A Randomized Controlled Trial of Prenatal Air Pollution Exposure and the Development of Allergic Sensitization in Infancy

By
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Ethics Statement

The author, whose name appears on the title page of this work, has obtained, for the research described in this work, either:

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or

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or has conducted the research

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Abstract

Background: Prenatal exposure to $PM_{2.5}$ has been associated with the development of allergic sensitization in children. We conducted a single-blind, randomized controlled trial in Ulaanbaatar, Mongolia to test the effectiveness of HEPA filter air cleaner use during pregnancy on the risk of allergic symptoms in the first year of life.

Methods: We enrolled 540 pregnant women at 10.3 weeks' gestation, on average, and randomly assigned them to the intervention group (N = 217), which received one or two air cleaners (depending on home size) to use from enrollment until childbirth, or the control group (N = 187). We measured indoor $PM_{2.5}$ concentrations over 7-days at ~11 weeks' gestation and again at ~31 weeks' gestation. We surveyed mothers about eczema, wheeze, respiratory infections and otitis media in the first year of life. The effectiveness of the intervention was analyzed using logistic regression in intention-to-treat analyses.

Results: Baseline characteristics were similar between the two groups. $PM_{2.5}$ concentrations were 29% lower, on average, in intervention homes than control homes (95% CI: 21-37%). The prevalence of outcomes ranged from 8.2% for wheeze to 54% for eczema. The intervention was significantly associated with a reduction in wheeze (OR: 0.47, 95% CI: 0.22 – 0.97). For eczema (OR: 1.12, 95% CI: 0.76 – 1.66), otitis media (OR: 1.07, 95% CI: 0.64 – 1.76) and chest infections (OR: 0.91, 95% CI: 0.58 – 1.43), the 95% confidence intervals indicated both potential harmful and beneficial effects of the intervention.

Conclusion: The use of HEPA filter air cleaners during pregnancy reduced the odds of parent-reported wheeze in the first year of life.

Dedication

Mom

Your strength and dedication made me the person I am today.
Thank you for everything.

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Sean, thank you for all your love and sacrifice. I couldn't have done this without your encouragement and unwavering support.

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List of Acronyms

AD	Atopic Dermatitis
BMI	Body mass Index
CLQI	Children's Life Quality Index
CONSORT	Consolidated Standards of Reporting Trials
COPSAC	The Copenhagen Prospective Study on Asthma in Childhood
CRP	C-reactive protein
DALYS	Disability Adjusted Life Years
ETS	Environmental Tobacco smoke
HEPA	High Efficiency Particulate Air
ISAAC	International Study of Asthma and Allergies in Childhood
LRTI	Lower respiratory tract infection
$PM_{2.5}$	Particulate Matter with diameter 2.5 microns or less
QoL	Quality of life
TCRS	Tucson Children's Respiratory Study
UGAAR	Ulaanbaatar Gestation and Air Pollution Research Study
UN	United Nations
WHO	World Health Organization

Overview

Air pollution is a global health problem. In 2013, 87% of the world's population lived in areas where fine particulate matter ($PM_{2.5}$) concentrations exceeded the World Health Organizations (WHO) annual average guideline of 10 $\mu g/m^3$ (1). The impacts of air pollution on the cardiovascular and respiratory health of adults are well established, and there is growing evidence that exposure to air pollution in early life may affect immune development and risk of atopic conditions such as wheeze and eczema (2-4). Allergic diseases impose a large burden on society with more than 300 million people suffering from asthma and over 350 million people suffering from eczema globally (5). Conditions like asthma, wheeze and eczema can significantly reduce a child's quality of life and pose a large financial burden on families and healthcare systems (6). Moreover, among children rates of allergic diseases such as eczema and asthma have been increasing (7). Several studies have investigated the role of air pollution on the development of allergic sensitization in early life, but few have looked specifically at the role pre-natal air pollution exposure plays in the development of atopic conditions (8-10). The objective of this thesis research was to investigate the effectiveness of high efficiency particulate air (HEPA) filter air cleaner (henceforth "HEPA cleaner") use during pregnancy on the risks of wheeze and eczema in the first year of life in a highly polluted community.

Chapter 1. **Background**

The prevalence of atopic conditions such as wheeze and eczema are increasing in children. Air pollution exposure in early life has been identified as a possible risk factor for allergic conditions, but results have been mixed and it has been challenging to disentangle the impacts of exposures in the prenatal and postnatal periods (11).

Previous studies have shown that HEPA cleaners are effective at reducing indoor PM concentrations (12, 13). The objective of my research was to test the effectiveness of HEPA cleaner use during pregnancy in reducing odds of wheeze and eczema in the first year of life. This research was conducted as part of an ongoing randomized controlled trial in Ulaanbaatar, Mongolia, a city with some of the world's worst air pollution.

1.1 Eczema and Wheeze

1.1.1 **Eczema**

Eczema, which often indicates the initiation of allergic sensitization, is a chronic inflammatory disease of the skin. (2). The terms "eczema" and "atopic dermatitis" (AD) are often used interchangeably, but there are important differences in mechanisms and clinical manifestations. For example, the presentation of eczema does not necessarily indicate an IgE-mediated response (14). AD is a dry, scaly, skin rash that, similar to eczema, usually develops early in life, with more than 60% of cases developing before 12 months of age and 85% of cases manifesting within the first 5 years of life (15). The early development of these conditions suggests that the most significant drivers act primarily before, or just after, birth. AD, asthma, and allergic rhinitis (hay fever) often develop together or sequentially over time and are known as the "atopic triad" in which AD is often a precursor to subsequent asthma and allergies (16).

Atopic dermatitis usually develops on the cheeks and face first, and then on the arms in later stages (17). Infantile forms of atopic dermatitis are often characterized by swelling, oozing and scabbing, which are easy for mothers to recall (17). AD predisposes children to staph infection, herpes and molluscum contagiosum (5,16).

Eczema is a leading cause of physician visits among young children (2, 18, 19). A 2018 UN report described a steady increase in eczema incidence, and predicted that rates will continue

to increase over the next few years due to increased urbanization (20). Physical manifestations of eczema include inflamed, red itchy skin with dry swollen patches that ooze or crust, depending on the severity of the disease (21). Symptoms can last from a few days up to several weeks. Sex plays a role in the timing of atopic eczema (22-25). Boys are at greater risk of atopic dermatitis during early childhood, while the inverse is observed in adolescence (26, 27).

My thesis is focused on atopic eczema. Atopic eczema is thought to result from a defective skin barrier due to a mutated protein, Filaggrin, which is presents in the epidermal layer of over 50% of all patients with eczema (16, 28-30). The most common presentation of atopic eczema is flexural eczema, an itchy rash in the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck or ears or eyes (5, 31). In babies, it often appears in red, weepy patches (5). Infantile eczema generally presents before three months of age in high contact areas associated with crawling; in older children the elbows, knees, and face are most often affected (32, 33). Another hallmark of eczema is susceptibility to bacterial and viral infections as well as physical and chemical irritation (34).

Eczema poses a considerable burden on children's quality of life (35). Recurrent bouts of atopic eczema can lead to psychosocial stress, which can further exacerbate symptoms of AD by initiating an immune response through activation of certain T-lymphocytes, eosinophils and natural killer cells (16). Increased physical manifestations of this condition are often difficult on a child and may lead to poorer outcomes in social situations including school, sports and outdoor activities (16). Many children with AD experience stomach aches and sleep problems from itching, frequent waking and excessive worrying (16). Globally, eczema poses a significant cost to healthcare systems. For example, in the United States adult patients with eczema pay more out-of-pocket in healthcare, have more sick days off work, increased healthcare usage and physician visits, urgent emergency care and hospitalizations, and increased prescription costs relative to their non-sensitized counterparts (35). Childhood eczema is estimated to cost over $5 billion (USD) per year in the United States alone (35).

1.1.2 **Wheeze**

Wheeze is an indication of abnormal airway hyper-responsiveness and retarded lung development (36-39). Although no universal definition exists, wheeze is most frequently defined as "whistling or wheezing from the chest"; it does not include noisy breathing from the nose",

(36, 40-45). Wheeze is a predictor for the development of asthma and greater decline in lung function later in life (37-39, 45).

Wheeze can substantially impact children's quality of life. A 2006 Dutch study found that children aged two months to 5 years with wheeze had lower reported health-related quality of life (46). Infants and children who wheeze are significantly more likely to have emergency room visits and hospitalizations (47, 48). Wheezing also impacts the quality of life for families and caregivers as wheezing often causes sleep disturbances and anxiety for both children and parents (47).

Wheeze is often classified by the type of trigger or its onset and persistence (49). Wheeze can be triggered by a virus, specific mechanism, or by multiple sources (49). The onset of wheezing is defined by the time at which symptoms first occur, how often they occur, and whether or not they persist (49). Commonly used categories of childhood wheeze include early-transient, persistent, and late-onset wheeze (43). Early transient wheeze refers to wheeze that occurs before three years of age, but does not persist up to age 6 (43). Persistent wheezing develops during lower respiratory tract infections (LRTIs) before age three years and lasts to at least six years, while late-onset wheeze is defined by no LRTI or wheeze before three years of age but wheezing at 6 years (43, 50). Recurrent wheeze is defined as three or more episodes of wheeze in the first year of life (47).

In a multi-centered study of over 30,000 infants across Latin America and Europe, over 45% (95% CI: 44.7-45.8) experienced wheeze before 15 months of age, while 20% (95% CI: 19.8-20.7) experienced recurrent wheeze (47). Wheeze affects nearly half of all children in the first 6 years of life. The prevalence of wheeze has increased worldwide, with the greatest burden occurring in "westernized" or industrialized countries, but rates of wheeze vary largely in and between nations (51, 52). For instance, current rates in Germany at age 4 are less than 2%, rates in Spain exceed 55%, while approximately 30% of children in China experience wheeze before they reach school age (51, 53).

1.1.3 Eczema and wheeze as predictors of asthma

Asthma afflicts approximately 300 million people globally and is one of the largest contributors to morbidity among young children, contributing to approximately 1% of total global disability adjusted life years (DALYs) (54). Asthma, the most severe endpoint in the development of

allergic sensitization (5) (55), is a chronic condition characterized by hyper-responsiveness and inflammation of the lungs and airways (7). The combination of inflammation and swelling leads muscles around the airways to constrict, causing wheezing, shortness of breath, coughing and tightness of the chest (7). Individuals who experience asthma are at greater risk of developing numerous lung conditions over the life course such as infections and reduced lung function (56).

Wheeze and eczema are both risk factors for the development of asthma and sensitization to inhaled allergens (57). AD is highly predictive of asthma development; 50% of those who experience acute AD develop asthma over the life-course (15). AD is more predictive than eczema for later asthma and as noted previously the conditions are often confused clinically. Children who have the most severe forms of AD are at greatest risk for developing asthma (15). A synthesis of thirteen prospective cohort studies found that children with AD were 1.7 (95% CI: 1.05-2.75) times more likely to develop asthma than their non-symptomatic counterparts (15). The strength of this association increases if the children are younger at first onset of AD (58).

Wheeze is also a predictor of asthma development later in childhood (59). The Tucson Children's Respiratory Study found that 22% of children who experienced late-onset persistent wheeze had doctor diagnosed asthma by the age six (59). A 2015 meta-analysis of 24 asthma predictive models indicated that wheezing, in addition to at least one other atopic condition, was the best predictor of asthma in children from birth to 14 years of age (59, 60). In a study of 703 children aged 4-12 with physician diagnosed asthma, 79% had previously experienced at least one atopic symptom and 26% had suffered from asthma, eczema and rhino-conjunctivitis collectively (61). These studies indicate that eczema and wheeze are the most appropriate outcomes for characterizing the development of allergic sensitization in the first year of life and risk for future development of asthma.

1.1.4 Risk Factors for Eczema and Wheeze

Family history of atopy is a strong predictor of whether a child will develop atopic conditions like eczema (22). Parental atopy, specifically, is the most reliable predictor of early life development of eczema (22, 62, 63). However, the increased prevalence of eczema over the last few decades cannot be explained by genetic changes, indicating that environmental factors may play an important role (32).

Several possible explanations for the increase in asthma have been identified. Several studies provide support for the "hygiene hypothesis" - the theory that early life exposure to microbes has a protective effect on the development of allergic diseases (32, 64). For example, a study in Sweden reported that children who grew up on farms had lower rates of eczema than those not raised on a farm (OR: 1.14, 95%CI: 1.04-1.25) (22). Additional support for the hygiene hypothesis comes from studies reporting that children born to larger families have a reduced incidence of allergic conditions, including eczema (32). Parity is also associated with decreased incidence of allergic diseases, with first-born children being at increased risk of developing eczema (64). Numerous studies also support the "parasite hypothesis" - the theory that parasitic infection may be protective against the development of numerous allergic conditions including eczema, wheeze and asthma (65-67). This theory also helps to explain lower incidence of allergic conditions in developing and/or rural areas where parasitic infections are more prevalent (68, 69). Exposure to tobacco smoke, both active and passive, in the prenatal period is another well-established risk factor for the development of childhood respiratory illnesses and allergic sensitization (70-72).

Numerous risk factors for development of wheeze in the first year of life have also been identified. The most well-established risk factor is maternal smoking during pregnancy and during the child's first year of life (72).

1.1.5 Air Pollution as a Risk Factor in the Development of Eczema and Wheeze

Results from studies of air pollution exposure and eczema development have been mixed (2). A systematic review conducted in 2012 found no significant association between PM exposure and eczema development in children (73). In contrast, longitudinal birth cohort studies conducted in Poland and New York found that prenatal PM exposure and post-natal environmental tobacco smoke exposure synergistically increased the risk of developing eczema in the first year of life (74).

For wheeze, the evidence of increased risks with acute exposure to air pollution has been relatively consistent, while the evidence from chronic exposure studies has been mixed (8, 75, 76). A South American birth cohort study reported that a short-term increase in $PM_{2.5}$ of 10 $\mu g/m^3$ was associated with a 5-9% increase in wheezing episodes within one to nine days after exposure (77). Similarly, the Copenhagen Prospective Study on Asthma in Childhood

(COPSAC) study reported that increased concentrations of ambient air pollution (specifically PM_{10}, NO_x, NO_2 and CO) were associated with an increase in wheezing symptoms 4 days later (18). Other large cohort studies have failed to find similar associations between acute air pollution and wheeze in children (78). Several of the chronic exposure studies have focused on traffic-related air pollution. A South African study found that children living in areas with trucks passing most of the day were at increased risk of developing 'ever-wheeze' (OR 1.32, 95% CI: 1.01-1.73), and had more cases of severe wheeze than those living in areas with less traffic (79). A population-based study in Jimma, Ethiopia found a 17% (OR 1.17, 95% CI: 1.01-1.36) increase in risk of wheeze among those who lived within 60m of a roadway compared to those who lived >150m (80).

1.1.6 Potential Biological Mechanisms Linking Air Pollution Exposure with Wheeze and Eczema

The fetal origins hypothesis postulates that prenatal adaptive changes are initiated by an altered maternal environment that results in restricted growth in-utero leading to increased risk of respiratory morbidity and mortality (40, 81-83). Specifically, air pollution may lead to impaired lung function through the impairment of fetal growth, resulting in smaller airways and reduced lung volume (84).

Another plausible mechanism involves inflammation leading to altered immune development. Air pollution, specifically PM, is linked to inflammatory responses including increased IgE, C-reactive protein (CRP), fibrinogen, IL-6 and white blood cell counts (61, 81, 85). Increased levels of circulating cytokines and T-helper cells (type 1 (Th1) and 2 (Th2)) in mothers during pregnancy may also alter the development of the immune response in the developing fetus (83). The presence of Th2 may be most influential on this modulation due to its role in atopic reactions (4, 86). Fetal exposure to CRP is associated with an inflammatory response in the developing fetus, leading to alterations of the fetal immune system that result in the development of allergic conditions such as asthma and wheeze (83). A study of 244 mother-child pairs in Chicago found that children born to mothers with increased levels of CRP during pregnancy were at increased risk of developing wheeze in the first year of life (OR 1.7, 95% CI: 1.1-2.4), even after adjusting for small for gestational age, prematurity and genetic variations, suggesting that a mechanism independent of growth may influence the development of wheeze

in childhood (83). This relationship persisted after adjustment for smoke exposure during pregnancy.

Similarly, intra-uterine environmental exposures may increase the risk of infantile eczema by activation of an IgE-mediated response in the mother. It is hypothesized that increased IgE responses in the mother are carried over to the child via fetal-placental interaction. One hypothesis involves the activation of CD23, which is responsible for the regulation of IgE synthesis, in the gastrointestinal tract of the child. Activation of CD23 has been shown to increase IgE production and hypersensitivity reactions (87). A second hypothesis is that activation of cytokines during pregnancy may transpose across the fetal-placental barrier and activate an immune response, though evidence has been mixed as to the role cytokines play in later development of eczema (88, 89).

1.2 Study Setting: Ulaanbaatar, Mongolia

My thesis is part of the Ulaanbaatar Gestation and Air Pollution Research (UGAAR) study conducted in Ulaanbaatar, Mongolia. Ulaanbaatar is one of the most polluted cities in the world, with annual fine particulate matter ($PM_{2.5}$) concentrations up to 15 times the WHO guideline concentration of 10 $\mu g/m^3$ (90, 91). Currently, nearly half of all Mongolians reside in Ulaanbaatar, where the population has increased by over 70% in the past two decades (92). Ulaanbaatar has long, cold winters and the largest source of $PM_{2.5}$ is residential coal combustion in the city's ger (traditional Mongolian yurt) districts, where over 60% of the city's residents live (93). In addition to residential coal burning the city also relies on coal-fired power plants for electricity generation and central heating. Air quality problems are exacerbated by traffic congestion and the city's topography.

Air pollution is a widely-recognized public health issue in Ulaanbaatar (20). The UN has recently declared air pollution a public health crisis (20). It has been estimated that air pollution is responsible for 10% of mortality in the city (20, 94).

About 20% of the population in Ulaanbaatar experienced some form of eczema in their life (95, 96). Higher rates of allergic sensitization are also reported in Ulaanbaatar (31%, 24.5-37.5%) than in rural towns and villages throughout the country (97).

A study conducted in 2009 used a translated version of the validated questionnaire from the International Study of Asthma and Allergies in Childhood (ISAAC) to assess the rates of asthma

and allergy in children 6-7 years of age. The investigators reported that 32% of Mongolian children aged 6-7 have ever experience wheeze, while 21% of children living in Ulaanbaatar experienced wheeze within the last year (95). The prevalence of wheeze in Ulaanbaatar was significantly higher than in the Asia-Pacific region (95).

Chapter 2. **Methods**

2.1 The UGAAR Study

My thesis made use of data collected in the UGAAR randomized controlled trial (98), which was designed to evaluate the associations between air cleaner use during pregnancy, fetal growth, and early childhood development. A total of 540 women were recruited between January 9, 2014 to May 1, 2015 based on the following criteria: 18 years or older; in the early stages (≤18 weeks) of a single-gestation pregnancy; non-smoker; living in an apartment; planning to give birth in a maternity hospital in Ulaanbaatar; and not using an air cleaner in the home at enrollment. Sample size calculations were based on birth weight as a continuous outcome and assumptions on the effect of $PM_{2.5}$ on birthweight (99, 100), outdoor $PM_{2.5}$ concentrations (101), infiltration of outdoor $PM_{2.5}$ (30), effectiveness of HEPA filters to reduce indoor $PM_{2.5}$ (102, 103) and time spent indoors during pregnancy (104). Results indicated that 460 participants, in equal numbers in both groups, were needed to detect a 120-gram difference in mean birth weight between intervention and control groups. Assuming 18% attrition, due to both dropout and pregnancy loss, resulted in a target population of 540 participants. While a large proportion of the population in Ulaanbaatar lives in gers (yurts), these women were excluded from the study because electricity is unreliable in ger neighbourhoods and gers may have higher indoor-outdoor air exchange rates, which reduces HEPA cleaner effectiveness. In addition, gers generally have higher indoor pollution emissions, and UGAAR was primarily focused on the potential benefits of the air filter intervention among those exposed primarily to air pollution of outdoor origin.

Participants were recruited at one of two reproductive health clinics in the centrally-located Sukhbaatar district. This district was targeted due to its large population living in apartments, its relatively high pollution concentrations, and relationships with clinic staff. We randomly assigned participants to the intervention or control group using sealed opaque envelopes containing randomly generated “filter” or “control” allocations and labeled with participant identification numbers from one to 580. Allocation was done on a 1:1 ratio. Once an individual was deemed eligible and provided written consent, a sealed envelope was drawn in sequential order and opened by a study coordinator who informed the participant of her allocation. Only one envelope was opened per participant; if a participant did not agree to her allocation she was not enrolled in the study. The envelope was then discarded and a new one was opened when the next

participant was enrolled. “Sham” air cleaners were not used, so participants were not blinded to their intervention status. The study protocol was approved by the Simon Fraser University Office of Research Ethics (2013s0016) and the Mongolian Ministry of Health Medical Ethics Approval Committee (Decree No.7).

Two hundred and seventy-two participants were randomized to the control group and 268 were randomized to the intervention group. Participants in the intervention group received one or two HEPA cleaners (Coway AP-1009CH) to use in their home throughout their pregnancy; participants in the control group received no air cleaners. The number of air cleaners deployed was dependent on home size; participants with homes <40m^2 were allocated one air cleaner, while those with homes ≥40m^2 received two. In homes receiving one air cleaner it was placed in the main living area; in homes with two air cleaners the second unit was placed in the participant’s bedroom. The air cleaners have a clean air delivery rate for tobacco smoke (particles sized 0.09-1.0 µm) of 149 cubic feet per minute, which is appropriate for rooms up to approximately 22 m^2. Two features, an internal PM sensor and light that changes colour based on PM concentration, were disabled to avoid biasing participants’ behaviour. The units were set to operate only on the second-highest fan setting because the highest fan setting was too noisy.

$PM_{2.5}$ concentrations were measured at two points in pregnancy, once shortly after enrollment during early pregnancy (~11 weeks, on average) and again during late pregnancy (~31 weeks, on average). Both measurements were done over a 7-day period using Dylos laser particle counters, which measure particles ranging from 0.5 - 2.5 µm (105). Particle counts were logged at 5-minute resolution (105). $PM_{2.5}$ was also measured gravimetrically in a subset of the homes (n=90) using Harvard personal environmental monitors (HPEMS) to quantify the relationship between the Dylos particle counts and $PM_{2.5}$ mass concentrations. There was strong agreement (R^2 = 0.94) between 7-day Dylos and HPEM measurements (98).

As previously reported, the overall reduction in $PM_{2.5}$ in intervention homes was 29% (95% CI: 21, 37), but air cleaner effectiveness was substantially reduced over time (Figure 2.1) (98). The greatest reductions in $PM_{2.5}$ concentrations were observed in winter months, while the air cleaners were least effective in summer. Housing units with two air cleaners had greater reductions in $PM_{2.5}$ concentrations. The intervention also reduced exposure to cadmium by 14% (95% CI: 4 - 23%), as indicated by blood samples collected late in pregnancy.

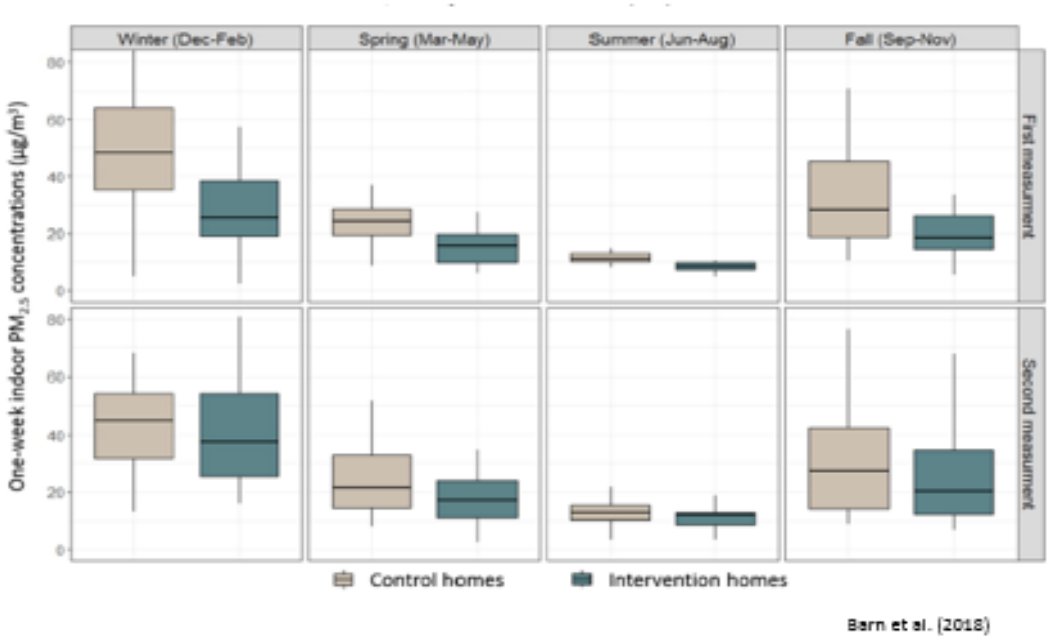

Figure 2.1. Season stratified indoor $PM_{2.5}$ concentrations in control and intervention homes at first trimester allocation and follow-up (from Barn et al., 2018).

2.1.1 Follow-up of the UGAAR Cohort

Children in the UGAAR cohort were born between July 2014 and December 2015. There were 463 live births. Starting in the summer of 2016, all mother-child dyads in the UGAAR cohort were invited to participate in an extended follow-up study designed to observe the growth and development of children in the UGAAR cohort until four years of age. The protocol for the extended follow-up study was approved by the Simon Fraser University Office of Research Ethics and the Mongolian Ministry of Ethics Approval Committee. Participants received an honorarium of 40,000 Mongolian tugriks (approximately $25 Canadian) annually.

2.2 Hypotheses

Using data from the UGAAR cohort, I sought to test two hypotheses:

1. Children born to mothers who were randomly assigned to receive HEPA cleaners during pregnancy will experience fewer cases of parent-reported wheeze in the first year of life than children born to mothers who did not receive HEPA air filter cleaners.

2. Children born to mothers who were randomly assigned to receive HEPA cleaners during pregnancy will experience fewer cases of parent-reported eczema in the first year of life than children born to mothers who did not receive HEPA air filter cleaners.

2.3 Methods

2.3.1 Data collection

We assessed symptoms in the first year of life using questionnaires adapted from previous studies including the Canadian Healthy Infant Longitudinal Development (CHILD) study, Infancia y Medio Ambient (INMA), and ISAAC (2, 106, 107). Questionnaires were written in English, translated into Mongolian, then back-translated to ensure translation accuracy.

Upon enrollment into the extended follow-up phase of the study, mothers were provided with materials to assist in documenting their child's health. This included 1-page diary cards at weekly resolution on which they were asked to record any instances of wheeze, cough, eczema, respiratory infections, medication use, or contact with the healthcare system (unscheduled doctor's visits, emergency room visits, or hospitalizations). They also received images demonstrating dermatitis and eczema on Mongolian children.

Due to the range of ages of children at re-enrollment (7-24 months) some parents received one questionnaire while others received two. All parents were administered a baseline questionnaire immediately at enrollment. Children <12 months at enrollment received an additional questionnaire at 12 months of age to capture all information in the first year of life. Baseline questionnaires were all administered by Mongolian technicians via telephone and lasted roughly 30 minutes. Technicians administering the questionnaires were not aware of the participant's intervention status. The baseline questionnaire captured information on family history of relevant health outcomes, as well as the child's health (wheeze, eczema, allergic symptoms, infections, medication use, scheduled and unscheduled doctors' visits, emergency room visits, and hospitalizations) from birth to the age at enrollment. In addition, the baseline questionnaire captured information on housing characteristics, family structure, parental income and employment, as well as the child's diet, sleep patterns, time-location-activity patterns, and exposure to SHS.

We administered 12-month questionnaires over the phone (~30 minutes) for participants who had not reached their first birthday at the time baseline questionnaire was administered.

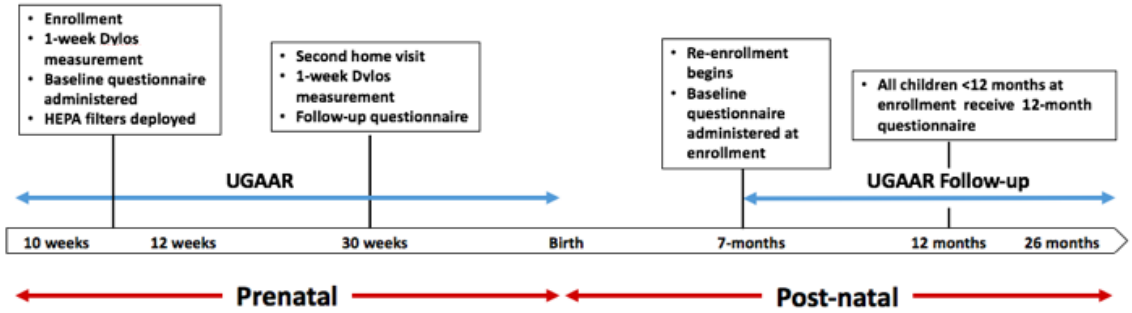

Figure 2.2 Study Timeline enrollment-1st year follow-up.

2.3.2 Outcomes

2.3.2.1 Primary Outcomes

The primary outcomes in this study were wheeze and eczema in infancy. The presence of these outcomes was assessed from questions on the presence of symptoms and, in the case of the baseline questionnaire, the child's age at first occurrence (Table 2.1).

Table 2.1 Primary Outcome Evaluation Questions.

Questionnaire	Wheeze Question(s)	Eczema Question(s)
Baseline	Has your child ever had a "wheezing" or whistling noise coming from his/her chest?	Has your child ever had an itchy skin rash that was coming or going?
	How old was your child when the first wheezing episode occurred? (0-3 months, 4-6 months, 7-12 months, >12 months)	How old was your child when this itchy skin rash first occurred? (0-3 months, 4-6 months, 7-12 months, >12months)
12-month	Over the past 6 months, has your child ever had a "wheezing" or whistling noise coming from his/her chest?	Over the past 6 months, has your child had an itchy skin rash that was coming and going?

2.3.2.2 Secondary outcomes

In addition to the primary outcomes, we also examined associations between the air cleaner intervention and development of chest infection and otitis media. Like the primary outcomes, chest infection and otitis media were assessed via questionnaires administered to the child's mother or primary caregiver (Table 2.2).

Table 2.2 Secondary Outcome Evaluation Questions.

Questionnaire	Chest infection Question(s)	Otitis media Question(s)
Baseline	Has a doctor ever told you that your child had a chest infection, bronchitis, bronchiolitis, pneumonia, or pneumonitis?	Has a doctor ever told you that your child had any ear infections?
	How old was your child the first time a doctor told you your child had a chest infection, bronchitis, bronchiolitis, pneumonia, or pneumonitis? (0-3 months, 4-6 months, 7-12 months, >12 months)	How old was your child when the first ear infection occurred (0-3 months, 4-6 months, 7-12 months, >12months)
12-month	In the past 6 months, has a doctor told you that your child had a chest infection, bronchitis, bronchiolitis, pneumonia, or pneumonitis?	In the past 6 months, did your child have any ear infections?

2.3.3 Statistical Analysis

We calculated medians and interquartile ranges to measure central tendencies and variation for all outcomes and relevant covariates for intervention and control groups. Randomization was expected to minimize confounding bias, however, baseline characteristics were compared between intervention and control participants.

The association between intervention status and outcomes were assessed using logistic regression, with binary outcomes (presence/absence of symptom[s] at any time during the first year of life) regressed on intervention status. Consistent with Consolidated Standards of Reporting Trials (CONSORT) methodological guidelines, outcomes were assessed using intention-to-treat analyses.

2.3.3.1 Effect Modification

Potential effect modifiers identified *a priori* included sex of child, household smoking status, and family history of allergy (11, 108, 109). Effect modification was tested using interaction terms in the logistic regression models. We measured second hand smoke exposure via questionnaires administered at clinical visits early (5-18 weeks) and late (24-37 weeks) in pregnancy. SHS exposure was coded as a binary variable defined as living with a smoker at any time during pregnancy. Family history of allergy was defined using methods consistent with the Canadian Asthma Primary Prevention Study (CAPPS). Specifically, family history was defined as having either one first-degree relative with asthma or two first-degree relatives with any other IgE-

mediated allergic disease (110, 111). Models were also run after stratifying by number of air cleaners deployed, since previous research demonstrated that $PM_{2.5}$ reductions were greater in homes that received two air cleaners (98)

To evaluate possible selection bias resulting from loss to follow-up, I compared three populations: the originally recruited UGAAR cohort (N = 540), participants whose pregnancies ended in a live birth (N = 460), and those who re-enrolled in the extended follow-up study and were analyzed in my thesis (N = 404) (Table 3.1).

I also conducted a sensitivity analysis to evaluate any differences in outcome reporting over time. For this analysis, children were dichotomized into two groups: those <15 months at enrollment and those >15 months to determine if age at enrollment (and the use of only the baseline questionnaire vs. the baseline questionnaire and the 12-month follow-up questionnaire) influenced the reporting of outcomes.

To explore the validity of the wheeze questions, I used logistic regression to determine if wheeze was associated with likely risk factors (family history of allergy and living with a smoker) and the other outcomes (eczema, chest infection, and otitis media) (Table 3.5).

Chapter 3. **Results**

3.1 Cohort Characteristics

We initially recruited 540 pregnant women in the UGAAR Study (Figure 3.1); 272 were randomly allocated to the control group and 268 were randomly allocated to the intervention group. A total of 75 participants (27 in the intervention group and 48 in the control group) were lost between enrollment and childbirth due to withdrawal, loss of contact, or a pregnancy loss; one child from each group was excluded due to a chromosomal abnormality. Of women in the original study, 55 (20 in intervention and 25 in control) failed to re-enroll in the follow-up study. Thus, of the 460 participants with a live birth who were eligible to continue with the follow-up study, 404 (88%) re-enrolled, and 187 mother-child dyads from the control group and 217 dyads from the intervention group were analyzed in my thesis (Figure 3.1). Despite attrition, the characteristics of dyads included in my analysis were similar to those who were originally enrolled in UGAAR and those whose pregnancy ended in a live birth (Table 3.1).

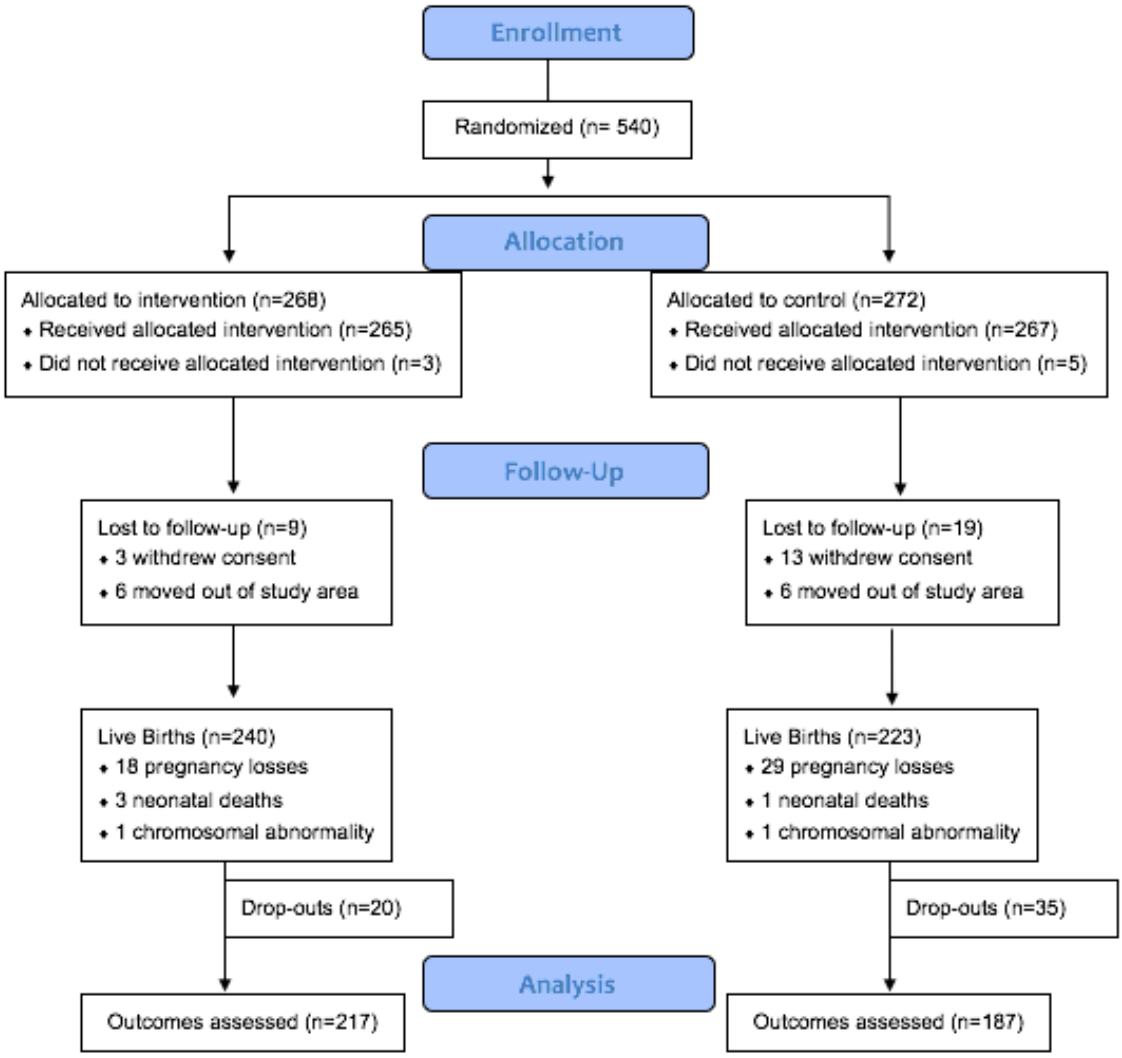

Figure 3.1 Trial Profile.

Table 3.1 Comparison of participants loss to follow-up.

	Enrolled in UGAAR (N=540)	Live Births (N=460)	Re-enrolled in Extended follow-up (N=404)
Characteristic	Median, 25th-75th or N, %	Median, 25th-75th or N, %	Median, 25th-75th or N, %
Maternal age at enrollment	29.0 (25-33)	29.0 (25-33)	29.0 (25-33)
Mother's marital status			
Married/Common-law	439 (81%)	374 (81%)	330 (82%)
Not married/common law	87 (16%)	81 (18%)	70 (17%)
Missing	14 (3%)	5 (1%)	4 (1%)
Mother's Education			
University	434 (80%)	391 (85%)	349 (86%)
< University	60 (11%)	33 (7%)	25 (6%)
Missing	47 (9%)	36 (8%)	30 (7%)
Mother's Pre-pregnancy BMI	21.7 (19.7-24.0)	21.6 (19.6-24.0)	21.6 (19.6-24.1)
Missing	42 (8%)	29 (6%)	0 (0%)
Parity			
0	48 (9%)	45 (10%)	36 (9%)
1	198 (37%)	174 (38%)	155 (38%)
≥2	123 (23%)	102 (22%)	96 (24%)
Missing	171 (31%)	139 (30%)	117 (29%)
Lived with smoker during pregnancy			
Yes	241 (45%)	208 (45%)	186 (46%)
No	276 (51%)	240 (52%)	211 (52%)
Missing	23 (4%)	12 (3%)	7 (2%)

3.1.1 Baseline characteristics

Initial maternal enrollment into UGAAR occurred at 10.3 weeks' gestation, on average. Nearly half of the women in the study (46%) lived with a smoker during pregnancy. The average age of the children and mothers at re-enrollment was 15.8 months (± 3.8 months) and 29.2 years (± 5.5 months), respectively. The prevalence of breastfeeding was high in this cohort (99%) and approximately 63% of the study children had at least one sibling. No significant differences were found between groups for birthweight, breastfeeding patterns, gestational age at birth, number of siblings, parity, season of birth, sex, or type of delivery (caesarean vs. vaginal), maternal age

at birth, maternal education, or household income (Table 3.2). There were also no differences in family history of wheeze, eczema, food allergy, pet allergy, rhinitis, or asthma (Table 3.3).

Table 3.2 Baseline Characteristics.

Characteristic	Control (n=187) (Median, 25-75 or N, %)	Intervention (n=217) (Median, 25-75 or N, %)	p-value
Mother's age at enrollment, years	29.0 (25.0-33.0)	30.0 (25.0-33.0)	0.67
Weeks pregnant at enrollment	10.0 (8.0-12.0)	11.0 (9-13)	0.62
Gestational Age, weeks	39.5 (39.0-40.0)	39.5 (38.5-40.0)	0.59
Caesarean delivery	73 (39%)	79 (36%)	0.60
Birth Weight, grams	3,450 (3100, 3800)	3,550 (3200, 3800)	0.39
Parity			
0	15 (8%)	21 (10%)	
1	74 (40%)	81 (37%)	0.63
≥2	41 (22%)	55 (25%)	
Missing	57 (30%)	60 (28%)	
Breastfed (1st year)			
Yes	183 (98%)	214 (99%)	
No	3 (1.5%)	3 (1%)	0.85
Missing	1 (0.5%)	0 (0%)	
Season of Birth			
Winter	23 (12%)	32 (14%)	
Spring	41 (22%)	58 (27%)	0.45
Summer	62 (33%)	69 (32%)	
Fall	61 (32%)	58 (27%)	
Child's age at enrollment, months	15.0 (13.0-17.0)	15.0 (13.0-18.0)	0.77
Sibling			
Yes	119 (64%)	134 (62%)	
No	67 (36%)	83 (38%)	0.65
Missing	1 (<1%)	0 (0%)	
Sibling Allergy			
Yes	60 (32%)	61 (28%)	
No	127(68%)	156 (72%)	0.38
Missing	0 (0%)	0 (0%)	
Lived with smoker (1st year)			
Yes	106 (57%)	111 (51%)	
No	81 (43%)	106 (49%)	0.65
Missing	(0%)	(0%)	
Pets in home (1st year)			
Yes	16 (9%)	22 (10%)	0.59
No	171 (91%)	195 (90%)	
Missing	(0%)	(0%)	
Water leaks (1st year)			
Yes	50 (26%)	50 (23%)	0.38
No	134 (73%)	164 (76%)	
Missing	3 (1%)	3 (1%)	
Lived >4th Floor (1st year)			
Yes	94 (50%)	125 (58%)	0.13
No	92 (49%)	90 (41%)	
Missing	1 (<1%)	2 (1%)	
Pests/Bugs (1st year)			
Yes	46 (25%)	69 (32%)	0.13
No	138 (74%)	147 (68%)	

Missing	3 (1%)	1 (<1%)	[1] [1]
Monthly Household Income, Mongolian Tugriks[1]			
0-1,999,999	132 (71%)	162 (75%)	0.19
2,000,000- 2,399,999	13 (7%)	18 (8%)	
More than 2,400,000	12 (6%)	13 (6%)	
Prefer not to answer	24 (13%)	14 (6%)	
Missing	6 (3%)	10 (5%)	
Maternal Education			
High School	5 (3%)	9 (4%)	0.56
Completed University	174 (93%)	196 (90%)	
College/Other	4 (2%)	7 (4%)	
Missing	4 (2%)	5 (2%)	
Mold in home during pregnancy			
Yes	20 (11%)	24 (11%)	0.57
No	166 (89%)	191 (88%)	
Do not know	0 (0%)	1 (<1%)	
Missing	1 (<1%)	1 (<1%)	

Canadian dollar = 1,894.21 Mongolian Tugriks

Table 3.3 Family History of Allergies.

	Maternal History		Paternal History	
	Control (n=187)	Filter (n=217)	Control (n=187)	Filter (n=217)
Wheeze				
Yes	6 (3%)	12 (6%)	17 (9%)	10 (5%)
No	181 (97%)	205 (94%)	170 (91%)	202 (93%)
Do not know	0 (0%)	0 (0%)	0 (0%)	5 (2%)
Eczema				
Yes	64 (34%)	75 (35%)	34 (18%)	49 (22%)
No	123 (66%)	142 (65%)	152 (82%)	165 (76%)
Do not know	0 (0%)	0 (0%)	1 (<1%)	3 (1%)
Rhinitis				
Yes	61 (33%)	83 (38%)	42 (22%)	51 (24%)
No	126 (67%)	134 (62%)	144 (77%)	158 (72%)
Do not know	0 (0%)	0 (0%)	1 (<1%)	8 (4%)
Pet allergies				
Yes	12 (6.5%)	5 (2%)	3 (2%)	4 (2%)
No	174 (93%)	211 (97%)	184 (98%)	209 (96%)
Do not know	1 (<1%)	1 (0.3%)	0 (0%)	4 (2%)
Food allergies				
Yes	29 (15.5%)	37 (17%)	22 (12%)	23 (11%)
No	157 (84%)	179 (82.5%)	165 (88%)	192 (88%)

Do not know	1 (<1%)	1 (<1%)	0 (0%)	2 (1%)
Asthma				
Yes	5 (3%)	5 (2%)	4 (2%)	2 (1%)
No	182 (97%)	212 (98%)	182 (98%)	212 (98%)
Do not know	0 (0%)	0 (0%)	1 (<1%)	3 (1%)

3.2 Effect of the Intervention on Outcomes

Overall, the prevalence of wheeze in the first year of life was 8.2%, with significantly fewer cases in the intervention group (OR: 0.47, 95% CI: 0.22-0.97), (Table 3.4). Eczema was reported by 53% of participants, with a similar number of cases in both groups (Table 3.4) Twenty-five percent of participants reported at least one case of chest infection, bronchitis, bronchiolitis, pneumonia, or pneumonitis; (OR: 0.91, 95% CI: 0.58-1.43), while 18% percent of children experienced at least one occurrence of otitis media (OR: 1.07 95%CI: 0.64-1.76). For these outcomes 95% confidence intervals indicated both potential harmful and beneficial effects of the intervention.

Table 3.4 Associations between the HEPA filter air cleaner intervention and outcomes.

Outcome	Cases in Control (N = 187)	Cases in Intervention (N = 217)	Odds Ratio	95% Confidence Interval	
Wheeze	21 (11%)	12 (5.5%)	0.47	0.22	0.97
Eczema	96 (51%)	117 (54%)	1.12	0.76	1.66
Chest Infection	49 (26%)	54 (25%)	0.91	0.58	1.43
Otitis Media	32 (17%)	39 (18%)	1.07	0.64	1.76

3.2.1 Effect Modification

We used stratified analyses and interaction terms in logistic regression models to examine potential modification of the association between intervention and wheeze by sex, smoking in

the home during pregnancy, and family history of allergies (Figure 3.2). In logistic regression models, exponentiating an interaction term coefficient gives the ratio of stratum-specific odds ratios. To aid interpretation, interaction terms were coded with 1 representing the stratum in which the intervention was more protective and 0 representing the stratum in which the intervention was less protective (i.e., coded to generate ratios < 1). For no household smoking, female sex, and no family history of allergies the ratios were 0.37 (95% CI: 0.08, 1.66), 0.28 (95% CI: 0.05, 1.70), and 0.35 (95% CI: 0.08, 1.61), respectively. Separate estimations of the effects of one or two air cleaners indicated a significant reduction in wheeze only for participants who received two air cleaners. (Figure 3.2).

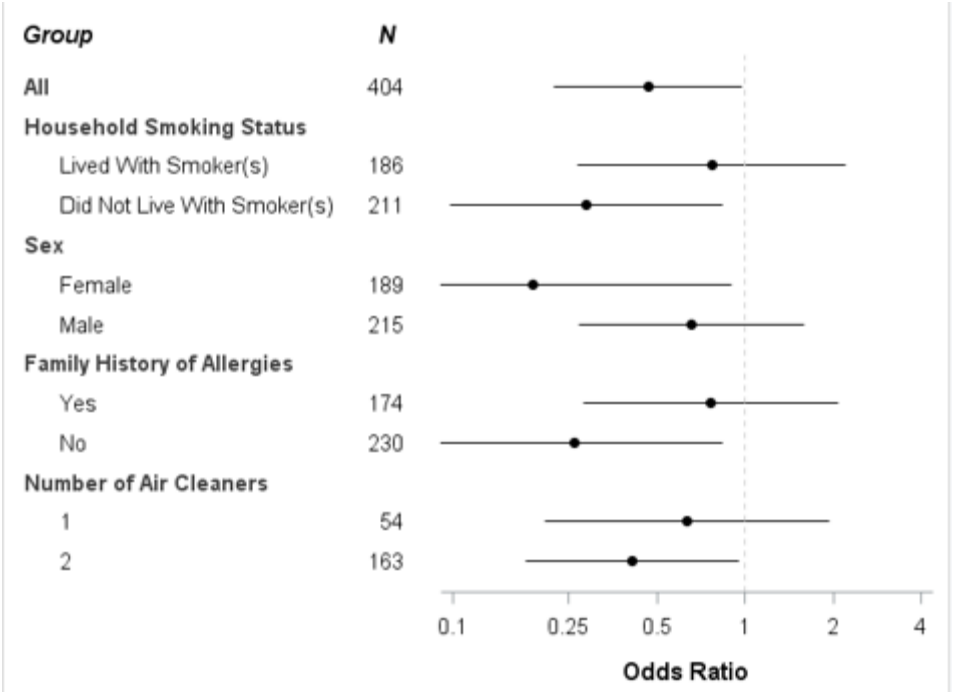

Figure 3.2

Figure 3.2 Estimated odds ratios and 95% confidence intervals for wheeze within strata.

3.2.2 Sensitivity Analyses

Children ranged from seven to 26 months of age at the time of re-enrollment (Table 3.5). Thirty–five participants (8.6%) were younger than 12-months old at re-enrollment. Mothers of participants in this age group received both the baseline questionnaire and a follow-up questionnaire once their child reached 12-months of age to capture all relevant data for the first

year of the child's life. Caregivers of all children over the age of 12 months at enrollment (91.4%) reported all relevant information on the first year of life retrospectively on the baseline questionnaire.

Overall, no meaningful differences in reporting were observed between those <15 months and those >15 months, though prevalence was higher among the older children for all outcomes.

Table 3.5 Summary of children's age (in months) at re-enrollment into the extended follow-up phase of UGAAR.

Age in Months	Control N (%)	Intervention N (%)	Baseline questionnaire administered	12-month questionnaire administered
0-6 months	0 (0.0%)	0 (0.0%)	At enrollment	At child's 1-year birthday
6-9 months	4 (2.1%)	3 (1.4%)	At enrollment	At child's 1-year birthday
9-12 months	14 (7.5%)	14 (6.5%)	At enrollment	At child's 1-year birthday
12-15 months	71 (38.0%)	85 (39.2%)	At enrollment	ASAP after enrollment
15-18 months	52 (27.8%)	63 (29.0%)	At enrollment	Not administered
18-26 months	46 (24.6%)	52 (23.9%)	At enrollment	Not administered

We found that wheeze was reported infrequently for both parents and children in both the intervention and control groups. This raised concerns that the wheeze questions had been poorly understood by participants. Logistic regression was used to determine if wheeze was associated with likely risk factors (family history of allergy and living with a smoker) or other outcomes (eczema, chest infection, and otitis media) (Table 3.6). Chest infection was strongly associated with wheeze in the first year of life (OR 5.34, 95% CI: 2.55-11.19). For family history of allergy, eczema, and otitis media, point estimates were in the expected direction but 95% confidence intervals indicated the potential for both a positive or inverse relationship.

Table 3.6 Relationship between Wheeze and Other Variables.

Variable	**N** (404)	**Wheeze Cases** N (%)	**Odds Ratio**	**95% Confidence Interval**
Family history of Allergy				
No	230	16 (7.0%)	**Reference**	
Yes	174	17 (9.8%)	1.45	0.71 – 2.96
Mother lived with smoker(s) during pregnancy				
No	211	18 (8.5%)	**Reference**	
Yes	186	15 (8.1%)	0.94	0.46 – 1.92
Missing	8	(0%)		
Eczema				
No	191	11 (5.8%)	**Reference**	
Yes	213	22 (10.3%)	1.90	0.89 – 4.00
Chest Infection				
No	301	13 (4.3%)	**Reference**	
Yes	103	20 (19.4%)	5.34	2.55 – 11.19
Otitis Media				
No	333	24 (7.2%)	**Reference**	
Yes	71	9 (12.7%)	1.87	0.83 – 4.22

Chapter 4. **Discussion**

This study assessed the impacts of a HEPA filter air cleaner intervention during pregnancy on the development of allergic sensitization in the first year of life among a highly exposed cohort in Ulaanbaatar, Mongolia. The air cleaners were previously shown to reduce indoor $PM_{2.5}$ concentrations by 29% (21-37%) during pregnancy (98). The intervention was associated with reduced odds of wheeze in the first year of life (OR 0.47, 95% CI: 0.22-0.97). For eczema (OR 1.12, 95% CI: 0.76-1.66), chest infection (OR 0.91, 95% CI: 0.58-1.43), and otitis media (OR 1.07, 95% CI: 0.64-1.76) the 95% confidence intervals indicated both potential harmful and beneficial effects of the intervention. Stratified analyses and models with interaction terms were used to explore effect modification by household smoking status, child's sex, and family history of allergy. In stratified analyses there was some suggestion that the intervention was more effective among those in non-smoking households, girls, and those with no family history of allergy, but interaction terms were estimated imprecisely. After stratifying by number of air cleaners deployed, a significant reduction in wheeze was found only for participants who received two air cleaners. This is likely due to the larger sample size and increased precision in the estimate among that group, and possibly also to the larger exposure reductions in apartments that received two air cleaners (98).

These results are consistent with findings from previous cohort studies in which the development of wheeze in early life was associated with increased exposure to PM, NO_2 and soot (8, 75, 76). Korten et al. suggest that the fetal period may be critical in the development of lung conditions such as wheeze and eczema due to the enhanced susceptibility of rapidly growing fetal cells to environmental factors (112). Additionally, repair systems are inferior to those of mature systems making them less capable of repairing damage (112). Prolonged exposure to air pollution may be especially toxic to the developing lungs because their development occurs over a longer duration than most other organs (112). Given that the most rapid development of the lung occurs during the fetal period it is logical that this period plays a large role in lung modulation, particularly on the growth and modelling that occurs later in the gestational period, though little research has been done to determine what trimester is the most critical (112). Another hypothesis suggests that air pollution may cause an inflammatory response leading to elevated CRP levels during pregnancy, altering the fetal immune system and making the infant more susceptible to allergic conditions (83).

Effects estimates were too imprecise to definitively identify the relationship between the HEPA filter intervention and of the development of eczema in the first year of life (Table 4.5). Previous literature on the relationship between air pollution and the development of eczema has been mixed (2, 73). While some studies have found a significant association between $PM_{2.5}$ exposure and eczema development, others have only found significant relationships between CO, SHS and VOCs exposure and eczema (113). It is possible that our intervention, which was instituted at 10 weeks' gestation, may have missed a critical window for the development of eczema. Alternatively, some studies have indicated that early life exposures may be more critical than those in-utero on eczema development. One proposed mechanism of early life sensitization is the hygiene hypothesis, which suggests that exposure to certain antigens in early life may have a protective effect on the development of atopic conditions. This would suggest that factors like family size, pet ownership, daycare attendance and caesarean section may play a greater role in the initiation of atopy.

Overall, reporting of wheeze (8.2%) was lower in our cohort than observed in previous studies of children living in South America and Latin America where 45% (95% CI: 44.7,45.8%) of participants reported at least one episode of wheeze in the first year of life (114, 115). Overall, reporting of eczema was high in this cohort (53%) indicating a need for further investigation into potential underlying mechanisms. Reporting of otitis media (18%) was consistent with a previous Tibetan-Mongolian study of children under five (116). Twenty-five percent of participants reported experiencing some form of respiratory infection (pneumonia, bronchitis, bronchiolitis), which is lower than previously reported in a cross-sectional study of children under 5 in rural Mongolia, where 38.9% of children had a LRTI hospitalization (117).

Confounding, selection bias, and information bias can all affect estimates in epidemiologic studies (6, 118). This research is somewhat novel in that it utilized a randomized controlled trial study design, which minimizes the influence of measured and unmeasured confounders. Similarities between intervention and control participants included in this analysis provide some evidence that the association between the intervention and wheeze was not attributable to other differences between groups.

Participant re-enrollment was high (89%) and characteristics of the cohort were generally similar at original enrollment, childbirth, and outcome assessment (Table 3.1). Overall, participant retention was higher among participants in the intervention group than the control group (81% vs. 69%), likely because participants were not blinded to their intervention status. Additionally,

among pregnancies that ended in a live birth, intervention participants were more likely to re-enroll in the second phase of UGAAR than participants in the control group (90% vs. 84%). Selection bias must be considered in randomized control trial study designs, however different rates of dropout between groups does not necessarily introduce selection bias unless attrition is related to the outcomes of interest (119). Similarities between participants within the control and intervention arms included in this analysis and the original cohort of 540 mothers suggests that attrition was not related to the outcomes, and provides some evidence that results are not due to selection bias. Another way to test the impact of these missing participants on my results would be to use multiple imputation, but this is beyond the scope of this thesis (120).

Participants in the control group did not receive a placebo (sham filter) and therefore were not blinded to their intervention status. This may introduce information bias, a systemic error that arises when exposure or disease are incorrectly identified, because knowledge of intervention status may have affected the reporting of outcomes. Information bias due to a lack of blinding is not expected to be major limitation in this study because of the substantial time from when mothers received the intervention to the time of reporting and may not associate reporting of wheeze and eczema after birth with their intervention status during pregnancy. Information bias may have been introduced as women in the control group may have been more likely to report symptoms (particularly of wheeze) than women in intervention group. As a result we may expect to see some differential misclassification of symptoms between groups, and if control participants over-report symptoms it would lead to an overestimation of the intervention effect. Analysis of chest infection, another outcome that participants might intuitively have linked with air pollution, was reported with approximately equal frequency by parents of control and intervention participants. This provides indirect evidence that intervention status did not make participants more likely to report respiratory symptoms.

We assessed all outcomes using questionnaire data, which may also result in information bias. While questionnaires are one of the most widely utilized methods of data collection in epidemiology, their reliability has been called into question given the subjective nature of self-report. For example, parents may feel the need to give inaccurate responses that they believe are more socially desirable. Self-report of allergic outcomes is less objective than skin-prick tests, particularly with eczema reporting, as parents may report non-allergic skin rashes as eczema. However, previous studies have found that the ISAAC question for ever-wheeze was relatively sensitive (80.6%), while the ISAAC question used to define “ever wheeze’ in our questionnaire had 74.9% specificity for doctor-diagnosed asthma in children (121). We do not

expect that the sensitivity or specificity of the questions differed among intervention or control participants (non-differential) and as a result, misclassification would result in a bias toward the null.

Because there was a gap between birth and re-enrollment into the extended follow-up study, children ranged from 7 months to >2 years when outcome assessment began, so for some children symptoms in the first year of life were reported retrospectively. All four outcomes were reported slightly more frequently among older participants, though the differences were not statistically significant. This suggests a possible lack of specificity, perhaps because the caregivers of older children correctly recalled the occurrence of symptoms, but incorrectly identified them as having occurred in the first year of life. Given that we could not detect significant differences in outcomes between younger and older children, it seems unlikely that retrospective reporting had a major impact on disease classification. Moreover, the distribution of ages at re-enrollment did not differ between intervention and control groups (Table 3.2). This suggests that the lack of specificity was similar between intervention and control participants, and this non-differential misclassification would result in a slight bias towards the null. This issue was addressed in a similar matter in the INMA cohort, where in some locations caregivers were asked about their children's symptoms at 6 months when their child was over a year old and in other locations caregivers were asked about symptoms prospectively (2). Children's ages ranged from 12.4 $\pm$ 1.1 months to 29.2 $\pm$ 5.7 months (mean $\pm$ standard deviation) (2). Results indicated that mothers who had older children when reporting noted more symptoms than those with younger children (2). However, excluding older children made no significant difference to results (2).

Overall, the prevalence of wheeze (among children and parents) in this cohort was low. The low reporting may have been a result of a relatively low-risk study population (e.g., relatively high socioeconomic status and maternal education). The questions used to assess wheeze may have also led to underreporting. Although the question used to assess wheeze has been standardized in over 98 countries and is the most widely accepted question for the assessment of wheeze globally (122), the question may have lacked sensitivity in this context. The translation into Mongolian was reviewed among several health professionals in Mongolia to ensure the issue was not one of semantics. Despite these efforts, anecdotal evidence suggests some participants were unclear as to what the question was asking and required additional clarification. To further evaluate the wheeze outcome ascertainment, we assessed relationships between wheeze and expected risk factors (family history of allergies and living with a smoker)

and the other outcomes. We found that wheeze was associated with chest infections and marginally associated with eczema, otitis media, and family history of allergies, which provides indirect evidence that cases of wheeze identified were associated with other allergic outcomes. However, we did observe a small non-significant protective effect of living with a smoker during pregnancy on the development of wheeze, which may suggest that the wheeze question lacked sensitivity (positive predictive value).

Due to the nature of recruitment most women were not enrolled in UGAAR until 10-18 weeks into their pregnancy, and as a result HEPA filters were not installed in homes until the second trimester. This may be a minor limitation as existing evidence suggests that the most vulnerable stages of fetal respiratory and immunological development and consequent allergic sensitization may be in the second and third trimesters (123, 124). The intervention also only influenced exposure when mothers were indoors at home, which likely reduced the effectiveness of the intervention.

An important limitation of previous studies has been an inability to tease apart the influence of pre-natal and post-natal exposures as they are often highly correlated (2, 125, 126). Because women in UGAAR received air filters early in pregnancy and returned them once their child was born, the reduction in odds of wheeze among intervention participants suggests an important role for prenatal exposure. In addition, the use of HEPA cleaners also reduces collinearity between concentrations of PM and gases. Because HEPA cleaners remove only PM from the air and this is a randomized design, benefits are likely to result from the reduction in PM and not gaseous co-pollutants.

These results may have limited generalizability since Ulaanbaatar has some of the highest $PM_{2.5}$ concentrations in the world, and the exposure reductions achieved with HEPA filtration in Ulaanbaatar will not be possible in cities with lower levels of pollution. As a result, HEPA cleaners may have less effectiveness in settings with lower pollution levels. In addition, HEPA cleaners are most effective at low air exchange rates, so these results may not be generalizable to warmer climates, where windows and doors may be opened more frequently.

4.1 Conclusions

Results from this study support the hypothesis that the use of air cleaners during pregnancy reduces the odds of wheeze in the first year of life. We found no impact of air cleaner use on

the development of eczema in the first year of life suggesting that the air cleaners may have influenced non-atopic wheeze. This work contributes to the growing literature on air pollution's early-life impacts and provides evidence in support of an available household-level intervention that may provide benefits for pregnant women exposed to high levels of particulate matter air pollution.

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Appendix A.
Previous studies on air pollution exposure during pregnancy and morbidity in children under 7 years of age.

Table A1. ***Previous studies on air pollution exposure during pregnancy and Respiratory conditions in children under 7 years of age.***

Study	N	Ages	Location	Assessment Method	Results
Early-Life Exposure to Outdoor Air Pollution and Respiratory Health, Ear Infections, and Eczema in Infants the INMA Study(2)	2199	1-1 ½	Spain (Asturias, Gipuzkoa, Sabadell, and Valencia)	Land use Regression (NO_2)	Mothers who are exposed to higher levels of NO_2 during pregnancy (10 µg/m^3) during pregnancy have children with increased risk of developing lung infection (RR 1.05 [0.98-1.41]) and ear infection (RR 1.18 [0.98-1.41].
Polycyclic aromatic hydrocarbons, environmental tobacco smoke, and respiratory symptoms in an inner-city birth cohort (3)	303	Up to age 2	Manhattan, New York	Polycyclic Aromatic Hydrocarbons measured through personal monitors Questionnaire.	Exposure to Polycyclic Aromatic Hydrocarbons and post-natal ETS led to increased risk of wheeze (OR, 1.49 [CI 1.00 -2.22]) and cough by 12 months.
Prenatal ambient air exposure to polycyclic aromatic hydrocarbons and the occurrence of respiratory symptoms over the first year of life (126)	333	First year of life	Poland	48-hr personal PAH measurement during 2nd or 3rd trimester of pregnancy.	Prenatal PAH exposure associated with cough (RR, 4.80 [CI 2.73-8.44] wheezing without cold (RR, 3.83 [CI 1.18-12.43]) and ear infection(RR, 1.82 [CI 1.03-3.23]) assessed by questionnaire.

Atopic Diseases, Allergic Sensitization and exposure to traffic related Air pollution in children (4)	2436	Brith-6 years	Munich, Germany	42-hour seasonal sampling PM2.5 and NO2 across 40 monitoring sites	Increase in doctor diagnosed Asthmatic/Spastic/ Obstructive Bronchitis or Asthma (OR 1.56 [1.03–2.37]) per IQR increase in $PM_{2.5}$. Increase in doctor diagnosed eczema (OR 1.18 [1.00–1.39]) for IQR increase in $NO_{2.}$ Increase in doctor and parental Asthmatic/Spastic/ Obstructive Bronchitis or Asthma if living <50 m of main road (OR 1.66 [1.01–2.59] and 1.24 [1.01–1.52]) respectively

Table A2. ***Previous studies on air pollution exposure during pregnancy and atopy and eczema in children under 7 years of age***

Study	N	Ages	Location	Assessment Method	Results
Early-Life Exposure to Outdoor Air Pollution and Respiratory Health, Ear Infections, and Eczema in Infants the INMA Study(2)	2199	1-1 ½ years	Spain (Asturias, Gipuzkoa, Sabadell, and Valencia)	Land use Regression (NO_2)	Mothers exposure to higher levels of NO_2(10 µg/m^3) and benzene (1µg/m^3) during pregnancy showed non-significant effects on the development of eczema by 18 months .
GINI-plus and LISA-plus cohorts inner-city birth cohort (3)	2112	Birth-6 years	Germany, (Bad Honnef, Munich, Leipzig, Wesel)	Land use Regression for $PM_{2.5}$ and No_2.	Increase in inner 90% range: 0.5 10^{5} m^{1} PM2.5 absorbance and 9 mg/m^3 NO2.(as a marker of soot) at address of birth led to an increase in doctor diagnosed eczema by age 6 (RR 1.69 [OR 1.04-2.75])
Perinatal Exposure to Traffic-Related Air Pollution and Atopy at 1 Year of Age in a	2477	Birth - 1 year	Canada (Edmonton, Toronto, Vancouver, Winnipeg)	LUR, Road/Land-use models. Skin-prick tests, questionnaires	TRAP exposure increased risk of atopy (OR 1.16 [CI 1.00-1.41]) for a 10 µg/m^3 increase in NO_2 after birth. Non-significant effect on development of atopy for found

Multi-Center Canadian Birth Cohort Study(11)					for fetal exposure (OR 1.02 [CI 0.86-1.22])
Atopic Diseases, Allergic Sensitization and exposure to traffic related Air pollution in children (4)	2436	Brith-6 years	Germany (Munich)	42-hour seasonal sampling PM2.5 and NO2 across 40 monitoring sites	Increase in doctor diagnosed eczema (OR 1.18 [1.00–1.39]) for a 6.4 μg/m^3 increase in NO_2. This relationship increased for atopic dermatitis (defined as eczema + allergic sensitization [specific IgE against inhaled and food allergens with CAPRAST & FEIA])

Appendix B. Questions Used to Identify Wheeze and Eczema

Table B1. Wheeze Questions

	Baseline Questionnaire	6-Month Questionnaire	12-Month Questionnaire
Assessment Question(s)	Has your child ever had a "wheezing" or whistling noise coming from his/her chest?	Over the first 6 months of your child's life, has he/she ever had a "wheezing" or whistling noise coming from his/her chest?	Over the past 6 months, has your child ever had a "wheezing" or whistling noise coming from his/her chest?
Sub-question:* First Occurrence *of Wheezing	How old was your child when the first wheezing episode occurred? (0-3 months, 4-6 months, 7-12 months, >12 months)		
***Sub-question:* Frequency of Wheezing**		How many wheezing episodes did your child have in the first 6 months of his/her life? (1,2,3,4,5, 6 or more)	How many wheezing episodes did your child have over the past 6 months? (1,2,3,4,5,6 or more)
***Sub-question:* Wheezing without a cold**	Has your child ever had a wheezing episode that was not associated with a cold?	How many of these wheezing episodes were not associated with a cold? (0,12,3,4,5,6 or more)	How many of these wheezing episodes were not associated with a cold? (1,2,3,4,5, 6 or more)

Sub-question(s): **Contact with the health care system**	Has your child had any of the following as a result of a wheezing episode or shortness of breath? • Unscheduled doctor's visit • Emergency room visit • Hospital admission	Over the first 6 months of your child's life, did your child have any [unscheduled doctor's visits, emergency room visits, hospitalizations]? • Number • Date • Reason	Over the first 6 months of your child's life, did your child have any [unscheduled doctor's visits, emergency room visits, hospitalizations]? • Number • Date • Reason
Sub-question(s): **Medication use**	Has your child ever been prescribed medication for wheezing or shortness of breath?	In your child's first 6 months of life, was your child given any medications for wheezing or shortness of breath? • Medication name • Over the counter or prescription • Date medication started • Date medication stopped	In the past 6 months, was your child given any medications for wheezing or shortness of breath? • Medication name • Over the counter or prescription • Date medication started • Date medication stopped

Table B2. Eczema Questions

	Baseline Questionnaire	6-Month Questionnaire	12-Month Questionnaire
Assessment Question(s)	Has your child ever had an itchy skin rash that was coming or going?	Over the first 6 months of your child's life, has he/she ever had an itchy skin rash that was coming and going?	Over the past 6 months, has your child had an itchy skin rash that was coming and going?
Sub-question 1: Location of eczema	Has this itchy skin rash at any time affected any of the following places:	Has this itchy skin rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck or ears?	Has this itchy skin rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck or ears?
Sub-question 2: First occurrence	How old was your child when this itchy skin rash first occurred? (0-3 months, 4-6 months, 7-12 months, >12months)	At what age did this itchy skin rash first occur? (0-2, 3-4, 5-6, >6 month)	At what age did this itchy skin rash first occur? (0-3, 4-6, 7-9 months, 9-12 months, >12 months)
Sub-question: Clearing of rash	Since the rash first occurred has it ever cleared completely?	Since this rash first occurred, has it ever cleared completely?	Since this rash first occurred, has it ever cleared completely?
Sub-question: Contact with the health care system	Has this rash been seen by a doctor?	Has this rash been seen by a doctor?	Has this rash been seen by a doctor?
Sub-question: Diagnosis	What was the diagnosis? (Eczema, Atopic Dermatitis, Hives, Diaper Rash, Do not know, Other, Specify)	What was the diagnosis? (Eczema, Atopic Dermatitis, Hives, Diaper Rash, Do not know, Other, Specify)	What was the diagnosis? (Eczema, Atopic Dermatitis, Hives, Diaper Rash, Do not know, Other, Specify)

Sub-question(s): Medication use (ever)	Has your child ever been prescribed medication for this rash?		
Sub-question: **Medication use (past 6 months)**		In your child's first 6 months of life, was your child given any medications for this itchy skin rash?	Over the past 6 months, was your child given any medications for this itchy skin ash?