include decreased lung function, aggravated asthma, arrhythmia, and premature death[6,7].

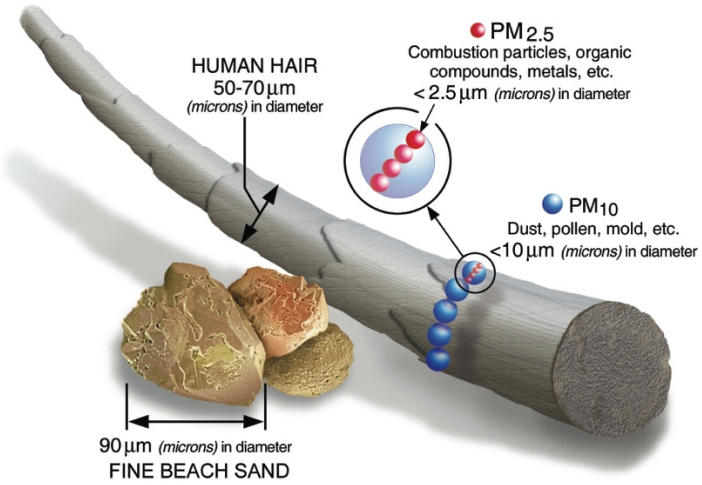

Figure 1: Size comparison of $PM_{2.5}$ Reprinted from "Particulate Matter (PM) Basics" by U.S. Environmental Protection Agency.[6]

While the effects of $PM_{2.5}$ exposure are experienced by the entire population, certain populations are more susceptible to the adverse health outcomes. These susceptible populations include: children, elderly, and those with pre-existing cardiopulmonary or respiratory disease[7].

1.2 Childhood Asthma

Asthma is a chronic respiratory condition marked by hyperactive and/or inflamed obstructions in the lungs. There are a range of symptoms associated with asthma, including wheezing, coughing, shortness of breath, and chest pain[9]. Asthma attacks can be defined as periods of reversible airflow obstruction. This chronic disease currently does not have a cure, but can be managed with bronchodilators and corticosteroids administered through inhalers and oral pills[10]. Airway stress can be present without the overt signs and symptoms of asthma[11]. Asthma also has the potential to cause other health issues later in life. The tendency for asthmatics to have lower than average lung function increases their risk of cardiovascular diseases[12,13]. With an estimated 235 million people in the world affected by asthma,[3] it is a significant public health concern.

While asthma affects people of all ages, children are uniquely susceptible to this disease. Age related differences in asthma prevalence have been documented for some time. In the 1980s, over half of all asthma hospital admissions in the United Kingdom were children[14]. More recently, in 2008 the International Study of Asthma And Allergies in Childhood (ISAAC) has estimated that 14% of children worldwide experience asthmatic symptoms[15]. Hospitalization and other debilitating effects of asthma result in the loss of millions of school days annually[16]. The loss of school days for young children can influence academic standing and their overall base knowledge. The prevalence of childhood asthma, along with the negative health and social consequences make its prevention, control, and treatment a major public health issue.

Air pollution is one of the triggers of asthma attacks and is even considered a possible cause of asthma (although the evidence is not consistent). The main pollutants of concern are ozone and particulate matter. Many studies have been conducted to elucidate the relationship between ambient air pollution and negative health consequences for susceptible populations, such as asthmatics[17–19]. Even at relatively low concentrations of $PM_{2.5}$ (below 15μg/m^3) significant relationships are found between ambient $PM_{2.5}$ concentrations and asthma related emergency room visits by children[20]. Air pollutant exposure causes changes in biological markers such as pH, 8-isoprostane, and cytokines, which are indicators airway inflammation and oxidative stress[21]. Asthmatic children experience these negative respiratory effects and have heightened responses due to their existing asthmatic status.

In China the prevalence of asthma varies between urban and rural, as well as between cities. A survey conducted in 10 Chinese cities from 2010-2012 showed that the prevalence of physician-diagnosed asthma varied from 1.7% to 9.8% with a mean of 6.8%. The city with the highest prevalence of childhood asthma was found to be Shanghai with 9.8%[22]. Additionally, prevalence of asthma in Shanghai have been increasing from 1990 to 2011[23]. As shown in Figure 2, across age groups and genders, childhood asthma has ubiquitously increased. The age group with the highest prevalence of asthma in this study were children ages 3-7 followed by children ages 8-12. These age categories of increased asthma occurrence present a uniquely susceptible subset of the population to the effects of air pollution.

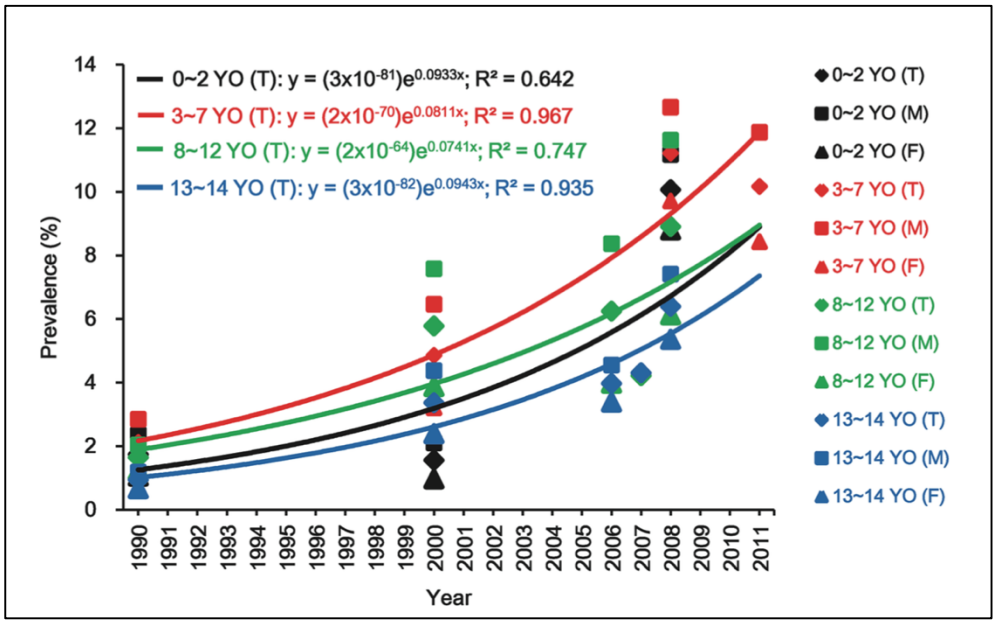

Figure 2: Time-trend prevalence of asthma among children in Shanghai, China. Reprinted from "Updated prevalences of asthma, allergy, and airway symptoms, and a systematic review of trends over time for childhood asthma in Shanghai, China," By C. Huang, *PLoS One*. 10(4), pg 10. 2015.
"YO" stands for "years old". T: Total; M: Male; F: Female. The solid lines are exponential trend lines[23].

1.3 Indoor Air Interventions

While ambient (outdoor) air pollution is a major public health concern, indoor air pollution is also a significant contributor to air pollutant exposures. Individuals spend upwards of 80% of their time indoors,[24] indicating the significance of indoor environments to overall exposure to air pollutants. In the past it has been recommended that people with severe allergies or asthma to use air filtration systems, i.e. an air filtering vacuum cleaner and HEPA air filtration devices[25]. These recommendations have been based on the thought that the presence of filtration systems will reduce indoor air pollutants and subsequently protect health. Multiple intervention studies have been conducted to research the exposure and human health effects of the use of these household air filtration devices. However, these studies have not been consistent in their findings of health effects resulting from indoor air filtration.

Air purifiers and household filtration devices are commonly used by families in order to reduce air pollutants and suspended particles (dust) in the house. To study the effects of the use of these devices intervention studies can be conducted. Intervention studies involve a systematic change controlled by the researchers and are meant to test the efficacy of a specific action or product. Intervention studies on air quality and human health effects are an important part of the scientific literature. They greatly differ from toxicology and laboratory studies, but their differences complement each other and create opportunities for greater scientific findings. Some of the main differences between laboratory studies and intervention studies are the study of acute vs. chronic effects, population size, extrapolation, mixtures, and dose exposure[26].

Intervention studies allow for unique insights unavailable through laboratory testing, with one of the key advantages being the inclusion of human behavior and culture. Within these studies, individuals and/or populations can be studied with the individual or population itself serving as its own control[26]. Individual intervention studies, such as air filtration devices, allow for the practicality of the intervention, along with its effectiveness to be tested. Even through it is impossible to fully control the study and collect all the data produced value of real world data outweighs these uncertainties.

Multiple intervention studies have been conducted to research the exposure and human health effects of the use of these household air filtration devices. There is a great variety in cohorts and situations in which the effects of air filtration units have been explored. Many studies focus on the effects of air filtration systems on adults[27]. Symptom reduction has been seen in trials of air filtration systems with adults,[28,29] however validated scales of clinical symptoms and quality of life are lacking. Many studies have used reported symptoms and measures of airway mechanics such as PEF and FEV_1 as outcome parameters of study[27].

Additionally, filtration studies have been conducted with cohorts of asthmatic children, but only in areas with low levels of outdoor pollution[27,30] and with the inclusion of additional variables such as living in households with one or more smokers[31,32]. These studies showed that the filters used did reduce the particulate exposure of the children, but did not prevent all exposure to secondhand smoke.

This study aims to fill the gaps presented by the filtration intervention studies already employed. Indoor air filtration studies in a cohort of asthmatic children without any other diagnosed diseases and not being exposed to indoor smoking has not been done previously. In all, this study focuses on the effects of filtration intervention on PEF values within the susceptible pollution of asthmatic children in areas with moderate levels of outdoor air pollution.

1.4 Filtration Units

Household filtration units are a common addition to a home as an environmental control measure in order to reduce exposure to indoor pollutants[33,34]. Also, air filtration units are used by those with respiratory issues and also the general population. In heavily polluted areas these interventions are often sought out. For example, in Shanghai, after a period of high air pollution in 2015 and 2016 sales of portable air purifiers increased by 300%[35].

High-Efficiency Particulate Air Filtration units (HEPA) are a common filtration system. These filters use mechanical filtration,[36] meaning the filter has many layers of mesh which particulates cannot get through. The particulates are intercepted by the mesh and are physically trapped in the net-like filter. HEPA filters are standardized, with "a minimum 99.97% efficiency rating for removing particles greater than or equal to 0.3μm (1/83,000 of an inch) in diameter"[36].

Within this study the Amway Atmosphere™ filtration unit was utilized. Amway is the world leading seller of premium in home filtration units[37]. The Amway Atmosphere™ system

includes a pre-filter, a carbon (odor) filter, and HEPA filter. This portable, in home filtration unit has an adjustable clean air delivery rate of 1.4 to 7.1m^3/min and available on the market for $1,700 (USD)[38].

1.5 Peak Expiratory Flow

A common measure of lung function for asthmatics is peak expiratory flow (PEF). PEF is a measure of the maximum speed of expiration from the lungs, measured in liters per minute. Low or decreased PEF readings are seen as indications of lung obstruction. PEF can be measured with a variety of instruments including pneumotachometers, spirometers, turbines, anemometers, and flow meters (peak flow meters). Peak flow meters are the most often used instrument due to their portability and relative low cost[39]. PEF readings are a relatively easy in-home measurement of lung obstruction. Readings can be taken once a day, or multiple times a day, thereby allowing for temporal changes in lung function to be identified and quantified.

Many factors can affect PEF readings include: physical lung dimensions, volume history of the lungs, sex, age, and health status[39]. This is why individual's PEF readings are often compared to standard reference values which have been developed for many different demographics. However, over time an individual is able to establish their own baseline values, and can distinguish significant personal changes in PEF on an individual basis.

According to the American Academy of Allergy, Asthma, and Immunology, PEF can be monitored for a variety of reasons including[40]:

- To quantitatively determine severity of asthma attacks or asthma symptoms
- Monitor response to treatment during asthmatic episode
- Monitor response to treatment of chronic asthma
- Detect worsening of lung function, and allow for appropriate activity and medication changes to be made

1.6 Specific Study Aims

The goal of this project was to assess the respiratory health impacts of an indoor air filtration intervention within asthmatic children's bedrooms. The pathway of interest for this research is shown in Figure 3. The intervention of a portable indoor air filtration unit was hypothesized to reduce indoor pollutant concentrations, thereby reducing personal exposure to air pollutants, and finally having positive effects on health endpoints. Within this study the pollutant of concern is $PM_{2.5}$ and the health endpoint was PEF. This research was conducted through a double blind, placebo controlled, 2x2 crossover trial in Shanghai, China.

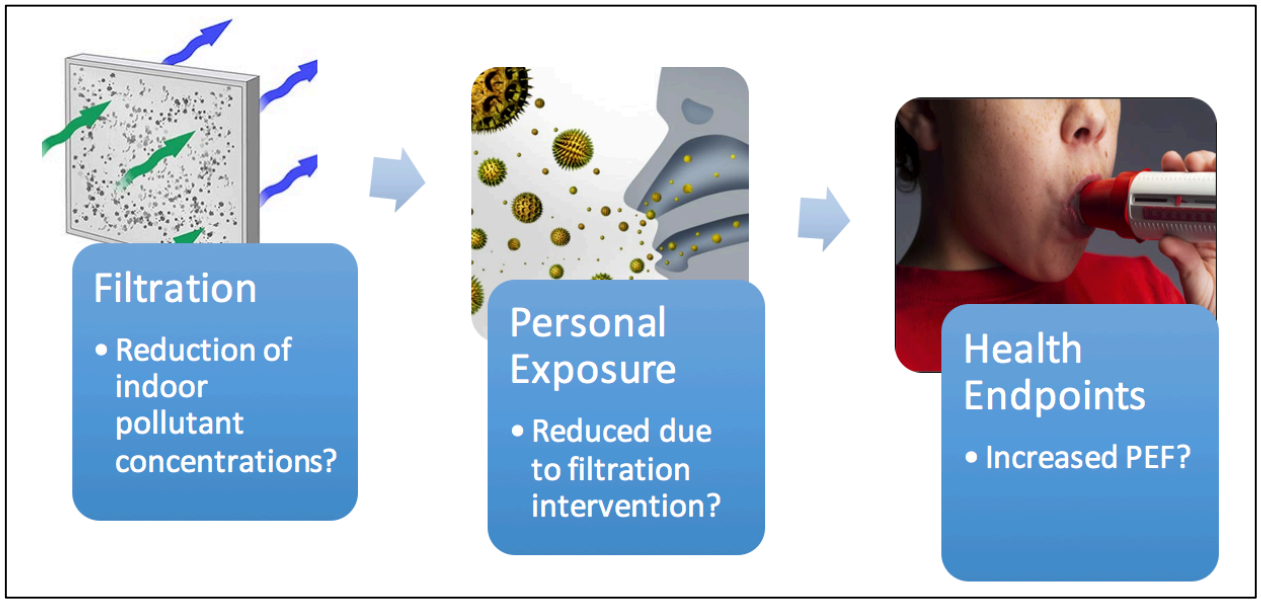

Figure 3: Pathway of concern for study. Implementation of a filtration unit, reducing indoor pollutant concentrations and exposure, thereby improving health endpoints.[41–43]

The specific aims of this research were three-fold:

- Aim 1: Examine the diurnal variability of PEF;
- Aim 2: Assess impact of indoor air filtration on PEF; and
- Aim 3: Examine temporal relationships between length of filtration intervention and PEF.

2. Methods

2.1 Study Design

2.1.1 UL Project

This master's project is part of the UL project (i.e., principally funded by the Underwriters Laboratory) which took place from February to April, 2017 in Shanghai China. A multidisciplinary team from Duke University designed and led this project, including Xiaoxing Cui, Dr. Junfeng Zhang, Dr. Zhen Li, Karoline Johnson, Christina Norris, Dr. Michael Bergin, and Dr. James Schauer. A brief summary of the full project will be presented here.

The objective of the UL project is to determine the effects of filtration interventions on asthmatic children in urban China. More specifically, whether the intervention of air filtration units in asthmatic children's bedrooms has an effect on indoor air pollutant concentrations and various health measurement endpoints. Recruitment of study participants was lead by Dr. Zhen Li of Shanghai First People's Hospital and Xiaoxing Cui. To be included in the study, participants had to meet a set of criteria: Subjects all had to live within 30 km of Shanghai First People's Hospital to allow for easy of clinical visits and greater monitoring of ambient pollutant concentrations. Additionally, all of the individuals were diagnosed by Dr. Li with mild or moderate asthma in line with the guideline of the Global Initiative of Asthma (GINA) [44], and had at least one asthma attack in the past 12 months as well as being free from any other disease diagnosis prior to enrolment in the study.

After recruitment, the study participants were then divided into two groups to receive the interventions. The study design was a randomized double-blind, placebo-controlled, 2x2 crossover trial. The two intervention conditions were defined as "true" and "sham" with a "washout" period in-between. True filtration was defined as the use of an Amway Atmosphere[38]

filtration device. The device has a variety of flow rates to choose from between 1.4 and 7.1 m^3/min. For this study "wind speed 2" was used, which had a clean air delivery rate of 2.8 m^3/min. This CADR was adopted due to its relatively lower levels of noise. The true filtration device included a pre-filter, a high efficiency particulate air (HEPA) filter, and an active carbon filter (Figure 4). The sham filters were filtration devices which look identical to the true filters but did not contain the HEPA or active carbon filters. The wash out period was a time between the two intervention periods in which no filtration unit was present or used.

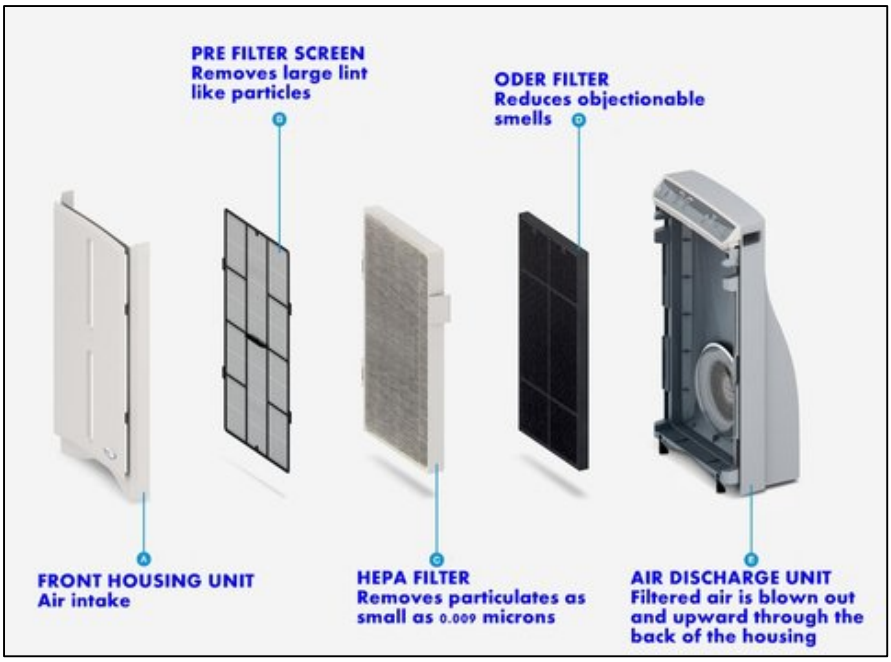

Figure 4: Schematic of Amway Atmosphere unit, Reprinted from "Atmosphere air purifier review." by *Medium*. 2017.[37]

Both study groups had the same amount of time with the filtration device, the washout period, and sham filter. The use of these "sham" filters allowed for the study to be double-blind, meaning both the participants and researchers did not know the order of interventions. During the first two weeks one group of participants received the true filtration devices and the other group received the sham filtration devices. These air filters were placed in the children's bedrooms. After two weeks of intervention, the filtration devices were removed for two weeks,

allowing for a washout period. After this washout period, the second intervention period began with the filtration systems switching between the two groups. In this way the cohort that previously received the true filters received the sham filters, and those that previously received the sham filters received the true filters. This crossover design allows for each study participant to serve as his/her own control. Figure 5 exhibits the timeline of this study design.

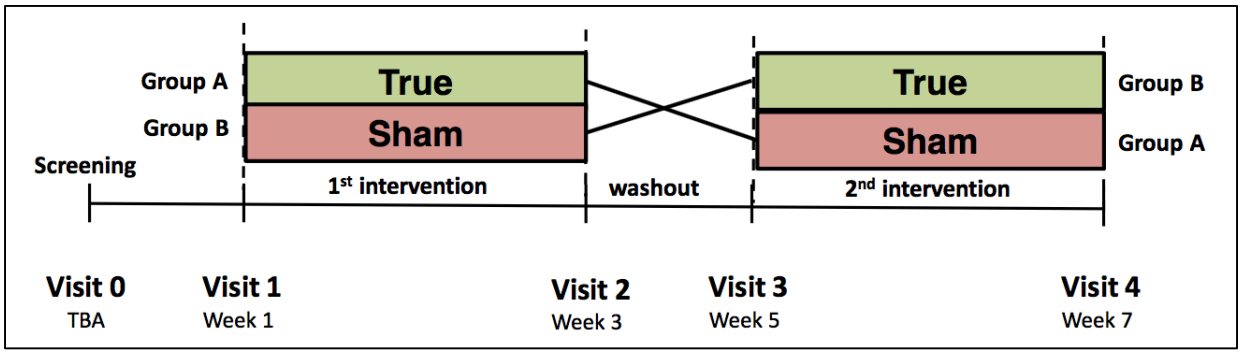

Figure 5: Study Design (credit: Xiaoxing Cui)

Throughout the study period the participants provided various measurements and biological media. These measurements are described in Appendix 2. Symptom and medication diaries were also collected. The majority of these measurements and collections occurred at five clinical visits throughout the study for each participant. The time periods of the clinical visits are indicated in Figure 4 (Visit 0 was the screening visit, Visit 1 was conducted before the first intervention, Visit 2 was conducted after the first intervention, Visit 3 was conducted before the second intervention, and Visit 4 was conducted after the second intervention). Peak expiratory flow (PEF) was a unique measurement in this study, in that personal measurements were taken two times a day with a peak expiratory flow meter. PEF is the focus of this research project and the methods of these measurements will be further defined in the following sections.

Air quality measurements were also collected throughout the study period. Indoor $PM_{2.5}$ concentrations were measured inside the subjects' rooms during two randomly selected 48-hour

periods, one during the sham and the other during the true intervention period. Personal air sampling pumps (XR5000, SKC AirCheck, USA) were used to pull air through a $PM_{2.5}$ personal modular impactor (SKC, USA) at 3L/min. 37mm Polytetrafluoroethylene (PTFE) filters (Pall Laboratory, USA) were used to collect $PM_{2.5}$. To quantify the $PM_{2.5}$ concentrations the PTFE filters were weighed before and after sample collection with a microbalance with a precision of 0.001 mg. Before being weighed, all filters were placed under controlled conditions: 22-24°C and 40-50% relative humidity.

Personal exposure to $PM_{2.5}$ was estimated using the same sampling equipment, but having the subject carry around the portable measurement device throughout the 48-hour collection period. The bag containing the personal sampling pump was carried throughout the day by the participant, and placed at breathing height in the bedroom while the participant slept.

2.1.2 2x2 Crossover Study Design

The crossover study design is a type of randomized control trial in which the selected cohort is divided into separate groups and the experimental timeline is blocked into at least two different units. During the first unit of time, one study group is given the intervention while the other either receives a placebo or retains natural conditions. At the second time unit the groups are switched, those that initially received the intervention then receive the placebo and those that received the placebo then receive the intervention. Also included within the experimental timeline can include “washout periods” in which neither the intervention or placebo is deployed to each subgroup.

In testing the environmental and human health effects of an indoor filtration intervention the 2x2 crossover design is the most prominently utilized design. This is due to a variety of reasons, including:

- Subjects are able to act as their own controls within the analysis.
- All study participants receive both the intervention and control thus equally receiving any benefits associated with the intervention.
- Allows quantification of acute health effects associated with short term changes in exposure[29].

2.1.3 Specific PEF Methods

Within this research only PEF measurement are the health endpoint of concern. The pathway of interest being explored is the addition of a filtration unit thereby reducing indoor exposure and improving health endpoints, in this case increasing PEF values. PEF measurements within the UL study are unique in that it is the only health measurement recorded every day. This greater resolution of health data allows for temporal changes in lung function associated with the intervention of air filtration units to be explored.

PEF is measured with peak flow meters. These are portable lightweight devices, which are commonly given out to asthmatic patients in order to provide a general self record of their lung function. The PEF meters used in this study are *KOKA Peak Flow Meters* (Figure 6). This device can record PEF readings of 60-850 L/min, which contains the expected PEF values of children in the 3-15 age group[45,46]. The measurements obtained from the PEF meter are indicated on the side of the device, with the distance between closest tick marks indicating 5 L/min. This can be conceptualized as the resolution of the measurements.

Figure 6: KOKA Peak Flow Meter utilized in the research project. Reprinted from "Adult peak flow meter Peak velocity instrument" by Aliexpress[47].

All subjects and their parents/guardians were trained by medical professionals on how to properly use and read their peak flow meter following the proper technique recommended by American Academy of Allergy, Asthma, and Immunology [40]:

1. Ensure the device is set at zero, or is at its base level
2. Stand up
3. Place meter in mouth and close lips around mouthpiece
4. Take a deep breath, then blow out as hard and fast as possible (should be one to two seconds)
5. If the user coughs, spits, or lets their tongue block the mouthpiece re-set the device to zero and re-do the measurement
6. Repeat two more times, and record the highest achieved PEF value

Within the research period PEF readings were conducted two times a day, the first at 7:00am and the second at 9:00pm. These times were selected in order to provide readings that represent lung function at the beginning of the day after waking up and with minimal outdoor ambient air pollution exposure for the 7:00am measurements. The 9:00pm measurements were

chosen so that the recorded PEF corresponded to lung function after a full day of activities and return back to the home environment prior to sleeping.

At each measurement session the children would blow three times and the highest PEF reading of the three exhales would be recorded on a provided data sheet. Measurements were done three times to allow for more confidence in the recorded values.

2.1.4 Self-reported Illness and Medication Usage

At each clinical visit throughout the study, subjects reported medication usage and were questioned about recent illness by a trained professional. The variables collected within these visits that will be used in this analysis include indication of upper respiratory tract infections (URI) and fever along with reported use of regulatory and emergency medications.

All of these variables were related to the two weeks leading up to the clinical visit. Upper respiratory tract infections were defined by asking the following question: "Do you have a fever OR feel like you have a cold (typically associated with runny nose and cough) during the previous two weeks?". However, the designation of URI could be confounded by other symptoms of asthma or allergies. This is why the indication of fever was also included, being defined as the response to the following question: "Did you have a fever during the previous two weeks?". The indication of use of regulatory medication was given by the following question: "Did you take long-asthma control medications during the previous two weeks". The regulatory medication was then further broken down to inhaled corticosteroids (ICS), long-acting beta agonists (LABA), H_1 receptor antagonists, leukotriene receptor antagonists, and other forms of medication. The indication of use of attack medication was defined as the response to the following question: "Did you take asthma fast relief medication to cope with asthma attack during the previous two weeks?". The attack medication was then further broken down to short-

acting beta agonists (SABA), anticholinergic medications, corticosteroids, and other medications.

This information is important because the presence of illness and use of medication during the study period can have effects on recorded PEF values. These potential influences are addressed within the analysis of this report.

2.2 Data Acquisition and Quality Control

Data for this research project was provided by the UL project team. All data provided was de-identified and included daily PEF readings, physical and health descriptors of subjects, medication and illness records, and health/biomarker recordings taken throughout the research period.

PEF data was recorded two times daily by a parent/guardian of each subject on a provided datasheet (Figure 7). Subjects and their parents were trained on use and reading of the PEF flow meter prior to the initiation of the study period by physicians. PEF recording sheets were collected at each clinical visit and photographed for data preservation and sharing. The handwritten records were transcribed to excel workbooks by two independent researchers. These two records were compared and any discrepancies between the recorded measurements were resolved by referring back to the original handwritten recordings.

Figure 7: Example of PEF flow chart completed throughout the study period.

At every clinical visit throughout the study multiple health and wellness measures were recorded. The clinical visits were all performed by medical professionals at Shanghai First People's Hospital. The data was provided on medical charts and transferred to excel documents by members of the project team. Any uncertainties found within the visit notes were addressed directly with Dr. Zhen Li and her team at Shanghai First People's Hospital. Data received during these visit includes use of different regulatory and emergency asthma medications along with indications of sickness within the prior two-week period. While specific dates of sickness were included, the dates of medication use were generalized to the entirety of the two-week period prior to the clinical visit.

After review of all data, and comparison to raw recordings when uncertainties arose, the data was determined to be valid and then further utilized within this analysis.

2.3 Statistical Analysis Methods

2.3.1 Normality of the Data

PEF data including morning and evening values for all subjects was tested for normality with a Shapiro-Wilk normality test. Additionally, PEF distributions for the individual subjects were analyzed. Baseline PEF capabilities are variable throughout a population based on sex, age, height/weight, as well as other respiratory health factors. Thus, raw PEF values between individuals are not always comparable. Therefore, a subject by subject analysis of PEF normality was conducted.

2.3.2 Diurnal Variability

Measuring PEF values two times a day every day provides many benefits in analysis, including the evaluation of diurnal variability with in the cohort. Various studies have explored the presence and cause of diurnal variations in PEF values[48–50]. Past cohort studies of PEF have shown the presence of diurnal variability in PEF measurements[48,49]. Diurnal variability means that the morning and evening PEF values are consistently different. Studies have shown some consistency in that morning PEF measurements are often times associated with lower PEF values[48,49]. The lower morning values are often attributed to the presence of nocturnal and morning asthma. However, diurnal variability can be caused by a variety of factors including timing of medication, indoor and outdoor pollution exposures, allergens, as well as temperature.

In order to examine the presence/absence of diurnal variability within this cohort a variety of analysis methods were employed. This includes data visualization, the Mann-Whitney test and the Wilcoxon signed-rank test. Findings of diurnal variability will be used to group the participants into those with and without diurnal variability. Further testing was done on these

groups to determine if there are any significant relationships between presence of diurnal variability and medication usage through Fisher's exact test.

2.3.3 Filtration Effect

To further explore the effect of filtration on PEF values, linear mixed-effects models were created. The data used for this analysis only included PEF values corresponding to sham and true intervention periods. The additional data was not used since the main focus of this analysis is the effects of the filtration unit utilized within these two intervention periods. In these models the health outcome of PEF was set as the response (dependent variable). Statistical analysis were conducted using the *lme4* [51] and *lmerTest* packages in R statistical software[52]. The following models were created:

- *Final Model Development* – In development of a final model in addition to subject id as a random effect and intervention as a categorical variable illness and medication usage was considered. Final model creation was facilitated by a step down method. This entailed starting with a full model including all measures of sickness, time of PEF measurement, and medication usage, then taking out variables one by one based on significance measured within the model. The final model was decided based on comparison of models via ANOVA analysis as well as comparison of Akaike information criterion (AIC) and Bayes information criterion (BIC) values. (Equation 1)
    - Stratified analysis was also employed on the final model considering all PEF values, just morning PEF, just evening, or an average daily value as the explanatory variable.
- *Effect Modification Analysis Model* – The indications of diurnal variability found presented reason to evaluate if PEF measured at different the time of the day demonstrate different filtration effects. (Equation 2)

- Filtration intervention was included as a categorical fixed effect variable and PEF timing (morning/evening) was added as an interaction term with filtration intervention. Subject id was also included as a random effect variable.

- Sensitivity Analyses – To ensure that all significant variables were included in the analysis, and that the removal or addition of variable did not have a significant change to the effects of filtration on PEF sensitivity analyses were preformed.
  - *Fever Sensitivity Analysis* – Further sensitivity analysis was completed by removing the dates in which fever was indicated for a subject. After this removal the full model was re-run with this new response variable.
  - *Longitudinal Models* – To continue the analysis of temporal variability in PEF values between interventions longitudinal models were created including the days since intervention initiation as a variable. Two models were created, one with correlated random effects and one without. (Equations 3 and 4)
    - Allowing for correlated effects allows for subjects with a higher initial reaction to the filtration intervention to be more strongly affected by the intervention over time as well.

Equation 1: Final conservative linear mixed effects model

$$Y_{ijlm} = \beta_0 + \beta_1 FIL_{ij} + \beta_2 URI_{il} + \beta_3 REG_{im} + W_i + \varepsilon$$

Equation 2: Linear mixed effects model exploring the effect of time of day on PEF values.

$$Y_{ijlm} = \beta_0 + \beta_1 FIL_{ij} + \beta_2 TIM_{ij} + \beta_3 \left(FIL_{ij} * TIM_{ij}\right) + \beta_4 URI_{il} + \beta_5 REG_{im} + W_i + \varepsilon$$

Equation 3: Modeling the longitudinal data with a linear mixed effects model with correlated random effects. The correlated random effects allow for subjects with a higher initial reaction to the filtration intervention to be more strongly affected by the intervention over time as well.

$$Y_{ijk} = \beta_0 + \beta_1 FIL_{ij} + \beta_2 SEQ_{ijk} + (1 + U_{ik}) + \varepsilon$$

Equation 4: Modeling the longitudinal data with a linear mixed effects model with uncorrelated random effects.

$$Y_{ijk} = \beta_0 + \beta_1 FIL_{ij} + \beta_2 SEQ_{ijk} + W_i + (0 + U_{ik}) + \varepsilon$$

i = the participant id (i = RS01, RS02,…, RS43)

j = the two filtration interventions (j =1, 2)

k = reported fever (k = 1, 2)

l = reported upper respiratory tract infection symptoms (l = 1, 2)

m = reported use of regulatory medication (m = 1, 2)

k = days since start of intervention period (k = 0, 1,…, 13)

Y_{ij} = PEF value

FIL_{ij} = the type of filtration intervention (1 = true filtration, 0 = sham filtration)

TIM_{ij} = time of day in which PEF was recorded (1 = 9:00pm, 0 = 7:00am)

FEV_{ik} = fever confirmation (1 = yes, 0 = no)

SEQ_{ijk} = number of days since start of intervention period

URI_{il} = URI confirmation (1 = yes, 0 = no)

REG_{im} = regulatory medication confirmation (1 = yes, 0 = no)

W_i = subject-specific random intercept

U_{ik} = subject-specific random intercept and slope with respect to days since start of intervention for each subject

ε = residual

2.3.4 Temporal Changes in PEF

Within this analysis one of the main goals was to evaluate whether the intervention of filtration within the bedroom had a significant effect on PEF over time. The data for each individual was visualized to garner general trends. However, additional analyses were necessary to make any conclusions about PEF changes over time across the participants.

In order to evaluate differential changes over time between the true and sham interventions methods from Zhang et al. (2009) were replicated[53]. First, the PEF measurements were categorized into days since initiation of intervention. The day in which the intervention (sham or true) began was coded as 0, the second day as 1, and so on. This coding allows for the different days of intervention period to be compared between interventions and between subjects.

In order for this analysis to be done on all the subjects a comparable metric was created. Percent change was used as an indicator of temporal change for the two different intervention periods. With the average PEF value during the sham intervention set as the "baseline" and changes during the intervention period quantified with Equation 5.

Equation 5: Percent change equation

$$\frac{Y_2 - Y_1}{Y_1} * 100 = Percent\ Change$$

Y_1 = Average PEF value during the sham intervention period set as the baseline value achieved without inclusion of filtration intervention.
Y_2 = the subsequent PEF readings which are being compared to the baseline Y_1 value.

The percent change metric was used to evaluate differential temporal changes in PEF between the sham and true intervention periods. Mann Whitney tests were employed as well as paired t-tests. Paired t-tests were used in lieu of the non-parametric Wilcoxon sign-ranked test to create a comparison of PEF percent change values matching for day since initiation of intervention, which is not accomplished by the non-parametric tests. Additional linear mixed effect models were created to determine if there was a significant relationship between the day of intervention (sequence) and filtrations effect on PEF (Equation 6).

Equation 6: Linear mixed effects model used to evaluate temporal relationship between day of intervention and PEF.

$$Y_{ijk} = \beta_0 + \beta_1 FIL_{ij} + \beta_2 SEQ_{ijk} + \beta_3 (FIL_{ij} * SEQ_{ijk}) +_. W_i + \varepsilon$$

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i = the participant id (i = RS01, RS02,…, RS43)

j = the two filtration interventions (j =1, 2)

k = days since start of intervention period (k = 0, 1,…, 13)

Y_{ij} = PEF value

FIL_{ij} = the type of filtration intervention (1 = true filtration, 0 = sham filtration)

SEQ_{ijk} = number of days since start of intervention period

W_i = subject-specific random intercept

ε = residual

3. Results

3.1 Participant Characteristics

43 asthmatic children between the ages of 5 and 13 were recruited to participate in the UL study. A description of the cohort recruited for this research can be found in Table 1.

Table 1 Study participants' description

Descriptor	Mean (min, max)
Age (years)	7.814 (5,13)
Weight (kg)	31.23 (19,59)
Height (cm)	132.3 (110, 166)

Gender	No. of Subjects (%)
Male	26 (60%)
Female	17 (40%)

All 43 subjects provided PEF data for parts of the study period. However, the number of days in which subjects provided data ranged from 13 days (~ 2 weeks) to 55 days (~ 8 weeks), with a mean of 44.4 and median of 45 days (~ 6.3 weeks). The average of six weeks is significant because the entire study period; including intervention 1, washout, and intervention 2, required six weeks. Some subjects provided data for more than six weeks due to the fact that they started recording values prior to their first intervention and/or continued recording PEF values after their last intervention period ended. This occurred because the initial clinical visit and PEF recording training occurred prior to the start of the intervention period, and the last clinical visit occurred after the final intervention was concluded. For other data for less than the entire six-

week period was acquired. This was due to a variety of reasons including incomplete data recording and loss of data.

However, the majority of subjects did provide adequate PEF data during the intervention periods for analysis, as shown by Table 2.

Table 2 Quantity of PEF data recorded by subjects. Days of complete data indicates the minimum number of days completed for both the sham and true intervention periods.

Days of Complete Data for Sham and True Intervention Periods	Number of Subjects Meeting Criteria (Percentage)
14 days (2 weeks of complete data)	10 (23.3%)
13 days	27 (62.8%)
12 days	37 (86.0%)
1 or more days	40 (93.0%)

Data on incidence of illness and medication usage was also collected throughout the study period. These data were collected by trained medical professionals during each clinical visit throughout the study period. A summary of reported illnesses and medication usage can be found in Table 3. 36 out of the 43 individuals (83.7%) indicated URI symptoms during the previous two-week period at least one of the clinical visits. However, only 9 out of the 43 individuals (20.9%) indicated having a fever during the previous two-week period. Medication use was widely present for regulatory medicines with 36 subjects (83.7%) indicating use, while attack medicine was not as widely reported with only 5 individuals (11.6%) indicating use of attack medicine during at least one of the two-week periods prior to a clinical visit.

Table 3: Summary of illness and medication recorded by the subjects.

Sickness/Medication Usage Indicated	Yes	No
URI	36 (83.7)	7 (16.3)
Fever	9 (20.1)	34 (79.1)
Regulatory Medicine	36 (83.7)	7 (16.3)
Attack Medicine	5 (11.6)	38 (88.4)

3.1.1 PEF Distribution

Initial analysis of PEF values included a total cohort view, and then also segmented by individual subjects. There was a large range in PEF values recorded by the cohort (50 to 450), with a mean of 251.5, median of 245.0, and standard deviation of 62.4 L/min (Figure 8).

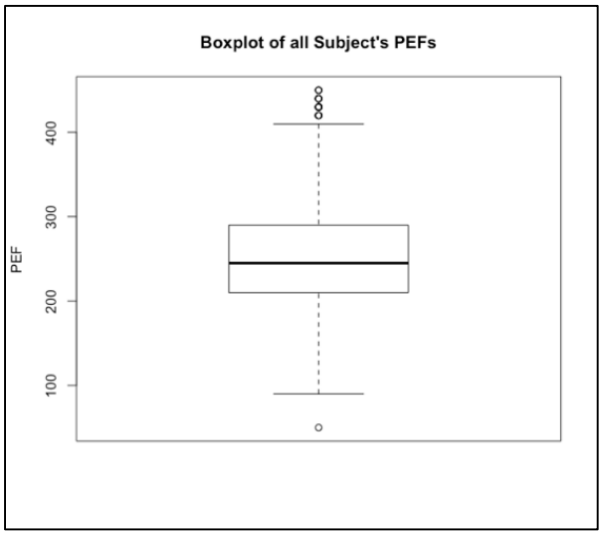

Figure 8: Distribution of all participant's PEF values.

After examining the entire cohort's PEF distribution, subject specific PEF analysis was completed. As shown in Figure 9 PEF distributions and average values were greatly variable and significantly different throughout the cohort. This is due to population variability of PEF capabilities. Therefore, raw PEF values are not always comparable between subjects and

standardized values such as ratios or percent change can be used, which will be addressed later in this report.

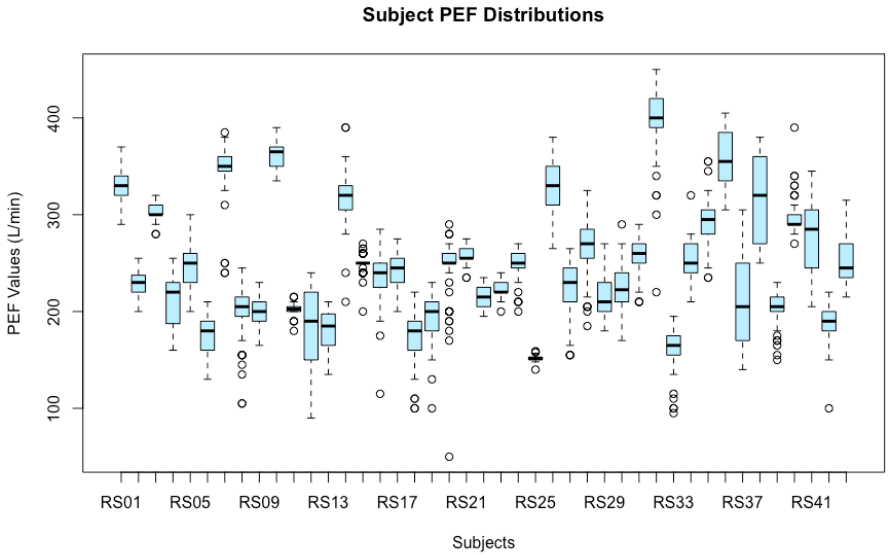

Figure 9: Subject specific distributions of PEF values.

3.1.2 Tests of Normality

Shapiro Wilks Normality tests conducted indicated that the total PEF data collected for all subjects was not normally distributed ($p < 0.001$). Multiple transformations were performed on the data to achieve normality, but none were successful. However, when visualizing the data in a histogram (Figure 10), the data does not appear greatly skewed.

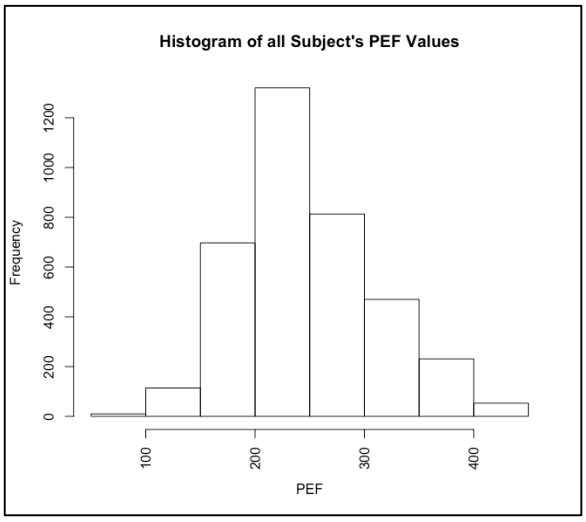

Figure 10: Distribution of all 43 Subjects' PEF values.

The subsequent analysis included subject specific Shapiro-Wilk tests on PEF distribution. Distributions of individual PEF values can be seen in Figure 11. From visual inspection is does not appear that the data is largely skewed, but additional Shapiro-Wilk normality tests were performed. From these tests significant values indicating lack of normality were found for 38 out of the 43 subjects within the study. Subsequent transformations of the data were unsuccessful in improving the normality of the data. Therefore, within this analysis the raw PEF data will be used without transformations, and non-parametric tests will be used.

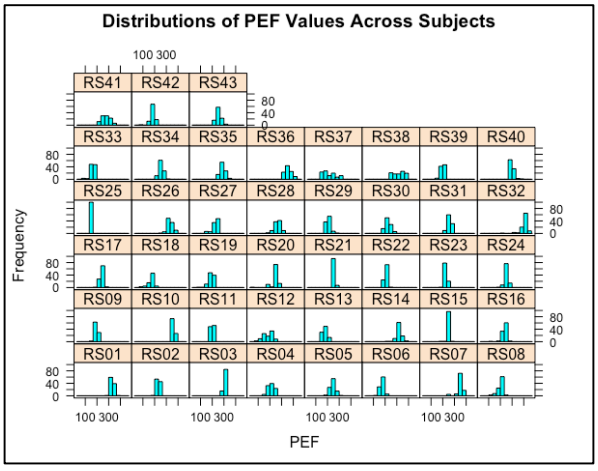

Figure 11: Distribution of subject's PEF values.

3.2 Air Quality Measurements

Indoor air quality measurements were recorded during the study period during 48-hour windows within the sham and true intervention periods. Additionally, ambient outdoor $PM_{2.5}$ measurements were taken. Results from these measurements can be seen in Table 4. The intervention of the true filtration device was found to significantly reduce the bedroom concentrations of $PM_{2.5}$, with a median percent change between sham and true concentrations of 60%.

Table 4: Indoor and outdoor $PM_{2.5}$ concentrations during study period.

Measurement Situation	Mean $PM_{2.5}$ ($\mu g/m^3$)	Median $PM_{2.5}$ ($\mu g/m^3$)	Range of $PM_{2.5}$ ($\mu g/m^3$)
Indoor with Sham Filtration	34.1	29.0	15.7-84.8
Indoor with True Filtration	14.8	12.1	1.4-52.1
Outdoor	54.6	50.0	2.0- 185.0

Personal exposure measurements were also taken during 48-hour periods during the study period. These results are shown in Table 5. A decrease in $PM_{2.5}$ exposures was seen when going from sham to true filtration intervention periods, however this difference was not found to be significant.

Table 5: Personal $PM_{2.5}$ exposure measurements during study period.

Measurement Situation	Mean $PM_{2.5}$ ($\mu g/m^3$)	Median $PM_{2.5}$ ($\mu g/m^3$)	Range of $PM_{2.5}$ ($\mu g/m^3$)
Indoor with Sham Filtration	67.6	64.3	10.7- 127.0
Indoor with True Filtration	65.1	49.2	3.2- 165.8

3.3 Diurnal Variability

3.3.1 Data Visualization

First, the data was separated in to morning and evening values. Subsequently, each subject's mean PEF and standard deviation for their morning and evening PEF values were calculated and visualized in a box plot (Figure 12). This graph visually does not indicate a large difference between the morning and evening values recorded or the standard deviations of these values on a per subject basis. While this initial visualization does not present a case for a presence of diurnal variability within the subjects' additional statistical tests were completed to further evaluate this.

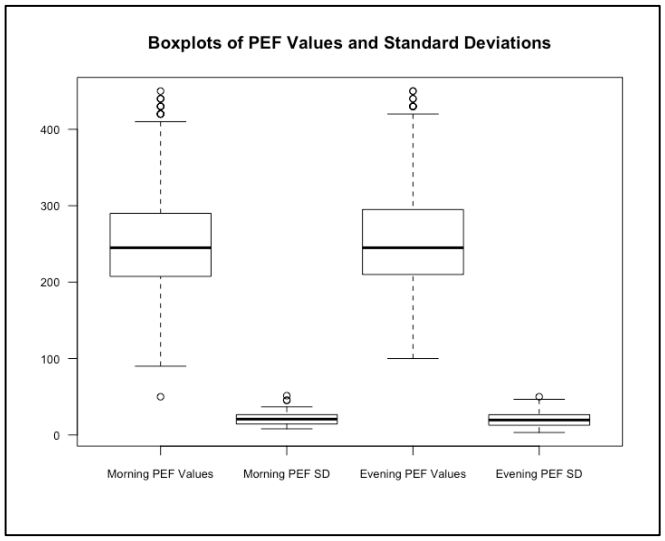

Figure 12: Distribution of morning and evening PEF values.

3.3.2 Statistical Analysis

Since the PEF data are not normally distributed non-parametric tests were utilized in the analysis of morning and evening values. First a Mann Whitney test was performed comparing the morning and evening recorded PEF values for the entire dataset, yielding an insignificant p value (0.30). This shows that there is not a significant difference between the morning and evening PEF values of all subjects.

Additionally, tests comparing the morning and evening PEF values were completed for each subject. Through this analysis Mann Whitney tests, comparing mean subject PEF values for morning and evening, as well as Wilcoxon sign-ranked tests, matching up values in a test similar to a paired t-test, were utilized. 17 subjects (40%) yielded significant p values for the Mann Whitney and/or Wilcoxon sign-ranked tests. This indicates that 40% of the subjects did have significantly different PEF values when comparing morning and evening measurements.

To further explore this, analysis was undertaken to determine if morning or evening values were consistently higher amongst those subjects with significant differences in PEF measurements. 16 out of the 17 subjects (94%) had mean PEF values higher in the evening than in the morning. This finding strongly suggests the presence of diurnal variability within the subjects.

3.3.3 Diurnal Variability Stratified Analysis

Through the analysis of diurnal variability within the subjects, two groups were identified: those with diurnal variability in PEF readings and those without. Further analysis of these groups was undertaken to determine if there were any underlying trends or relationships between the presence of diurnal variability and some other uncontrolled variable. The variables included within this analysis are use of regulatory and attack medications as well as fever.

Initial data exploration included in creation of contingency tables in which the total dataset was classified based on presence of diurnal variability and use of regulatory (Table 6) or attack medications (Table 7), and indication of fever (Table 8). The 1,911 data points used correspond to all of the daily recordings by subjects throughout the study period.

Table 6: PEF diurnal variability and use of asthma regulatory medication.

		Presence of Diurnal Variability		
		Yes	**No**	**Total**
Use of Asthma Regulatory Medication	**No (# and row %)**	147 (25.2%)	420 (74.1%)	567 (100%)
	Yes (# and row %)	574 (42.7%)	770 (57.3%)	1344 (100%)

Table 7: PEF diurnal variability and use of asthma attack medication.

		Presence of Diurnal Variability		
		Yes	**No**	**Total**
Use of Asthma Attack Medication	**No (# and row %)**	707 (38.4%)	1136 (61.6%)	1,843 (100%)
	Yes (# and row %)	14 (20.6%)	54 (79.4%)	68 (100%)

Table 8: PEF diurnal variability and indication of fever.

		Presence of Diurnal Variability		
		Yes	**No**	**Total**
Reporting of Fever	**No (# and row %)**	693 (62.8%)	1171 (37.2%)	1864 (100%)
	Yes (# and row %)	28 (40.4%)	19 (59.6%)	47 (100%)

Subsequent Fisher's exact tests were conducted to evaluate the relationship between the presence of diurnal variability and the use of medications and indication of fever. The Fisher's test including regulatory medication usage and diurnal variability yielded a significant result ($p < 0.001$), rejecting the hypothesis of no relationship between these variables. The odds ratio from this test was 2.12, with a 95% confidence interval of 1.7 to 2.7. This can be interpreted as the

odds of having diurnal variability for a subject using regulatory medication is 2.1 times that for a subject that does not use regulatory medication.

The Fisher's test evaluating the relationship between use of attack medication and presence of diurnal variability in PEF measurements also yielded a significant result ($p = 0.003$), rejecting the hypotheses of no relationship between these variables. The odds ratio was 0.42, with a 95% confidence interval of 0.21 to 0.77. This can be interpreted as the odds of having diurnal variability for a subject using attack medication is 0.42 times that for a subject that does not use attack medication.

The relationship between diurnal variability and fever indication was also analyzed with a Fisher's test. This test yielded a significant result ($p = 0.0022$), and an odds ratio of 1.49 with a 95% confidence interval of 1.33 to 4.75. This is interpreted as the odds of having diurnal variability for a subject who had a fever is 1.49 times that for a subject that did not have fever.

These analyses were all replicated with the use of Chi-square tests and found to have consistent results, showing lack of independence between the fever, regulatory medication, and attack medication variables with diurnal variability. Additional analysis was completed on a medication by medication basis, and can be found in Appendix 3.

3.3.3.1 Sensitivity Analysis

Due to the significant effect of fever found in this analysis, and its potential confounding effects, additional analyses were completed in which all days in which fever was indicated were removed. There were 47 days of indicated fever which were removed for this analysis.

With the removal of fever indicators similar results were obtained:

- The Fisher's test including regulatory medication usage and diurnal variability yielded a significant result ($p < 0.001$), rejecting the hypothesis of no relationship between these

variables. The odds ratio from this test was 2.17, with a 95% confidence interval of 1.7 to 2.7. This can be interpreted as the odds of having diurnal variability for a subject using regulatory medication is 2.17 times that for a subject that does not use regulatory medication.

- The Fisher's test evaluating the relationship between use of attack medication and presence of diurnal variability in PEF measurements also yielded a significant result ($p = 0.03$), rejecting the hypotheses of no relationship between these variables. The odds ratio was 0.52, with a 95% confidence interval of 0.26 to 0.97. This can be interpreted as the odds of having diurnal variability for a subject using attack medication is 0.52 times that for a subject that does not use attack medication.

Table 9: Comparison of results of Fisher's Exact test with and without fever indicators.

Inclusion of Fever Data	Metric being related to Diurnal Variability	Odds Ratio	95% CI	p value
Fever Data Included	Regulatory Medication	2.12	1.7, 2.7	< 0.001*
	Attack Medication	0.42	0.21, 0.77	0.003*
No Fever Data Included	Regulatory Medication	2.17	1.7, 2.7	< 0.001*
	Attack Medication	0.52	0.26, 0.97	0.03*

3.4 Filtration Effect

Multiple mixed effects models were created in the analysis of filtration effect within this study. Results of these models can be found below.

3.4.1 Final Model Development

In utilizing the step down methods of model development the "full model" included subject id as a random effect and intervention, time of PEF measurement, indications of illness, and medication usage as categorical variables. The final model included filtration, time of PEF

measurement, upper respiratory tract infection, and use of regulatory medications and can be seen in Table 10.

Table 10: Final model output.

Variable		β	95% CI	p
Filtration	β_1	4.19	(2.36, 6.01)	< 0.001 *
Upper Respiratory Tract Infection	β_3	-21.70	(--24.49, -18.92)	< 0.001 *
Regulatory Medication	β_4	-5.33	(-9.12, -1.53)	0.006*

3.4.1.1 Stratified Analysis

Due to the presence of diurnal variability within the dataset, stratified analysis was completed creating models using all recorded PEF values as well as just the morning or evening values. The results of these stratified analyses as well as the full model (Equation 1) are described in Table 11.

Table 11: Output comparison from stratified analysis.

Response Variable (Y_{ij}), PEF	β_1	95% Confidence Interval	p
All	4.19	(2.36, 6.01)	< 0.001 *
Morning	4.43	(1.91, 6.95)	< 0.001 *
Evening	4.05	(1.37, 6.73)	0.003 *
Average	4.25	(1.83, 6.67)	< 0.001 *

3.4.1.2 Effect Modification Analysis

Further analysis on the final developed model found that the time of day in which PEF was taken to be significant ($p < 0.001$), but the interaction between time of day and interaction to

not be significant (p = 0.90). Using Equation 2, the results of this model support the presence of diurnal variability with significance attributed to the PEF timing variable and filtration intervention. The model outputs can be interpreted as switching from sham to true filtration interventions corresponds to a 4.31 (95% CI: 1.75, 6.87) L/min increase in PEF, in taking PEF measurements in the evening instead of in the morning there is a corresponding 5.34 (2.83, 7.84) L/min increase in PEF, and the interaction of intervention and timing leads to a decrease 0.23 ((-3.78, 3.31) L/min decrease in PEF (summarized in Table 12).

Table 12: Effect modification analysis. Including the time of day in which PEF is measured as an interaction variable with the filtration intervention.

Variable	β	95% CI	p
Filtration	4.31	(1.75, 6.87)	< 0.001 *
Time of Day PEF Taken	5.34	(2.83, 7.84)	< 0.001 *
Presence of Upper Respiratory Tract Infection	-21.71	(-24.47, -18.94)	< 0.001 *
Use of Regulatory Medication	-5.35	(-9.11, -1.58)	0.005*
Interaction between Time of Day and Filtration Intervention	-0.23	(-3.78, 3.31)	0.90

3.4.2 Sensitivity Analysis

3.4.2.1 Fever Sensitivity Analysis

Due to the interaction of Fever with PEF readings, additional sensitivity analyses were conducted on the final model. In these analyses the days in which fever was indicated by a subject were removed and the final model was re-run. The results of this model were not greatly different than that of the model including fever indicator (Table 13).

Table 13: Final model output (sensitivity analysis removing data in which fever indicator was positive)

Variable	β	95% CI	p
Filtration	4.18	(2.36, 6.01)	< 0.001 *
Upper Respiratory Tract Infection	-21.71	(-24.49, -18.92)	< 0.001 *
Regulatory Medication	-5.33	(-9.12, -1.47)	0.006 *

3.4.2.2 Longitudinal Model with Correlated Effects Analysis

Continuing the temporal analysis of PEF values throughout the two-week intervention periods mixed effect models for longitudinal data were created. The response variable within these analyses were daily average PEF values. This average value was used as a daily representative since change over time, with days as the unit, were explored. Within these models the days since initiation of intervention was used as an additional variable. The two models explored within this analysis included a model with correlated random effects (Equation 3) and one without correlation (Equation 4). Within both models created, the days since onset of intervention was not found to be a significant fixed effect variable (Table 14), which is consistent with the findings within the previous temporal analysis.

Table 14: Output for longitudinal analysis.

Model Type (Equation)	β_1 (Filtration Intervention)	95% CI	p	β_2 (Sequence Variable)	95% CI	p
Correlated Random Effects (Equation 3)	3.27	(0.71, 5.83)	0.01*	0.045	(-0.40, 0.49)	0.83
Uncorrelated Random Effects (Equation 4)	3.25	(0.69, 5.81)	0.01*	0.040	(-0.40, 0.48)	0.86

3.5 Temporal Changes in PEF

Prior to this analysis it was predicted that a trend of increasing PEF over time would be associated with the true filtration intervention, and a subsequent decreasing trend in PEF over time with the sham filtration intervention. However, when looking at the trends graphs produced for individual subjects (Figure 13) and the entire study group (Figure 14), there did not appear to be an obvious trend in PEF value percent change over the sham or true intervention periods.

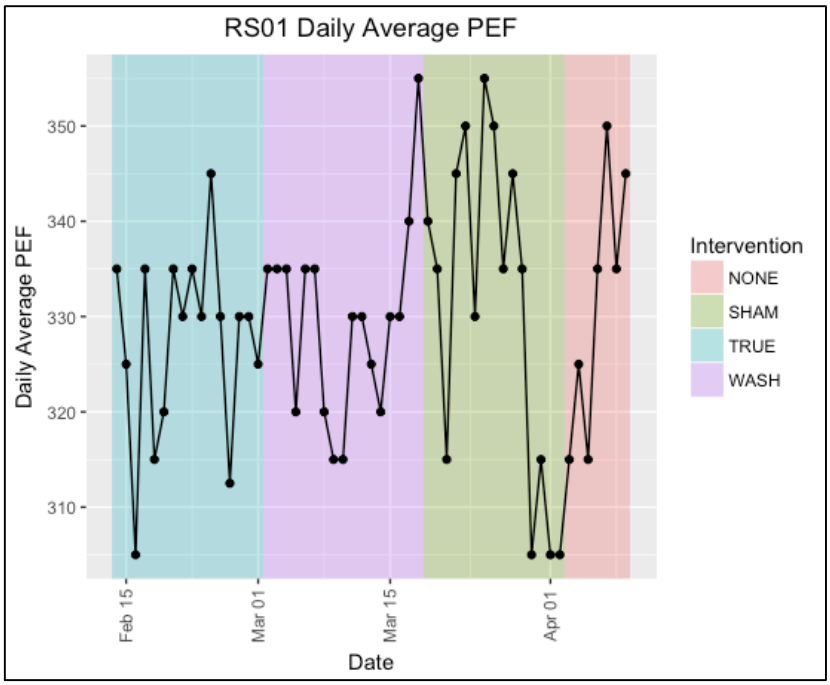

Figure 13: Visualization of average daily PEF values over time for subject RS01. This subject first started with a two-week intervention of the true filtration device, two-week washout period (with no filter), two weeks with the placebo sham filter, then an additional few days after the study period commenced.

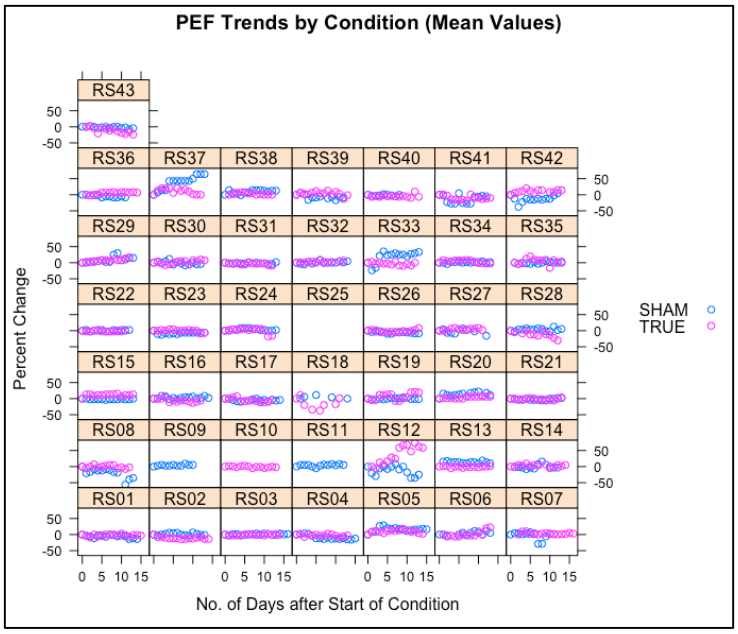

Figure 14: Percent change in daily mean PEF over time for sham and true intervention periods by subject.

This lack of divergent trend lines held constant when all subjects were compiled into a full cohort analysis of PEF percent change over time (Figure 15). The percent change for all subjects was collapsed by day since intervention to create Figure 15. It is shown that the percent change in PEF values are significantly different between sham and true interventions via Mann Whitney tests ($p < 0.001$) and Wilcoxon sign ranked tests ($p < 0.001$). Additionally, although the data was not normally distributed a paired t-test was performed to analyze if there was a significant difference in sham and true PEF percent change when matching for days since intervention. This analysis was also significant ($p < 0.001$), further showing the differential percent changes in PEF across the sham and true interventions.

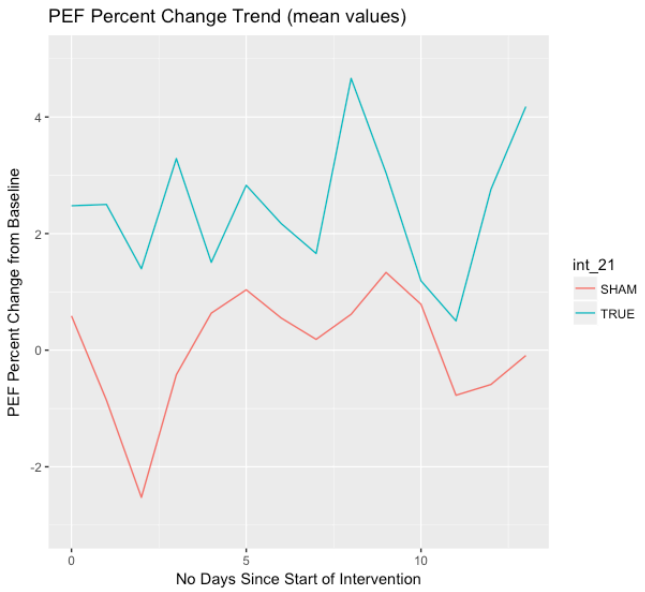

Figure 15: Percent change in daily mean PEF values across all subjects over the sham and true intervention periods.

Additional analysis was conducted to determine if there were any trend in PEF Percent Change from Baseline over the intervention periods. To do this a linear mixed effects model was developed in which intervention and sequence were included as interacting fixed variables and subject specific id was included as a random effects variable. Through this analysis it was found that the sequence variable and the interaction variable were not significant within the model, while the intervention variable was still significant (Table 15).

Table 15: Results from linear mixed effects model investigating the temporal trends of PEF.

Variable	***β***	**95% CI**	***p***
Filtration	4.08	(0.48, 7.84)	0.03 *
Sequence of Intervention	0.18	(-0.15, 0.51)	0.30
Interaction Between Sequence and Intervention	-0.16	(-0.63, 0.31)	0.52

4. Discussion and Conclusions

4.1 Discussion

In the examination of the effects of a filtration intervention on the peak expiratory flow of asthmatic children, a randomized crossover 2x2 study was employed. To examine the changes in PEF associated with the used of an air filtration device, we examined data from all participants, and also conducted between and within subject analysis on PEF variability.

4.1.1 Diurnal Variability

Within this analysis significant evidence of diurnal variability was found with 40% of the subjects exhibiting significant differences between morning and evening recorded PEF values. The higher evening values within this subsection of the cohort were consistent with past studies of diurnal variability[48,49]. The causes of diurnal variability within previous studies have been attributed to temperature changes[54] and normal changes associated with circadian rhythm[48]. While the exact causes of diurnal variability within this study were not identified, medication usage was different between those that exhibited diurnal variability and those that did not. Those who took regulatory medication had higher odds of having diurnal variability, and those that took emergency/attack medication had lower odds of having diurnal variability. The hypothesized reason for these differences is those that consistently take regulatory medication do not use emergency attack medication for emergency events as much as those that do not regularly manage their asthma with consistent medication usage.

There are other factors that may influence the presence of diurnal variability that were not included within this analysis including nighttime allergen exposures. Allergens can be ubiquitous throughout a household in the dust, carpet, bedding, etc[55]. However, these allergen concentrations in the subjects' rooms were not measured and the subjects' allergen profiles were

not included in this analysis. The allergen concentrations within the children's rooms could have influenced the findings of diurnal variability.

4.1.2 Filtration Analysis

Use of linear mixed effects models showed that the intervention of a filtration unit had significant positive effects on PEF readings within this study group. In the final model the variables of upper respiratory tract infection and regulatory medication usage were also found to significantly influence PEF readings.

The time of the day (either 7am or 9pm) was found to be significant as a categorical variable, but the interaction term between the time of the day and filtration type was not statistically significant. This is consistent with the earlier study findings of diurnal variability within a large percentage of the study group. The lack of interaction showed that PEF measurements at both time points responded similarly to the filtration interventions, and thus time of day in which PEF was recorded was not included in the final model.

Longitudinal analyses did not yield significant effects. The effect of the filtration intervention on PEF did not increase over time. Previous studies have shown particulate exposure over time leading to an increased effect on PEF values[53], however this was not shown in this study. The hypothesis that the effects of the filtration intervention would increase over time was not supported by the mixed effects longitudinal analysis or the temporal relationship analysis. The lack of change in PEF over time suggests that the effects of filtration intervention on PEF are relatively stable over time. This is most likely because PEF is a variable but sensitive measure of lung function. Changes in the ambient environment are quick to effect PEF values, both positively and negatively.

The final model created included the filtration intervention, indications of upper respiratory tract infection, and use of regulatory medication, and the random effect of individual subjects. When controlling for all of these other variables there was still a significant improvement in PEF with the implementation of a filtration unit. The decrease in PEF associated with URI was expected since respiratory sickness is also marked by lung obstruction reflected by PEF. However, the use of regulatory medication was also associated with a decrease in PEF readings. This finding was not expected but thought to have occurred due to the variable medication usage throughout the study period by individuals. Throughout the study individuals were not constant in the type or frequency of regulatory medication usage. Therefore, if an individual was not feeling well or having increased asthmatic symptoms they could be prescribed further regulatory medications. Therefore, the use of regulatory medications could have been skewed towards those with greater symptoms and times in which the subjects experienced lower PEF values. This is similar to what has been found in studies of adverse health effects of air pollution and use of inhaled corticoid steroids[56]. Asthmatic children using ICS can be found to have greater adverse health outcomes to pollution compared to those that do not use this medication, however it is thought that children with greater symptomatic asthma may use ICS more often[18].

Through these analyses it was found that the filtration intervention within children's bedrooms did have a significant effect on $PM_{2.5}$ concentrations and PEF values. The significant decrease in $PM_{2.5}$ concentrations is consistent with other studies on the efficacy of HEPA filtration devices[32,34]. The existing literature on positive PEF effects associated with filtration interventions support the findings of this study[27-29]. However, there are few studies focused on the effects of air pollution in asthmatic children and the use of filtration devices. Studies with

low levels of outdoor air pollution have found significant health improvements[27,30], as well as studies including household smoking as a variable[31,32]. This research adds to the growing evidence of home filtration units providing positive health effects for asthmatic children.

4.1.3 Temporal Relationship

It was hypothesized that the intervention of a true filtration device would lead to a gradual increase in PEF values over the intervention period in a linear fashion. Linear relationships between exposures and PEF values have been found in previous short term studies of exposure along a busy roadway[53]. However, the exploration of temporal changes in PEF value over the two-week intervention showed that PEF values between the sham and true interventions were significantly different, but that there was not a linear trend in PEF values over the intervention periods. PEF is a sensitive measure to air pollution exposures, in that changes in exposures and asthmatic symptom onsets are often quickly expressed in PEF measurement[39], which is supported by this study.

4.1.4 Limitations

The limitations of this study have been touched on throughout this report. These include data availability, pollutant exposure measurements, and inherent uncertainties when working with human subjects.

In the analysis of diurnal variability additional data on time of day in which medication was taken and allergen exposures were not collected. This additional information could have helped to explain why diurnal variability was not consistent throughout the study participants.

Also, the exposure measurements used in this study are related to $PM_{2.5}$, which is one of the many pollutants of concern. $PM_{2.5}$ is a known human health hazard and able to exacerbate asthma[6,7], but inclusion of additional pollutants would have created a more robust study.

The participants in the study were young children, which presents some uncertainty in the accuracy of certain recorded measurements. While all of the children and parents/guardians were trained on PEF data collection and asked to accurately report medication usage and sickness information, this data could be inaccurate. However, the field teams involved in this study were trained to minimize errors in recording and in obtaining accurate information. Due to this, the confidence in the data used within this analysis is high.

4.1.5 Future Studies

While this study was able to find a significant effect of an indoor air filtration system on $PM_{2.5}$ concentrations and increases in PEF during filtration interventions in children with stable asthma, further studies are warranted to address the following issues. PEF is one measurement of lung function that is relatively easy to record, but other more precise measurements of lung obstruction and function are needed to fully elucidate the respiratory health benefits of a filtration intervention. Additionally, the causes of diurnal variability in PEF are still unclear from previous research and these findings. Decreasing lung function variability within asthmatic children is important for long term asthma management and for maintaining optimal lung function in the adulthood. Further research into the factors affecting diurnal variability in PEF could be beneficial in the overall suite of asthma management practices.

4.2 Conclusions

The findings of this study show that for asthmatic children residing in places with moderate levels of outdoor air pollution, using a portable filtration unit within the bedroom for two weeks significantly increased peak expiratory flow (PEF), reflective of reduced lung obstruction. Diurnal variability was found within the cohort, with greater PEF values generally occurring in the evening compared to morning values. The use of regulatory medication and

indications of upper respiratory tract infections were also found to have significant effects on PEF values.

The results of this analysis support the use of air filtration devices in the households of asthmatic children in alleviating the impact of particulate matter pollution. However, it should be noted that indoor air filtration should only be regarded as a ‘last resort’, as the reduction of ambient air pollution should be the ultimate goal in order to protect the health of the general population including children and those with preexisting disease such as asthma.

5. Appendices

5.1 Appendix 1: Air Pollutant Standards

The table below includes the ambient air quality guidelines set by the World Health Organization, and the enforceable air quality standards of China.

Pollutant	WHO Guidelines[57]	China Air Quality Standards[58]
$PM_{2.5}$	10 μg/m^3 annual 25 μg/m^3 24 hour	35 μg/m^3 annual 75 μg/m^3 24 hour
PM_{10}	20 μg/m^3 annual 50 μg/m^3 24 hour	70 μg/m^3 annual 150 μg/m^3 24 hour
O_3	100 μg/m^3 8 hour mean	160 μg/m^3 daily, 8-hour max 200 μg/m^3 hourly
NO_2	40 μg/m^3 annual 200 μg/m^3 1 hour	40 μg/m^3 annual 80 μg/m^3 24 hours 200 μg/m^3 hourly
SO_2	20 μg/m^3 24 hour 500 μg/m^3 10 minute mean	60 μg/m^3 annual 150 μg/m^3 24 hour 500 μg/m^3 hourly
CO		4 mg/m^3 24 hour 10 mg/m^3 hourly

5.2 Appendix 2: Measurements of health indicators performed in UL study

Category	Measurement/Biological Media	Parameters	Description	Biological Significance
Airway Mechanics	Spirometry	FEV_1	Forced expiratory volume in the first second of a maximum expiration [59]	Lung Obstruction
		FVC	Forced vital capacity- amount of air that can be exhaled from the lungs after a deep breath [59]	Lung restriction
		$FEF_{25-75\%}$	Average forced expiratory flow during the middle portion (25-75%) for the FVC test [59]	Small airway obstruction
	Impulse Oscillometry (See figure 2)	R_5	Representative of total airway resistance (forward pressure of conducting airways) [60]	Airway resistance at 5Hz
		X_5, R_5-R_{20}, Fres	R_5-R_{20} indicates small airway resistance, X_5 and Fres reflect change in degree of obstruction in peripheral airways [60] (Figure 2)	Small airway mechanics
		PEF	Peak expiratory flow	Airway Obstruction
Respiratory Oxidative Stress and Inflammation	Exhaled NO	FeNO	Fractional exhaled nitric oxide is a measure of airway inflammation	Airway inflammation
	Nasal fluid	MDA	Malondialdehyde is an indicator of lipid peroxidation from oxidative stress	Lipid peroxidation by oxidative stress
	Saliva	ECP	Eosinophil cationic protein, marker of asthma disease activity.[61]	Eosinophil activity
		IL-6	Interleukin 6. Inflammatory cytokine.	Proinflammatory cytokine
		MDA	Malondialdehyde is an indicator of oxidative stress. Increases in free radicals increase production of MDA which is a final product in the peroxidation of polyunsaturated fatty acids[62]	Lipid peroxidation by oxidative stress
Systemic Oxidative Stress	Urine	8-OHdG	8-hydroxydeoxyguanosine is an oxidized nucleoside of DNA, and an indication of DNA lesion due to oxidative stress[63]	DNA damage by oxidative stress
		MDA	Malondialdehyde is a bioindicator of pulmonary oxidative stress. Increases in free radicals increase production of MDA which is a final product in the peroxidation of polyunsaturated fatty acids[62]	Lipid peroxidation by oxidative stress
		Specific gravity	Used to normalize urine samples due to dilution	Adjust for urinary dilution

5.3 Appendix 3: Analysis of Diurnal Variability and Medication Usage

Within the report the relationship between diurnal variability and medication usage was explored. However, this analysis only used the general indicators of regulatory and attack medications. This analysis does similar testing on each type of medication to evaluate whether a specific medication is the driver in the relationship between medication usage and diurnal variability found within the report.

Medication Category	**Medication**	**Subjects Taking Medication (# data points)**	**P value**	**Odds Ratio (95% CI)**
Regulatory	Inhaled Corticosteroid (ICS)	22 (644)	2.6e-07	1.67 (1.37, 2.04)
Regulatory	Long-Acting Beta Agonist (LABA)	2 (28)	0.24	1.66 (0.73, 3.79)
Regulatory	ICS +LABA	33 (1,110)	9.3e-13	2.01 (1.65, 2.45)
Regulatory	H1 Receptor Antagonist	14 (333)	<2.2e-16	4.39 (3.39, 5.71)
Regulatory	Leukotriene Receptor Antagonist	5 (113)	0.0036	0.53 (0.33, 0.82)
Attack	Short-Acting Beta Agonist	3 (41)	0.75	0.85 (0.41, 1.70)
Attack	Anticholinergic	0 (0)	NA	NA
Attack	Corticosteroid	2 (27)	2.94e-06	0 (0, 0.24)
Attack	Other	0 (0)	NA	NA

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