Effects of Reducing Indoor Air Pollution on the Adult Asthmatic Response (INHALE 2)

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Study Protocol and Statistical Analytical Plan

Title: The Effect of Reducing Air Pollution on the Adult Asthmatic Response (INHALE2)

Abstract

Asthma is one of the most common chronic diseases in adults, and inner-city residents, who typically live in poorly maintained urban housing, suffer a disproportionate burden of asthma morbidity (1). Many factors contribute to this disparity, including the observation that the urban indoor environment has been shown to have higher concentrations of indoor air pollutants than suburban counterparts (2). An increasing amount of evidence has shown that air pollutants, which contain particulate matter, including coarse ($PM_{2.5-10}$) and fine ($PM_{2.5}$) particles, are associated with greater respiratory morbidity in asthmatics (3-9). While the bulk of this data focuses on ambient air pollution, accumulating evidence suggests that indoor air pollution, which (unlike outdoor pollution is not EPA regulated) may be even more harmful (10). Moreover, exposure to these pollutants may be prolonged, as Americans spend most of their time indoors (11). Fortunately, the indoor environment is more amenable to modifications by the individual, thus making it an attractive target for interventions aiming to improve asthma health.

One such intervention is introduction of a HEPA air cleaner. We have previously shown that introduction of a HEPA air cleaner results in sustained improvements in indoor pollution concentrations and respiratory symptoms (12,13). Our prior work has investigated the effects of indoor particulate matter on biological and clinical markers of respiratory health in a cohort of inner city children in Baltimore. However, given the age of our participants and research procedure restrictions, we have been limited by the inability to collect bronchoscopic specimens, which could reveal important information regarding lung-specific immune responses within the lower airway. The aim of this project is to extend these findings to a population of urban non-smoking adults with asthma, and characterize both local and systemic responses to the indoor environment. In addition, we hypothesize that actively removing these pollutants through an air cleaner intervention will attenuate their impact on asthma morbidity. This study, INHALE 2, extends evaluation of a subgroup of participants from a parent study, INHALE 1.

In the parent study, 100 adult subjects will be studied longitudinally during a 1-week period at baseline and again at 3 months, during which environmental monitoring of indoor air quality, as well as health assessments (respiratory symptoms, lung function and serum markers) will be conducted. As part of this initial study, we aim to further characterize the inflammatory and oxidative stress pathways that have been implicated in the airway's response to PM in the published literature. To this end, markers in the blood, will be analyzed and linked to changes in indoor particulate matter. Subsequently, a subset of 40 subjects from this cohort that meet safety criteria will then be randomized to having one of two interventions—HEPA air cleaners or sham air cleaners--placed in the home for 1 month's duration. After this month, the true or sham air cleaner will be removed from the home, and no machines will be present in the home for at least another month (washout period). In the final month of this study, the two intervention arms will be crossed over in a blinded fashion, and true/sham air cleaners will be placed in the home again for 1 month. During the first and third months, homes will undergo continuous environmental monitoring and participants will undergo personal environmental monitoring, along with simultaneous health assessments that include questionnaires, diaries, lung function testing, and blood testing. In addition, during the last week of each month with the intervention, participants will undergo bronchoscopy, during which we will obtain airway samples in order to compare lower airway response to the interventions.

In summary, more evidence is needed to understand the local pulmonary and systemic mechanisms that contribute to the burden of asthma in susceptible populations such as urban dwellers exposed to high levels of indoor pollution. Furthermore, by examining the potential alleviating effect of actively reducing chronic exposure to air pollution in the indoor environment, we aim to strengthen the causal relationship between PM and worsening asthma. Such evidence has the promise to lay the groundwork for future clinical recommendations and public policies for environmental control practices.

Objectives (include all primary and secondary objectives)

Primary Objective:

The aim of this project is to investigate the effects of an air cleaner intervention, compared to sham air cleaner, on the change in indoor air pollution, notably fine and coarse particulate matter (PM), in the home of adult asthmatics.

Secondary Objectives:

We will also investigate the effects of an air cleaner intervention, compared to sham air cleaner on clinical markers of asthma health, specifically day and nighttime symptoms, medication usage, and asthma-related quality of life using questionnaires. The effects on lung function using spirometry and alterations in airway and systemic biomarkers of inflammation will also be explored. Finally, the effects of the intervention compared to sham on the indoor air nicotine concentration will be assessed.

Background

The mechanisms by which indoor air pollution potentially worsens asthma morbidity are unclear. In epidemiologic studies, higher indoor PM levels have been associated with increased respiratory symptoms, decreased lung function, and more frequent rescue medication use. Potential mechanisms behind this observed relationship have been investigated in numerous studies, but these have largely been limited to animal models, in vitro systems, or human challenge models that high experimental loads of PM. Regardless, these studies have demonstrated that exposure to air pollutants triggers the release of specific cytokines (Il-6, Il-8) which play a central role in cell-to-cell communication, stimulating immune cells, and regulating inflammatory processes within lung tissue, and that this effect is potentiated in patients with asthma. Such inflammatory effects have been demonstrated in bronchoalveolar lavage fluid and cultured bronchial epithelial cells, but also been shown to generate systemic inflammatory responses (as evident by elevated circulating levels of IL-6 and TNFα, as well as CRP), suggesting that inflammation is one of the main responses to PM. However, because this proposal investigates the effect of exposures in the native environment of human subjects, it will provide the opportunity to corroborate these findings in a real-world scenario. Furthermore, this study is novel in that it will investigate the effects of pollution abatement and examine the effect on these asthmagenic processes when real-time PM exposure is actively reduced.

A number of preliminary studies conducted by our group set the stage for this proposal(1). We have extensive experience performing environmental monitoring within Baltimore city and have found that the city has high levels of biologically active indoor PM. In our prior cohort study of 150 asthmatic children, the mean ($\pm$SD) indoor PM concentration for $PM_{2.5-10}$ (coarse) was 17.4 $\pm$ 21.1 μg/m3 and for $PM_{2.5}$ (fine) was 40.3 + 35.4 μg/m3, both of which were significantly higher than the average ambient measurements made over the same time period (10.3 ± 21.0 μg/m^3 and 12.4 ± 6.2; $p < 0.01$ for both comparisons). Eighty-five percent of homes had indoor levels of $PM_{2.5}$ exceeding the EPA limit for ambient pollution (2, 14). In addition, we found that this indoor pollution is associated with increased asthma morbidity. Specifically, each 10 μg/m^3 increase in $PM_{2.5-10}$ was associated with increases of 8% in the number of days of symptoms

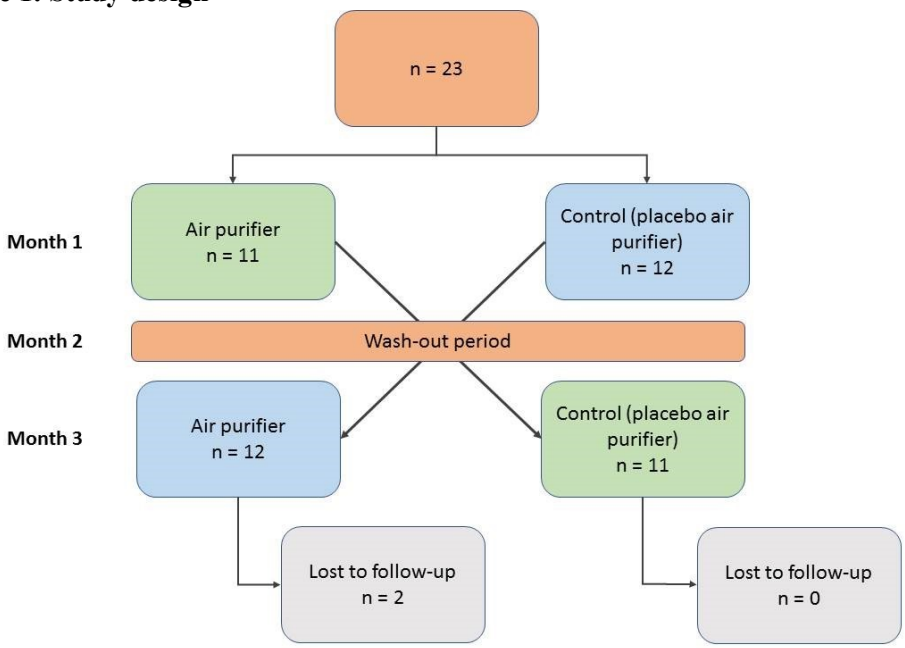
severe enough to slow activity, 8% in nocturnal symptoms, 11% in wheezing that limited speech, 6% in rescue medication use, and 6% in overall asthma symptoms (3). We have successfully reduced these in-home PM levels in our prior experience with HEPA air cleaners. In a randomized controlled trial of home environmental interventions in urban Baltimore children with asthma, concentrations of PM_{10} decreased 30% compared to the control group after 6 months of air cleaner use (12). Asthma symptoms also significantly decreased over this time period. A subsequent study of air cleaners in urban homes of children with asthma showed similar improvements in fine and coarse PM after 6 months, along with improvement in symptom-free days compared to a control group (13). Therefore, we have demonstrated that HEPA air cleaners are able to reduce PM and improve asthma health in inner city children with asthma. However, this has not yet been investigated in adults, and we also do not have an understanding of the biological mechanisms behind such an improvement in asthma symptoms (4). Lastly, our collaborators in the basic sciences have demonstrated that particulate matter has measurable effects on epithelial barrier function, showing that a single dose of PM (150 µg/ml) is associated with enhancement of barrier function and decreased permeability, but repeated exposures result in barrier disruption and increased permeability (15). This evidence supports the hypothesis that chronic pollution exposure can induce the natural airway epithelial barrier to become more leaky, allowing further entry of PM or allergens and triggering further inflammation.

Currently, our research group is actively involved in gathering and analyzing environmental and health data from questionnaires, serum, urine, and exhaled breath samples in children with asthma in several Baltimore studies, and this study will draw upon this expertise, especially with regard to study protocols and operation of equipment. Our field workers have many years of experience in recruiting both children and adult participants with asthma in inner city Baltimore. Furthermore, colleagues in our division are currently engaged in research bronchoscopy in order to collect lower airway samples for their respective studies, and we will be modeling our protocols after these established studies.

Study Procedures

Study design:

Figure 1. Study design



Eligible participants for this protocol will be recruited from the community and health care facilities. All study procedures will be performed as part of this research proposal, with none of the investigations part of routine care. However, clinically significant study results will be shared with participants as needed.

Over the course of 3-5 years, 40 participants that meet criteria will be recruited from the parent study (INHALE 1) which occurs over a 3 month period, and enrolled for an additional months of investigations (i.e. this study will pick up immediately after the parent study leaves off). Informed consent will be obtained at the beginning of the parent study, and hereafter, the participant will be enrolled in both INHALE 1 and INHALE 2 studies, though study procedures for Inhale 2 will not commence until the study period of INHALE 1 is completed.

The study period is broken up into 1st, 2nd, and 3rd assessment periods. During the first month, assessments of each participant's indoor air quality will be accomplished by environmental monitoring of air pollution (PM, nicotine) inside the home. During this month, either true or sham air cleaners will be placed for the entire duration of the month (see figure 1). To measure the air cleaner use compliance, air cleaners will be outfitted with a HOBO data logger, Onset Corporation (Bourne, MA) that has been exempted by Clinical Engineering. Participants will be blindly randomized into receiving one or the other during this time. During the last week of the month, health assessments will be conducted, which include in-home health questionnaires, symptom-, and activity- diaries/recalls, blood, and handheld spirometry. Participants will also be asked to wear a light backpack with air monitoring devices during the course of the day during the last week in order to measure their exposures to pollutants. Finally, at the end of the month, participants will be asked to report to the Johns Hopkins outpatient endoscopy suite for bronchoscopy, during which airway sampling will occur under conscious sedation.

Bronchoscopy: Women of childbearing age will have a repeat pregnancy test (one is already performed in the parent study) during the first month of the study to ensure eligibility as pregnant subjects would be excluded from the study). All bronchoscopies will be performed at the Johns Hopkins Hospital Endoscopy Suite, and will be consented again for the bronchoscopy on the appropriate Johns Hopkins Endoscopy Procedure consent form. Participants who meet safety criteria (including FEV_1>60% predicted) will fast at least 8 hours prior to the procedure and conscious sedation will be administered in accordance to Conscious Sedation Guidelines using intravenous anxiolytics. All participants will have

peripheral blood drawn and nasal rinse prior to bronchoscopy. Subjects will undergo a research fiberoptic bronchoscopy procedure with BAL fluid collected following instillation of room temperature saline in the lung. BAL and blood will be processed for the measurement of cell count and inflammatory mediators. Weekly telephone calls and home visits will occur throughout the study as needed to trouble-shoot and perform quality checks for the study.

At the completion of the first month, the subjects will enter a wash out period of at least 1 month, during which there are no interventions or assessments made. After the wash out period, the subjects will then cross over with regard to the air cleaner-sham cleaner intervention and receive the opposite intervention. During the last month of the study period, all study procedures from the 1st month are repeated. The study is concluded after the completion of the repeat bronchoscopy.

Subjects and study staff will be blinded to whether a true or sham air cleaner is randomly assigned to each home. This blinding is to reduce bias on the part of researchers and participants. Due to the crossover design, each participant serves as his/her own control. Since all participants receive the true air cleaner for one month of the study, they are not deprived of any potential benefits of the air cleaner.

1. Inclusion/Exclusion Criteria

Inclusion Criteria:

1. Age 18-50 years of age
2. Non-smoker (<100 cigarettes in lifetime)
3. Physician diagnosis of asthma
4. Symptoms of asthma and/or reliever medication use in the past 6 months
5. Living in the current residence >= 6 months within Baltimore

Exclusion Criteria:

1. Current diagnosis of another major pulmonary disease, other significant morbidity
2. Pregnancy (as defined by a positive urine pregnancy test at screening of all women of child-bearing potential)
3. Planning to relocate residence or activity that necessitates travel away from home for prolonged period of time during the study period
4. Current use of an air cleaner in the home

2. **Study Statistics**

A. Primary outcome variable

The change in concentration of fine and coarse particulate matter ($PM_{2.5}$ and $PM_{2.5-10}$) with the intervention of an air cleaner, compared to sham air cleaner.

B. Secondary outcome variables

1. Asthma control will be compared between the intervention and sham groups. This will include evaluation of changes in respiratory symptoms from self-reported diaries, asthma morbidity and asthma-related quality of life from questionnaires.

2. In addition, we will assess the effects of the intervention compared to the sham on other markers of asthma health. This includes lung function as measured by spirometry, and biomarkers of inflammation as measured in the blood and the lower airways via bronchoscopy.
3. Finally, we will assess the effects of the intervention compared to the sham on the indoor air nicotine concentration.

C. Statistical plan including sample size justification and interim data analysis.

We aimed to enroll 40 participants in this crossover design in order to detect with 80% power (and an alpha of 0.05) a 40% difference in PM concentrations between groups, accounting for an ultimate drop out/loss to follow up rate of approximately 10-15%. The estimate in sample size was based on a prior study from Butz et al. (18), which showed that a sample size of 77 participants was adequate to detect a 44% difference in PM concentrations between the intervention and control groups. [Note that over the course of the study, the planned sample size of 40 was not attained due to difficulties with recruitment. Only patients in the parent observational study willing to undergo bronchoscopies were recruited, resulting in a total of only 23 patients followed, with 2 lost to follow-up by the end of the study.]

A descriptive analysis will be performed with calculation of means, standard deviations, and medians for continuous variables and proportions for categorical variables. Bivariate analyses to assess differences before and after the intervention in each group will be conducted using t-tests or the Wilcoxon rank-sum test for continuous variables and χ^2 or Fisher's exact test for categorical variables.

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