A Randomized Controlled Trial of Air Cleaner Use during Pregnancy and Wheeze in Early Childhood

by

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Abstract

Background: Air pollution is a major threat to public health. I investigated the impact of HEPA filter air cleaners use during pregnancy on wheezing in childhood using data from the Ulaanbaatar Gestation and Air Pollution Research (UGAAR) randomized controlled trial.

Methods: Study staff randomly assigned 540 pregnant women to an intervention group that received HEPA cleaners during pregnancy or a control group that received no air cleaners (N = 268 intervention and 272 control). During the children's first four years of life, staff administered a questionnaire to caregivers at six-month intervals to assess wheezing in children. I identified the presence or absence of wheezing in each year and categorized children into four wheeze phenotypes: ever wheezers, persistent wheezers, late-onset wheezers, or early-transient wheezers. I also quantified the number of wheezing episodes in the first and second years of life and the third and fourth years of life. The primary analysis was intention to treat. In a secondary analysis, I estimated the relationship between modelled indoor $PM_{2.5}$ concentrations, averaged over pregnancy and each trimester, and wheeze outcomes.

Results: My analysis included 481 children (236 intervention, 245 control) born at a median gestational age of 39.5 weeks. The intervention reduced average indoor $PM_{2.5}$ by 29% (95% CI: 21, 37%). Over half (54%) of the children experienced a wheezing episode before age four. The intervention was not associated with the frequency of wheeze or with any wheezing phenotypes. In my secondary analysis, an interquartile range increase in indoor $PM_{2.5}$ during the first trimester was associated with increased odds of late-onset wheeze (OR: 1.84, 95% CI: 1.13, 3.01). There were no associations between $PM_{2.5}$ concentrations and other phenotypes.

Conclusion: The HEPA air cleaner intervention during pregnancy did not reduce the frequency of wheeze episodes or the odds of wheeze phenotypes. Future research is needed to investigate the impact of air pollution interventions on late-onset wheeze.

Keywords: Wheeze; Children's Health; Air Pollution; Air Cleaner; Randomized Controlled Trial

Dedication

I am convinced that a mysterious cosmic law conspires to shield the loved ones of graduate students from ever reading their works. Nevertheless, I am incredibly grateful to my mom, dad, and my two sisters, Keatin and Hutton, for their unending love and support. To Emma, thank you for being by my side and providing me with invaluable encouragement. This work is dedicated to all of you, the ones who have braved the impenetrable forces of the universe to stand by me. Having you all by my side has made all the difference.

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I would also like to extend my appreciation to my committee members, Dr. Lawrence McCandless and Dr. Bruce Lanphear. Your expert guidance and insightful feedback have been instrumental in shaping the direction of my research. It has been inspiring to collaborate with such an amazing group of researchers, and I am grateful for the time and dedication you have committed to this work. Working alongside you all has given me a profound understanding of what it means to be an expert.

In addition, I would like to acknowledge the support and encouragement from my friends and family. Your belief in my abilities has been a constant source of motivation, and I am grateful for your support. Thank you to Maggie Liu and Bocheng Jing for lending their coding expertise and helping me create a function that would run ZIP regression within MICE.

I would like to also express sincere gratitude to the UGAAR team and UGAAR participants. This work would not have been possible without you. It has been an honour and privilege to have had the opportunity to work on this study.

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List of Acronyms

ALSPAC	Avon Longitudinal Study of Parents and Children
API	Asthma predictive index
BMI	Body mass index
BP	Blood pressure
CI	Confidence intervals
CO	Carbon monoxide
GRAPHS	Ghana Randomized Air Pollution and Health Study
GUSTO	Growing up in Singapore towards Healthy Outcomes
HAPIN	Household Air Pollution Intervention Network
HEPA	High efficiency particulate air
HOME	Home Observation Measurements of the Environment
IQR	Interquartile range
ISSAC	International Study of Asthma and Allergies in Children
ITT	Intention-to-treat
LMIC	Low-middle income countries
LPG	Liquefied petroleum gas
MICE	Multiple imputations with chained equations
OR	Odds ratio
OS	Oxidative stress
PIAMA	Prevention and Incidence of Asthma and Mite Allergy
PM	Particulate matter
PSS	Perceived Stress Scale
RCT	Randomized controlled trial
RESPIRE	Randomized Exposure Study of Pollution Indoors and Respiratory Effects
ROS	Reactive oxygen species
RSV	Respiratory syncytial virus
TCRS	Tucson Children's Respiratory Study
TRAP	Traffic-related air pollution
UGAAR	Ulaanbaatar Gestation and Air Pollution Research
WHO	World Health Organization

Preface

This document is formatted in accordance with the manuscript-based thesis guidelines provided by the Faculty of Health Sciences at Simon Fraser University. This thesis is based on a peer-reviewed manuscript. Chapter one is an introductory chapter that describes my objectives and the rationale for my research. Chapter two provides a brief review of the relevant scientific literature. In Chapter four, I provide some discussion and suggestions for future research. Chapter three is a research chapter written as a manuscript that I intend to submit for publication:

Tanner Noth, Enkhjargal Gombojav, Chimeglkham Banzrai, Sarangerel Batsukh, Enkhtuul Enkhtuya, Buyantushig Boldbaatar, Bruce Lanphear, Lawrence McCandless, Tim Takaro, and Ryan W. Allen. *Randomized Controlled Trial of Air Cleaner Use during Pregnancy and Wheeze in Early Childhood.*

I developed the data analysis plan with input from my supervisory committee. I conducted all statistical analyses and drafted the manuscript.

Chapter 1. Objectives and Rationale

1.1. Background

Ambient air pollution is a prominent public health concern and contributes significantly to disease and death worldwide.[1] Particulate matter with an aerodynamic diameter less than 2.5 micrometres ($PM_{2.5}$) is a crucial component of ambient air pollution. The small size of $PM_{2.5}$ particles allows them to penetrate the gas exchange region of the lung, but the harmful impacts of particulate pollution extend beyond the airways.[2,3] $PM_{2.5}$ is a leading contributor to the global burden of disease and causes chronic obstructive pulmonary disease, type 2 diabetes, ischemic heart disease, lower respiratory infections, lung cancer, and adverse pregnancy outcomes.[4] The State of Global Air estimates that 6.7 million people died in 2019 from $PM_{2.5}$ exposure.[5]

There is increasing evidence of adverse health effects at low concentrations.[6] In 2021, the WHO reduced its annual average guideline concentration for $PM_{2.5}$ from 10 ug/m^3 to 5 ug/m^3.[7] Over 99% of the world's population is breathing air with $PM_{2.5}$ concentrations that exceed this new guideline. $PM_{2.5}$ concentrations in low- and middle-income countries (LMIC) often far exceed those found in high-income countries.

$PM_{2.5}$ is a heterogeneous mixture of solid and liquid particles suspended in air. Ambient $PM_{2.5}$ in urban environments is produced by both natural and anthropogenic sources. Major sources of exposure to particulate pollution include motor vehicle transportation, fossil fuel emissions from power plants and factories, and indoor cooking and heating with biomass.[8] Natural sources of particulate pollution include dust, sea salt, and emissions from wildfires.[9] But the major sources of $PM_{2.5}$ vary between cities around the world.[10] $PM_{2.5}$ can also differ significantly between and within cities, as meteorological conditions and the topology of a region can influence the dispersion of pollutants.[11] For instance, a study in China showed that temperature, humidity, wind, precipitation, radiation, and precipitation individually influenced $PM_{2.5}$ concentrations throughout the country.[11] In Ulaanbaatar, Mongolia, the topography of the region plays a crucial role in the cities pollution concentrations.[12]

1.2. Rationale

The objective of my thesis was to investigate if HEPA filter air cleaner ("HEPA cleaner") use during pregnancy reduces the odds of parent-reported wheeze from birth to age four. I used data collected in the Ulaanbaatar Gestation and Air Pollution Research (UGAAR) study.

This study was, to my knowledge, the first RCT investigating the potential benefits of air cleaners use during pregnancy on wheeze phenotypes and frequency of wheeze episodes in childhood. Moreover, respiratory symptoms in the first year of life are often transient, and symptoms during this time are not strong predictors of respiratory health later in life.[13] Studies have shown that the many young children that suffer wheeze in the first months or years of life will outgrow it in childhood and adolescence, as their airways mature and increase in size[13,14] Including early childhood wheezing symptoms from birth to four years of age provides valuable insight into temporal trends in wheeze, while allowing for the use of phenotypes that are predictive of respiratory morbidities later in life. Understanding the risk factors associated with wheeze and respiratory health in early life and possible interventions in mitigating those impacts may help to improve the health of children worldwide.

My thesis also addresses many limitations in previous observational studies, such as exposure misclassification. The randomized study design of the UGAAR study minimizes residual confounding. In previous studies, researchers have had difficulties distinguishing between pre- and postnatal exposures due to the high correlation between $PM_{2.5}$ during pregnancy and after childbirth.[15] The residence of the mother during pregnancy is often the same residence where their children spend their first years of life. Because the intervention was only in place during pregnancy for UGAAR participants, any differences observed between the intervention and control groups can be attributed to differences in exposure during the prenatal period.

Chapter 2. Literature Review

2.1. Wheeze

Wheeze is a symptomatic manifestation of any disease that causes airway obstruction or narrowing of the airways.[16] In children, wheezing manifests as a high-pitched whistling noise emitted from the chest on inhalation or exhalation. The most common causes of wheeze in children are asthma, bronchitis, allergies, and respiratory infections.[14] Roughly one-third of school-age children will experience wheeze in the first five years of life,[16] making wheeze the most common respiratory symptom in young children. Wheeze can lead to significant morbidity and decreased quality of life for children and their caregivers. Moreover, recurrent wheezing in childhood can require frequent use of health care systems and result in considerable economic cost.[17]

2.1.1. Wheeze and asthma

Wheeze is the most frequently used symptom for diagnosing childhood asthma - a disease that impacts 300 million children worldwide and is the most common chronic disease in children.[18] Asthma is a chronic inflammatory condition of the airways, where inflammation causes recurring episodes of coughing, wheezing, chest tightness, and breathlessness.[19] In the United States alone, it is estimated that the 20-year total cost associated directly with asthma exceeds 300 billion dollars; and it is thought that this number will continue to grow.[20] Phase One of the International Study of Asthma and Allergies in Children (ISSAC) found large variations in the prevalence of asthma in populations with similar genetic and ethnic backgrounds, suggesting that environmental factors play an important role in the development of asthma.[21] For these reasons, it is important to understand the environmental risk factors associated with wheeze and asthma, and possible interventions to improve respiratory health in children and adults.

Although wheezing and asthma are closely associated, wheezing is not specific to asthma. It is common for young children to wheeze early in life, and many children with respiratory infections will experience wheezing.[22] In asthmatic individuals, wheezing is due to the narrowing of the lower airways.[23] Many children who wheeze in early life will not wheeze at a later age when respiratory infections become less common.[16] Moreover, the number of wheezing episodes associated with respiratory infections

appears to be a strong predictor of respiratory health outcomes later in life, with children who experience a small number of wheezing episodes associated with a viral infection being at a low risk of asthma later in life.[24]

2.1.2. Risk Factors for Wheeze and Asthma

Genetic predisposition, environmental exposures, viral infections, and the interaction between these factors play an important role in the development of recurrent wheeze and asthma in children.[16] Research suggests that these broader categories of specific risk factors may differ by wheeze phenotypes.[25] Moreover, the factors that influence wheeze and asthma also differ between high-risk and general populations.[26]

Genetics

In children under 5 years of age, parental history of asthma and atopy are among the strongest predictors of recurrent wheeze and asthma.[27,28] The Tucson Children's Respiratory Study (TCRS) reported that maternal asthma was associated with persistent wheezing at 6 years old.[29] Moreover, paternal asthma has repeatedly been used as one of the two major predictors in multiple iterations of the Asthma Predictive Index (API).[28]

Personal history of atopy and allergic sensitization in early life also increases the risk of children developing recurrent wheeze and asthma.[30] Multiple studies have reported skin prick tests and allergen-specific IgE (allergic sensitization to common household allergens) as independent predictors of persistent wheeze later in life[31–33] and asthma.[34–36] Moreover, medically diagnosed eczema, allergic rhinitis, and number of wheeze episodes per year have been included as predictive variables in the API.[37,38]

Sex

Some research also suggests that male sex is a risk factor for wheeze and asthma.[29,32,39] The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study found that males were at an increased risk of experiencing persistent wheezing (OR: 2.06 95% CI: 1.34, 3.16).[39]

Environmental Exposures

Environmental exposures have also been shown to influence the development of recurrent wheeze and asthma. For instance, research has shown that breastfeeding for

a minimum of 12 weeks[39] and exposure to animals in early life[40] may decrease the risk of developing asthma later in life.

Tobacco smoke exposures, both in prenatal and in early life, are established risk factors for wheeze and asthma.[41] This includes maternal smoking during pregnancy,[42] second-hand smoke exposure during pregnancy,[43] and children's exposure to environmental tobacco smoke in early life.[44] The TCRS reported that maternal smoking during pregnancy was an independent predictor of persistent and transient early wheeze phenotypes.[29]

Research has suggested that exposure to ambient air pollution in early life increases the risk of children developing wheeze symptoms and asthma.[45–47] Two recent reviews reported that early life exposures to traffic-related air pollution (TRAP) increased the risk of children being diagnosed as asthmatic.[45,48] One study investigating 10 European cities found that living near high-traffic roadways accounted for approximately 14% of all asthma cases.[49] However, these associations tend to differ between cities, and additional unmeasured confounding likely exists.[50] For instance, in some cities low-socioeconomic-status (SES) communities are more likely to both reside in highly polluted areas,[50] and the develop asthma as a result of other factors associated with low SES.[47]

A review and meta-analysis concerned with point source pollutants and asthma-related outcomes (wheeze, asthma, and bronchiolitis) found a weak association between pollution and respiratory outcomes, claiming that heterogeneity in study designs and exposure assessment precluded conclusive results.[51] The evidence of a link between air pollution exposure and wheeze outcomes remains inconclusive and results tend to vary by pollutant, wheeze phenotype, and exposure timing (prenatal vs postnatal exposures).[48]

Viral Infections

Viral infections are a common trigger of wheezing in young children, and can interact with environmental and host factors to increase the risk of recurrent wheeze and asthma.[52] In some children, respiratory viral infections can cause transient wheezing episodes that do not persist into later life. In others these viral infections can increase the risk of developing asthma.[52] Some viruses impact the lower airways and can result in

inflammation causing airway obstruction in children.[53] A study of 108 children aged nine to eleven found that viral infections were detected in 80% of reported wheeze episodes and 85% of reported upper respiratory symptoms.[54] Children with severe respiratory illness induced by rhinovirus or respiratory syncytial virus (RSV) in the presence of wheeze are at particular risk of developing asthma.[52] Moreover, in individuals with asthma, viral infections can drastically exacerbate asthma symptoms, with 80% and roughly 50% of asthma exacerbation attributable to rhinoviruses in children and adults, respectively.[55]

2.1.3. Wheeze Phenotypes

Respiratory symptoms in early life are often transient, and accurately characterizing wheeze phenotypes is crucial for determining the risk of a child developing respiratory morbidities later in life.[56] In this regard, birth cohort studies have offered valuable insight into early life wheezing phenotypes. The first study to classify wheeze phenotypes in early life was the TCRS, a long-term, longitudinal study investigating the origins of respiratory illness.[29]

The TCRS study identified four wheezing phenotypes in children from birth to 6 years of age: never wheezed, transient-early wheeze, persistent wheeze, and late-onset wheeze. Transient-early is characterized by children who reported wheezing by age three but not between the ages of four and six. In TCRS, children who reported wheezing from birth to three and four to six were considered persistent wheezers. Lastly, late-onset wheezing was characterized by the onset of wheezing symptoms from ages four to six. Of these four phenotypes, persistent wheezing and late-onset wheezing were shown to be predictive of wheezing at 16 years old.[57] To be considered a wheezer for any of these periods, the children had to have been reported at least one wheeze episode in the 12-months prior to the questionnaire.

Epidemiological studies that have adopted these wheeze phenotypes have often adapted the onset and duration of symptoms based on the study period of interest. For instance, a birth cohort in Paris investigating wheeze symptoms from birth to the age of four used the same four wheeze phenotypes as TCRS.[58] However, in this study, children were classified according the onset of symptoms before or after two years of age.[58]

Subsequent studies to TCRS applied latent class analysis techniques and identified similar wheezing phenotypes in children.[33,59] The Avon Longitudinal Study of Parents and Children (ALSPAC) has since identified two additional wheezing phenotypes: prolonged early wheeze and intermediate-onset wheeze.[33] In the ALSPAC cohort, prolonged early wheezers were defined as children that wheezed from 5-54 months but not after 69 months, whereas intermediate-onset wheezers were children with the onset of wheeze symptoms at 18 months or older that persistent past 42 months.[33] These methods of characterizing wheeze phenotypes by temporality and duration of symptoms have garnered criticism, with some citing that the phenotypes are not useful for accurately assessing asthma risk in clinical practice.[16]

Syndromes

The TCRS group subsequently expanded on the initial four wheeze phenotypes and classified wheeze into three syndromes: transient infant wheezers, nonatopic wheezers, and atopic wheezers. This classification aimed to differentiate between atopic wheezers, who are more likely to experience persistent respiratory symptoms later in life, and other wheezers.

Transient infant wheezers were identified as children who experienced periodic wheezing in the first three years of life but did not wheeze after age three. Risk factors for transient infant wheezers in TCRS were low lung function before lower respiratory infection (LRI), maternal smoking, and younger mothers.[60] While the lower lung function in transient infant wheezers improved over time, it did not reach the lung function of children who never reported wheezing. Notably, these children were not more likely to wheeze later in life than children who did not wheeze in infancy.[57]

Children categorized with the second syndrome identified by TRCS, nonatopic wheezers, were more likely to develop acute airway obstruction from viral infections. However, like transient infant wheezers, the prevalence of wheezing in nonatopic children also decreased with age.

Most children in TRCS who developed atopic asthma displayed their first symptoms by the age of six. This group was categorized into early atopic wheezers (before age three) and late atopic wheezers (onset of symptoms after age three). Of these subgroups, early atopic wheezers had the lowest lung function at ages six and

11.[61] As a result, the onset of symptoms and allergic sensitization in the first three years of life may be important risk factors for asthma later in life.

The categorization of wheeze symptoms can provide useful insights into how differences in the onset and duration of wheeze symptoms and atopy can influence the risk of developing respiratory morbidities later in life. Birth cohorts have provided important information on how patterns of wheeze early in life can be predictive of recurrent wheeze and asthma later in life. The TCRS study expanded on the wheeze phenotypes defined by the onset and duration of symptoms and highlighted the importance of distinguishing between atopic and nonatopic wheezers. Since the identification of wheeze phenotypes in the TRCS, there has been increasing research interest in using latent trajectory methods to identify wheezing patterns.[26]

2.2. Air Pollution Exposure and Children's Respiratory Health

Although exposure to air pollution can impact health at any age, early life is a particularly vulnerable period. Due to their developing physiology, children are more likely than adults to experience the adverse impact of exposure to air pollution.[62] Children breathe more air relative to their body weight and have a higher surface area-to-bodyweight ratio than adults. As a result, children receive higher doses of environmental pollutants than adults.[62]

Increasing evidence suggests that early life exposure to air pollution can influence respiratory and immune system function and development, leading to health complications later in life.[63] Exposure to $PM_{2.5}$ during pregnancy and early childhood may increase the risk of children developing atopy[64] and asthma.[48] In addition, exposure to air pollutants during pregnancy can impact the fetus during critical stages of development that may influence health outcomes across the entire life course through developmental programming.[65]

2.2.1. Prenatal Air Pollution Exposures and Wheeze

There is strong epidemiologic evidence to suggest that early life exposure to air pollutants impacts lung function and can increase risk asthma in children.[63,66–70]

However, less is known about how prenatal air pollution exposure during gestation influences the trajectory of respiratory health. Furthermore, there is limited evidence of benefits from exposure interventions during pregnancy in mitigating the impacts of air pollution on respiratory development.[64-66] Previous household-level intervention studies have investigated the use of updated cooking stoves and liquefied petroleum gas (LPG) fuel.

Randomized Controlled Trials

Previous work investigating the role of household-level interventions in reducing prenatal exposure has focused primarily on indoor pollution exposure from solid fuel cooking and heating. RCTs have offered valuable insights into how prenatal exposure may be mitigated through updating cooking stoves, particularly in LMIC.

The Randomised Exposure Study of Pollution Indoors and Respiratory Effects (RESPIRE) is an RCT that investigated the use of a chimney stove intervention in the San Marcos region of Guatemala.[71] The investigators randomly assigned 534 residents to an intervention group that received an updated wood stove with a chimney or a control group that continued cooking on open woodfires. The intervention reduced participants average carbon monoxide exposure by 50%, but was not associated with a reduction in physician-diagnosed pneumonia in childhood.[71] However, the intervention group did experience a reduction in severe pneumonia outcomes.[71] An exposure-response analysis revealed that a larger reduction in carbon monoxide (CO) exposure was associated with a greater reduction in pneumonia risk.[71] If the chimney stove intervention had a greater reduction in exposure or if more statistical power had been available, a significant effect on physician-diagnosed pneumonia may have been detected.

The Ghana Randomized Air Pollution and Health Study (GRAPHS) investigators enrolled 1,414 pregnant women in a randomized cookstove intervention trial in rural Ghana.[72] The researchers measured prenatal CO exposures over four 72 hours periods using personal monitors.[72] Children born to mothers with high CO exposures were at an increased risk of impaired lung function measured one month after birth, with female children being at particularly increased risk.[72] Moreover, impaired lung function in these children increased their risk of physician-assessed pneumonia in their first year of life.

Investigators in the Household Air Pollution Intervention Network (HAPIN) enrolled 3,195 households with pregnant women to examine the use of a LPG fuel intervention in Guatemala, India, Peru, and Rwanda.[73] The trial is currently underway, but early results indicate that the LPG intervention reduced participants' average $PM_{2.5}$ exposure by 66% (71.5 vs 24.1 μg/m^3).[73]

Observational Studies

Intervention studies have provided valuable information into methods for reducing indoor air pollution. Outside these few RCTs, researchers have relied primarily on observational designs to investigate the role prenatal air pollution exposure plays in early childhood wheezing, with differing results. Some studies reported an association between prenatal exposures and wheezing,[74–77] while others report no meaningful associations.[78,79] However, there are considerable differences between study designs, exposure assessment methods, and covariates included in the analyses.

It is important to highlight the fundamental difference in research questions between the RCTs and the observational studies. The RCTs investigate the association between the use of interventions to reduce indoor air pollution and respiratory health. In contrast, the observational studies examine the association between air pollution exposure or concentrations and respiratory health.

The GUSTO birth cohort in Singapore included 953 children and reported that compared to children whose mothers were in the lowest quartile of outdoor $PM_{2.5}$ concentration during pregnancy, those whose mothers were in higher quartiles (Q3-Q4) experienced more frequent wheezing episodes from birth to two years old.[74] Zhang et al. estimated ambient $PM_{2.5}$ concentrations during gestation and the first year of life for 30,325 preschool children in mainland China. The investigators found that for each IQR increase in prenatal $PM_{2.5}$, there was an associated increased odds of ever wheeze (OR: 1.08, 95% CI: 1.01, 1.16) and asthma (OR: 1.18, 95% CI: 1.01-1.29) in childhood, with reference to the lowest quintile.[80] Another study in China reported that prenatal exposure to NO_2 was associated with a lower remission of wheezing in early life.[75] Jedrychowski et al. reported that children whose mothers had $PM_{2.5}$ exposures above the median during pregnancy had more frequent wheezing episodes from birth to two years old (IRR = 1.38; 95% CI: 1.25, 1.51) than children whose mothers had exposure below the median. However, this association did not persist when children were three or years old.[81]

Studies of cohorts in Mexico and Norway reported weaker associations between prenatal exposure to air pollutants and wheezing symptoms from birth to four years old.[78,79]

Due to limitations in data and varying study designs, many existing observational studies investigating prenatal or early-life air pollution exposure have classified wheeze phenotypes within the constraints of their data, with many studies assessing health outcomes for current wheeze[75,78,82] or ever wheeze.[79,80] Some studies have assessed outcomes based on the phenotypes identified by TRCS,[58,83,84] to consider the onset and persistence of wheezing symptoms. Even within the group of studies that assessed health outcomes using the wheeze phenotypes defined by TRCS, the definitions of the phenotypes vary considerably. Other observational studies analyzed the frequency of children's wheeze episodes.[74,85]

2.2.2. Trimester-Specific Exposures to Air Pollution and Wheeze outcomes

A subset of studies of prenatal pollution have investigated the impact of exposures during specific weeks of gestation on wheeze and asthma outcomes to determine vulnerable periods during pregnancy. These studies suggest that particular periods of pregnancy have a significant impact on determining respiratory health outcomes.[86,87] For instance, the early stages of fetal lung development play a critical role in establishing the foundation for health lung and airway structure. Insults during this period may result in impaired development.[87] Understanding the timing and vulnerability of these developmental phases is important to better understand how prenatal air pollution exposure influences respiratory health.

Researchers in Mexico reported that among children born to mothers exposed to high stress, outdoor air pollution during the first trimester of pregnancy increased the risk of current wheeze at 48 months (RR =1.35; 95% CI: 1.00,1.83 per 3.5 μg/m^3 contrast in $PM_{2.5}$).[78] This association was not observed among children with mothers that reported low stress during pregnancy. In a prospective birth cohort study in China, Chen et al. found that $PM_{2.5}$ exposure during pregnancy increased the risk of wheeze/asthma among 3,725 children three to four years old.[88] Moreover, effect estimates were highest for exposures during the pseudoglandular (6-16 weeks) and canalicular stages (16-24

weeks) of fetal lung development, and these periods significantly influenced wheeze/asthma in the first three years of life.

2.2.3. Potential Biological Mechanisms

Epidemiologic evidence has suggested that prenatal air pollution exposure can impair normal fetal development and influence adverse pregnancy outcomes that can increase the risk of respiratory symptoms and asthma in children.[89] Although the biological mechanisms are not fully understood, oxidative stress (OS) and epigenetic changes are thought to play crucial roles.[62,90]

Oxidative Stress

Oxidative stress appears to play a key role in adverse pregnancy outcomes and may contribute to fetal programming and influence the trajectory of health and disease into adulthood.[91] Inhaling particulate matter can cause inflammation in the lung and induce OS in pregnant women. OS refers to an imbalance of reactive oxygen species (ROS) and antioxidant defence systems that can lead to tissue damage and inflammation.[91] The proinflammatory signalling from oxidative stress can then set off a series of events that can impact distant organs in the body.[92] Maternal oxidative stress and proinflammatory cytokines can result in placental dysfunctions and increased fetal stress,[91] and lead to airway remodelling and airway hyperresponsiveness in the fetus.[93] Moreover, specific periods of pregnancy, particularly early stages of gestation, may be more vulnerable to exposures due to the fetus having less developed antioxidant capabilities.[93]

Air pollution exposure during pregnancy may also directly impair placental development and impact the delivery of nutrients and oxygen to the fetus during critical periods of development.[94] A study in mice found that exposure to TRAP produces cellular changes in the placenta that lead to pregnancy complications that impact both the health of the mother and offspring.[95] Moreover, human epidemiological evidence suggests that prenatal exposure to $PM_{2.5}$ is associated with adverse birth outcomes such as low birth weight, preterm birth, and small gestational age.[95,96] In particular, low birth weight has been associated with an increased risk of asthma, impaired lung function in adulthood, and increased respiratory symptoms in early life.[97]

Epigenetic Changes

Exposure to air pollutants can cause epigenetic changes in the developing fetus, leading to developmental deficits and disease later in life.[90] Prenatal exposures are associated with changes in DNA methylation that can influence fetal programming of respiratory health.[65,98] In addition, exposures during early gestation may have a disproportionate impact due to the considerable epigenetic reprogramming occurring in embryogenesis.[65,99,100]

Chapter 3. Randomized Controlled Trial of Air Cleaner Use during Pregnancy and Wheeze in Early Childhood

3.1. Introduction

Exposure to fine particulate matter ($PM_{2.5}$) air pollution during pregnancy can influence fetal growth and pregnancy outcomes.[89] There is increasing evidence that air pollution exposures during pregnancy can impact the fetus during critical stages of respiratory development and increase the risk of respiratory disease later in life.[70,86,94,101–103] Prenatal exposure to $PM_{2.5}$ has been associated with both wheeze and asthma outcomes in children.[75,80,81,88,104]

Wheeze is the symptomatic manifestation of any disease that causes a narrowing or obstruction of the airways.[16] Roughly one-third of school-age children will experience wheeze in the first five years of life,[16] making wheeze the most common respiratory symptom in young children. Wheeze is the most frequently used symptom for diagnosing childhood asthma - a disease that impacts 300 million people worldwide and is the most common chronic disease in children.[18] Although wheeze and asthma are closely associated, wheezing is not specific to asthma. It is common for young children to wheeze early in life, and many children with respiratory infections will experience wheezing.[22] Many children who wheeze in early life will not wheeze at a later age when respiratory infections become less common.[16] Moreover, the number of wheezing episodes associated with respiratory infections appears to be a strong predictor of respiratory health outcomes later in life, with children that experience a small number of wheezing episodes associated with a viral infection being at a low risk of asthma later in life.[24]

There is limited evidence of benefits from exposure interventions during pregnancy in mitigating the impacts of air pollution on respiratory development.[64-66] RCTs have focused on household-level interventions, such as chimney stoves,[71] cookstoves,[72] and liquefied petroleum gas (LPG) fuel interventions,[73] in reducing prenatal exposures. While these interventions have shown promising results in reducing exposure, their effects on respiratory symptoms have been mixed. Observational studies have provided additional insights, with some reporting associations between prenatal air

pollution exposure and wheezing,[74–77] while others report no meaningful associations.[78,79] However, variations in study designs, exposure assessment methods, and covariates included in the analyses may contribute to the heterogeneity of results.

Portable HEPA filter air cleaners ("HEPA cleaners") are a promising intervention to reduce exposure to $PM_{2.5}$. Previous studies have reported that HEPA cleaners can reduce indoor $PM_{2.5}$ concentrations by 29 to 82%.[105] However, no previous studies have investigated the impact of HEPA cleaner use during pregnancy on wheezing in early childhood. Evidence suggests that there may be short-term cardiovascular and respiratory benefits of using indoor air cleaners, but that the overall certainty for the evidence remains low.[106–108] Moreover, work has shown that HEPA cleaner use in the home may improve airway mechanics and asthma and allergic symptoms in children.[109–111] Considering the ubiquity of air pollution exposure and its persisting threat to public health for the foreseeable future, even a modest reduction in subclinical health indicators justifies the widespread adoption of indoor air cleaners as a means to improve health.[105]

I investigated the effect of the HEPA cleaner intervention on caregiver-reported wheezing symptoms in the first four years of life. In a secondary analysis, I evaluated the association between modelled indoor $PM_{2.5}$ concentrations during pregnancy and wheeze outcomes.

3.2. Materials and Methods

The Ulaanbaatar Gestation and Air Pollution Research (UGAAR) randomized controlled trial (RCT) was designed to evaluate the impacts of using HEPA cleaners during pregnancy on fetal growth and early childhood development.[112–115] UGAAR investigators have previously reported that the intervention was associated with an increase in mean term birth weight and improvements in obesity-related outcomes.[112,114] The UGAAR study has been described previously.[112] Briefly, the study was conducted in Ulaanbaatar, Mongolia's capital city, which is among the most polluted cities in the world. The primary source of air pollution in the city is residential coal burned in home heating stoves.

We recruited participants at one of two health clinics. We enrolled 540 women who met the following criteria: ≥18 years of age, ≤ 18 weeks into a single child gestation

pregnancy, non-smokers, residing in an apartment, not using HEPA cleaners at the time of enrollment, and planning to give birth in an Ulaanbaatar hospital.

3.2.1. Randomization and blinding

Prior to randomization, study staff confirmed participants' eligibility for the study and obtained written informed consent. Staff assigned participants to either the intervention or control group at a 1:1 ratio using sealed opaque envelopes containing randomly generated cards indicating "filter" or "control". Study staff drew the envelopes in sequential order and informed the participant of their allocation. The envelope and cards were then discarded, and the process was repeated for the next participant. The women enrolled in the study were not blinded to their intervention status.

3.2.2. Intervention

Depending on the size of the residence, staff deployed one or two HEPA cleaners (Coway AP-1009CH) in the homes of participants in the intervention group. In every home, UGAAR personnel placed an air cleaner in the living room. In apartments ≥ 40m^2, we placed a second air cleaner in the participant's bedroom. The control group received no HEPA cleaners. Staff installed the HEPA cleaners' the participants' homes shortly after enrollment and encouraged participants to use the HEPA cleaner continuously throughout pregnancy. The HEPA filters were not replaced during the study and staff retrieved the HEPA cleaners shortly after the pregnancy ended.

3.2.3. Prenatal data collection

Staff measured indoor $PM_{2.5}$ concentrations over two seven-day sampling campaigns, first at a median of 11 weeks' gestation and again at a median of 30 weeks' gestation, using Dylos DC 1700 laser particle counters. As described elsewhere, the $PM_{2.5}$ measurements were used to develop a blended multiple linear / random forest regression model that was used to predict weekly indoor $PM_{2.5}$ concentrations during pregnancy.[116]

At five-19 weeks' gestation and again between 24 and 37 weeks, staff administered a questionnaire to collect information on demographics, maternal health,

housing, and lifestyle. Each participant's body mass index (BMI) was calculated using height and current weight at enrollment. UGAAR personnel measured self-perceived psychological stress in participants on both questionnaires using the four question Perceived Stress Scale (PSS-4).[117] After birth, staff obtained data on birth weight, length, head circumference, gestational age, mode of delivery, and the sex of the child from medical records. We also recorded information on stillbirths and pregnancy complications from medical records. Participants self-reported the occurrence and timing of spontaneous abortions.

3.2.4. Postnatal data collection

At a median age of 15.4 months (range: 7.7 – 28.9 months), staff invited all living mother-child dyads to re-enroll in a follow-up study of childhood development. At re-enrollment staff administered a questionnaire to capture relevant information on the child's diet, health, activities, and home environment since birth. Subsequent questionnaires were administered to participants at six-month intervals.

Staff made annual visits to the participants' homes roughly around the child's birthday. At that time, $PM_{2.5}$ was measured again over seven days in a sub-sample of homes depending on availability of monitors. During the first of the home visits, staff assessed nurturing and stimulation of the child using the Home Observation Measurements of the Environment (HOME) inventory.

3.2.5. Assessment of Wheezing Symptoms

On each of the post-natal questionnaires, staff collected information about the child's respiratory symptoms using questions adapted from the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire. Because children were enrolled into this follow-up study between 7.7 and 28.9 months of age, the first post-natal questionnaire asked parents if their child had experienced wheeze from birth to the time of postnatal enrollment and if so, how old the child was when the first episode occurred. Subsequent bi-annual questionnaires asked participants the number of wheeze episodes that the child experienced over the past six months. The questionnaires were written in English, translated by native Mongolian speakers, then back-translated to English to ensure accuracy.

3.2.6. Sample Size

The UGAAR study was originally designed to assess the role of the intervention on fetal growth. As a result, our sample size calculations were based on term birth weight. We targeted a sample of 540 participants assuming 18% attrition from pregnancy loss and withdrawal, a type I error rate of 0.05 (2-sided), and a type II error rate of 0.20.

3.2.7. Statistical Analyses

The primary analysis was by intention-to-treat (ITT) and included 481 children (245 intervention and 236 control) (Figure 1). A secondary complete case analysis included 316 children (170 intervention and 146 control) with complete wheeze data from birth to four years of age. The participants included in the ITT analysis represent the full cohort except for individuals that withdrew prior to baseline data collection (n=8), pregnancy losses (n=46), and neonatal deaths (n=5).

I imputed the frequency of wheeze episodes in each year of life for participants that failed to answer one or more of the wheeze questions, assuming the data were missing at random. I imputed 80 datasets stratified by treatment group using multiple imputation with chained equations (MICE) (R mice package).[118] Other work from UGAAR investigators have used 20 imputations for single health outcomes.[114,115,119] I used 80 imputations because I was using a single imputation model to impute data for four outcomes: first year wheezing, second year wheezing, third year wheezing, and fourth year wheezing.

My objective with the imputation model was to impute missing data for participants who did not complete the wheeze questions. This required including in the imputation model important demographic variables among participants that were predictive of missingness in wheeze. Moreover, to include variables in the imputation model that are predictive of missingness in wheeze, the variables themselves could not be missing. I employed different thresholds to select predictor variables in my imputation model. To be considered as a predictor variable, variables had to be at least 85% complete. I then included variables that were associated ($p< 0.05$) with missingness or predictive of the frequency of wheeze episodes ($p < 0.20$). This approach allowed for a

more comprehensive consideration of potential predictors, considering both statistical significance and the practical relevance of the variables to the research question. The selected variables included birth season, preterm birth, maternal high blood pressure, PSS-4 score in early pregnancy, PSS-4 score in late pregnancy, marital status, age of participant at enrollment, sex of the child, delivery type, gestational age at birth, and history of parental asthma.

My primary outcomes were four wheeze phenotypes: ever wheeze, persistent wheeze, early transient wheeze, and late onset wheeze (Figure A.1 in appendix). Ever wheeze was defined as children whose caregivers reported any wheeze episodes from birth to four years old. Persistent wheeze was defined as children that were reported to have wheezed both in year one or two and in year three or four. Early transient wheeze was defined as children that wheezed in year one or two and did not wheeze in years three or four. Late-onset wheeze was defined the onset of wheezing symptoms in the third or fourth year of life. Secondarily, I analyzed the total number of caregiver-reported wheeze episodes in three time periods: the first and second years of life, the third and fourth years of life, and from birth to four years.

The wheeze phenotypes were created by aggregating the questionnaire data from 6-month intervals to the frequency of wheezing episodes in the first, second, third, and fourth year of life. To have been considered a wheezer in a particular year, the child had to have been reported to wheeze at least once in the corresponding year.

I used unadjusted logistic regression to test the effect of the HEPA cleaner intervention on binary wheeze outcomes.

I also used an unadjusted zero-inflated Poisson regression to estimate the effect of the intervention on the frequency of wheezing symptoms. The zero-inflated Poisson regression is two-part model that allows for an excess of observed zeros in count data, where the excess zeros are considered in a separate model than the count data.[120,121] The model applies a logistic regression to estimate the probability of observations being excess, or “always” zeros. The Poisson portion of the model is applied to the count data. The results for each portion of model are presented using separate effect estimates: the estimates for the logistic portions of the model are presented as odds ratios (OR), while the Poisson portions are presented as incidence rate ratios (IRR).[81] The logit portion of

the model is presented as inverse odds ratio (1/OR) to help interpret the results more intuitively.[81] In this context, the inverse odds ratio represents the likelihood of a child not belonging to the excess zero group.

In my secondary analysis, I used multiple logistic regression models and zero-inflated Poisson regression models to estimate the association between full-pregnancy and trimester-specific averaged indoor $PM_{2.5}$ concentrations and wheeze outcomes. I used a directed acyclic graph (DAG) (Figure A.2 in appendix) to select control variables and included intervention status (control/intervention), maternal age (continuous), birth season (winter, spring, summer, fall), living with a smoker (yes/no), education (university/ no university), parental allergies (yes/no), and parental asthma (yes/no). Models assessing exposures for each trimester also controlled for $PM_{2.5}$ concentrations in other trimesters. To improve interpretability and comparability, I scaled the effect estimates to interquartile range (IQR) increases in $PM_{2.5}$ exposure.

As a sensitivity analysis, I also used inverse probability weighting (IPW) to account for missing observations. I also evaluated how the intervention effect estimates differed between preterm and term children. This was motivated by the observation in previous UGAAR analyses that preterm birth was more common in the intervention group. UGAAR investigators have hypothesized that this association between the intervention and preterm birth may be due to the live birth bias.[122] I also conducted a sensitivity analysis to assess the relationship between modelled indoor $PM_{2.5}$ concentrations during specific trimesters and wheeze symptoms that did not adjust for concentrations during other trimesters.

3.3. Results

UGAAR investigators recruited 540 pregnant women from January 2014 to May 2015 and randomly assigned 272 participants to the control group and 268 to the intervention group (Figure 1). Intervention and control participants were enrolled into the study at a median (25^{th}, 75^{th} percentile) of 11 weeks (9, 13) and 10 weeks (9, 12), respectively. A total of 514 participants were followed to the end of pregnancy (253 in control and 261 in intervention). There were 469 live births (243 intervention and 225 control), 46 known pregnancy losses, and 5 neonatal deaths. From February 2016 to January 2017, we enrolled 416 participants into the postnatal study.

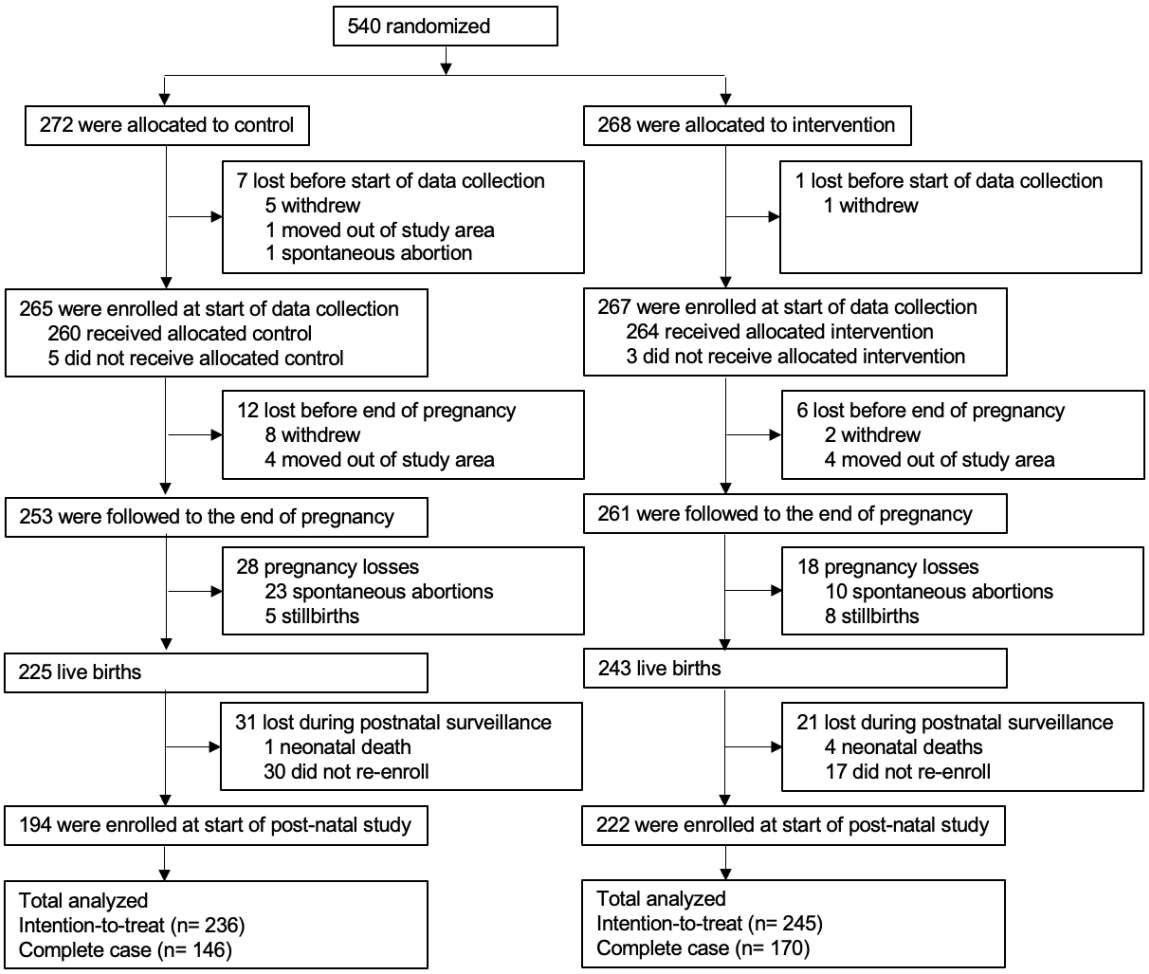

Figure 1. UGAAR trial profile.

3.3.1. Baseline characteristics

The intervention and control groups had comparable characteristics at baseline (Table 1). The median (25^{th}, 75^{th} percentile) ages at enrollment were 28 (25, 33) years in the control group and 29 (25, 33) years in the intervention group. Just under half of the women in each group reported living with a smoker at enrollment. A history of parental allergy was reported slightly more commonly in the intervention group (51%) than in the control group (37%).

Table 1. Baseline characteristics.

	Treatment group	
	Control (n = 236)	**Intervention (n = 245)**
Characteristic	**Median (25th, 75th percentile) or *n (%)***	**Median (25th, 75th percentile) or *n (%)***
Maternal BMI (Pre-Pregnancy)	21.7 (19.6, 23.9)	21.4 (19.7, 24.0)
Missing, n (%)	21 (9%)	8 (3%)
Age at Enrollment (years)	28.0 (25.0, 33.0)	29.0 (25.0, 33.0)
Missing, n (%)	11 (5%)	10 (4%)
Weeks pregnant at enrollment	10.00 (8.75, 12.25)	11.00 (9.00, 13.00)
Missing, n (%)	0 (0%)	0 (0%)
Parity		
None	23 (10%)	24 (10%)
One	92 (39%)	88 (37%)
2 or more	47 (20%)	60 (25%)
Missing, n (%)	74 (31%)	73 (31%)
Marital status		
Married of common law	226 (96%)	239 (97%)
Not married or common law	7 (3%)	3 (1%)
Missing, n (%)	3 (1%)	3 (1%)
Enrollment season		
Fall	60 (19%)	75 (31%)
Spring	79 (33%)	67 (27%)
Summer	24 (10%)	32 (13%)
Winter	73 (31%)	71 (29%)
Missing, n (%)	0 (0%)	0 (0%)
Monthly household income		
≥ 800,000 Tugrik	181 (77%)	189 (77%)
< 800,000 Tugrik	45 (19%)	46 (19%)
Missing, n (%)	10 (4%)	10 (4%)
Maternal education		
Completed university	188 (80%)	196 (80%)
Did not complete university	32 (14%)	29 (12%)

Characteristic	Treatment group	
	Control (n = 236)	Intervention (n = 245)
	Median (25th, 75th percentile) or *n (%)*	Median (25th, 75th percentile) or *n (%)*
Missing, n (%)	16 (7%)	20 (8%)
Maternal smoking		
Yes	18 (8%)	18 (7%)
No	217 (92%)	224 (91%)
Missing, n (%)	1 (0%)	3 (1%)
History of parental asthma		
Yes	9 (4%)	7 (3%)
No	178 (75%)	210 (96%)
Missing, n (%)	49 (21%)	28 (11%)
History of parental allergy		
Yes	87 (37%)	110 (51%)
No	100 (42%)	107 (49%)
Missing, n (%)	49 (21%)	28 (11%)
Lives with a smoker at enrollment		
Yes	108 (46%)	111 (45%)
No	122 (51%)	128 (52%)
Missing, n (%)	6 (3%)	6 (2%)

[1] Median (IQR); n (%)

3.3.2. Postnatal characteristics

Birth and postnatal characteristics were generally similar among the intervention and control groups (Table 2). There were a similar number of vaginal and cesarian deliveries in each group. Missing data was more common in the control group than the intervention group. In addition, missing data for wheeze symptoms was more common among children who were 15 months or older at baseline. Among children with non-missing wheeze outcomes, those younger than 15 months old at the time of baseline questionnaire were reported to have experienced a greater number of wheeze symptoms in the first two year of life compared to older children (Table A.1 in appendix).

This variation in caregiver-reported wheeze symptoms may be due to missing data or to the fact that parents of older children, at the time of enrollment, were asked to recall wheeze symptoms over a longer period than caregivers of younger children.

Breastfeeding duration was similar between the two groups, with 141 (73%) and 157 (71%) of control and intervention participants, respectively, breastfeeding their child for at least 12 months. Season of birth, the presence of visible mould, and living with a smoker from birth to four were also similar between the two groups. Over half of the participants in each group reported living with a smoker in the first four years of the child's life.

UGAAR investigators previously reported that the HEPA cleaners reduced average indoor $PM_{2.5}$ concentrations in the homes of the intervention group by 29% (95% CI: 21%, 37%), from a geometric mean 24.5 $\mu g/m^3$ in the control group to 17.3 $\mu g/m^3$ in intervention group.[112] Post-natal indoor $PM_{2.5}$ concentrations were similar between groups.[113]

Table 2. Birth and postnatal characteristics.

Characteristic	Treatment group	
	Control (n = 236) Median (25th, 75th percentile) or *n (%)*	Intervention (n = 245) Median (25th, 75th percentile) or *n (%)*
Season of birth		
Fall	75 (32%)	66 (27%)
Spring	51 (22%)	58 (24%)
Summer	71 (30%)	79 (32%)
Winter	26 (11%)	35 (14%)
Missing, n (%)	13 (6%)	7 (3%)
Sex		
Female	111 (47%)	110 (46%)
Male	113 (48%)	128 (54%)
Missing, n (%)	12 (5%)	7 (3%)
Delivery type		
Cesarian	88 (39%)	88 (36%)
Vaginal	135 (61%)	151 (62%)
Missing, n (%)	13 (5%)	6 (2%)
Birth term		
Preterm (<37 wk)	10 (4%)	21 (9%)
Term (≥37 wk)	213 (90%)	218 (89%)
Missing, n (%)	13 (6%)	6 (2%)
Visible mould in home		
Yes	34 (14%)	32 (13%)
No	161 (68%)	190 (78%)
Missing, n (%)	41 (17%)	23 (9%)
Breastfed		
Never	6 (3%)	5 (2%)
<12 months	44 (19%)	54 (22%)
≥12 months	141 (60%)	157 (64%)
Missing, n (%)	45 (19%)	29 (12%)
Lives with a smoker at enrollment		
Yes	119 (50%)	137 (56%)

Characteristic	Treatment group	
	Control (n = 236) Median (25th, 75th percentile) or *n (%)*	Intervention (n = 245) Median (25th, 75th percentile) or *n (%)*
No	65 (28%)	67 (27%)
Missing, n (%)	52 (22%)	41 (17%)
Postnatal HEPA filter air cleaner use (birth to four)		
Yes	88 (37%)	97 (40%)
No	86 (36%)	102 (42%)
Missing, n (%)	62 (26%)	46 (19%)
Ever wheeze		
Yes	115 (49%)	144 (59%)
No	54 (23%)	56 (23%)
Missing, n (%)	67 (28%)	45 (18%)
Persistent wheeze		
Yes	43 (18%)	46 (19%)
No	133 (56%)	159 (65%)
Missing, n (%)	60 (25%)	40 (16%)
Late onset wheeze		
Yes	32 (14%)	43 (18%)
No	132 (56%)	153 (62%)
Missing, n (%)	72 (31%)	49 (20%)
Early transient wheeze		
Yes	27 (11%)	43 (18%)
No	134 (57%)	149 (61%)
Missing, n (%)	75 (32%)	53 (22%)

[1] n (%); Median (IQR)

3.3.3. Intervention effects

In the primary ITT analyses of 481 participants, I observed that, beyond the first year of life, the intervention group reported more wheeze episodes than the control group (Figure 2). Furthermore, a greater proportion of children in the intervention group exhibited each wheeze phenotype (Table 3). However, all wheeze effect estimates in

these analyses were imprecise and had large confidence intervals that spanned no effect. Similarly, the intervention was associated with an increase in the frequency of caregiver-reported wheeze phenotypes, particularly in the third and fourth year of life (OR: 1.33, 95% CI: 1.00, 1.76) (Table 4). These results did not change considerably after adjusting for preterm birth. The results for the complete case analyses and IPW were similar to those observed in the primary ITT analyses using MICE (Table A.2 in appendix).

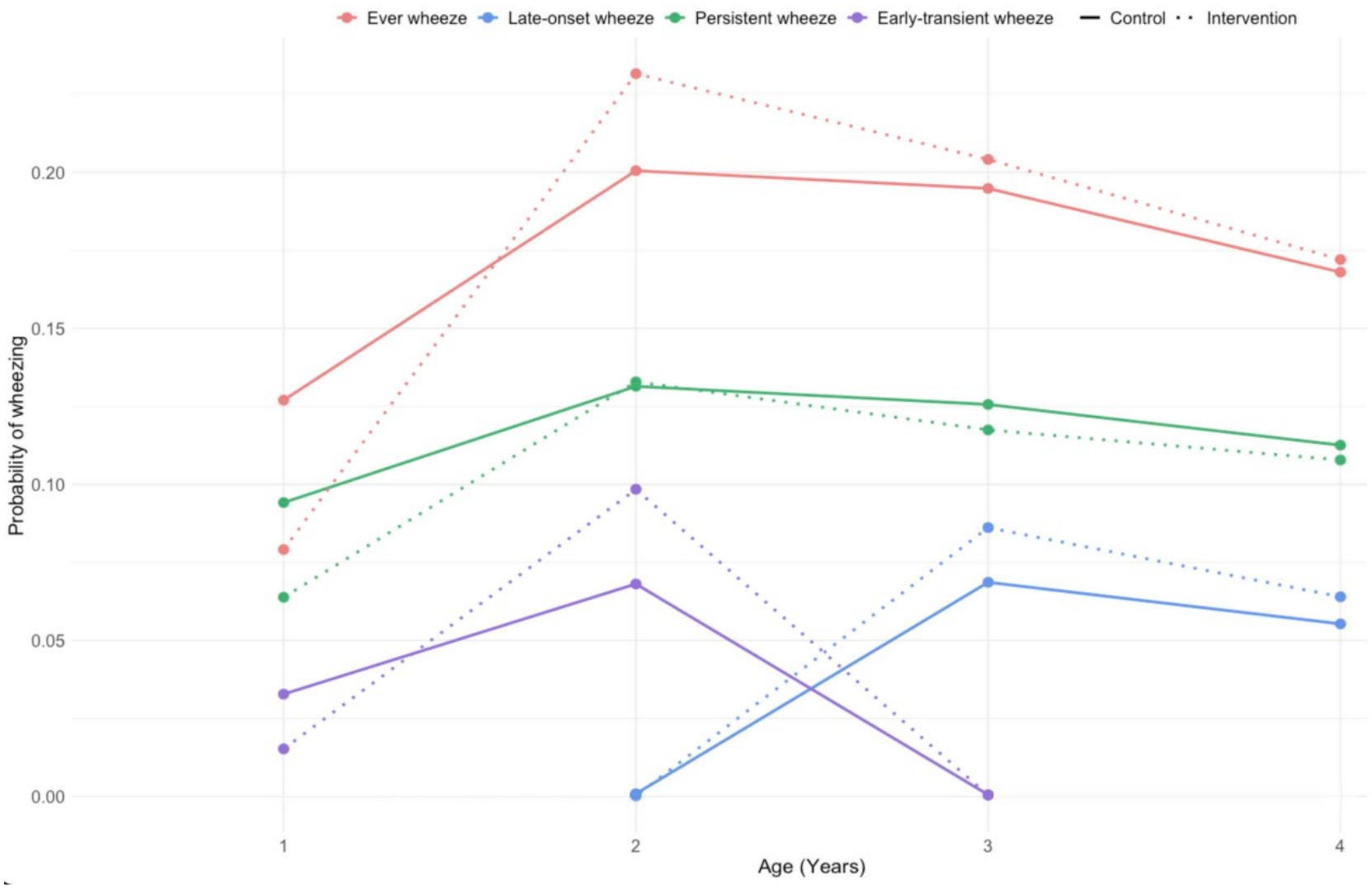

Figure 2. **Probability of wheezing in each year for ever wheezers, late-onset wheezers, persistent wheezers, and early-transient wheezers.**

Table 3. Effect of intervention on wheeze phenotypes.

Phenotypes	N	Cases by treatment group		Effect of Intervention on wheeze
		Control (n = 236)	Intervention (n = 245)	(OR 95% CI)
Ever wheeze	369	115 (68%)	144 (72%)	1.22 (0.80, 1.88)
Persistent wheeze	381	43 (24%)	46 (22%)	0.92 (0.58, 1.48)
Late onset wheeze	360	32 (20%)	43 (22%)	1.05 (0.64, 1.72)
Early transient wheeze	353	27 (17%)	43 (22%)	1.40 (0.83, 2.34)

Table 4. Effect of intervention on wheeze frequency.

Years	N	Total number of episodes by treatment group		Effect of Intervention on wheeze
		Control (n = 236)	Intervention (n = 245)	(IRR 95% CI)
Year 1 & 2	375	121	133	1.11 (0.72, 1.73)
Year 3 & 4	337	145	186	1.33 (1.00, 1.76)
All years	379	288	370	1.11 (0.90, 1.35)

3.3.4. Indoor $PM_{2.5}$ effects

In my secondary analyses, IQR increases in indoor $PM_{2.5}$ in first trimester (IQR = 20.8 μg/m^3) was associated with an increased odds of late onset wheeze (OR: 1.84, 95% CI: 1.13, 3.01) (Table 5). An IQR increase in $PM_{2.5}$ over full pregnancy was also associated with increased odds of children experiencing late onset wheeze, but confidence intervals spanned no effect (OR: 1.35, 95% CI: 0.90, 2.02). For ever wheeze, persistent wheeze, and early transient wheeze, effect estimates were imprecise and had confidence intervals that also spanned no effect.

In my secondary analyses of the frequency of wheeze episodes, IQR increases in $PM_{2.5}$ exposure during second trimester (IQR= 20.9 μg/m^3) and full pregnancy (IQR=

9.3 μg/m^3) were associated with an increase in the number of caregiver-reported wheeze episodes in the first two years of life (Table 6) (2^{nd} trimester: IRR: 1.46, 95% CI: 1.13, 1.89, Full pregnancy: IRR: 1.31, 95% CI: 1.04, 1.31). All other effect estimates for the Poisson portion of the zero-inflated Poisson models had confidence intervals that spanned no effect. Results among compete cases were similar (Table A.3 in appendix).

The effects of indoor $PM_{2.5}$ concentrations and wheeze symptoms appear to differ between wheeze phenotypes and wheeze frequency. In the phenotype analysis, I observed that IQR increases during the first trimester increased the odds of the onset of wheeze symptoms in the third or fourth years of life. In contrast, my wheeze frequency results suggests that increases in $PM_{2.5}$ concentrations during the second trimester and full pregnancy may increase the number of wheeze episodes reported in first and second year of life.

For trimester-specific $PM_{2.5}$ concentrations and wheeze outcomes, I conducted a sensitivity analysis that did not adjust for trimester concentrations in other trimesters. . Generally, not adjusting for trimester-specific concentrations had only small effects on the effect estimates trimester-specific exposures and wheeze symptoms (Table 4 and Table A.5 in appendix). For instance, the association between 1^{st} trimester concentrations and late onset wheezing in a model that did not adjust for concentrations in other trimesters (OR: 1.68, 95% CI: 1.06, 2.66) was similar to the estimate from a model that adjusted for other trimesters (OR: 1.84, 95% CI: 1.13, 3.01). Similarly, the estimated effect of 2^{nd} trimester $PM_{2.5}$ concentration on wheeze frequency in the first two years of life was similar when not adjusting for other trimesters (IRR: 1.42, 95% CI: 1.07, 1.89) and when other trimesters were adjusted for (IRR: 1.46, 95% CI: 1.13, 1.89).

Table 5. Associations between indoor $PM_{2.5}$ concentrations and wheeze phenotypes.

	Estimated effect of an IQR contrast in indoor $PM_{2.5}$ concentration and the odds of wheeze phenotypes (Adjusted OR, 95% CI)			
	Ever wheeze (n= 350)	Transient early wheeze (n=89)	Late onset wheeze (n=101)	Persistent wheeze (n=160)
1st Trimester (IQR= 20.8 µg/m^3)	1.15 (0.72, 1.84)	0.68 (0.38, 1.22)	1.84 (1.13, 3.01)	0.88 (0.53, 1.46)
2nd Trimester (IQR= 20.9 µg/m^3)	0.94 (0.50, 1.77)	1.17 (0.57, 2.39)	0.73 (0.35, 1.54)	1.08 (0.56, 2.09)
3rd Trimester (IQR= 13.3 µg/m^3)	1.04 (0.67, 1.64)	0.98 (0.58, 1.65)	1.22 (0.74, 2.01)	0.92 (0.59, 1.43)
Full Pregnancy (IQR= 9.3 µg/m^3)	1.06 (0.73, 1.52)	0.86 (0.55, 1.33)	1.35 (0.90, 2.02)	0.93 (0.63, 1.37)

Table 6. Effect of indoor PM2.5 concentrations on frequency of wheeze episodes.

	Effect of prenatal $PM_{2.5}$ exposure on wheeze (Adjusted OR, 95% CI)		
Wheeze Frequency	Years 1 and 2	Years 3 and 4	All years
Poisson Portion- IRR			
1st Trimester (IQR= 20.8 μg/m^3)	1.09 (0.80, 1.48)	1.11 (0.91, 1.37)	1.06 (0.90, 1.26)
2nd Trimester (IQR= 20.9 μg/m^3)	1.46 (1.13, 1.89)	0.87 (0.71, 1.07)	0.98 (0.85, 1.14)
3rd Trimester (IQR= 13.3 μg/m^3)	0.91 (0.73, 1.14)	0.99 (0.83, 1.18)	0.98 (0.86, 1.12)
Full Pregnancy (IQR= 9.3 μg/m^3)	1.31 (1.04, 1.66)	0.96 (0.80, 1.15)	1.01 (0.87, 1.16)
Logit Portion- 1/OR			
1st Trimester (IQR= 20.8 μg/m^3)	0.34 (0.10, 1.18)	1.35 (0.85, 2.17)	1.11 (0.66, 1.86)
2nd Trimester (IQR= 20.9 μg/m^3)	0.36 (0.07, 1.94)	0.78 (0.49, 1.24)	0.93 (0.56, 1.53)
3rd Trimester (IQR= 13.3 μg/m^3)	1.35 (0.27, 6.64)	1.38 (0.89, 2.16)	1.22 (0.76, 1.95)
Full Pregnancy (IQR= 9.3 μg/m^3)	0.35 (0.09, 1.36)	1.02 (0.69, 1.51)	1.02 (0.66, 1.58)

3.4. Discussion

To my knowledge, this is the first RCT to investigate the relationship between HEPA cleaner interventions, indoor $PM_{2.5}$ concentrations, and wheeze phenotypes and frequency in children 4 years of age. In this cohort of women living in a highly polluted city, I found no evidence that HEPA cleaner use during pregnancy reduced the risk of four wheeze phenotypes or the frequency of wheezing episodes in children from birth to four years of age. Unexpectedly, beyond the first year of life, families randomly assigned to the intervention group reported that children had a greater number of wheezing

episodes than children in the control group, however the difference was not statistically significant. In a secondary analysis, I observed that indoor $PM_{2.5}$ concentrations during the first trimester increased the odds of children experiencing the onset of wheezing symptoms in the third or fourth year of life. Moreover, 2nd trimester and full pregnancy indoor $PM_{2.5}$ concentrations were associated with increases in the frequency of caregiver-reported wheeze episodes in the first two years of life. However, most estimates were imprecise, with some point estimates suggesting a potential protective effect of increased $PM_{2.5}$ exposure. Collectively, the results from this study indicate that indoor $PM_{2.5}$, particularly in early pregnancy, may impact wheeze symptoms in early childhood. However, caution is needed when interpreting these results due to multiple comparisons.

Although HEPA cleaners effectively reduce indoor PM concentrations,[123–126] the evidence regarding their health benefits remains inconclusive and is likely to vary across regions, populations, and health outcomes of interest.[127] Research indicates that indoor air cleaners may offer short-term cardiovascular and respiratory benefits, but that the overall certainty for the evidence was low.[106–108]. Furthermore, studies have demonstrated that the use of HEPA cleaners in households can enhance airway mechanics and alleviate asthma and allergic symptoms in children.[109–111] Although there are variations across settings and health outcomes, the pervasiveness of air pollution and its threat to public health in LMIC for the foreseeable future justifies the widespread use of indoor air cleaners, even for modest reductions in subclinical health indicators.[105] However, it is important that such individual-level interventions be adopted alongside broader efforts to mitigate emissions.

There are several potential reasons why the HEPA cleaner intervention was shown to have no effect on wheezing in this cohort. The intervention was deployed in intervention group participants' homes at a median of 11 wks gestation. It is possible that exposures earlier in pregnancy are particularly important in influencing respiratory outcomes, and that this study missed an important exposure window by deploying the intervention late in the 1st trimester. Moreover, although the intervention was randomized among participants, there may be residual confounding between the HEPA cleaner intervention and wheeze outcomes that was not accounted for in this analysis. It is also possible that the 29% reduction in indoor $PM_{2.5}$ was insufficient to influence respiratory development.

Respiratory symptoms in early life are often transient, and accurately characterizing wheeze phenotypes is important for determining the risk of developing respiratory morbidities later in life.[56] Birth cohort studies have provided valuable insights into these wheeze phenotypes.[33,61,128] Notably, the TCRS study found that persistent wheezing and late-onset wheezing have shown strong predictive associations with wheezing at 16 years old.[61] These findings may be important in the context of my findings suggesting that first trimester $PM_{2.5}$ exposures were associated with late-onset wheezing. It may be that exposures in early pregnancy disproportionately impact the risk of children going on to experience wheeze symptoms that are predictive of respiratory morbidities later in life. This highlights the importance of considering late-onset wheezing as an outcome and its potential relevance for assessing asthma risk in clinical practice.

The association observed between prenatal $PM_{2.5}$ exposure and wheezing in children is consistent with several observational studies. Jedrychowski et al.[81] reported that prenatal $PM_{2.5}$ exposure, measured using personal exposure monitors and dichotomized as above and below median concentrations, was associated with more frequent wheezing in children from birth to two years old. In Singapore, the GUSTO birth cohort study investigators found that children of overweight or obese mothers who were exposed to upper quartiles (Q2-Q4) $PM_{2.5}$ in the first trimester experienced more wheeze than children whose mothers had exposure in the bottom quartile.[74] A study in Mexico found that greater $PM_{2.5}$ exposure during the first trimester was associated with an increased risk of current wheeze at 48 months among children with mothers who reported high stress during pregnancy (RR: 1.35, 95% CI: 1.00, 1.83 per IQR increase of 3.8 µg/m3), but not among low stress mothers (RR: 0.84, 95% CI: 0.61, 1.16 per IQR increase).[78] In a prospective birth cohort study in China, Chen et al.[88] reported that increases in $PM_{2.5}$ exposure during pregnancy were associated with an increased risk of wheezing and asthma among 3,725 children aged three to four years old. In this group, exposures early in pregnancy, specifically during the pseudo glandular stage (6-16 weeks) and the canalicular stage (16-24 weeks) of fetal lung development, were found to impact wheezing and asthma outcomes. In some observational studies, wheezing outcomes were evaluated based on specific wheeze phenotypes, as considered in the present study, with a focus on the onset and duration of wheeze symptoms.[58,83,84] However, it should be noted that the definitions of these wheeze phenotypes tend to vary considerably across the studies.

The biological mechanisms through which prenatal exposure to air pollution affects respiratory development are not yet fully understood. However, it is believed that oxidative stress (OS) and epigenetic changes play important roles.[62,90] Particulate matter can trigger lung inflammation and induce OS.[94] Maternal OS and the release of proinflammatory cytokines can disrupt placental function and increase fetal stress levels.[91] These factors can contribute to airway remodeling and heightened airway responsiveness in the developing fetus.[93] Exposure to air pollution during pregnancy may also impair the development of the placenta, affecting the delivery of essential nutrients and oxygen to the fetus during critical developmental periods.[94]

This study had some limitations. First, because participants were not blinded to intervention status and because we relied on parent-reported wheeze, instead of objective lung function measurements or physician verified wheeze, these results might be influenced by recall bias. The lack of blinding may also have influenced participants' perception of their child's respiratory symptoms. Participants in the intervention group may have been more attentive to their child's development and wheezing episodes. Moreover, the lack of blinding may have contributed to the higher number of withdrawals from the control group, thereby potentially introducing selection bias, which I tried to mitigate through imputation of missing data and analyzing the cohort by intention-to-treat. The sample size was calculated based on term birth weight, which was the original outcome for this trial, and the study size may have been underpowered for assessing the relationship between the intervention and wheeze outcomes. Personal history of atopy and allergic sensitization in early life increases the risk of children developing wheeze[31–33] and asthma.[34–36] I did not have results from skin prick tests or allergen-specific IgE data to distinguish between atopic and non-atopic wheezers. In my secondary analysis, I did not adjust for air pollution exposures outside of the home. Participant's exposure outside of the home may be an important source of residual confounding in my secondary analysis.

In this study, I observed more frequent wheezing in the intervention group. The lack of blinding may have influenced this result. Air pollution is a visible hazard during much of the year in Ulaanbaatar, and it is possible that some participants enrolled hoping to receive a HEPA cleaner. Consequently, individuals who were more susceptible to and knowledgeable about the detrimental effects of pollution may have withdrawn from the study after being assigned to the control group. This could have

resulted in a higher proportion of susceptible participants remaining in the intervention group.

It is also possible that our study was affected by the live birth bias, a type of selection bias found in studies of exposures during pregnancy and health outcomes in childhood.[122] In previous work in this cohort, Barn and colleagues observed that the intervention group had fewer spontaneous abortions and more preterm births.[112] McCandless and colleagues hypothesized that the intervention may have allowed fetuses that might have otherwise died to survive and be born preterm.[122] If air pollution increases the likelihood of fetal loss predominantly in fetuses susceptible to respiratory morbidity, the control group would have fewer susceptible children, leading to an underestimation of the intervention's benefits.

This study also has several strengths. The randomization of the intervention during pregnancy minimized the influence of measured and unmeasured confounders. Previous observational studies have had difficulties distinguishing between prenatal and postnatal exposures to air pollution. In this study, the intervention was only in place only during pregnancy, which reduced the correlation between prenatal and postnatal $PM_{2.5}$ concentrations. Many previous studies have used outdoor $PM_{2.5}$ measurements as a proxy for exposure. In this study we used modelled concentrations indoors at home, where most people spend the majority of time.[129,130]

3.5. Conclusions

In this randomized controlled trial of pregnant women living in a highly polluted city, I found no benefit of reducing indoor air pollution during pregnancy on wheezing symptoms in children from birth to four years of age. To my knowledge, this is the first randomized controlled trial to examine the impact of a household-level intervention on the frequency of wheezing and wheeze phenotypes in childhood. In a secondary analysis, I found that IQR contrasts in indoor $PM_{2.5}$ in the first trimester of pregnancy were associated with an increased risk of children experiencing late onset wheezing. I also found that increases in $PM_{2.5}$ exposure during full pregnancy and the second trimester increased the odds of children experiencing a higher number of wheezing episodes in the first and second year of life. The results suggest that $PM_{2.5}$ exposure during early to middle pregnancy may influence the onset and frequency of wheezing

symptoms in children. Extended follow-up is needed to investigate the impact of the air cleaner intervention on late onset wheezing in children.

Chapter 4. Discussion, Limitations and Future Research

4.1. Discussion

In this thesis, I investigated the benefits of a household level intervention during pregnancy on wheeze symptoms in early childhood among the UGAAR cohort in Ulaanbaatar, Mongolia. In a secondary analysis, I examined the relationship between prenatal indoor $PM_{2.5}$ concentrations and wheeze in this cohort. This work provides important insights into the relationship between a readily available and relatively inexpensive method for reducing indoor air pollution. In addition, this work adds valuable information to the existing literature aimed at investigating the impact of prenatal air pollution exposure and respiratory symptoms. The randomization of the HEPA cleaner among UGAAR participants allows for causal inference between the intervention and wheeze symptoms. The findings of the secondary analysis contribute to the growing literature to suggest that prenatal exposures to air pollution may impact respiratory development.

While pollution concentrations in developed countries have improved considerably over the past several decades, concentrations in low-middle income are expected to continue to rise.[127] In highly polluted settings, household-level interventions may provide an important method for reducing indoor pollution exposure until emissions can be reduced. But the feasibility and efficacy of these interventions may vary depending on the duration of their use, the baseline pollution concentrations, and the location where the intervention is being implemented.

While there is clear evidence that HEPA cleaners are effective at reducing indoor PM concentrations,[123–126] the evidence of health benefits remains inconclusive and likely differs by regions, populations, and the health outcome of interest.[127] For instance, there is evidence to suggest that there may be short-term cardiovascular and respiratory benefits of using indoor air cleaners, but that the overall certainty for the evidence was low.[106–108] In addition, some work has shown that HEPA cleaner use in the home may improve airway mechanics and asthma and allergic symptoms in children.[109–111] Despite some inconsistencies between settings and health outcomes, given the ubiquity of air pollution and the likelihood that air pollution will remain a public health threat in LMICs

for decades, even a modest reduction in subclinical health indicators potentially warrants widespread use of indoor air cleaners to improve health.[105] However, such individual-level interventions should be adopted alongside efforts to reduce emissions.

While indoor HEPA cleaners are an effective strategy to reduce indoor air pollution concentration in the short-term, they may have important limitations in highly polluted regions.[127] In settings with extraordinarily high levels of outdoor PM pollution year-round, HEPA cleaner use may be impractical for reducing indoor concentrations to levels where health benefits can be observed. This is particularly true for health outcomes for which a supralinear concentration-response relationship has been observed.[131] A group tested the efficacy of HEPA cleaners in Delhi, India and found that concentrations in the city were so high that a 30- 50% reduction in indoor pollution while using the filters still resulted in higher concentration than outdoors in the city.[132] As a result, HEPA cleaners may be most useful in regions with lower pollution concentrations or where increases in concentrations are a result of shorter-term events, such as wildfires. A group in California that evaluated multiple interventions during wildfire events found that an increased duration of HEPA cleaner use was associated with a reduced odds reporting adverse health effects of the lower respiratory tract.[133] The authors suggested this was related to the ease of air cleaner use for the duration of the wildfire events.

The economic cost of air pollution is considerable.[134,135] As a result, it is important to weight the cost of air filtration interventions to the economic benefit associated with a reduction in disease. Understanding the health benefits and cost of such interventions can help develop sustainable and adaptive strategies for mitigating the health burden of air pollution.[136] The cost effectiveness of air filters as an intervention differs by regions, populations, and the efficiency of the air filters used. A group in China reported that air purifiers are a cost-effective method for reducing the death rate attributable to $PM_{2.5}$, and that the benefit is greatest in areas with the highest pollution levels.[136] In Southern California, a group reported that the interventions benefit exceeds the cost in prevented deaths during wildfire events.[137] However, the interventions cost far exceeded its benefits in the reducing hospital admissions. The authors suggest that this may have been a result of the small number of hospital admissions associated with wildfire events.[137] Moreover, the benefit of the intervention may be most effective when targeted to vulnerable populations, such as individuals over 65 years old.[137]

The efficiency of the filtration systems may also play a crucial role in in determining how cost-effective the intervention is. A group in Detroit found that efficient filters in schools would reduce the $PM_{2.5}$ asthma burden by 13% annually and that this benefit would increase with more efficient filters.[138] As a result, the cost effectiveness of air purifier interventions varies between highly and lowly polluted settings, vulnerable populations, and the efficiency of the air filters used.

RCTs play a crucial role in establishing causal inferences that are not attainable through observational studies. By randomizing the intervention, potential confounding by measured and unmeasured variables is minimized. However, despite their importance, RCT designs are rarely used in environmental health research.[139] In many cases, interventions in this field focus on reducing exposures in one group while withholding the intervention from the control group. This raises ethical considerations about withholding a potentially beneficial intervention from some participants.

In Ulaanbaatar, air pollution is a public health concern that is prominent in the city and significantly impacts the residents' quality of life. In this context, the UGAAR design has provided valuable and practical insights into how residents can use an intervention to potentially mitigate the health impacts of an environmental threat that affects all residents in the city. Given that reducing air pollution emissions in Ulaanbaatar will likely require decades of effort, it is worthwhile to investigate a household-level intervention that is both readily available and affordable for many families.

4.2. Limitations

There were limitations in this study. The wheeze outcomes in the study were self-reported by participants and may be susceptible to recall bias, particularly during the first two years of the study. At enrollment in the post-natal portion of UGAAR, children were an average of 15 months old (range: 7 – 28 months). It is possible that the caregivers of children that were older at baseline were less likely to report wheeze symptoms in their children, as these individuals would have to recall symptoms over a longer duration from birth to the time enrollment. In some cases, participants were asked to recall wheeze episodes that may have occurred over 18 months prior. This period between the birth of the child and the baseline questionnaire may have resulted in participants inaccurately recalling wheeze symptoms, which could influence the findings in this study.

In the primary analyses, the effect estimates presented were imprecise. This may be a result of the sample size of the UGAAR cohort that was originally intended the examine the role of the intervention on term birth weight. The imprecision in the ITT analysis makes it difficult to draw conclusions about the role the HEPA cleaner intervention during pregnancy plays in respiratory symptoms in early life. Unexpectedly, the intervention group reported more wheeze symptoms than the control group. Despite this finding, I think it is unlikely that a reduction in air pollution during pregnancy increased the risk of children experiencing wheeze. Rather, I suspect that these results indicate that additional confounding or other types of bias may exist that were unaccounted for in this analysis.

It is also possible that the self-reported nature of the outcome failed to accurately capture the underlying wheeze symptoms present in this cohort. This may be exacerbated by the fact that the outcome was not associated with some common risk factors known to influence respiratory symptoms. For instance, I failed to find evidence to suggest that preterm birth influenced wheeze outcomes in this cohort, despite the literature suggesting that preterm birth is one of the strongest predictors of respiratory symptoms in early life. In addition, previous work in the UGAAR group has shown that preterm birth children in UGAAR repeatedly have worse health outcomes than term birth children.[122] UGAAR investigators have shown that preterm birth in this cohort likely influences many of the analyses examining the relationship between the intervention and health outcomes.[122] The fact preterm birth was not associated with wheeze in these analyses may be suggestive of the unreliable nature of caregiver-reported wheeze symptoms.

4.3. Future research

The findings of this study present important considerations for future research examining the role of an intervention in influencing wheeze symptoms. Future research should measure wheeze episodes using methods that do not rely solely on the caregivers' reporting of symptoms. This might include expanding the definition of wheeze to include biological measurements of lung function, physician-verified wheeze episodes, or asthma diagnoses. Expanding the definition of the health outcome may increase the power of the analyses and better capture the reality of wheezing symptoms in children.

Future research using an RCT should also consider using a latent class analysis approach to classify wheeze phenotypes. These methods of identifying wheeze phenotypes in a population can help highlight important patterns of wheezing. For instance, the ALSPAC study used a latent class analysis approach for wheeze classification and identified additional phenotypes to those outlined in TCRS.[33] The wheeze phenotypes outlined in previous research vary greatly, and the use of these methods may help to identify patterns of wheeze that are specific to each cohort.

In this study, I classified wheezing phenotypes in the cohort by the presence/absence of symptoms in the first or second and the third or fourth years of life. This structure of classifying symptoms is not uncommon in the epidemiological literature but may lack nuance. It is possible that the methods used for classifying wheeze in this study failed to capture important information in the patterns of respiratory symptoms among the UGAAR children.

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Appendix. Supplemental Figures and Tables

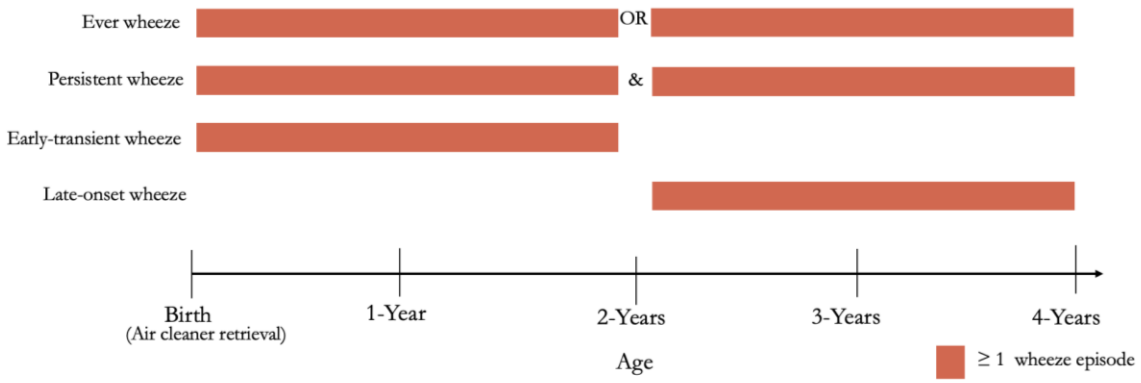

Figure A.1. Classification of wheeze phenotypes.

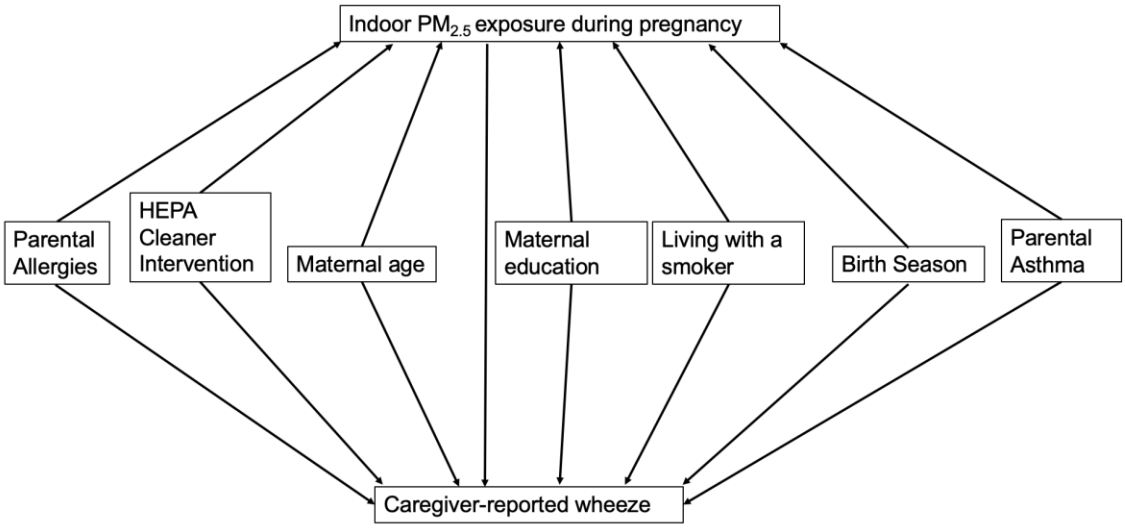

Figure A.2. Simplified DAG for association between indoor $PM_{2.5}$ concentrations and wheeze.

Table A.1. Presence of wheeze phenotypes by age of enrollment in post-natal follow-up.

	Age of child at baseline	
Wheeze phenotypes	**< 15 months** *n (%)*	**≥ 15 months** *n (%)*
Ever wheeze		
Yes	116 (62)	124 (60)
No	60 (32)	50 (24)
Missing, n (%)	10 (5)	32 (16)
Persistent wheeze		
Yes	39 (21)	41 (20)
No	138 (74)	147 (71)
Missing, n (%)	9 (5)	18 (9)
Early transient wheeze		
Yes	48 (26)	18 (9)
No	122 (66)	147 (71)
Missing, n (%)	16 (9)	41 (20)
Late onset wheeze		
Yes	22 (12)	52 (25)
No	153 (82)	118 (57)
Missing, n (%)	11 (6)	36 (17)

Table A.2. Inverse probability weighting for ITT analysis outcomes.

	OR (95% CI)
Wheeze year	
Poisson portion	
Year 1 & 2	0.74 (0.43, 1.30)
Year 3 & 4	1.34 (0.91, 1.96)
All years	1.35 (0.91, 2.01)
Logit portion	
Year 1 & 2	0.43 (0.00, 39.00)
Year 3 & 4	1.37 (0.72, 2.62)
All years	0.04 (0.01, 0.11)
Wheeze phenotype	
Persistent wheeze	0.81 (0.47, 1.40)
Ever wheeze	1.19 (0.73, 1.94)
Late onset wheeze	1.11 (0.62, 2.00)
Transient early wheeze	1.46 (0.80, 2.65)

Table A.3. Complete case analyses for wheeze frequency and phenotypes.

Wheeze years- frequency	OR (95% CI)
Poisson portion- count	
Year 1 and 2	0.78 (0.52, 1.16)
Year 3 and 4	1.17 (0.86, 1.57)
Total episodes frequency	0.89 (0.73, 1.09)
Logit portion	
Year 1 and 2	0.56 (0.16, 2.04)
Year 3 and 4	1.31 (0.71, 2.41)
Total episodes frequency	0.71 (0.37, 1.34)
Wheeze phenotypes	
Ever wheeze	1.19 (0.75, 1.90)
Persistent wheeze	0.71 (0.42, 1.19)
Late onset wheeze	1.24 (0.71, 2.17)
Transient early wheeze	1.51 (0.87, 2.62)

Table A.4. Associations between indoor $PM_{2.5}$ concentrations and wheeze phenotypes without adjusting for other trimester concentrations.

	Estimated effect of an IQR contrast in indoor $PM_{2.5}$ concentration and the odds of wheeze phenotypes (Adjusted OR, 95% CI)			
	Ever wheeze (n= 350)	Transient early wheeze (n=89)	Late onset wheeze (n=101)	Persistent wheeze (n=160)
1st Trimester (IQR= 20.8 µg/m^3)	1.12 (0.73, 1.72)	0.70 (0.40, 1.23)	1.68 (1.06, 2.66)	0.90 (0.56, 1.46)
2nd Trimester (IQR= 20.9 µg/m^3)	1.02 (0.58, 1.78)	1.04 (0.54, 1.99)	0.99 (0.52, 1.89)	1.00 (0.55, 1.80)
3rd Trimester (IQR= 13.3 µg/m^3)	1.01 (0.67, 1.54)	1.07 (0.67, 1.73)	1.02 (0.65, 1.60)	0.95 (0.63, 1.43)
Full Pregnancy (IQR= 9.3 µg/m^3)	1.06 (0.73, 1.52)	0.86 (0.55, 1.33)	1.35 (0.90, 2.02)	0.93 (0.63, 1.37)

Table A.5. Effect of indoor PM2.5 exposure on frequency of wheeze episodes without adjusting for other trimester concentrations.

	Effect of prenatal $PM_{2.5}$ exposure on wheeze (Adjusted OR, 95% CI)		
Wheeze Frequency	Years 1 and 2	Years 3 and 4	All years
Poisson Portion- IRR			
1st Trimester (IQR= 20.8 µg/m^3)	1.11 (0.84, 1.46)	1.10 (0.94, 1.28)	1.05 (0.93, 1.20)
2nd Trimester (IQR= 20.9 µg/m^3)	1.42 (1.07, 1.89)	0.88 (0.73, 1.07)	0.99 (0.85, 1.15)
3rd Trimester (IQR= 13.3 µg/m^3)	0.92 (0.75, 1.13)	0.93 (0.81, 1.06)	0.95 (0.86, 1.05)
Full Pregnancy (IQR= 9.3 µg/m^3)	1.31 (1.04, 1.66)	0.96 (0.80, 1.15)	1.01 (0.87, 1.16)