A randomized air filter intervention study of air pollution and fetal growth in a highly polluted community: the Ulaanbaatar Gestation and Air Pollution Research (UGAAR) study

by

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Thesis Submitted in Partial Fulfillment of the
Requirements for the Degree of
Doctor of Philosophy

in the
Doctor of Philosophy Program
Faculty of Health Sciences

SIMON FRASER UNIVERSITY

Fall 2018

Approval

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Degree:	**Doctor of Philosophy**
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Abstract

Background: Gestational exposure to fine particulate matter ($PM_{2.5}$) and cadmium may impair fetal growth. Portable high efficiency particulate air (HEPA) filter air cleaners can reduce indoor $PM_{2.5}$, but their effect on fetal growth has not been evaluated.

Objectives: We assessed (1) HEPA cleaner effectiveness in reducing residential indoor $PM_{2.5}$ and maternal blood cadmium, (2) the effect of HEPA cleaners on fetal growth, and (3) the relationship between maternal cadmium exposure and fetal growth, among non-smoking pregnant women in Ulaanbaatar, Mongolia.

Methods: We randomized 540 participants at ≤ 18 weeks gestation to an intervention (1-2 HEPA cleaners in homes from early pregnancy until childbirth) or control (no HEPA cleaners) group. We collected exposure, health, and demographic data through home and clinic visits and from clinic records. We measured one-week indoor $PM_{2.5}$ concentrations in early (~11 weeks gestation) and late (~31 weeks gestation) pregnancy, collected blood samples in late pregnancy for analysis of cadmium, and obtained birth data at delivery. We evaluated the effect of the intervention on our primary outcome, birth weight, and other fetal growth indicators using unadjusted linear and logistic regression and time-to-event analysis, in intention-to-treat analyses. We also used multiple linear and logistic regression to assess the relationships between log_2-transformed blood cadmium and fetal growth.

Results: HEPA cleaners reduced indoor $PM_{2.5}$ and blood cadmium concentrations by 29% (95% CI: 21, 37%) and 14% (95% CI: 4, 23%), respectively. Among 463 live births, the median (25th, 75th percentile) birth weights for control and intervention participants were 3450 g (3150, 3800 g) and 3550 g (3200, 3800 g), respectively, but the intervention was not associated with an increase in birth weight (18 g; 95% CI: -84, 120 g). In a pre-specified subgroup analysis of 429 term births the intervention was associated with an 85 g (95% CI: 3, 167 g) increase in mean birth weight. A doubling of blood cadmium was associated with an 86 g (95% CI: 26, 145 g) reduction in birth weight.

Conclusions: Our findings provide further evidence that $PM_{2.5}$ and cadmium exposures during pregnancy impair fetal growth and that exposure reduction during pregnancy can reduce these effects. Portable HEPA cleaners are an effective household-level intervention but reductions in air pollution emissions are needed to realize the largest public health benefits.

Keywords: $PM_{2.5}$, cadmium, RCT, portable HEPA filters, fetal growth, Mongolia

Dedication

To my favourite babies - Arjun, Naya, Anmol, Duncan, and Tuguldur.

Acknowledgements

This dissertation is a culmination of work by a large hard-working team. First and foremost, thank you to Dr. Ryan Allen for dreaming up this ambitious study and for being such a wonderful supervisor. Throughout the last five years you have been engaged, supportive, helpful, and so enthusiastic. You also introduced me to the best Indian food in Ulaanbaatar, for which I will remain eternally grateful. Thank you to Dr. Enkhee Gombojav for overseeing the day to day work involved with UGAAR, including the large amount of data collection. To my committee members, Dr. Bruce Lanphear and Dr. Patricia Janssen, thank you for giving so willingly of your time, expertise, and input. Thank you also to all the co-authors of our manuscripts, and in particular to Dr. Jennifer Hutcheon - your feedback made this work better.

My trips to Ulaanbaatar and getting to know the UGAAR study team were the highlights of my PhD experience. Thank you to the entire team for their hard work and dedication toward this study, and in particular to Buyan, Bolor, and Dr. Gerel. Also, thank you to the UGAAR participants who gave so freely of their time and without whom this study would not be possible. This study was funded by the Canadian Institutes of Health Research (CIHR) and I was fortunate to receive a CIHR doctoral award.

I am so grateful for my little community. Thank you Emily for always listening and giving the best advice, Soutomi for your positivity and much needed goofiness, Aman, my fellow grad student for understanding this journey, Meghan for your random “you are awesome” texts, Bolor for making Ulaanbaatar feel like home, and Anisha, my thesis angel, for getting me through the final stretch. My family has been my biggest support. Ma, thank you for always believing that I am smarter than I really am. Pan, thank you for your unconditional love, support, and silliness. You inspire me in so many ways and I am so lucky that you are my sister. Randy, thank you for your constant thoughtfulness. Maja and Phil, thank you for your support and encouragement. To my husband Aio, thank you for so many things.

Thank you for talking to anyone who would listen about this work, for celebrating each tiny success, for the many pep talks, and for always believing in me. The last five years have been full of so many special moments and I could not imagine going through this journey with anyone else. And finally, to my son Arjun, I love you so much – thank you for being the best motivation for completing this thesis.

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List of Acronyms

GC-MS/MS	Gas chromatography-tandem mass spectrometry
GM	Geometric mean
HEPA	High efficiency particulate air
ICP-MS	Inductively coupled plasma-mass spectrometry
IUGR	Intrauterine growth restriction
LBW	Low birth weight
LMIC	Low- and middle-income countries
LOQ	Limit of quantification
PM	Particulate matter
$PM_{2.5}$	Fine particulate matter
PTB	Preterm birth
RCT	Randomized controlled trial
RH	Relative humidity
SGA	Small for gestational age
SHS	Second hand smoke
TEOM	Tapered element oscillating microbalance
UGAAR	Ulaanbaatar Gestation and Air Pollution Research

Preface

This thesis is organized into five chapters. Chapter one is an introductory chapter that provides a background, rationale, and the research questions addressed in this work, and chapter five is a discussion chapter that provides a synthesis of the research conducted for this thesis. Chapters two, three, and four are research chapters that were written as manuscripts for publication. At the time of this thesis submission, chapter two had been published in *Science of the Total Environment* and chapter three had been accepted for publication in *Environment International.* Both papers are a result of feedback and input from many co-authors, all of whom have approved the final version of the published manuscripts.

Prabjit Barn, Enkhjargal Gombojav, Chimedsuren Ochir, Bayarkhuu Laagan, Bolor Beejin, Gerel Naidan, Buyantushig Boldbaatar, Jargalsaikhan Galsuren, Tsogtbaatar Byambaa, Craig Janes, Patricia A. Janssen, Bruce P. Lanphear, Tim K. Takaro, Scott A. Venners, Glenys M. Webster, Weiran Yuchi, Christopher D. Palmer, Patrick J. Parsons, Young Man Roh, Ryan W. Allen. The effect of portable HEPA filter air cleaners on indoor $PM_{2.5}$ concentrations and second hand tobacco smoke exposure among pregnant women in Ulaanbaatar, Mongolia: The UGAAR randomized controlled trial. *Science of The Total Environment.* 2018; 615:1379-89.

Prabjit Barn, Enkhjargal Gombojav, Chimedsuren Ochir, Buyantushig Boldbaatar, Bolor Beejin, Gerel Naidan, Jargalsaikhan Galsuren, Bayarkhuu Legtseg, Tsogtbaatar Byambaa, Jennifer A. Hutcheon, Craig Janes, Patricia A. Janssen, Bruce P. Lanphear, Lawrence C. McCandless, Tim K. Takaro, Scott A. Venners, Glenys M. Webster, Ryan W. Allen. The effect of portable HEPA filter air cleaner use during pregnancy on fetal growth: the UGAAR randomized controlled trial. *Environment International.* 2018. (Accepted)

Chapter four has been prepared for submission. As with the previous manuscripts, co-authors provided feedback and input on the version included in this thesis.

Prabjit Barn, Enkhjargal Gombojav, Chimedsuren Ochir, Buyantushig Boldbaatar, Bolor Beejin, Gerel Naidan, Jargalsaikhan Galsuren, Bayarkhuu Legtseg, Tsogtbaatar Byambaa, Jennifer A. Hutcheon, Craig Janes, Patricia A. Janssen, Bruce P. Lanphear, Lawrence C. McCandless, Tim K. Takaro, Scott A. Venners, Glenys M. Webster, Christopher D. Palmer, Patrick J. Parsons, and Ryan W. Allen. Gestational cadmium exposure and fetal growth in Ulaanbaatar, Mongolia.

Chapter 1.

Introduction

Fine particulate air pollution ($PM_{2.5}$) is a leading contributor to morbidity and mortality world-wide due to its well-established impacts on cardiovascular disease, chronic lung disease, respiratory infections, and lung cancer.[1] In 2016, 95% of the world's population lived in areas where outdoor $PM_{2.5}$ concentrations exceeded the World Health Organization's annual average guideline of 10 $\mu g/m^3$.[2] Although concentrations in high-income countries continue to decrease, largely due to stricter emissions regulations, improvements in technology, and a shift toward cleaner fuels, the global population-weighted $PM_{2.5}$ concentration increased by 18% from 2010 (43 $\mu g/m^3$) to 2016 (51 $\mu g/m^3$).[2] This increase was largely driven by low- and middle-income countries (LMIC), which bear the largest burden of the public health impacts of air pollution.[3]

Recent evidence suggests that exposures very early in life, particularly during fetal development, can have detrimental effects on health. Observational studies have linked outdoor $PM_{2.5}$ concentrations during pregnancy to decreased birth weight and increased risks of low birth weight, small for gestational age, and preterm birth.[4-10] Much of the research consists of observational studies that link fixed-site outdoor $PM_{2.5}$ concentrations to administrative data on fetal growth outcomes. These studies, while informative, are often limited in their ability to accurately assess exposure and account for confounding variables. Moreover, most studies have been conducted in high-income countries where air pollution concentrations are relatively low and pollution sources may be different from those in LMIC. The biological understanding of how air pollution affects fetal growth is also incomplete. Finally, few intervention studies have been conducted to understand how air pollution affects fetal growth. Intervention studies offer opportunities to study risk-reduction strategies and can strengthen causal links between air pollution and fetal growth.

Cadmium, a ubiquitous metal, has also been linked to impaired fetal growth, but the evidence is less consistent.[11-23,24] Several studies have reported larger effects on growth restriction in girls versus boys.[11,13,17,20,22,25] Most studies have focused on diet or tobacco smoke as the dominant sources of exposure. Sources of airborne cadmium other than tobacco smoke have not been well studied among pregnant women.

The aims of this thesis were to investigate the impact of portable high efficiency particulate air (HEPA) filter air cleaner (henceforth "HEPA cleaner") use on indoor residential $PM_{2.5}$ and maternal blood cadmium concentrations, as well as on fetal growth, and to study the relationship between cadmium and fetal growth.

1.1. Background

1.1.1. Impaired fetal growth and health

Birth weight and low birth weight are commonly used indicators of fetal growth. Low birth weight is typically defined as weighing less than 2,500 g regardless of gestational age. Birth weight is a relatively easy measure to collect with high precision and validity[26] and is also strongly correlated with health in early and later life.[27,28] Decreases in birth weight can occur due to fetal growth restriction and/or shorter gestational duration. To distinguish between these pathways, researchers have restricted analyses to term births, typically defined as ≥37 weeks or categorized fetal growth as small for gestational age or preterm birth. Small for gestational age is defined as being less than a given cut-off value of birth weight for gestational age and sex for a given population; commonly used cut-offs include the 3rd, 5th, or 10th percentiles or two standard deviations less than an average weight, for a given population.[29,30] Preterm birth is defined as delivery occurring <37 weeks of gestation.

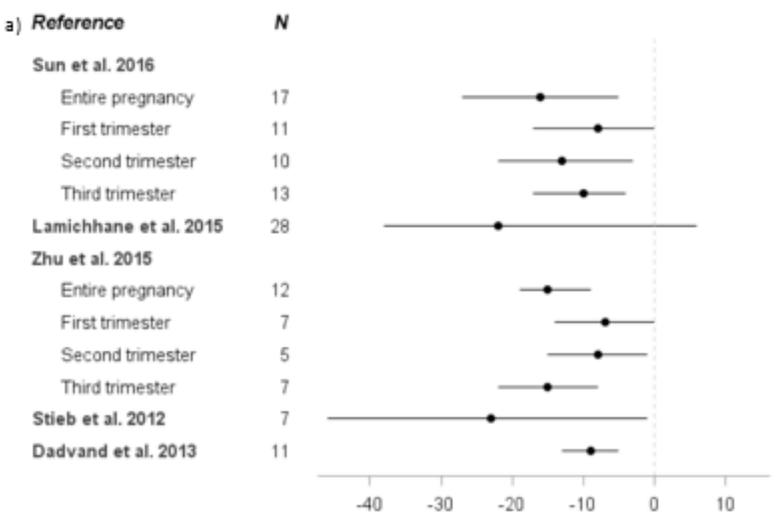
Fetal growth impairment and preterm birth elevate the risk of death, disease, and disability in early and later life.[31-33] Growth restricted babies are at increased risk of stillbirth, childhood obesity, and as adults, of type-2 diabetes, hypertension and coronary heart disease.[26,31-35] Preterm birth is associated with increased risks of neonatal mortality, and short- and long-term pulmonary and neurological morbidity, including wheeze and asthma in childhood.[36-38] The link between unfavorable intrauterine conditions and health in later life was first described by Barker and colleagues in what became to be known as the "Barker hypothesis" and was later expanded to the developmental origins of adult health and disease hypothesis.[39,40] This hypothesis centres on the idea that unfavorable intrauterine conditions force the fetus to make irreversible adaptions that favor immediate survival but have lasting effects on organ morphology, vasculature, physiology, endocrine and metabolic functioning.[41,42]

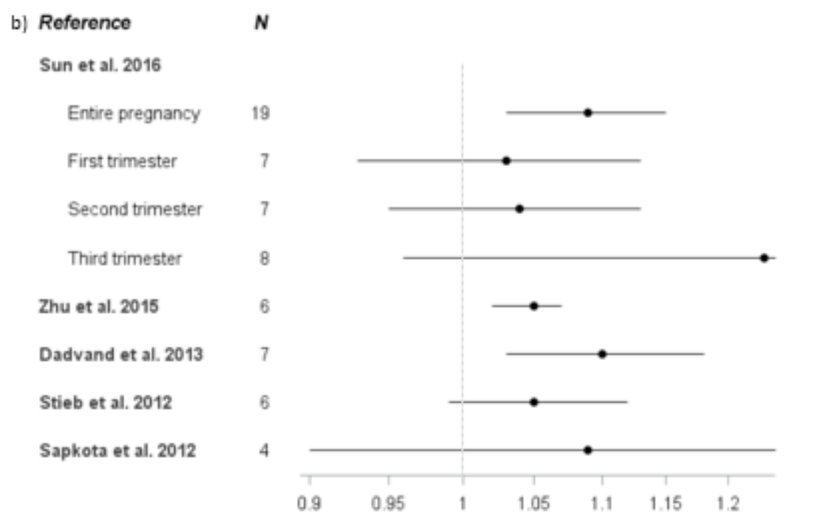
1.1.2. $PM_{2.5}$ and fetal growth

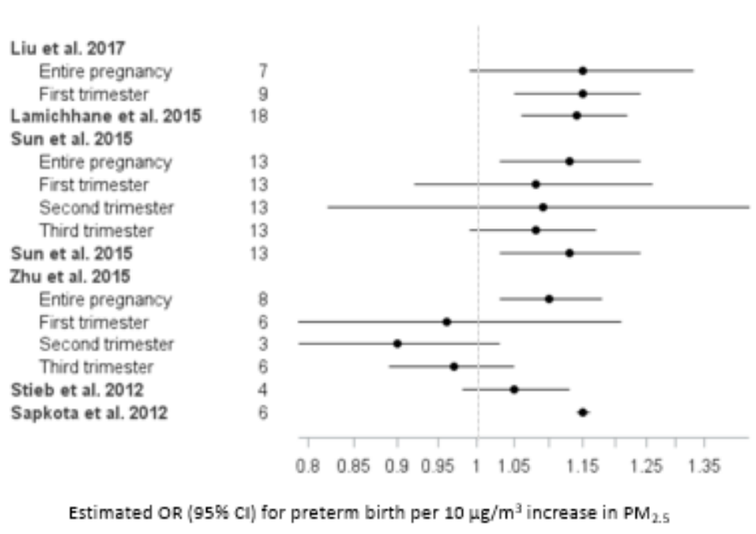
There is growing evidence of a link between air pollution and fetal growth. Over 150 studies and 11 meta-analyses investigating this relationship have been conducted, with most studies focusing on $PM_{2.5}$ as the main pollutant of interest.[4-10,43-46] The bulk of the research consists of large observational studies that link data from outdoor government monitoring networks to administrative data on birth outcomes. More recently, researchers have attempted to develop more refined measures of exposure using satellite data, land use regression models, or a combination of assessment methods.[47-49] Overall, the bulk of the current research reports small but relatively consistent effects of $PM_{2.5}$ on birth weight, low birth weight, preterm birth, and small for gestational age.[4-10,43-45]

A recent meta-analysis of 32 observational studies reported a 16 g (95% CI: 5, 27 g) reduction in birth weight and an odds ratio (OR) of 1.09 (95% CI: 1.03, 1.15) for low birth weight per 10 $\mu g/m^3$ increase in $PM_{2.5}$ over full pregnancy.[4] The majority of the studies in the paper limited their analyses to term births, generally defined as $\geq$ 37 weeks gestation, as a measure of "normal" fetal growth. Other meta-analyses have reported similar effects

of $PM_{2.5}$ on birth weight and low birth weight, in addition to increased risks of preterm birth and small for gestational age (Figure 1.1).[5-10,43-45] Exposure in the latter half of pregnancy may play a particularly important role (Figure 1.1).







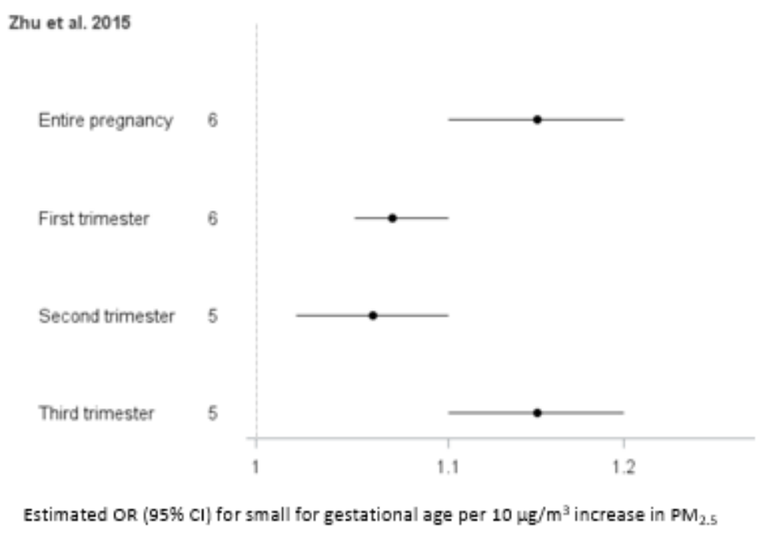


Figure 1.1. Summary of meta-analyses investigating relationships between $PM_{2.5}$ and (a) birth weight, (b) low birth weight, (c) preterm birth, and (d) small for gestational age, where N is the number of studies included in each meta-analysis

There are several limitations of the existing research. Most studies have been conducted in high-income countries where air pollution levels are relatively low and vary little over the course of pregnancy. Outdoor air pollution concentrations may also not provide an accurate measure of total exposures since exposures inside the home or in other microenvironments, such as at work or during a commute, are not considered. Much of the previous research has also not adequately accounted for factors that could bias interpretation of study findings, such as maternal smoking, second hand smoke (SHS) exposure, and maternal nutrition. Finally, few studies have looked at the composition of $PM_{2.5}$ to understand how different pollutant mixes may impact toxicity.

1.1.3. Cadmium and fetal growth

Cadmium is a ubiquitous metal found in the environment. Diet and tobacco smoke are typically the main sources of cadmium among the general public.[50] Tobacco smoke is the largest source of cadmium among smokers[51] while SHS is an important source among non-smokers.[52-55] Emissions from coal combustion, waste incineration and battery manufacturing and recycling may be important sources in some communities,[51,56-58] but have not been adequately studied among pregnant women.

The links between cadmium exposure and health effects such as cancer, and kidney and bone disease are well-established.[50,51] Research also links maternal cadmium exposure during pregnancy, typically measured as concentrations in blood or urine, to impaired fetal growth although findings are mixed (Table A.1).[11-18,20-25,59-73] The inconsistent findings are likely due, in part, to differences in study design, sample size, and exposure levels. Several studies have also reported greater effects in girls versus boys.[11,13,17,20,22,25] Most of these studies have focused on tobacco smoke or diet as the main sources of exposure, but few studies have been conducted among non-smoking pregnant populations in communities heavily impacted by coal smoke.[17,74,75]

1.1.4. Biological mechanisms

$PM_{2.5}$ and cadmium may exert their toxicity on fetal growth through overlapping pathways. Once inhaled, $PM_{2.5}$ and cadmium can cause local oxidative stress and inflammation, which initiates a cascade of systemic oxidative stress and inflammatory responses that not only cause direct damage to cells but also lead to secondary processes such as endothelial dysfunction and increases in blood coagulation and blood pressure.[76-78] During pregnancy, these pathways are thought to interfere with the development and functioning of the placenta, ultimately decreasing the transfer of oxygen and nutrients to the fetus.

Both pollutants may also work through additional direct pathways. $PM_{2.5}$ may directly damage DNA by reacting with molecules to form chemical bonds with DNA called adducts.[79] Unrepaired DNA adducts can disrupt gene expression and create abnormal proteins that can impair cellular growth and differentiation and interfere with the production of growth factors and hormones.[80,81] Cadmium, which accumulates in the placenta, can impair the transfer of essential nutrients[59,82] and the release of progesterone.[83] $PM_{2.5}$ and cadmium may both cause epigenetic changes that alter gene expression without changing DNA sequence, primarily through DNA methylation, histone modifications, and microRNA activity.[84] Epigenetic mechanisms play a critical role in fetal development by coordinating apoptosis, cell growth, and cell differentiation.[85] During pregnancy, cadmium has been suggested to cause hypomethylation of growth genes in girls resulting in larger growth deficits.[17]

1.1.5. Portable air cleaners

Portable HEPA cleaners are a promising intervention to improve our understanding of the relationship between $PM_{2.5}$ and fetal growth and to reduce the potential risks. HEPA cleaners lower $PM_{2.5}$ concentrations through mechanical ventilation. By definition HEPA filters reduce 99.7% of particles sized 0.3 μm, with lower efficiency for larger and smaller

particles. The effectiveness of HEPA cleaners at reducing indoor particle concentrations also depends on the volume of air that can be cleaned by the unit, which in turn is related to the size of the room in which it is placed, as well as the air exchange in the room or home. Although portable air cleaners are designed to clean air in a single room, they have been found to reduce whole house $PM_{2.5}$ concentrations in some studies.[86]

Portable HEPA cleaner use has been linked to reductions of 25-79% in indoor residential $PM_{2.5}$ concentrations (Table 1.1).[87-95] All but two of these studies were conducted in high-income countries where $PM_{2.5}$ concentrations were relatively low (<12 $\mu g/m^3$ for most studies); little is known about the impact of these air cleaners in highly polluted settings. Additionally, few studies have tested HEPA cleaner use over periods longer than two weeks. The effects of portable air cleaners on fetal growth have not been studied, but their use has been linked to improvements in cardiovascular effects that may be also be important to fetal growth such as improved endothelial function, reduced systemic inflammation and decreased blood pressure.[88,91,95,96]

Table 1.1. Summary of studies investigating reductions in residential indoor particulate matter associated with portable HEPA cleaner use

Study	Source(s), location, and study design	% Reduction
Zhan et al. 2018[87]	No specific source Beijing, China One unit was operated in homes for 48 hrs with the filter in place (filtering period) and 48 hrs without the filter (control period); the filtering period was randomly assigned (n=5).	79 (from a mean of 49.0 to 8.5 $\mu g/m^3$)
Shao et al. 2017[88]	No specific source Beijing, China One unit was operated in homes for two weeks with the filter in place (filtering period) and two weeks without the filter (control period); the filtering period was randomly assigned (n=20).	60 (from a mean of 60.0 to 24.0 $\mu g/m^3$)
Kajbafzadeh et al. 2015[89]	Wood smoke and traffic Vancouver, Canada Two units were operated in homes for one week with the filters in place (filtering period) and one week without the filters (control period); the filtering period was randomly assigned (n=44).	40 (from a mean of 7.1 to 4.3 $\mu g/m^3$)
Batterman et al. 2012[90]	No specific source (total suspended particles) Detroit, US Homes of asthmatic children were randomly assigned to one of three groups for three to four consecutive seasons: (i) control (n=37); (ii) one unit (n=47); (iii) one unit and an air conditioner (n=42).	45 (from mean of 21.4 to 11.8 $\mu g/m^3$)
Allen et al. 2011[91]	Wood smoke Smithers, Canada Two units were operated in homes for one week with the filters in place (filtering period) and one week without the filters (control period); the filtering period was randomly assigned (n=25).	60 (from mean of 11.2 to 4.6 $\mu g/m^3$)

Butz et al. 2011[92]	Second hand smoke Baltimore, US Homes of children exposed to indoor second hand smoke were randomly assigned to one of three groups over six months: (i) control (n=44); (ii) two units (n=41); (iii) two units plus home visits from a health coach (n=41).	47 (from mean of 33.9 to 17.9 $\mu g/m^3$)
Lanphear et al. 2011[93]	Second hand smoke (particles > 0.3 µm) Cincinnati, US Homes of children exposed to indoor second hand smoke were randomly assigned to one of two groups for one-year months: (i) two sham units (n=115); (ii) two units (n=110).	38 at six months (from 4.0 x $10^6/ft^3$ to 2.5 x $10^6/ft^3$) 25 at one year (from 4.0 x $10^6/ft^3$ to 3.0 x $10^6/ft^3$
Barn et al. 2008[94]	Wildfire and wood smoke British Columbia, Canada One unit was operated in homes for 24 hrs with the filter in place (filtering period) and 24 hrs without the filter (control period); the filtering period was randomly assigned (n=53).	58 (from mean of 6.7 to 4.2 $\mu g/m^3$)
Brauner et al. 2008[95]	Traffic Copenhagen, Netherlands Two units were operated in homes for 48 hrs with the filter in place (filtering period) and 48 hrs without the filter (control period); the filtering period was randomly assigned (n=21).	62 (from geometric mean of 12.6 to 4.7 $\mu g/m^3$)

1.2. Rationale

There is growing evidence that air pollution exposures during pregnancy can impair fetal growth. Outdoor $PM_{2.5}$ exposure during pregnancy has been linked to small but consistent reductions in fetal growth. Cadmium, an important component of tobacco and coal smoke, has also been linked to impaired fetal growth. Few studies have been conducted in highly polluted settings, and even fewer randomized intervention studies have been conducted to understand how reductions in air pollution may benefit fetal growth. Given that air pollution is ubiquitous and increasing in much of the world, and the importance of fetal growth to health in early and later life, it is important to understand how air pollution exposure during pregnancy affects fetal growth and the potential benefits of exposure reduction.

This work investigates the impact of portable HEPA cleaners on fetal growth in Ulaanbaatar, Mongolia, one of the most polluted cities in the world. The population-weighted annual average $PM_{2.5}$ concentration in the city is approximately 70 $\mu g/m^3$.[97] The high concentrations of air pollution are primarily due to emissions from coal combustion in the city. Household coal use occurs in neighborhoods of traditional Mongolian felt-lined dwellings (gers) and poorly constructed one or two-story wood and brick homes. Roughly 60% of the city's residents live in these neighborhoods. Each ger stove burns an average of five tons of coal per year, and coal stoves in ger neighborhoods are responsible for 45-70% of total $PM_{2.5}$ concentrations in the city.[98-100] Air pollution emissions linked to household coal use are expected to increase further as the population in ger neighbourhoods increases.[101] The remainder of Ulaanbaatar's residents live in apartments, which receive electricity from three coal-fired power plants. These power plants and an increasing number of motor vehicles also contribute to air pollution in the city,[102] although the majority of air pollution comes from gers.[99,100] Smoking rates are also high in Mongolia; nearly 40% of men smoke compared with roughly 7% of women.[97,103]

We conducted a randomized controlled trial in which 540 non-smoking pregnant women were randomized into an intervention group that received one or two HEPA cleaners to use in their apartments from enrollment to delivery, or a control group that received no HEPA cleaners. This thesis explores three research questions, which are addressed in chapters 2, 3, and 4, respectively:

1) To what extent do portable HEPA cleaners reduce indoor $PM_{2.5}$ and blood cadmium concentrations in a highly polluted community? (Chapter 2)
2) Can portable HEPA cleaner use during pregnancy improve fetal growth and birth outcomes in a highly polluted community, as measured by birth weight, length, head circumference, ponderal index, low birth weight, small for gestational age, and preterm birth? (Chapter 3)
3) What is the relationship between cadmium exposure during pregnancy and fetal growth? (Chapter 4)

Chapter 2.

The effect of portable HEPA filter air cleaners on indoor $PM_{2.5}$ concentrations and second hand tobacco smoke exposure among pregnant women in Ulaanbaatar, Mongolia

2.1. Abstract

Background: Portable HEPA filter air cleaners can reduce indoor fine particulate matter ($PM_{2.5}$), but their use has not been adequately evaluated in high pollution settings. We assessed air cleaner effectiveness in reducing indoor residential $PM_{2.5}$ and second hand smoke (SHS) exposures among non-smoking pregnant women in Ulaanbaatar, Mongolia.

Methods: We randomized 540 participants to an intervention group receiving 1 or 2 HEPA filter air cleaners or a control group receiving no air cleaners. We followed 259 intervention and 253 control participants to the end of pregnancy. We measured one-week indoor residential $PM_{2.5}$ concentrations in early (~11 weeks gestation) and late (~31 weeks gestation) pregnancy and collected outdoor $PM_{2.5}$ data from centrally-located government monitors. We assessed blood cadmium in late pregnancy. Hair nicotine was quantified in a subset (n=125) to evaluate blood cadmium as a biomarker of SHS exposure. We evaluated air cleaner effectiveness using mixed effects and multiple linear regression models and used stratified models and interaction terms to evaluate potential modifiers of effectiveness.

Results: The overall geometric mean (GM) one-week outdoor $PM_{2.5}$ concentration was 47.9 $\mu g/m^3$ (95% CI: 44.6, 51.6 $\mu g/m^3$), with highest concentrations in winter (118.0 $\mu g/m^3$; 95% CI: 110.4, 126.2 $\mu g/m^3$). One-week indoor and outdoor $PM_{2.5}$ concentrations were correlated (r=0.69). Indoor $PM_{2.5}$ concentrations were 29% (95% CI: 21, 37%) lower in intervention versus control apartments, with GMs of 17.3 $\mu g/m^3$ (95%

CI: 15.8, 18.8 μg/m^3) and 24.5 μg/m^3 (95% CI: 22.2, 27.0 μg/m^3), respectively. Air cleaner effectiveness was greater when air cleaners were first deployed (40 %; 95% CI: 31, 48%) than after approximately five months of use (15%; 95% CI: 0, 27%). Blood cadmium concentrations were 14% (95% CI: 4, 23%) lower among intervention participants, likely due to reduced SHS exposure.

Conclusions: Portable HEPA filter air cleaners can lower indoor $PM_{2.5}$ concentrations and SHS exposures in highly polluted settings.

2.2. Introduction

Outdoor fine particulate matter ($PM_{2.5}$) air pollution is a leading global public health risk factor.[1,104] The enormous public health impact of $PM_{2.5}$ is due in part to the large number of people exposed. In 2013, 87% of the world's population lived in areas where $PM_{2.5}$ concentrations exceeded the World Health Organization annual average guideline of 10 μg/m^3.[105] Despite decreasing concentrations in many high-income countries, the global population-weighted $PM_{2.5}$ concentrations increased by over 20% between 1990 and 2013 due largely to increasing concentrations in Asia.[105] $PM_{2.5}$ is a risk factor for numerous health conditions including ischemic heart disease, stroke, chronic obstructive pulmonary disease, cancer, and lower respiratory infections.[1,104] A growing body of evidence also links $PM_{2.5}$ exposure with impaired fetal growth, an important indicator of health in early childhood and over the life course.[31-33]

Reducing $PM_{2.5}$ concentrations results in substantial public health benefits.[106-108] From a public health perspective, interventions that reduce pollution emissions and exposure among large populations are generally preferable to those that reduce exposure at the individual or household level. However, because community-wide improvements in air quality usually occur over decades,[109] it is important to identify interventions that can

reduce household exposures in the near term until emissions can be reduced to acceptable levels.

Portable HEPA filter air cleaners are a promising household level intervention to reduce indoor $PM_{2.5}$ concentrations. $PM_{2.5}$ readily infiltrates into buildings,[110-112] so a substantial portion of exposure to $PM_{2.5}$ of outdoor origin actually occurs indoors, where individuals spend the majority of their time.[113] Many countries with high outdoor air pollution concentrations also have a high prevalence of smoking, so air cleaners have the potential advantage of reducing exposure to both outdoor pollution that infiltrates indoors and indoor-generated pollution from cigarettes and other sources. Air cleaners are widely available and relatively inexpensive to purchase and operate.[114] Previous studies have linked portable air cleaner use in residences to reductions of 32-68% in concentrations of particles from various outdoor and indoor sources, including traffic, wildfire and residential wood smoke, and second hand tobacco smoke (SHS).[89-95,115-117] Much of this work has been conducted in high-income settings where $PM_{2.5}$ concentrations and smoking rates are relatively low,[118] so little is known about the efficacy of portable air cleaners in highly polluted settings. Additionally, most studies of air cleaner use have been conducted over short periods ranging from a few days to weeks, with few evaluations of efficacy over longer durations.[119]

The Ulaanbaatar Gestation and Air Pollution Research (UGAAR) study is a randomized controlled trial designed to assess the effect of portable HEPA filter air cleaner use during pregnancy on fetal growth and early childhood development (ClinicalTrials.gov Identifier: NCT01741051). Our study was conducted in Ulaanbaatar, Mongolia's capital city, which is home to roughly one-half of the country's total population of three million.[120] Ulaanbaatar is one of the coldest and most polluted cities in the world. The population-weighted annual average $PM_{2.5}$ concentration in the city is approximately 70 $\mu g/m^3$.[97] Ulaanbaatar is located in a valley with mountains to the north and south, which together with cold temperatures, contribute to inversions that exacerbate the poor air quality in

winter. Wintertime $PM_{2.5}$ emissions are dominated by residential heating with coal.[97] Coal combustion is also linked to other pollutants, including cadmium.[121] Household coal use occurs in ger (a traditional felt-lined Mongolian dwelling) neighbourhoods surrounding the city where roughly 60 % of the city's population resides.[98] In 2013, there were an estimated 164 000 to 185 000 ger households in the city,[101] each burning an average of approximately five tons of coal per year.[98] Air pollution emissions linked to household coal use are expected to increase further as the population in ger neighbourhoods increases.[101] The remainder of Ulaanbaatar's residents live in apartments, which receive electricity from three coal-fired power plants. These power plants and an increasing number of motor vehicles also contribute to air pollution in the city.[102] We have previously estimated that approximately 10% of the mortality in Ulaanbaatar is attributable to outdoor $PM_{2.5}$.[122] The objective of this analysis was to quantify the impact of HEPA filter air cleaner use during pregnancy on indoor residential $PM_{2.5}$ and blood cadmium concentrations.

2.3. Methods

2.3.1. Study population

Our study population consisted of women in Ulaanbaatar who met the following eligibility 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. Initially, recruitment of participants was done in coordination with the reproductive health clinic at the Sukhbaatar district Health Centre in Ulaanbaatar. This city district was targeted due to its large population living in apartments, its proximity to the ger area north of the city centre, and our relationships with staff at the district hospital. To increase participant recruitment, we established a second study office in September 2014 at the first branch location of the Sukhbaatar Health Centre (see Figure B.1). We excluded women living in gers due to concerns about the reliability of electricity in ger neighbourhoods and the possibility that higher air exchange rates in gers would make portable HEPA filter air cleaners ineffective.

2.3.2. Study design

We randomly assigned 540 participants to the intervention or control group. Randomization was done using sealed opaque envelopes containing randomly generated "filter" or "control" allocations and labelled with participant identification numbers that ran from one to 580. Allocation was done on a 1:1 ratio. Participants in the intervention group received one or two portable HEPA filter air cleaners (AP-1009CH, Coway, Korea) depending on the size of their apartment, and air cleaners were used from the first home visit until childbirth. Apartments with a total area less than 40 m^2 received one air cleaner and those with areas greater or equal to 40 m^2 received two air cleaners. The air cleaners had a clean air delivery rate for tobacco smoke (particles sized 0.09-1.0 µm) of 149 ft^3/m, which is appropriate for use in rooms up to approximately 22 m^2. The commercially available model has an internal PM sensor and "mood light" that changes colour based on the PM concentration, but this feature was disabled to avoid biasing the behaviour of UGAAR participants. The air cleaners used in UGAAR were also modified to operate only on the second-highest fan setting with an internal timer that counted total hours of use. Timer data were retrieved once each participant completed the study. Unfortunately, the internal timers proved to have limited value because initiating the timer required the air cleaner to be turned on while also pressing specific buttons. Participants were given instructions on the procedure, but if a participant turned on the air cleaner (e.g., after the unit was turned off, unplugged, or in the event of a power failure) without initiating the timer then subsequent air cleaner usage was not logged. For smaller apartments, air cleaners were placed in the main living area of the home, and for larger apartments, the second unit was placed in the participant's bedroom. Air cleaners were deployed with new pre-filters, which help to remove large debris, and HEPA filters. Participants were shown how to clean the pre-filter, but we did not replace pre-filters or HEPA filters during the study. Participants were encouraged to use the air cleaners continuously throughout the study period. The control group received no air cleaners.

2.3.3. Data collection

Data collection took place from January 2014 to December 2015. We collected data at home and clinic visits that occurred in early (5-18 weeks gestation) and late (24-37weeks gestation) pregnancy (Figure 2.1). We collected air pollution measurements over one-week periods following the two home visits. Whole blood and hair samples were collected during the second clinic visit. We administered questionnaires at both clinic visits to collect data on housing and lifestyle (e.g. SHS exposures, time activity patterns) characteristics. Participants were compensated with a payment of 65,000 Mongolian tugriks (approximately $45 Canadian) upon completion of data collection, and a pro-rated amount was provided to participants who withdrew before completion of the study. The study protocol was approved by the Simon Fraser University Office of Research Ethics (2013s0016) and the Ministry of Health Medical Ethics Approval Committee (No.7). Written consent was obtained from participants prior to their enrollment into the study.

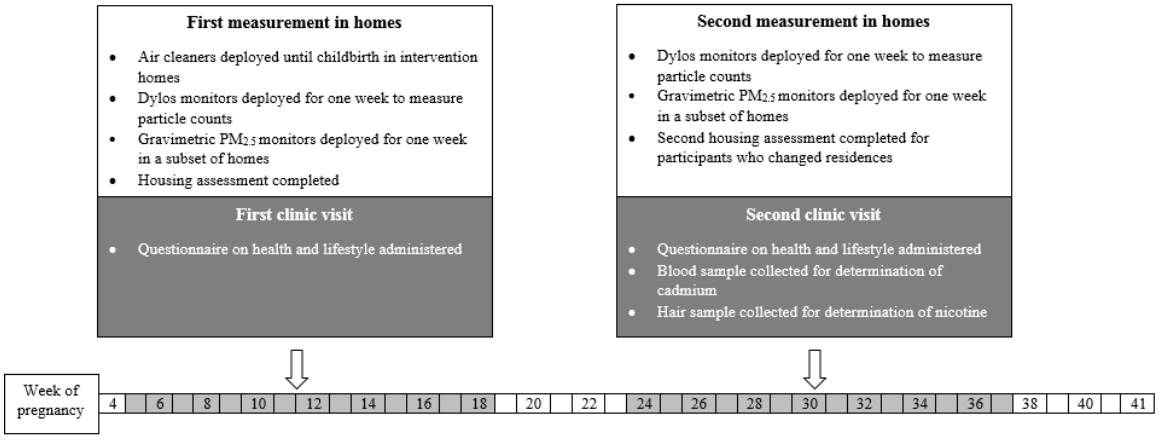


Figure 2.1. Summary of data collection

Indoor residential air pollution measurements

We measured particle number concentrations in all apartments during two one-week sampling campaigns using Dylos laser particle counters (DC1700; Dylos Corporation,

Riverside, California, USA). These instruments quantify particle count concentrations in two particle size ranges: >0.5 µm and >2.5 µm. The commercially available Dylos monitors log particle counts at one-minute intervals and display counts in real time, but the units used in UGAAR were modified to log data at five-minute intervals (to allow one-week of data to be logged). Real-time particle count displays were disabled to avoid biasing participants' behavior. We used the difference between the small and large particle size counts since it has previously been shown to provide the best approximation of $PM_{2.5}$ concentrations, with reported Dylos-$PM_{2.5}$ correlations ranging between 0.55 and 0.99.[48,123-127] We conducted co-location tests of all Dylos monitors to identify and discontinue the use of monitors showing poor performance (see Text B.1).

We collected co-located Dylos particle counts and gravimetric $PM_{2.5}$ measurements in a subset of 90 apartments, roughly 20 % of our sample. The data were used to establish the empirical relationship between Dylos particle counts and $PM_{2.5}$ mass concentrations (in units of $\mu g/m^3$) since this relationship depends on the optical properties of the aerosol being measured. These apartments represent a convenience sample because although they were randomly chosen to capture a representative sample of intervention and control apartments across multiple seasons, measurements were only conducted if participants gave permission for additional sampling. Gravimetric $PM_{2.5}$ samples were collected onto 37-mm Teflon filters using Harvard Personal Environmental Monitors (HPEM; Air Diagnostics and Engineering, Inc., Harrison, ME) connected to mass flow controlled BGI 400 air pumps (BGI, Inc., Waltham, MA) operated at 4 L/min. Filters were weighted in triplicate before and after sampling, and the average of the three measurements was taken. The air pollution sampling equipment was placed in the main activity room, typically on a table or shelf, as far as possible away from the air cleaner, pollution sources, ventilation systems, and bright light sources.

Outdoor air pollution data

Outdoor $PM_{2.5}$ concentrations were obtained from two centrally-located government-run monitoring stations. Measurements were made using tapered element oscillating microbalance (TEOM) monitors.

Relative humidity

Continuous measurements of relative humidity (RH) were made using HOBO loggers (ux100-011; Onset Computer Corporation; Bourne, MA, USA) in the subset of apartments selected for gravimetric $PM_{2.5}$ monitoring. RH was of interest since it can impact the light scattering properties of particles, thereby influencing the relationship between Dylos particle counts and $PM_{2.5}$ mass concentrations. The Dylos has previously been shown to record artificially high particle counts when RH exceeds approximately 90%.[128]

Blood cadmium

Whole blood samples were collected from 382 participants by a nurse at the reproductive health clinic during the second clinic visit. Samples were refrigerated and shipped to the Wadsworth Center (New York State Department of Health, Albany, New York, USA) for analysis within six weeks of collection. Samples were analyzed for cadmium using quadrupole-based inductively coupled plasma-mass spectrometry (ICP-MS), with matrix-matched calibration.[129] The limit of quantification (LOQ), which was based on US Environmental Protection Agency recommendations, was 0.043 µg/L. Two samples were below the LOQ; concentrations of LOQ/2 were assigned to these samples.[130]

Hair nicotine

Hair samples were collected during second clinic visits for analysis of nicotine, an indicator of SHS. Approximately 30-50 strands of hair (>30 mg) were cut close to the scalp at the occipital area of the head. Participants were asked if they had chemically treated their hair in the previous three months since chemical treatment can affect hair nicotine concentrations.[131] After collection, hair samples were placed into a plastic bag and stored

at room temperature before being shipped for analysis to the Clinical Pharmacology Laboratory at the University of California, San Francisco. Hair samples were used primarily to evaluate blood cadmium as a biomarker of SHS exposure, so 125 hair samples were selected for analysis to capture potentially low and high SHS exposures among intervention and control participants, based on whether participants lived with a smoker. Samples were additionally limited to participants who had a blood cadmium measurement and those who did not chemically treat their hair. Four-cm samples were analyzed to represent SHS exposures occurring in the approximately four months prior to data collection. Hair samples were washed, digested, and then analyzed by gas chromatography-tandem mass spectrometry (GC-MS/MS). Five samples were below the LOQ of 0.036 ng/mg; concentrations of LOQ/2 were assigned to these samples.[130]

Other data

Study technicians conducted a home assessment during the first home visit to determine the area and volume of each room, and total area of the home. Study technicians also determined the building location using a global positioning system (GPS). If a participant moved between visits, study technicians also conducted an assessment during the second home visit. During both clinic visits, staff administered a questionnaire to obtain information on health, medical history, and lifestyle factors such as alcohol use, smoking, and exposure to SHS. We quantified air cleaner use in intervention apartments using information provided on the questionnaire administered at the second clinic visit. Specifically, participants were asked to estimate the percentage of time that air cleaner units were used since they were installed in the home. For apartments with two air cleaners, we averaged the reported use for both units.

2.3.4. Data analysis

We conducted a series of quality control and data cleaning steps on particle count data prior to analysis, including removing incomplete data, which resulted in the removal of 464

(51 %) one-week Dylos measurements. We assessed baseline housing, personal, and behavioral characteristics among participants with zero and one or two Dylos measurements. Although participants with no measurements spent less time at home in early pregnancy (15.7 hours/day, 95% CI: 15.1, 16.2 hours/day) compared with participants with one or two measurements (16.3 hours/day, 95% CI: 15.9, 16.8 hours/day, p=0.02), we found no other significant differences between these groups (Table B.1), indicating that the participants and homes included in our analysis are representative of the full UGAAR cohort. The effect of RH on particle count data was determined to be negligible since hourly RH measured in apartments never exceeded 85%. We found strong agreement between the one-week particle counts and gravimetric $PM_{2.5}$ concentrations (R^2=0.94, n=22), and used this relationship to convert Dylos particle counts to mass concentrations (see Text B.2). We averaged outdoor $PM_{2.5}$ concentrations measured at the two monitoring sites and calculated one-week averages corresponding to each week of indoor $PM_{2.5}$ monitoring in apartments and examined correlations between indoor and outdoor concentrations. Potential differences by intervention assignment in baseline housing, personal and behavioral characteristics were assessed using Fisher's exact tests, t-tests, and Mann-Whitney tests as appropriate.

Linear and mixed effects regression models were used to assess the impact of the intervention on indoor $PM_{2.5}$ and blood cadmium concentrations. All exposure variables were log-transformed to improve the normality of model residuals, and results are presented as percent concentration reductions in the intervention group relative to the control group. Since one-week indoor $PM_{2.5}$ concentrations were measured twice for participants, we assessed the effect of the intervention based on all data using mixed effects models, and for each visit separately using multiple linear regression. For mixed effects models, we used an unstructured covariance matrix and entered intervention status as a fixed effect and apartment (participant) as a random intercept to account for repeated measurements in apartments. Results of indoor $PM_{2.5}$ models are shown both unadjusted and adjusted for outdoor $PM_{2.5}$ concentrations. All analyses comparing intervention and control groups were based on randomized intervention assignments, and all analyses

involving the number of air cleaners were based on the actual number deployed in homes by study staff. Standard regression diagnostics were conducted on all models.

To evaluate effect modification, we also ran the regression models after stratifying by variables that we hypothesized might modify air cleaner effectiveness such as number of air cleaners, air cleaner density (number of air cleaners per 100 m^2 of home area), reported air cleaner use, season, window opening, living with a smoker, living in a home where smoking occurred indoors, and, for blood cadmium, time spent indoors at home. Information on time-dependent variables, such as living with a smoker and time spent at home, was obtained in both early and late pregnancy. For stratifications involving $PM_{2.5}$, we used data collected at both time points. For stratified models of blood cadmium, we used data collected in late pregnancy to reflect more relevant exposure periods. The half-life of cadmium in blood ranges from roughly 75-128 days.[132] Differences in air cleaner effectiveness between strata were evaluated using interaction terms in the regression models.

Finally, we evaluated the role of SHS as a source of cadmium exposure. We calculated correlations between blood cadmium and hair nicotine and compared concentrations of both biomarkers between smoking and non-smoking households.

2.4. Results

Five hundred and forty women were recruited at a mean gestation of 10.3 weeks (range: 4.0-18.0 weeks). Two hundred and seventy-two participants were randomized to the control group and 268 were randomized to the intervention group (Figure 2.2). Eight participants received incorrect treatments. These participants were retained in the dataset and analyzed according to their assigned treatment groups. Twenty-eight (5%) participants were lost to follow up, leaving for analysis 512 participants followed to the end of

pregnancy. In total, 236 and 211 one-week $PM_{2.5}$ concentrations measured in early (first measurement) and later (second measurement) pregnancy, respectively, were analyzed, as well as 382 whole blood samples and 125 hair samples. Differences in several characteristics that might influence exposure to $PM_{2.5}$ and cadmium were examined among participants who remained in the study and those who were lost to follow up. No significant differences were found for housing characteristics such as area of home, age of home, window usage, as well as other characteristics, such as time spent at home, living with a smoker and season of enrollment into the study (see Table B.2). Participants lost to follow up were more likely to use a non-UGAAR study air cleaner (i.e. not provided by the study; p=0.05).

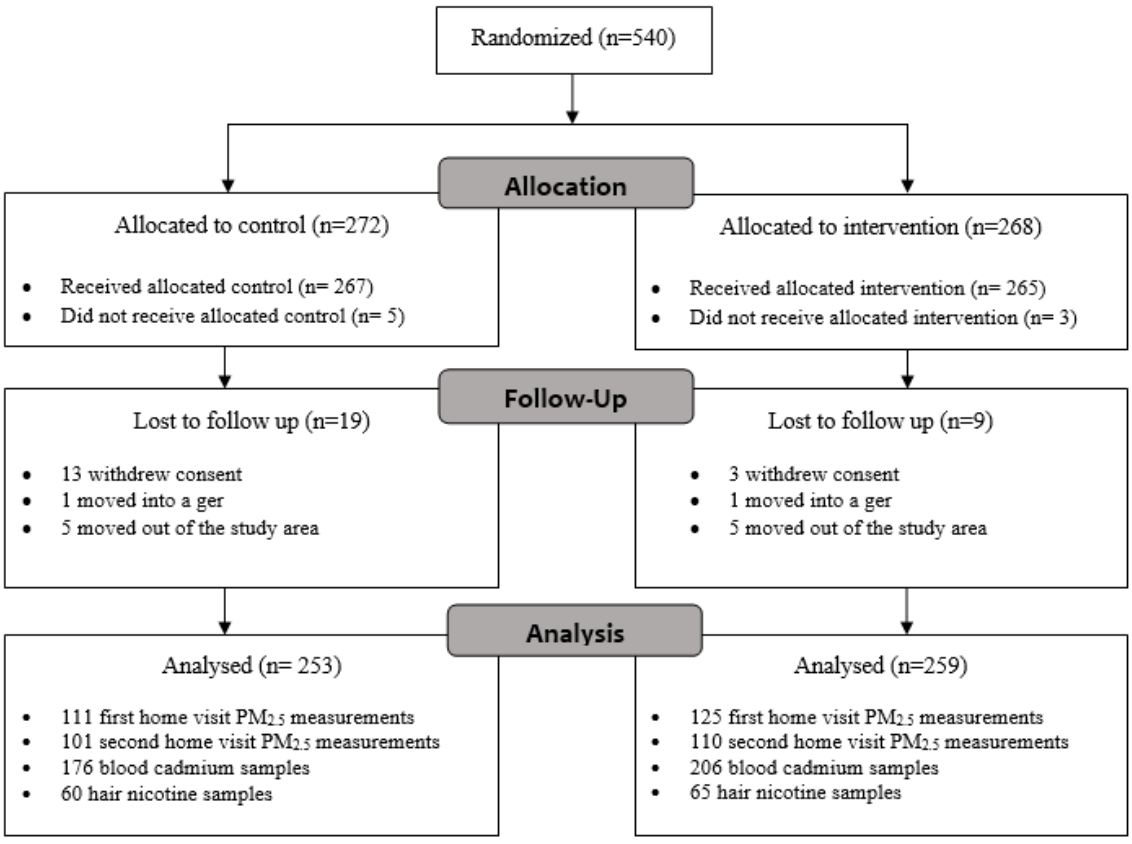


Figure 2.2. Trial profile

At baseline, control and intervention participants had similar home ages, total home areas, and window opening behaviour (Table 2.1). Approximately half of the participants in both groups reported living with a smoker at any time in pregnancy, and 8% of participants in both groups reported smoking at any time during pregnancy. Control and intervention participants spent on average 16 hours per day indoors at home in both early and late pregnancy. The majority of participants (80%) reported working outside the home during pregnancy More participants in the control group changed address (9%) compared with the intervention group (5%). Control participants were also more likely to live in apartments located on lower floors (56%) than intervention participants (46%). The number of participants enrolled into the study each season was similar for both groups, with the highest enrollment occurring during winter and fall. Among the intervention group, 70 households received one air cleaner and 186 households received two air cleaners. Air cleaner density, calculated as the number of air cleaners per total area of the home, was similar for apartments with one and two area cleaners, with geometric means of 3.0 air cleaners/100 m^2 (95% CI: 2.8, 3.2 air cleaners/100 m^2) and 2.9 air cleaners/100 m^2 (9% CI: 2.7, 3.1 air cleaners/100 m^2), respectively. Air cleaners were reported to be used for a geometric mean of 64% of the study duration, and use did not differ by the number of air cleaners deployed. Thirteen participants in the control group and seven in the intervention group reported using a non-UGAAR air cleaner.

Table 2.1. Summary of household, personal, and behavioural characteristics by intervention status

	Control Group (n = 253)		Intervention Group (n = 259)		p-value
	GM (95 % CI) or N	%	GM (95 % CI) or N	%	
Housing characteristics					
Total home area (m^2)	52.3 (48.7, 55.8)	94	54.6 (51.2, 58.2)	97	0.20
Not recorded		6		3	
Age of home (years)	10.6 (8.6, 13.1)	66	11.2 (9.4, 13.3)	73	0.96
Not recorded		34		27	
Window opening in winter					
Open < half the month	118	47	130	50	0.50
Open ≥ half the month	129	51	126	49	
Not recorded	6	2	3	1	
Window opening in summer					
Open < half the month	24	9	35	13	0.17
Open ≥ half the month	224	89	222	86	
Not recorded	5	2	2	1	
Outdoor $PM_{2.5}$ ($\mu g/m^3$)	54.3 (50.5 58.4)	96	55.0 (51.6, 58.6)	99	0.85
Not available		4		1	
Personal and behavioral characteristics					
Week of pregnancy at enrollment into the study	9.9 (9.6, 10.2)	100	9.9 (9.6, 10.3)	100	0.94
Season of enrollment into the study					
Winter (Dec-Feb)	89	35	78	30	0.46
Spring (Mar-May)	72	28	70	27	
Summer (Jun-Aug)	27	11	35	14	
Fall (Sep-Nov)	65	26	76	29	
Time spent indoors at home in early pregnancy (hours/day)	16.0 (15.5, 16.5)	79	16.3 (15.9, 16.8)	74	0.41
Not recorded		21		26	
Time spent indoors at home in late pregnancy (hours/day)	15.6 (14.9, 16.3)	47	15.8 (15.1, 16.5)	60	0.69
Not recorded		53		40	
Lived with a smoker at any time in pregnancy					
No	118	47	131	51	0.47
Yes	127	50	123	47	
Not recorded	8	3	5	2	
Smoking occurred in the home at any time in pregnancy					
No	173	53	176	56	0.70
Yes	73	29	81	31	
Not recorded	7	19	2	13	

The geometric means of one-week outdoor $PM_{2.5}$ concentrations corresponding to indoor residential $PM_{2.5}$ measurement periods were 58.2 $\mu g/m^3$ (95% CI: 52.9, 63.9 $\mu g/m^3$) and 38.0 $\mu g/m^3$ (95% CI: 34.2, 42.2 $\mu g/m^3$) for the first and second measurements, respectively. Outdoor concentrations were similar for control and intervention homes. Across the seasons, geometric mean outdoor $PM_{2.5}$ concentrations were 118.0 $\mu g/m^3$ (95% CI: 110.4, 126.2 $\mu g/m^3$) and 60.0 $\mu g/m^3$ (95% CI: 54.9, 65.7 $\mu g/m^3$) in winter and fall, and 31.7 $\mu g/m^3$ (95% CI: 29.5, 34.0 $\mu g/m^3$) and 20.3 $\mu g/m^3$ (95% CI: 19.3, 21.3 $\mu g/m^3$) in spring and summer, respectively. One-week indoor and outdoor $PM_{2.5}$ concentrations were correlated (r=0.69, n=429), with higher correlations for control (r=0.78, n=203) than intervention apartments (r=0.63, n=226; see Figure B.2).

The overall geometric means of one-week indoor $PM_{2.5}$ concentrations were 22.5 $\mu g/m^3$ (95% CI: 20.5, 24.6 $\mu g/m^3$) and 18.3 $\mu g/m^3$ (95% CI: 16.6, 20.1 $\mu g/m^3$) for the first and second measurements, respectively. Over half (64%) of the first home measurements were made in fall and winter reflecting higher indoor $PM_{2.5}$ concentrations compared with the second measurements, the majority of which (61%) were made in spring and summer when concentrations were lower. Overall, the intervention reduced indoor $PM_{2.5}$ concentrations by 29% (95% CI: 21, 37 %, Table 2). We observed larger reductions when the air cleaners were first deployed in early pregnancy (40%, 95% CI: 31, 48%), compared with after roughly five months of use (15%, 95% CI: 0, 27%, Table 2; Figure 3). Apartments that received two air cleaners had larger reductions in $PM_{2.5}$ concentrations (33%, 95 % CI: 25, 41%) than apartments with one air cleaner (20%, 95% CI: 6, 32%). This trend was seen for measurements made both early and late in the air cleaners' deployment. No differences in effectiveness were observed for reported air cleaner use. Stratification by season revealed a higher non-significant difference in air cleaner effectiveness between winter (36%, 95%: 20, 49%) and summer (18%, 95% CI: 4, 30%). Greater wintertime reductions were observed for apartments where windows were opened less frequently. Significantly higher indoor $PM_{2.5}$ concentrations were seen in apartments of participants who lived with smokers. Higher concentrations were also seen in apartments where smoking occurred

indoors, although differences were not significant. Behaviours related to smoking in the home did not influence air cleaner effectiveness.

Table 2.2. Effect of portable HEPA filter air cleaner use on one-week residential indoor $PM_{2.5}$ concentrations.

	GM (95% CI) µg/m³		% change[a] (95% CI)	
	Control	**Intervention**	**Crude**	**Adjusted for outdoor $PM_{2.5}$**
All data	24.5 (22.2, 27.0) n = 212	17.3 (15.8, 18.8) n = 235	-30 (-38, -22)	-29 (-37, -21)
Duration of air cleaner use				
First measurement	30.3 (26.7, 34.3) n = 111	17.3 (15.4, 19.4) n = 125	-43 (-52, -32)	-40 (-48, -31)
Second measurement	19.4 (16.9, 22.3) n = 101	17.3 (15.1, 19.7) n = 110	-11 (-26, 8)	-15 (-27, 0)
Number of air cleaners deployed				
1 air cleaner	-----	18.7 (15.7, 22.3) n = 64	-23 (-35, -9)	-20 (-32, -6)
2 air cleaners	-----	16.7 (15.1, 18.4) n = 167	-31 (-39, -21)	-33 (-41, -25)
Air cleaner density[b]				
< 3.0 air cleaners/100 m^2	-----	17.9 (15.7, 20.3) n = 102	-27 (-36, -16)	-28 (-37, -18)
≥ 3.0 air cleaners/100 m^2	-----	16.5 (14.6, 18.6) n = 123	-32 (-41, -22)	-30 (-38, -20)
Air cleaner use[c]				
< 63 % of study period	-----	17.1 (14.7, 19.7) n = 87	-30 (-40, -18)	-33 (-42, -23)
≥ 63 % of study period	-----	17.2 (15.2, 19.4) n = 121	-31 (-40, -20)	-30 (-39, -20)
Season				
Winter	44.5 (39.0, 50.9) n = 59	28.5 (23.7, 34.4) n = 54	-36 (-49, -20)	-36 (-49, -20)
Spring	22.6 (19.3, 26.5) n = 47	15.6 (13.6, 17.9) n = 64	-31 (-44, -15)	-35 (-48, -19)

Summer	11.7 (10.5, 13.1) n = 53	9.5 (8.4, 10.8) n = 51	-19 (-31, -4)	-18 (-30, -4)
Fall	28.3 (23.9, 33.5) n = 53	20 (17.5, 22.8) n = 66	-29 (-43, -13)	-31 (-43, -18)
Window opening in winter (Dec - Feb)				
Open < half the month	46.9 (38.6, 57.1) n = 34	25.7 (18.9, 35.0) n = 29	-45 (-61, -22)	-45 (-61, -22)
Open ≥ half the month	40.8 (34.0, 49.0) n = 24	32.2 (26.4, 39.3) n = 25	-21 (-39, 3)	-23 (-4, 10)
Lived with a smoker at any time in pregnancy				
No	22.8 (19.8, 26.3) n = 98	16.0 (14.2, 18.2) n = 120	-31 (-42, -19)	-26 (-37, -13)
Yes	26.0 (22.7, 29.8) n = 111	18.8 (16.6, 21.2) n = 112	-28 (-39, -16)	-29 (-40, -17)
Smoking occurred in the home at any time in pregnancy				
No	24.2 (21.5, 27.2) n = 144	16.7 (15.0, 18.6) n = 155	-31 (-41, -19)	-29 (-38, -19)
Yes	25.2 (21.2, 29.9) n = 65	18.4 (16.0, 21.2) n = 80	-32 (-44, -17)	-33 (-45, -19)

[a]Percent reduction comparing one-week indoor $PM_{2.5}$ concentrations in intervention to control apartments, except for analyses of number of air cleaners which compares indoor $PM_{2.5}$ concentrations in apartments with one and two air cleaners against apartments with no air cleaners.
[b]3.0 air cleaners/100 m^2 was the geometric mean air density calculated for intervention apartments.
[c]63% was the geometric mean air cleaner use reported by participants.

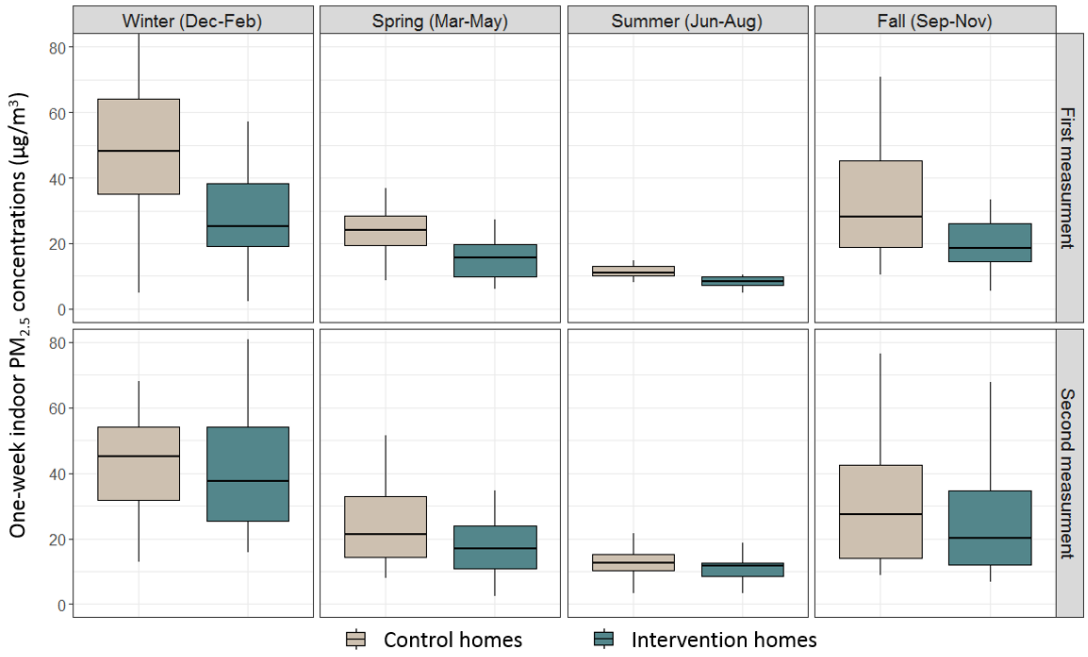


Figure 2.3. Distribution of one-week indoor $PM_{2.5}$ concentrations in control and intervention homes stratified by season and measurement (the first measurement was made when air cleaners were newly deployed and the second measurement was made after approximately five months of use).

The intervention reduced blood cadmium concentrations by 14% (95% CI: 4, 23%), from a geometric mean of 0.23 µg/L (95% CI: 0.21, 0.25 µg/L) to 0.20 µg/L (95% CI: 0.19, 0.21 µg/L). The effect of the air cleaners on blood cadmium concentrations was not significantly modified by smoking in the home, working outside the home, time spent at home, or number of air cleaners.

Blood cadmium and hair nicotine concentrations were more strongly correlated among participants who lived with a smoker (r=0.29, p=0.02, n=66) compared with those who did not (r=0.10, p=0.47, n = 56). Blood cadmium concentrations were 14% (95% CI: 2, 28%) higher among participants who lived with a smoker, and 24% (95% CI: 10, 41%) higher

among participants who lived in apartments where smoking occurred indoors, compared with participants from non-smoking households. Similarly, geometric mean hair nicotine concentrations were significantly higher among participants living in smoking (33 ng/mg; 95% CI: 0.23, 0.46 ng/mg) versus non-smoking households (0.10 ng/mg; 95% CI: 0.08. 0.14 ng/mg).

2.5. Discussion

In this relatively large randomized controlled trial we assessed the impact of HEPA filter air cleaners on indoor $PM_{2.5}$ and blood cadmium concentrations among pregnant women in Ulaanbaatar, Mongolia. Air cleaners reduced one-week indoor $PM_{2.5}$ concentrations by 29% (95% CI: 21, 37%) and blood cadmium concentrations by 14% (95% CI: 4, 23%). Larger $PM_{2.5}$ reductions were seen for the first measurement (40%, 95 % CI: 31, 48%), when the air cleaners were newly deployed, compared with the second measurement (15%, 95% CI: 0, 27%), which was made after roughly five months of air cleaner use. We found strong correlations between indoor and outdoor $PM_{2.5}$, indicating that outdoor $PM_{2.5}$ contributed substantially to indoor concentrations. Since filter effectiveness followed the same seasonal pattern as outdoor $PM_{2.5}$ concentrations, the impact of the intervention on indoor $PM_{2.5}$ concentrations was extraordinarily large in the winter months, when the geometric mean was reduced from 45 to 29 $\mu g/m^3$. Apartments with two air cleaners experienced larger reductions in indoor $PM_{2.5}$ than apartments with one air cleaner; in contrast, we did not observe differences in HEPA cleaner effectiveness by the density of air cleaners (number of air cleaners/100 m^2). No differences in effectiveness were found based on reported air cleaner use, which was crudely assessed from a question about overall use and was not based specifically on the periods of air pollution monitoring.

The reductions in residential indoor $PM_{2.5}$ in our study are consistent with findings reported by other studies evaluating portable air cleaner use in residential settings.[89-95,115,116] Only one study has been conducted in a similarly highly polluted setting. Chen et al. (2015)

evaluated the use of portable electrostatic precipitator air cleaners in 10 university dormitory rooms in Shanghai, China. The authors reported a 57% reduction in indoor $PM_{2.5}$, with mean (SD) concentrations decreasing from 96.2 (25.8) $\mu g/m^3$ during a 48-hour control period with sham filtration to 41.3 (17.6) $\mu g/m^3$ during a 48-hour period with active filtration.[116] Four US-based randomized controlled trials evaluated the use of portable air cleaners over six to 12 months in homes.[90,92,93,115] Authors reported mean reductions in $PM_{2.5}$ or particle counts (> 0.3 μm) of 32-66% (see Table B.3). In the only study to assess changes in air cleaner effectiveness over time, Lanphear et al. (2011) reported decreases in particle count concentrations (> 0.3 μm) of 38% in intervention apartments compared with control apartments after six months of air cleaner use, and a 25% reduction after 12 months of use (n=225).[93] In contrast, we saw greater decreases in effectiveness over the roughly five months between air pollution measurements in our study. This larger decrease may have been due to more rapid overloading of HEPA filters in this high pollution setting or lower compliance to the intervention.

Overall, participants reported using air cleaners for 64% of the study period. Although we did not systematically evaluate the reasons that participants shut off the air cleaners, anecdotal reports from participants revealed concerns about noise and electricity costs. For example, some participants reported consistently turning air cleaners off at night to minimize noise. Studies measuring compliance to air cleaner use have previously reported that participants used air cleaners approximately 34 to 79% of the time during study periods ranging from one to 12 months.[90,92,115,117] Batterman et al. (2012) also looked at changes in compliance over time. The authors conducted one-week indoor air quality monitoring in apartments for three to four consecutive seasons, with air cleaner use being monitored throughout this period.[90] Air cleaner use declined from a mean (SD) of 84% (24) during the first indoor air quality measurement to 63% (33) when indoor air quality measurements were collected in subsequent seasons. Compliance was lowest during periods outside of when indoor air quality measurements were taken, with a mean use of 34% (30).[90] Similar to our study, Ward et al. (2017) reported no relationship between air cleaner effectiveness

and compliance, which was assessed by comparing expected and measured energy consumption for air cleaner units during the study period.[117]

Air cleaners reduced average blood cadmium concentrations by 14%. A reduction in cadmium exposures, even from low levels, could have important public health implications.[50] Cadmium is a known human carcinogen and has also been linked with adverse cardiovascular and kidney effects.[50,133] Among pregnant women, blood cadmium concentrations have been linked to impaired fetal growth, as indicated by small for gestational age[14,62] and reduced birth weight.[69] Tobacco smoke exposures have been reported to be the greatest contributor to blood and urinary cadmium levels among smokers.[134] Similarly, among pregnant women, elevated blood cadmium levels have been reported among those who were active smokers or exposed to SHS.[135-137] Although blood cadmium concentrations cannot definitively be linked to SHS exposures, we found three pieces of compelling evidence to suggest that SHS exposure was an important source of cadmium in our population. First, we found higher blood cadmium concentrations among participants who reported living with smokers as well as among those living in homes where smoking occurred indoors, compared with those in non-smoking households. Second, we found higher correlations between blood cadmium and hair nicotine concentrations among participants who lived with smokers (r=0.29) compared with those who did not (r=0.10). Finally, we found lower blood cadmium concentrations among intervention participants, suggesting that airborne exposures were lower in this group. Other sources of airborne cadmium, including coal combustion, may have also contributed to blood cadmium exposures.[121] Our finding that air cleaner use decreased SHS exposure differs from previous studies. Lanphear et al. (2011) and Butz et al. (2011) reported no changes in hair, serum or urinary cotinine concentrations comparing intervention and control participants, or pre- and post-intervention levels, among children using portable HEPA filter air cleaners for six to 12 months.[92,93]

In our study, geometric mean blood cadmium and hair nicotine concentrations found among participants with and without SHS exposures ranged from 0.20-0.23 µg/L and 0.10-

0.33 ng/mg, respectively, which are relatively low compared with previously reported values among pregnant women. In a review of 24 studies assessing blood cadmium concentrations among pregnant women, Taylor et al. (2014) reported mean and median blood cadmium concentrations ranging from 0.09 to 2.26 µg/L among populations in several countries, including Poland, Russia, South Africa, Egypt, India, Norway, France, United States and China.[138] Few guidelines or levels of concern exist for blood cadmium. In Germany, a guideline of 1 µg/L has been established for the general public, which includes non-smoking adults aged 18–69 years.[138] Similarly, hair nicotine concentrations in our study population were substantially lower than concentrations reported among pregnant women living with partners who smoke (0.51 to 3.18 ng/mg).[139,140]

Our findings suggest that portable HEPA filter air cleaners are an effective household level intervention to reduce $PM_{2.5}$. The situation in Ulaanbaatar is similar to many other rapidly growing cities, where already dramatically high pollution concentrations are expected to increase, and strategies to effectively manage air quality will take years or decades to implement.[97] Proposed strategies in Ulaanbaatar have included dissemination of cleaner-burning coal stoves and use of cleaner-burning fuels in ger households, as well as improved emission controls for coal-fired power plants.[97] Cigarette smoke is the most important indoor source of $PM_{2.5}$ in non-ger households in Ulaanbaatar.[97] Nearly 40 % of Mongolian men smoke,[103] consistent with our finding that half of UGAAR participants lived with a smoker and 34% lived with someone who smoked inside the home. Portable air cleaners show promise because they are easy to operate and reduce concentrations inside residences, where individuals spend the largest portion of time. The costs, which include an initial purchase price typically starting at $200-300US,[141,142] as well as maintenance and operation costs, will be prohibitive for some. In addition, air cleaners must be appropriately sized for the volume of the home and the air exchange rate and may not be a viable intervention in situations when windows are frequently opened, or residences are not tightly sealed. This is consistent with our finding that in winter months air cleaners were more effective when windows were kept closed.

Some important limitations of our study should be noted. First, participants were not blinded to the intervention. Previous air cleaner studies have used sham filtration to blind participants to their intervention status, but instead of purchasing sham air cleaners we chose to recruit a larger number of participants and deploy two air cleaners in larger apartments. Moreover, our exposure measures were objective, which should minimize potential bias resulting from the lack of blinding. Another limitation of our study is that we did not replace HEPA filters during the study period, which has been done by others assessing long-term air cleaner use and performance.[90] We chose not to replace filters in our study period to assess air cleaner efficacy under more "real world" conditions and to minimize logistical challenges. Although we collected information on air cleaner use via questionnaires and internal timers, data from timers were flawed and did not allow us to assess how air cleaner use changed over time. We also did not assess air cleaner use in gers, where the highest exposures in Ulaanbaatar occur and where exposure reduction is needed most,[97] due to concerns about the lack of reliable electricity and high air exchange rates. Consequently, our findings on air cleaner effectiveness are likely not generalizable to ger households. Finally, we approximated $PM_{2.5}$ concentrations using the Dylos, a low-cost optical particle counter. Extensive quality control and data cleaning steps identified several instruments that provided unreliable data, which resulted in a large fraction of data being removed prior to analysis. Despite these data losses, our analysis made use of an extraordinarily large dataset (447 one-week indoor $PM_{2.5}$ concentration measurements in 342 apartments). Consistent with several previous studies, we found excellent agreement (R^2=0.94) between Dylos particle counts and $PM_{2.5}$ concentrations measured gravimetrically.[48,123-127]

2.6. Conclusions

In this randomized controlled trial, we found that air cleaners substantially reduced indoor $PM_{2.5}$ concentrations and SHS exposures as measured by blood cadmium among a group of pregnant women in a highly polluted city. Our findings suggest that portable air cleaners

are a useful household level intervention that can help reduce $PM_{2.5}$ exposures during pregnancy and other critical time periods.

Chapter 3.

The effect of portable HEPA filter air cleaner use during pregnancy on fetal growth: the UGAAR randomized controlled trial

3.1. Abstract

Background: Fine particulate matter ($PM_{2.5}$) exposure may impair fetal growth.

Aims/Objectives: Our aim was to assess the effect of portable high efficiency particulate air (HEPA) filter air cleaner use during pregnancy on fetal growth.

Methods: The Ulaanbaatar Gestation and Air Pollution Research (UGAAR) study is a single-blind randomized controlled trial conducted in Ulaanbaatar, Mongolia. Non-smoking pregnant women recruited at ≤ 18 weeks gestation were randomized to an intervention (1-2 air cleaners in homes from early pregnancy until childbirth) or control (no air cleaners) group. Participants were not blinded to their intervention status. Demographic, health, and birth outcome data were obtained via questionnaires and clinic records. We used unadjusted linear and logistic regression and time-to-event analysis to evaluate the intervention. Our primary outcome was birth weight. Secondary outcomes were gestational age-adjusted birth weight, birth length, head circumference, gestational age at birth, and small for gestational age. The study is registered at ClinicalTrials.gov (NCT01741051).

Results: We recruited 540 participants (272 control and 268 intervention) from January 9, 2014 to May 1, 2015. There were 465 live births and 28 losses to follow up. We previously reported a 29% (95% CI: 21, 37%) reduction in indoor $PM_{2.5}$ concentrations with portable HEPA filter air cleaner use. The median (25th, 75th percentile) birth weights for control and intervention participants were 3450 g (3150, 3800 g) and 3550 g (3200, 3800 g), respectively (p=0.34). The intervention was not associated with birth weight (18 g; 95% CI: -84, 120 g;), but in a pre-specified subgroup analysis of 429 term births the intervention was associated with an 85 g (95% CI: 3, 167 g) increase in mean birth weight.

Conclusions: HEPA filter air cleaner use in a high pollution setting was associated with greater birth weight only among babies born full term.

3.2. Introduction

Fine particulate ($PM_{2.5}$) air pollution is a leading contributor to the global burden of disease because exposure is ubiquitous and causes respiratory-, cardiovascular-, and cancer-related morbidity and mortality.[143] In 2016, 95% of the world's population lived in areas where $PM_{2.5}$ concentrations exceeded the World Health Organization annual average guideline of 10 $\mu g/m^3$.[2] Although air pollution levels are decreasing in many high-income countries, concentrations in low and middle-income (LMIC) countries remain unchanged or continue to increase.[105] Growing evidence from observational studies suggests that $PM_{2.5}$ exposures during pregnancy adversely affect fetal growth.[4,7] A recent meta-analysis of 32 studies presented pooled estimates of the effect of outdoor $PM_{2.5}$ on birth weight and/or low birth weight (LBW).[4] A 10 $\mu g/m^3$ increase in $PM_{2.5}$ over the full duration of pregnancy was associated with a 16 g (95% CI: 5, 27 g) reduction in birth weight and an increased risk of LBW (odds ratio (OR)=1.09; 95% CI: 1.03, 1.15).[4] Nearly all of the studies focused on term births (≥37 weeks), and the majority were conducted in the US. The only randomized controlled trial (RCT) of air pollution and fetal growth reported a trend toward greater birth weight (89 g; 95% CI: -27, 204 g) among participants who used a chimney stove (n=69)

compared with those who used traditional open fires (n=105) during pregnancy in rural Guatemala.[144]

Portable high efficiency particulate air (HEPA) filter air cleaners (henceforth "HEPA cleaners") are a promising intervention to lower $PM_{2.5}$ exposures at the household level. Their use has been shown to reduce indoor residential $PM_{2.5}$ concentrations by 29-65%.[55,89,91,92,94,95] These reductions in concentrations can have large impacts on exposure since individuals spend the majority of time indoors, and because HEPA cleaners target both outdoor pollution that infiltrates indoors and indoor-generated pollution from cigarettes, cooking, and other sources. The impact of portable air cleaners on fetal growth has not been previously studied, but their short-term use (days to weeks) may induce biological changes relevant to fetal growth,[76] including improvements in endothelial function,[95] inflammation,[91] and blood pressure.[96] The objective of this randomized trial was to determine if HEPA cleaner use at home from early pregnancy until childbirth among pregnant women in Ulaanbaatar, Mongolia was associated with improvements in fetal growth, compared with no HEPA cleaner use. Our primary motivation for this work was to introduce an exposure gradient from which to investigate the causal role of $PM_{2.5}$ on fetal growth. Secondarily, we sought to evaluate HEPA cleaner use as a possible household level intervention in high pollution settings.

3.3. Methods

3.3.1. Study design

The Ulaanbaatar Gestation and Air Pollution Research (UGAAR) study is a single-blind RCT designed to assess the effect of portable HEPA cleaner use during pregnancy on fetal growth and early childhood development in Ulaanbaatar, Mongolia (ClinicalTrials.gov: NCT01741051). This city is among the world's most polluted in wintertime, primarily due to coal combustion for heating in low income neighborhoods and emissions from three coal

fired power plants.[100] The population-weighted annual average $PM_{2.5}$ concentration in Ulaanbaatar is over seven times the World Health Organization (WHO) guideline concentration of 10 $\mu g/m^3$.[100] Household coal use occurs in gers, traditional felt-lined yurts, which house approximately 60% of the city's population [98]. Ulaanbaatar's other residents live in apartments that receive electricity and heat from the power plants. We previously reported that HEPA cleaners reduced indoor $PM_{2.5}$ by 29% (95% CI: 21, 37%) in this apartment-dwelling study population, with larger reductions in homes that received two air cleaners (33%, 95% CI: 25, 41%) than those that received one (20%, 95% CI: 6, 32%).[55]

The study was conducted at two branches of the Sukhbaatar district Health Center of Ulaanbaatar. 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).

3.3.2. Participants

We recruited women who met the following criteria: ≥ 18 years of age, ≤ 18 weeks of a single-gestation pregnancy, non-smoker, living in an apartment, planning to give birth in a medical facility in the city, and not using a residential portable air cleaner at enrollment. We excluded women who lived in ger households because electricity is unreliable in ger neighborhoods and gers may have higher indoor-outdoor air exchange rates, which reduces HEPA cleaner effectiveness. Moreover, gers generally have higher indoor pollution emissions, and we were primarily interested in the effects of community air pollution. We recruited participants 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 our relationships with clinic staff. All participants provided written informed consent prior to data collection. Participants were compensated with 65,000 tugriks (approximately $30 USD) upon completion of data collection; a pro-rated amount was provided to participants who withdrew before completion of the study.

3.3.3. Randomization and blinding

We used simple randomization to assign 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 by a principal investigator (RWA). 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 their 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. Participants were not blinded to their intervention status.

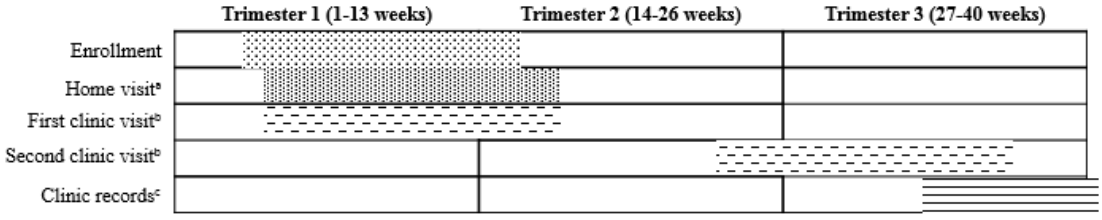
3.3.4. Intervention

The intervention group received one or two HEPA cleaners (Coway AP-1009CH), based on the size of their home, to use from enrollment to the end of pregnancy. The control group received no air cleaners.

3.3.5. Procedures

We installed one HEPA cleaner in the main living area of apartments with areas < 40 m^2; in larger apartments a second HEPA cleaner was installed in the participant's bedroom. We installed air cleaners at the first home visit, which occurred shortly after enrollment, and participants were encouraged to use the air cleaners continuously. The HEPA 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' behavior. The units were set to operate only on the second-highest fan setting due to noise at the highest fan setting.

Data were collected at clinic visits that occurred shortly after enrollment (5-19 weeks gestation) and later in pregnancy (24-37 weeks gestation; Figure 3.1). At these visits staff collected data on housing, lifestyle, and maternal health via questionnaires. During the second clinic visit we asked participants to estimate the percentage of time HEPA cleaners were used. After birth, we obtained birth weight, length, head circumference, gestational age, sex, and mode of delivery from clinic records. Participants self-reported the occurrence and timing of spontaneous abortions, and information on stillbirths was obtained from clinic records. We also collected information from clinic records on pregnancy complications and co-morbidities, including pre-existing and gestational diabetes and hypertension, anemia, and TORCH (Toxoplasmosis, Others [syphilis, varicella-zoster, parvovirus B19], Rubella, Cytomegalovirus, Herpes) infections. A full summary of UGAAR data collection activities is provided in the supplemental material (Figure C.1).



[a]Air cleaners were deployed in homes of intervention participants.
[b]Questionnaires on lifestyle and health were administered.
[c]Post delivery, the following data were extracted from clinic records: birth weight, length, head circumference, gestational age, sex, type of delivery, and health of participant during pregnancy (e.g. presence of infections, gestational diabetes and hypertension, preeclampsia).

Figure 3.1 Data collection

3.3.6. Outcomes

Our primary outcome was birth weight. We also analyzed secondary outcomes, including gestational age-adjusted birth weight, birth length, head circumference, and small for

gestational age (SGA) at birth, as additional measures of intrauterine growth restriction, as well as gestational age at birth. Birth weight was available to the nearest 10 g, and birth length and head circumference were available to the nearest one cm. Gestational age was available either as a completed week or as a one-week interval (e.g. 37-38 weeks); for the latter, the mid-point of the interval was used (e.g. 37.5 weeks). SGA was defined as a birth weight $<10^{th}$ percentile for sex and gestational age of the WHO fetal growth chart.[145] We also explored additional outcomes that were not pre-specified: ponderal index, LBW, and preterm birth (PTB). Ponderal index was calculated as 100 multiplied by birth weight (g) divided by crown-heel length cubed (cm^3). Low birth weight was defined as < 2,500 g, and PTB was defined as birth at <37 weeks gestation. Adverse events were spontaneous abortion, stillbirth, and neonatal death. Spontaneous abortion and stillbirth were defined as pregnancy loss at <20 weeks and ≥20 weeks, respectively. Neonatal death was defined as a death occurring within 28 days of a live birth. Stillbirth weight was not included in the analysis of birth weight since these data were not available.

3.3.7. Statistical analysis

Sample size calculations were based on term birth weight. We expected infants in the intervention group to weigh 120 g more at birth, on average, than infants in the control group (from a mean ± standard deviation of 3,490 g ± 520 g). This value was based on previous estimates of outdoor $PM_{2.5}$ effects on term birth weight,[146,147] as well as assumptions on indoor and outdoor $PM_{2.5}$ concentrations,[122] infiltration of outdoor $PM_{2.5}$,[148] the effect of HEPA cleaners on indoor $PM_{2.5}$,[91,94] and time spent in different microenvironments during pregnancy.[149] To detect a 120 g difference in mean birth weight with a type I error rate of 0.05 (2-sided) and a type II error rate of 0.20, we estimated that 460 participants, in equal numbers in both treatment groups, were needed. We assumed 18% attrition due to dropout and pregnancy loss, so we targeted a population of 540 participants.

We used unadjusted linear and logistic regression to assess the effect of the intervention on all continuous and categorical outcomes, respectively, except for gestational age. Since gestational age had a non-normal distribution, we used time-to-event analysis to calculate hazard ratios for time to a live birth comparing intervention with control participants; we censored lost to follow up participants and treated pregnancy loss from spontaneous abortion or stillbirth as a competing risk. Models of gestational age-adjusted birth weight were adjusted for gestational age using linear and quadratic terms to account for the non-linear relationship between fetal growth and gestational age. We conducted a complete case analysis among all live births, excluding those involving a chromosomal abnormality, as well as participants who were lost to follow up or who had a pregnancy loss. Participants were analyzed according to their original intervention assignments, regardless of which treatment they were given or used.

Because nearly all of the existing observational evidence,[4] including the studies used in our sample size calculations, is based on term births we stratified the analyses by gestational age (all births and term births, defined as $\geq$ 37 weeks) in *a priori* planned analyses. We also tested effect modification using stratified analyses and interaction terms in the models for variables identified *a priori*: gestational age at birth, exposure to second hand smoke (SHS), average time spent indoors at home during pregnancy, sex of the baby, season of birth, and self-reported air cleaner use. We additionally investigated income, as a proxy for socioeconomic status, as a potential effect modifier *post hoc*. Finally, we repeated all analyses to also estimate the effect of one and two air cleaners on our outcomes.

We assessed the sensitivity of the intervention effect estimates for birth weight to different factors. First, as an alternative to our intention-to-treat analysis, we estimated the effect of the intervention based on the treatment that participants received (i.e "per protocol"). We also estimated intervention effects on birth weight after excluding (i) neonatal deaths, (ii) participants who reported smoking at any time in pregnancy, and (iii) potential errors in gestational age or birth weight (identified as observations that exceeded the WHO fetal

growth chart 95th percentiles of birth weight for gestational age and sex by ≥20%). Finally, we estimated effects while adjusting for anemia status and PTB in the regression models.

3.3.8. Role of funding source

This study was funded by the Canadian Institutes of Health Research. Woongjin-Coway provided modified and discounted air cleaners. The funder and the company had no role in study design, data collection, data analysis, interpretation of study findings, or manuscript preparation.

3.4. Results

We recruited 540 participants from January 9, 2014 to May 1, 2015. Participants were enrolled in the study at a median (25th, 75th percentile) gestation of 10 weeks (8, 12 weeks). Two hundred and seventy-two participants were randomized to the control group and 268 were randomized to the intervention group (Figure 3.2). Five participants that were allocated to the control group mistakenly received the intervention, while three participants allocated to the intervention group did not receive HEPA cleaners; data from these participants were analyzed according to their original treatment assignments. Twenty-eight (5%) participants were lost to follow up, and there were 34 (6%) spontaneous abortions and 13 stillbirths (2%). In total, 465 participants (86%) had a known live birth, five of which resulted in neonatal deaths (1%) due to heart defects (n=2), respiratory failure (n=2), and brain injury (n=1). Two children were excluded due to chromosomal abnormalities (trisomy 18 and 21), leaving 463 live births in our complete case analysis.

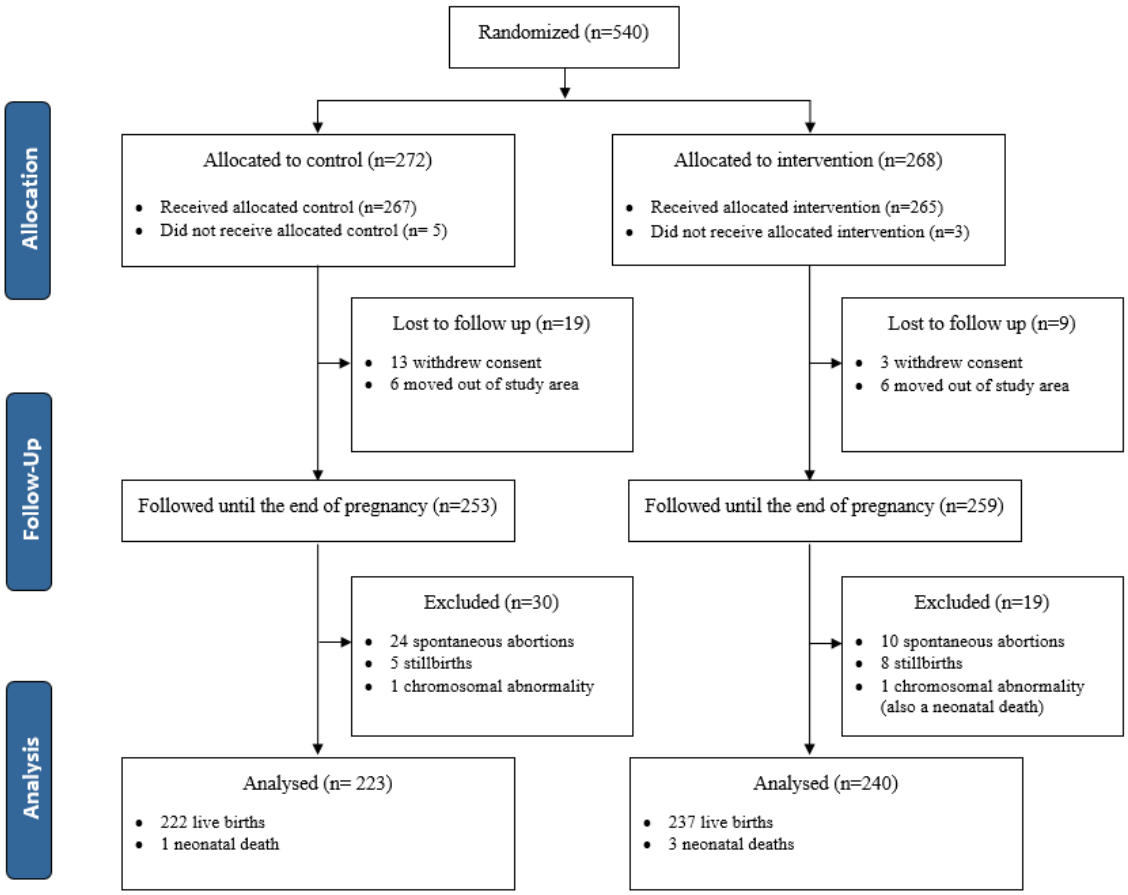


Figure 3.2 Trial profile

Participants lost to follow up and those who remained in the study had similar demographics and lifestyles, including age at enrollment, household income, maternal education, marital status, parity, and pre-pregnancy BMI (Table C.1). Some participants withdrew consent before our first questionnaire was administered resulting in more missing observations for these variables. More control participants were lost to follow up (19 vs. 9; p=0.06).

Baseline characteristics were similar among control and intervention participants (Table 3.1). The median (25^{th}, 75^{th} percentile) age at enrollment was 29 years (25, 33 years). Control and intervention participants were enrolled at median (25th, 75th percentile)

gestational ages of 11 (9, 12) and 11 (9, 13) weeks, respectively. The seasonal pattern of enrollment was also similar between the groups, with the most participants enrolled in winter (32%) and the fewest participants enrolled in summer (12%). Over half of the participants in both groups reported a monthly household income at or above the city's average of 800,000 Tugriks (approximately $360 US).[150] Most participants (≥80%) completed university or college and reported being married/common-law. Although all participants identified as non-smokers at enrollment, 8% of participants in both groups reported smoking in early pregnancy. Parity was similar between groups. Control participants had a shorter interval from the last pregnancy (24 vs 31 months), although the response rate to this question was poor with over 40% of observations missing. The intervention was implemented at a median (25th, 75th percentile) gestation of 11 weeks (9, 13 weeks). Seventy households received one HEPA cleaner and 186 households received two HEPA cleaners. The ratio of air cleaners to apartment area was similar for participants who received one (median: 3.0 air cleaners/100 m2; 25th, 75th percentile: 2.3, 3.7 air cleaners/100 m2) and two (median: 3.4 air cleaners/100 m2; 25th, 75th percentile: 2.4, 3.9 air cleaners/100 m2) HEPA cleaners. Participants reported using HEPA cleaners for a median of 70% of the time; reported use did not differ by the number of air cleaners received. We previously reported that outdoor $PM_{2.5}$ concentrations measured at centrally-located government monitoring stations during the study period were similar for control and intervention participants.[55]

Table 3.1. Summary of baseline characteristics for control and intervention participants.

	Control (n = 223)	**Intervention (n = 240)**
	Median (25th, 75th percentile) or N (%)	**Median (25th, 75th percentile) or N (%)**
Mother's age at enrollment, years	28 (25, 33)	30 (25, 33)
Gestational age at enrollment, weeks	11 (9, 12)	11 (9, 13)
Season of enrollment		
Winter (December, January, February)	77 (34)	71 (30)
Spring (March, April, May)	66 (30)	63 (26)
Summer (June, July, August)	23 (10)	33 (14)
Fall (September, October, November)	57 (26)	73 (30)
Monthly household income		
< 800,000 Tugriks[a]	69 (31)	83 (34)
≥ 800, 000 Tugriks	150 (67)	155 (65)
Not reported, N (%)	4 (2)	2 (1)
Mother's education		
Completed university	179 (80)	191 (80)
Did not complete university	29 (13)	28 (11)
Not reported, N (%)	15 (7)	21 (9)
Marital status		
Married/common-law	184 (83)	207 (86)
Not married/common-law	39 (17)	33 (14)
Not reported, N (%)	0 (0)	0 (0)
Worked/volunteered outside the home		
No	69 (31)	78 (32)
Yes	151 (68)	160 (67)
Not reported, N (%)	3 (1)	2 (1)
Parity		
0	21 (9)	24 (10)
1	88 (40)	86 (36)
≥2	44 (20)	59 (24)
Not reported, N (%)	70 (31)	71 (30)
Time since last pregnancy, months[b]	24 (10, 51)	31 (15, 61)
Not reported, N (%)	99 (44)	105 (44)
Previous poor pregnancy outcome[c]		
No	42 (19)	54 (23)
Yes	50 (22)	54 (23)
Not reported, N (%)	131 (59)	132 (54)
Pre-pregnancy BMI, kg/m^2	21.7 (19.6, 23.9)	21.4 (19.8, 24.0)
Not reported, N (%)	21 (9)	8 (3)
Time spent indoors at home in early pregnancy, hr/day	16.0 (14.0,18.7)	16.1 (14.0, 19.0)
Not reported, N (%)	46 (21)	63 (26)

[a]Approximate average monthly income in Ulaanbaatar in 2014.[150] At the time of data collection, 800,000 Tugriks was the equivalent of approximately $360 US.

[b]Defined as the period between the end of the last pregnancy, including live births and pregnancy losses, and start of current pregnancy.
[c]Previous poor outcome included spontaneous abortion, still birth, low birth weight, macrosomia, ectopic pregnancy, birth defect, and intrauterine growth restriction.

Maternal weight gain, second hand smoke exposure, and health complications during pregnancy were similar between groups (Table 3.2). Roughly half of control and intervention participants reported living with a smoker. A higher frequency of intervention participants reported anemia during pregnancy (22% vs 15%; p=0.07). No control or intervention participants had diabetes or gestational diabetes. Similarly, few participants had hypertension, gestational hypertension, or TORCH infections.

Table 3.2. Summary of variables assessed during pregnancy

	Control (n = 223)	Intervention (n = 240)	p-value[a]
	Median (25th, 75th percentile) or N (%)	Median (25th, 75th percentile) or N (%)	
Weight gain during pregnancy (kg)[b]	12 (8, 15)	11 (8, 15)	0.93
Not reported	43 (19)	31 (14)	
Smoked at any time in pregnancy			
No	203 (91)	217 (91)	0.99
Yes	19 (9)	20 (8)	
Not reported, N (%)	1 (0)	3 (1)	
Lived with a smoker at any time in pregnancy			
No	106 (48)	121 (51)	0.64
Yes	112 (50)	115 (48)	
Not reported, N (%)	5 (2)	4 (1)	
Health during pregnancy			
Anemia	34 (15)	53 (22)	0.07
Not reported, N (%)	0 (0)	0 (0)	
Hypertension	11 (5)	13 (5)	0.84
Not reported, N (%)	0 (0)	0 (0)	
Gestational hypertension	16 (7)	16 (7)	0.85
Not reported, N (%)	23 (10)	15 (6)	
TORCH infections[c]	3 (1)	5 (2)	0.72
Not reported, N (%)	10 (4)	4 (2)	
Type of delivery			
Caesarean delivery	88 (39)	86 (36)	0.50
Vaginal delivery	135 (61)	154 (63)	
Sex of child			
Female	108 (48)	109 (45)	0.58
Male	115 (52)	131 (55)	
Season of birth			
Winter (Dec, Jan, Feb)	26 (12)	35 (15)	0.56
Spring (Mar, Apr, May)	52 (23)	59 (24)	
Summer (Jun, Jul, Aug)	70 (31)	78 (33)	
Fall (Sep, Oct, Nov)	75 (34)	68 (28)	

[a]p-values were generated using Fisher's exact tests, 2-sample t-tests, and Mann-Whitney tests as appropriate.
[b]From approximately week 11 to week 31.
[c]Toxoplasmosis, Others [syphilis, varicella-zoster, parvovirus B19], Rubella, Cytomegalovirus, Herpes infections.

The birth weight distributions were skewed by PTBs (Figure 3.3). The median (25th, 75th percentile) birth weights for control and intervention participants were 3450 g (3150, 3800 g) and 3550 g (3200, 3800 g), respectively (p=0.34; Table 3.3). Regression results

indicated no significant intervention effect on mean birth weight (18 g; 95% CI: -84, 120 g), but after adjusting for PTB the intervention was associated with an 84 g (95% CI: -1, 170 g) increase in birth weight (Table C.2). The effect estimates from our other sensitivity analyses were generally similar to those from the main analysis (Table C.2). Gestational age, birth length, head circumference, ponderal index, and frequency of LBW and SGA were similar for control and intervention participants (Table 3.3). The intervention was associated with a significantly elevated risk of PTB (10% *vs.* 4%; OR=2.37; 1.11, 5.07). When stratified by late (34-36 weeks) versus early (<34 weeks) cases, a significantly elevated risk remained for late PTB (OR=3.55; 95% CI: 1.29, 9.73) but not early PTB (OR=1.18; 95% CI: 0.36, 3.94).

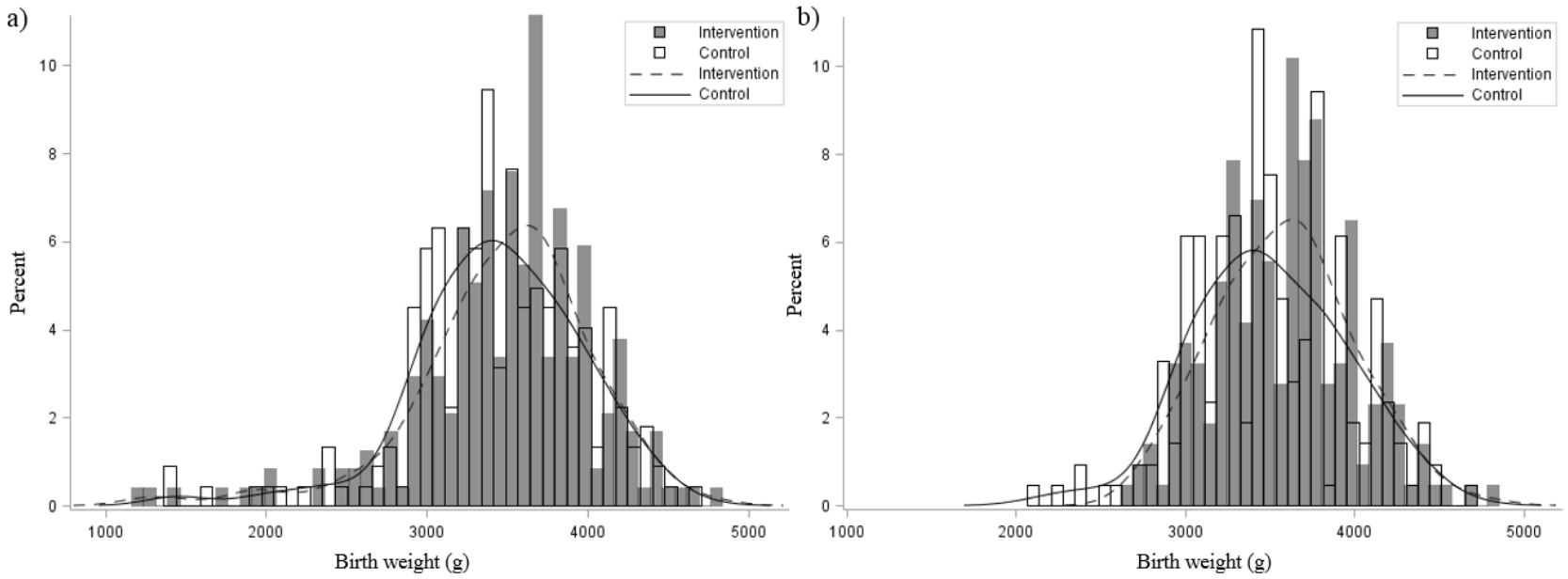


Figure 3.3 Distribution of birth weight by treatment assignment for all births (a) and term births (b).

Table 3.3. Effect of the intervention on fetal growth and birth outcomes

Outcome	Median (25th, 75th percentile) or N (%)			Effect of intervention		
	Control n = 223	Intervention n = 240	p-value[a]	Measure of association	All births n = 463	Term births[b] n = 429
Birth weight, g	3450 (3150, 3800)	3550 (3200, 3800)	0.34	Mean difference (95% CI)	18 (-84, 120)	85 (3, 167)
Gestational age-adjusted birth weight, g[c]	---	---	---	Mean difference (95% CI)	48 (-31, 126)	81 (2, 159)
Birth length, cm	50 (50, 52)	51 (50, 52)	0.63	Mean difference (95% CI)	-0.01 (-0.53, 0.51)	0.32 (-0.04, 0.68)
Head circumference, cm	35 (34, 36)	35 (34, 36)	0.23	Mean difference (95% CI)	-0.07 (-0.4, 0.26)	0.14 (-0.13, 0.4)
Ponderal index, g/cm^3	2.6 (2.5, 2.8)	2.6 (2.5, 2.8)	0.92	Mean difference (95% CI)	0.01 (-0.04, 0.07)	0.02 (-0.02, 0.06)
Gestational age	39.5 (38.5, 40.0)	39.5 (38.5, 40.0)	0.87	Hazard ratio for time to a live birth (95% CI)	1.12 (0.96, 1.32)	1.06 (0.90,1.25)
Small for gestational age	18 (8)	16 (7)	0.67	Odds ratio (95% CI)	0.81 (0.4, 1.64)	0.44 (0.19, 1.05)
Low birth weight[d]	10 (4)	13 (5)	0.60	Odds ratio (95% CI)	1.22 (0.52, 2.84)	-----
Preterm birth	10 (4)	24 (10)	0.03	Odds ratio (95% CI)	2.37 (1.11, 5.07)	-----

[a]p-values were generated using non-parametric Wilcoxon rank tests for continuous outcomes and Fisher's exact tests for categorical outcomes.
[b]Births occurring ≥ 37 weeks gestation.
[c]Models were adjusted for gestational week and gestational week squared.
[d]There were no cases of low birth weight among term births in the intervention group.

Among term births, the median (25th, 75th percentile) birth weights for control and intervention participants were 3500 g (3200, 3800 g) and 3600 g (3300, 3850 g), respectively. The intervention was associated with greater term birth weight (85 g; 95% CI: 3, 167 g; Figure 3.4) and gestational age-adjusted term birth weight (81 g; 95% CI: 2, 159 g), as well as a trend toward decreased risk of SGA (OR=0.44; 95% CI: 0.19, 1.05). No variables modified the intervention effects for all births or term births (Figure 3.4).

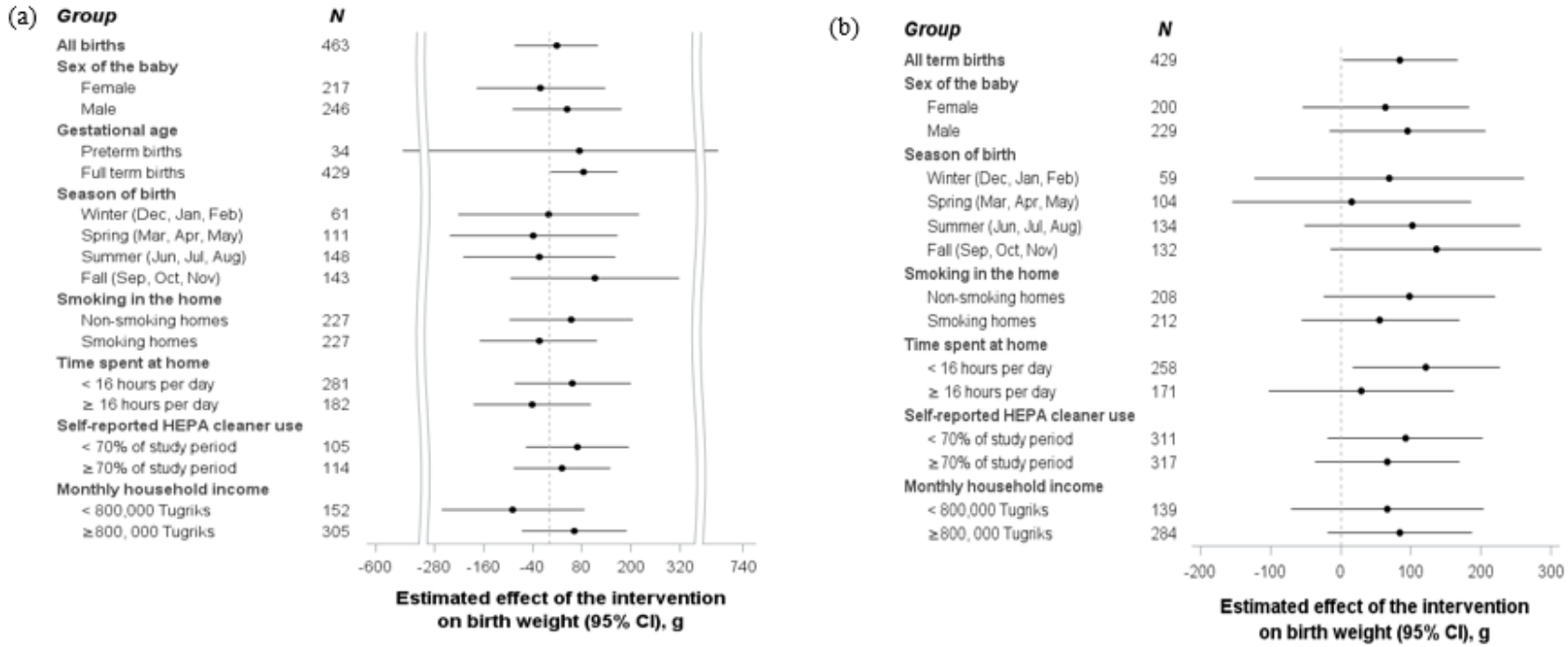


Figure 3.4. Effect of the intervention on birth weight in stratified analyses for (a) all births and (b) term births.

Note: 16 hours per day was the median time spent at home and 70% was the median self-reported use of the HEPA air cleaners. Numbers (Ns) reported for self-reported HEPA cleaner use reflect the number of intervention homes and effect estimates are relative to control homes. Monthly household income, as a proxy for socioeconomic status, was investigated as a potential effect modifier *post hoc*.

We also estimated the effects of using one or two air cleaners on birth outcomes separately because we previously reported greater $PM_{2.5}$ reductions among participants who received two air cleaners[55] Use of one HEPA cleaner was not associated with significant differences in birth weight (26 g; 95% CI: -100, 151 g) or gestational age-adjusted birth weight (17 g; 95% CI: -104, 138 g) among term births. For participants who received two HEPA cleaners, the intervention was associated with non-significant trends toward greater birth weight (85 g; 95% CI: -7, 177 g) and gestational age-adjusted birth weight (82 g; 95% CI: -5, 168 g) among term births.

There were 47 adverse events not prespecified as secondary outcomes, including 34 spontaneous abortions (24 control, 10 intervention) and 13 stillbirths (5 control, 8 intervention). Participants who had a spontaneous abortion were enrolled at a median (25th, 75th percentile) gestation of 8.0 weeks (7.0, 9.0 weeks), and participants who had a stillbirth were enrolled at a median (25th, 75th percentile) gestation of 10.0 weeks (5.0, 12.0 weeks). Spontaneous abortions occurred at a median (25th, 75th percentile) gestation of 12.0 weeks (9.5, 14.0 weeks) and stillbirths occurred at a median (25th, 75th percentile) gestation of 30.0 weeks (20.5, 36.0 weeks). There were no significant differences in the timing of spontaneous abortions or stillbirths between groups. The intervention was associated with a decreased risk of spontaneous abortion (OR=0.38; 95% CI: 0.18, 0.82), but there was no association with stillbirth (OR=1.58; 95% CI: 0.51, 4.90).

3.5. Discussion

In this single-blind RCT in a community exposed to very high air pollution concentrations, portable HEPA cleaner use during pregnancy was not associated with improvements in fetal growth among all births. However, the intervention was associated with an 85 g (95% CI: 3, 167 g) increase in term birth weight. Unexpectedly, we also saw an increased risk of PTB (OR=2.37; 95% CI: 1.11, 5.07) and a decreased risk of spontaneous abortion (OR=0.38; 95% CI: 0.18, 0.82) with intervention use.

Fetal growth restriction and shorter duration of gestation can both cause reductions in birth weight. To reduce the influence of gestational age and evaluate the effect of air pollution on "normal" fetal growth, others have restricted their investigations to term births.[4,28,151] We observed a 100 g greater median birth weight among the intervention group in our full study population, but this difference was not statistically significant based on a non-parametric test of medians or our linear regression model that tested for differences in means. However, adjusting for PTB resulted in a nearly identical intervention effect estimate (84 g; 95% CI: -1, 170 g) as that of our subgroup analysis of term births (85 g; 95% CI: 3, 167 g). This suggests that the intervention improved fetal growth in the full study population, but that improvement was offset by a higher frequency of PTB in the intervention group.

The effects of air pollution on fetal growth may be most detrimental in later pregnancy. For example, in their recent meta-analysis, Sun et al. (2016) suggested that the second and third trimesters might be a critical exposure window for $PM_{2.5}$.[4] Similarly, Rich et al. (2015) reported that infants born to women in Beijing who had their eighth month of pregnancy during the 2008 Olympics, when outdoor pollution levels were substantially reduced, had a 23 g (95% CI; 5, 40 g) greater mean term birth weight compared with infants whose eighth month fell in the same time period in the year before or after the Olympics.[152] Studies using repeated ultrasound measurements also suggest that air pollution may not alter growth trajectories until late in the second trimester.[153,154]

The observed relationship between the intervention and birth weight is biologically plausible. Air pollution has been linked with changes relevant to fetal growth, such as systemic oxidative stress, inflammation, endothelial dysfunction, blood coagulation, and blood pressure.[155] During pregnancy, these mechanisms are thought to decrease utero-placental blood flow from improper placental vascularization and increase blood flow resistance, among other effects.[76] The pathophysiology of growth restriction is thought to be rooted in the inability of the fetus to receive adequate nutrients and oxygen due to placental dysfunction brought upon by these mechanisms.[27] Constituents adsorbed onto particles may act through additional pathways. For example, heavy

metals such as cadmium may deregulate processes such as calcium transport and placental release of progesterone.[83] Randomized trials of portable air cleaner use over 4-14 days have demonstrated improved endothelial function, and reduced systemic inflammation and blood pressure, in healthy adults (20 to 75 years of age).[91,95,96] A recent RCT also reported lower diastolic blood pressure among 162 pregnant women using cleaner burning ethanol stoves compared with 162 pregnant women using more polluting kerosene or firewood stoves in Ibadan, Nigeria (p=0.04).[156]

The magnitude of our PTB-adjusted birth weight result and our term birth weight result is comparable with the only previous randomized trial of air pollution and fetal growth. Thompson et al. (2011) randomized 69 pregnant women in rural Guatemala to receive a chimney stove, and 105 pregnant women to a control group that continued to use open fires for cooking.[144] The intervention was associated with a 39% reduction in carbon monoxide exposure and an 89 g (95% CI: -27, 204 g) increase in mean birth weight.[144] Our estimated intervention effects on fetal growth are also comparable to those from maternal nutrition interventions aimed at increasing birth weight. A pooled analyses of 19 randomized trials conducted in countries such as Taiwan, India, Iran, England, and the US reported 74 g (95% CI: 30, 117 g) greater mean birth weights among women receiving protein energy supplementation compared with control participants consuming routine diets.[157] Another pooled analyses reported that dietary interventions were associated with greater mean birth weights of 94 g, starting from a weight of 3086 g, in low-income countries and 49 g, from a starting weight of 3406 g, in high-income countries.[158] Maternal malnutrition is a key contributor to poor fetal growth, and like air pollution, it disproportionately affects populations in LMIC.[3,159] However, unlike air pollution-related interventions, considerable emphasis has been placed on maternal nutrition intervention programs in LMIC to improve pregnancy and birth outcomes.[160]

We unexpectedly found the intervention was associated with a decreased risk of spontaneous abortion. There was no difference in timing of enrollment or spontaneous abortion between intervention and control participants. Active smoking and SHS exposures during pregnancy have been linked to spontaneous abortion,[161] but the evidence for air pollution is conflicting. Enkhmaa

et al. (2014) reported strong positive correlations between monthly outdoor air pollution concentrations and monthly hospital admissions for spontaneous abortion in Ulaanbaatar (r >0.80).[162] Monthly rates of spontaneous abortion were approximately 2.5 times greater in winter than in summer. The investigators did not consider other seasonally varying factors such as vitamin D or influenza exposure. In contrast, other studies conducted in Brazil[163] and China[164] reported no associations between outdoor PM and spontaneous abortion.

Although we also found an increased risk of PTB among intervention participants, the intervention did not significantly impact the risk of early (<34 weeks) PTBs (OR=1.18; 95% CI: 0.36, 3.94), which are less likely to reflect iatrogenic intervention. The risk of late (34-36 weeks) PTBs was significantly elevated among intervention participants. The reason for the surprising increase in PTB in the intervention group may be found, in part, in the higher frequency of spontaneous abortions in the control group; the presence of the intervention may have enabled fetuses to survive long enough to be born preterm. The downstream effects of $PM_{2.5}$-induced oxidative stress and inflammation on fetal growth may be seen in early pregnancy, resulting in pregnancy loss, or in later pregnancy, resulting in PTB and/or SGA.[165-168] Although unlikely, an increased risk caused by noise from the HEPA cleaners cannot be ruled out. No studies have investigated the potential effects of air cleaner-related noise, but limited research suggests that exposure to noise from aircraft and road traffic during pregnancy may increase the risk of PTB, possibly by increasing the release of stress hormones that interfere with the production and release of progesterone.[169] Our findings of an adverse effect on PTB and a decreased risk of spontaneous abortion merit further investigation.

Some important limitations of this study should be noted. Participants were not blinded to their intervention status, which likely contributed to the greater loss to follow-up among control participants. Although the treatment groups were similar in age, marital status, household income, pre-pregnancy BMI, and parity, it is possible that the groups differed in unmeasured ways despite randomization. Participants received air cleaners at a median of 11 weeks gestation so the HEPA cleaners did not influence exposure during much of the first trimester. Spontaneous abortions were

based on participant report, and we were not able to distinguish between spontaneous and medically indicated cases of PTB. Gestational age at birth was assessed from clinic records and was based on a combination of first trimester ultrasound, last menstrual period, and clinical assessment (symphyseal-fundal height measurements and/or Dubowitz or Ballard score). Participants reported using the HEPA cleaners for a median 70% of the study period but we were unable to assess how/if use changed throughout the study period. Anecdotal reports from participants indicated that HEPA cleaner use may have been reduced due to concerns about noise and electricity costs, and this may have reduced the benefits of the intervention.

3.6. Conclusions

Our motivations for studying the impact of HEPA cleaners on fetal growth were to investigate the causal role of $PM_{2.5}$ on fetal growth and to assess this household level intervention. We previously reported that HEPA filter air cleaner use was associated with significant reductions in indoor residential $PM_{2.5}$ concentrations.[55] In the present study, HEPA cleaner use was associated with greater birth weight, but the effect was offset by a higher frequency of PTB in the intervention group. We speculate that the apparent increase in risk of PTB was due, at least in part, to selection bias resulting from a reduction in spontaneous abortions. Our findings provide additional evidence for the health benefits of reducing air pollution. While HEPA cleaners can reduce exposures at the household level, this intervention is not accessible to or appropriate for everyone. Portable air cleaners require a constant supply of electricity, have costs related to initial purchase, operation, and maintenance that may be prohibitive to some, and are generally less effective in dwellings with high air exchange rates such as temporary or poorly constructed structures or in warm climates where windows are frequently opened. Thus, in any community, relying solely on such household level interventions to address air pollution exposures will not protect everyone, particularly those most vulnerable. In the long-term, strategies to reduce community-wide air pollution concentrations are needed to ensure that the benefits of exposure reduction are available to all.

Chapter 4.

Gestational cadmium exposure and fetal growth in Ulaanbaatar, Mongolia

4.1. Abstract

Background: Gestational cadmium exposure may impair fetal growth. Coal smoke has largely been unexplored as a source of cadmium.

Aims/Objective: We investigated the relationship between gestational cadmium exposure and fetal growth and assessed coal smoke as a potential source of cadmium among non-smoking pregnant women in Ulaanbaatar, Mongolia, where residential coal combustion is a major source of air pollution.

Methods: This observational study was nested within the Ulaanbaatar Gestation and Air Pollution Research (UGAAR) study, a randomized controlled trial of portable high efficiency particulate air (HEPA) filter air cleaner use during pregnancy, fetal growth, and early childhood development. We measured third trimester blood cadmium concentrations in 374 out of 465 participants who had a live birth. We used multiple linear and logistic regression to assess the relationships between $\log_2$-transformed maternal blood cadmium concentrations and birth weight, length, head circumference, ponderal index, low birth weight, small for gestational age, and preterm birth in crude and adjusted models. We also evaluated the relationships between $\log_2$-transformed blood cadmium concentrations and the density of coal-burning stoves within 5,000 m of each participant's apartment.

Results: The median (25th,75th percentile) blood cadmium concentration was 0.20 µg/L (0.15, 0.29 µg/L). A doubling of blood cadmium was associated with an 86 g (95% CI: 26, 145 g) reduction in birth weight in adjusted models. An interquartile range increase in coal stove density surrounding participants' homes was associated with an 11% (95% CI: 0, 23%) increase in blood cadmium concentrations.

Conclusions: Gestational cadmium exposure was associated with reduced birth weight. In settings where coal is a widely used fuel, cadmium may play a role in the putative association between air pollution and impaired fetal growth.

4.2. Introduction

Cadmium is a ubiquitous metal that is linked to cancer and kidney and bone disease.[50,51] Diet and smoking are the most important sources of cadmium.[50] Foods with the highest cadmium content include those grown or harvested in cadmium-rich environments such as leafy vegetables, grains, shellfish, and organ meats.[50] Tobacco smoke is the largest source of cadmium among smokers,[51] while second hand smoke (SHS) is an important source among non-smokers.[52-55] Cadmium can also be emitted into the environment from the combustion of solid fuel, such as coal, and through iron and copper smelting, waste incineration, and battery manufacturing and recycling.[51,56,170,171]

Gestational cadmium exposure may impair fetal growth. Several studies have linked maternal cadmium exposures to decreases in birth weight[11-13,15,17,20,60,63,69] and increased risks of low birth weight (LBW),[22,64] small for gestational age (SGA),[14,23,59,62] and preterm birth (PTB),[71] while others have reported no associations.[16,17,21,24,66,68,70] The inconsistent findings are likely due, in part, to differences in study design, sample size, and exposure levels. Most studies have focused on tobacco smoke or diet as the main sources of exposure. Few studies have been conducted among non-smoking pregnant populations in communities heavily impacted by coal smoke, with these studies reporting mixed findings on the importance of coal as a cadmium source.[17,74,75]

This study is part of the Ulaanbaatar Gestation and Air Pollution Research (UGAAR) study, a randomized controlled trial of portable high efficiency particulate air (HEPA) filter air cleaner use, fetal growth, and early childhood development (ClinicalTrials.gov Identifier: NCT01741051). Ulaanbaatar, the capital of Mongolia, has some of the world's highest air pollution concentrations. The population-weighted annual average $PM_{2.5}$ concentration is over seven times the World Health Organization (WHO) guideline concentration of 10 $\mu g/m^3$.[100] The high pollution levels are primarily due to wintertime residential coal use in neighborhoods of traditional Mongolian felt-lined yurts (gers) and poorly constructed one or two-story wood and brick homes. Roughly 60% of the city's residents live in these neighborhoods, which surround the apartment-dwelling population in the city center from which the UGAAR population was recruited.[99] Three coal-fired power plants supply electricity and heat to apartments and other buildings in the city.[98] The plants are a relatively minor contributor to $PM_{2.5}$ concentrations and spatial variability compared with residential coal emissions, which are responsible for 45-70% of total $PM_{2.5}$ concentrations in the city.[98-100]

We previously reported that SHS exposure was a source of cadmium based on our assessment of third trimester blood cadmium concentrations among this study population.[55] Close to half of our non-smoking study participants reported living with a smoker during pregnancy, which was not surprising considering the high smoking rates in Mongolia; nearly 40% of men smoke compared with roughly 7% of women.[100,103] We also assessed hair nicotine concentrations, as a marker of SHS, among a subset of the population (n=125). We found higher blood cadmium and hair nicotine concentrations, and stronger correlations between these measures, among participants who lived with a smoker (r=0.29 vs r=0.10; n=125).[55] We also reported that among this population, the HEPA cleaner intervention was associated with a 14% (95% CI: 4, 23%) reduction in blood cadmium concentrations,[55] suggesting that airborne cadmium contributed to exposure, and an 85 g (95% CI: 3, 167 g) increase in term birth weight (see Chapter 3). Here, we investigated the relationship between maternal blood cadmium concentrations and fetal growth. We also assessed residential coal stoves as a source of gestational cadmium exposure.

4.3. Methods

4.3.1. Data collection

The UGAAR study has been described previously.[55] Briefly, we enrolled women who were ≥ 18 years, ≤ 18 weeks into a single-gestation pregnancy, non-smokers, living in an apartment (i.e., not living in a ger neighborhood), planning to give birth in an Ulaanbaatar maternity hospital, and not using a portable air cleaner in the home at enrollment. We excluded women who lived in ger households because electricity is unreliable in these neighbourhoods and because we wanted to minimize the influence of indoor pollution emissions from coal stoves since we were primarily interested in the effects of community air pollution. Recruitment was conducted at two reproductive health clinics in the city's centrally-located Sukhbaatar district. Participants were randomly assigned to the intervention or control group. The intervention group received one or two HEPA filter air cleaners (henceforth, "HEPA cleaners"), depending on the size of their apartment, to use from early pregnancy until delivery, while the control group received no HEPA cleaners. Data were collected from medical records and at two clinic visits, which occurred in early (median of 11 weeks) and later pregnancy (median of 31 weeks).

Blood cadmium concentrations

Whole blood samples were collected by a nurse at the reproductive health clinic during the second clinic visit. In total, 378 samples were collected from 465 participants who went on to have a live birth. Some participants refused or were unavailable to provide a blood sample. Samples were refrigerated and shipped to the Wadsworth Center (New York State Department of Health, Albany, New York, USA) and analyzed within six weeks of collection using quadrupole-based inductively coupled plasma-mass spectrometry (ICP-MS), with matrix-matched calibration.[129] The limit of quantification (LOQ) was 0.043 µg/L. Two samples that were below the LOQ were assigned values of LOQ/2.[130]

Fetal growth outcomes

Our outcomes were birth weight, length, head circumference, ponderal index, LBW, SGA, and PTB. Data on birth weight, birth length, head circumference, and gestational age were obtained from clinic records after each delivery. We calculated ponderal index, a ratio of height to weight, as 100 multiplied by birth weight (g) divided by crown-heel length cubed (cm^3). Low birth weight was defined as <2,500 g, SGA was defined as $<10^{th}$ percentile for gestational age and sex using World Health Organization fetal growth charts[145], and PTB was defined as birth at <37 weeks gestation.

Determinants of cadmium exposure and co-variates

We collected information on potential sources of exposure as well as demographic and health factors via questionnaires that were administered at two clinic visits. Exposure to tobacco smoke was self-reported; we asked participants if they smoked and whether they lived with a smoker during pregnancy. Previously, we validated the self-reported data and found significantly higher median (25th, 75th percentile) hair nicotine concentrations [0.23 ng/mg (0.14, 0.72 ng/mg), n=66] among participants that reported living with a smoker in late pregnancy compared with participants who did not [0.09 ng/mg (0.05, 0.17 ng/mg), n=56, $p < 0.001$].[55] Here, we used the self-reported measures of tobacco smoke exposure since we had more complete data on these measures than on hair nicotine. We used responses collected in late pregnancy to reflect the relevant exposure period captured by concentrations in blood, which is roughly three to four months.[50] We used coal stove density as a proxy of residential coal smoke. We previously used high resolution aerial imagery and object-based image classification to map the location of over 108,000 gers in Ulaanbaatar,[172] and here we used those ger locations to approximate the density of coal-stoves surrounding each participant's apartment within a 5,000 m redius. The density of gers within 5,000 m of participants' apartments was predictive of indoor $PM_{2.5}$ concentrations in the UGAAR cohort and the locations of ger neighbourhoods explained 66% of the spatial variability in outdoor sulphur dioxide (SO_2) concentrations, a marker of coal smoke.[122] From clinic records, we also collected information on anemia, pre-existing and gestational hypertension and diabetes, placental disorders and TORCH

(Toxoplasmosis, Others [syphilis, varicella-zoster, parvovirus B19], Rubella, Cytomegalovirus, Herpes) infections during pregnancy.

4.3.2. Data analysis

We used linear and logistic regression to assess associations between cadmium exposure and fetal growth, after excluding three participants that reported active smoking during late pregnancy. The distribution of blood cadmium was skewed by four outliers so we log-transformed the concentrations. We chose $\log_2$ transformations to reduce the influence of extreme values on regression coefficients and to allow easy interpretation of regression coefficients.[24] We adjusted models of birth weight, length, head circumference, ponderal index and LBW for the following co-variates: maternal age at birth (<25, 25-29, 30-34, ≥35years), monthly household income (<600,000 Tugriks, 600,000 to <1,200,000 Tugriks, ≥1,200,000 Tugriks), pre-pregnancy BMI (continuous), anemia status (anemia, no anemia), sex of the baby, gestational age at birth and gestational age at birth squared (weeks, continuous), living with a smoker (yes, no), coal stove density (gers/hectare, continuous), and intervention status (control, intervention). Models of SGA were adjusted for this same list of co-variates, excluding gestational age, gestational age squared, and sex, while models of PTB were adjusted for all co-variates excluding gestational age and gestational age-squared. We used stratified models and interaction terms to evaluate effect modification by sex of the baby, living with a smoker, coal stove density, and intervention status. Results are presented per doubling of cadmium exposure for crude and adjusted models for all births and term births (≥37 weeks).

To investigate coal smoke as a source of maternal cadmium exposure, we regressed $\log_2$-transformed blood cadmium concentrations on coal stove density, while adjusting for the following variables: age of mother (<25, 25-29, 30-34, ≥35 years), monthly household income (<600,000 Tugriks, 600,000 to <1,200,000 Tugriks, ≥1,200,000 Tugriks), pre-pregnancy BMI (continuous), anemia status (anemia, no anemia), living with a smoker (yes, no), season in which the blood sample was collected (winter, spring, summer, fall), and intervention status (control, intervention).

4.4. Results

Blood samples were collected from 378 of the 465 participants who had a live birth in the full UGAAR cohort. One participant who had a child with a chromosomal abnormality and an additional three participants who reported active smoking in late pregnancy were excluded, leaving 374 participants in our final dataset. Participants with and without a blood cadmium measurement had similar demographics and lifestyles, including age at enrollment, household income, maternal education, marital status, and pre-pregnancy BMI. Birth weight, length, and head circumference were also similar between these groups (Table D.1). However, participants with a cadmium measurement were recruited earlier in pregnancy (10.0 vs. 12.0 weeks; p=0.003), gave birth later in pregnancy (39.5 vs. 39.3 weeks; p=0.01) and were less likely to have a baby that was LBW weight (4% vs 9%; p=0.04) or preterm (5% vs 17%; p=0.001) compared with those who did not provide a blood sample.

Participants with a blood cadmium measurement were enrolled at a median (25^{th}, 75^{th} percentile) age of 29.0 years (25.0, 33.0 years) and a gestational age of 10.0 weeks (8.0, 12.0 weeks). Most participants (86%) were married or in common-law relationships, completed university (81%), and 44% reported a monthly household income in the highest income bracket of ≥1,200,000 Tugriks (approximately $487 USD) (Table 4.1). Close to half (43%) of participants reported living with a smoker at any time in pregnancy. Seventy-six percent of participants reported taking iron, folate, calcium, or multivitamin supplements during pregnancy, but data for 24% of participants were missing. Few participants had anemia (19%), diabetes (0%), gestational diabetes (0%), gestational hypertension (8%), or TORCH infections (2%). The median (25th, 75th percentile) birth weight and gestational age were 3500 (3165, 3800) g and 39.5 (38.5, 40.0) weeks, respectively (Table 1). The median (25^{th}, 75^{th} percentile) birth length, head circumference and ponderal index were 51 cm (50, 52 cm), 35 cm (34, 36 cm), 2.6 g/cm^3 (2.5, 2.8 g/cm^3) , respectively.

The median (25th,75th percentile) blood cadmium concentration was 0.20 µg/L (0.15, 0.29 µg/L). In bivariate analyses, cadmium concentrations were marginally higher among women who

reported living with a smoker (p=0.08) and significantly higher among those living in an apartment surrounded by a higher density of coal stoves (p=0.02; Table 4.1). Blood cadmium concentrations were also highest among participants who delivered babies in the lowest birth weight tertile (p=0.02). Participants who had a blood sample collected in spring (p=0.03) and those in the intervention group (p=0.008) had lower blood cadmium concentrations.

Table 4.1 Maternal blood cadmium concentrations (µg/L) by maternal and newborn characteristics

	N (%)	Median (25th, 75th percentile)	p-value
MATERNAL			
Maternal age			
< 25 years	79 (21)	0.20 (0.15, 0.30)	0.49
25-29 years	118 (32)	0.20 (0.15, 0.27)	
30-34 years	129 (34)	0.19 (0.14, 0.29)	
>34 years	49 (13)	0.22 (0.18, 0.31)	
Maternal education			
Completed university	302 (81)	0.20 (0.15, 0.29)	0.17
Did not complete university	42 (11)	0.21 (0.16, 0.37)	
Marital status			
Married/common-law	320 (86)	0.20 (0.15, 0.29)	0.25
Not married/common-law	54 (14)	0.20 (0.16, 0.31)	
Monthly household income			
< 600,000 Tugriks[a]	92 (25)	0.16 (0.11, 0.29)	0.29
600,000 to <1,200,000 Tugriks	105 (28)	0.22 (0.16, 0.32)	
≥ 1,200,000 Tugriks	163 (44)	0.19 (0.15, 0.28)	
Parity			
0	39 (10)	0.22 (0.15, 0.31)	0.68
1	141 (38)	0.19 (0.15, 0.27)	
≥2	82 (22)	0.19 (0.12, 0.32)	
Missing	112 (30)	0.20 (0.16, 0.29)	
Pre-pregnancy BMI			
< 20	104 (28)	0.20 (0.15, 0.27)	0.87
20-22	134 (36)	0.20 (0.15, 0.31)	
≥ 23	110 (29)	0.19 (0.14, 0.29)	
Worked outside the home during pregnancy			
No	81 (22)	0.22 (0.15, 0.34)	0.20
Yes	281 (75)	0.19 (0.15, 0.28)	
Anemia status			
No	304 (81)	0.20 (0.15, 0.29)	0.71
Yes	70 (19)	0.19 (0.15, 0.27)	
Took iron, folate, calcium, or multi-vitamin supplements during pregnancy			
No	0 (0)	NA	0.80
Yes	283 (76)	0.19 (0.15, 0.29)	
Missing	91 (24)	0.20 (0.15, 0.31)	
Lived with a smoker in late pregnancy			
No	193 (52)	0.19 (0.15, 0.27)	0.08
Yes	160 (43)	0.21 (0.15, 0.33)	

Season in which blood sample was collected			
Winter (December, January, February)	71 (19)	0.20 (0.16, 0.29)	0.03
Spring (March, April, May)	119 (32)	0.17 (0.14, 0.26)	
Summer (June, July, August)	102 (27)	0.21 (0.16, 0.30)	
Fall (September, October, November)	82 (22)	0.23 (0.15, 0.30)	
Coal stove density (within 5000 m buffer of apartment)			
< 3.5 gers/hectare	127 (34)	0.18 (0.14, 0.25)	0.02
3.5-4.5 gers/hectare	130 (35)	0.20 (0.16, 0.3)	
>4.5 gers/hectare	115 (31)	0.21 (0.16, 0.31)	
Intervention status			
Control	173 (46)	0.22 (0.16, 0.31)	0.008
Intervention	201 (54)	0.19 (0.14, 0.27)	
NEWBORN			
Sex of baby			
Girls	169 (45)	0.20 (0.15, 0.29)	0.64
Boys	205 (55)	0.19 (0.15, 0.29)	
Birth weight			
< 3400 g	133 (35)	0.22 (0.16, 0.32)	0.02
3400-3700 g	123 (33)	0.19 (0.15, 0.27)	
> 3700 g	118 (32)	0.19 (0.14, 0.27)	
Low birth weight			
No	359 (96)	0.19 (0.15, 0.29)	0.85
Yes	15 (4)	0.22 (0.14, 0.38)	
Small for gestational age			
No	347 (93)	0.19 (0.15, 0.29)	0.16
Yes	27 (7)	0.25 (0.16, 0.32)	
Preterm birth			
No	355 (95)	0.20 (0.15, 0.29)	0.52
Yes	19 (5)	0.20 (0.14, 0.25)	

[a]At the time of data collection, 600,000 Tugriks was equivalent to approximately $243 USD.

Blood cadmium concentrations were associated with decreased birth weight in both crude and adjusted models (Table 4.2). In adjusted models, a doubling of blood cadmium concentration was associated with an 86 g (95% CI: 26, 145 g) and 84 g (95% CI: 27, 142 g) decrease in birth weight among all births and term births, respectively. A doubling in blood cadmium was also associated with a decrease in ponderal index (-0.04 g/cm^3; 95% CI: -0.08, 0.01 g/cm^3) among term births and

there was a trend toward increased risk of small for gestational age (OR=1.52; 95% CI: 0.93, 2.49). No other associations with fetal growth or duration of gestation were found.

Table 4.2 Effect of a doubling of maternal blood cadmium concentrations on fetal growth outcomes

		Crude		Adjusted[a]	
Outcome	**Type of effect estimate[b]**	**All births (n = 374)**	**Term births[c] (n =355)**	**All births (n = 324)**	**Term births[c] (n = 311)**
Birth weight, g	Mean difference (95% CI)	-71 (-136, -7)	-86 (-143, -28)	-86 (-145, -26)	-84 (-142, -27)
Birth length, cm		-0.21 (-0.52, 0.10)	-0.21 (-0.46, 0.05)	-0.17 (-0.45, 0.11)	-0.15 (-0.42, 0.12)
Head circumference, cm		-0.03 (-0.25, 0.19)	-0.09 (-0.28, 0.10)	-0.09 (-0.29, 0.10)	-0.09 (-0.29, 0.10)
Ponderal index, g/cm^3		-0.01 (-0.05, 0.02)	-0.03 (-0.06, -0.001)	-0.04 (-0.08, 0.002)	-0.04 (-0.08, -0.01)
Low birthweight	Odds ratio (95% CI)	0.90 (0.47, 1.72)	1.85 (0.72, 4.79)	1.16 (0.48, 2.80)	1.57 (0.60, 4.13)
Small for gestational age		1.43 (0.90, 2.26)	1.45 (0.87, 2.42)	1.52 (0.93, 2.49)	1.45 (0.84, 2.50)
Preterm birth		0.66 (0.36, 1.21)		1.52 (0.80, 2.87)	-----

[a]Models of birth weight, birth length, head circumference, ponderal index and low birth weight were adjusted for maternal age, monthly household income, pre-pregnancy BMI, anemia status, sex of the baby, gestational age and gestational age squared, living with a smoker in late pregnancy, ger density, and intervention status. Models of small for gestational age were adjusted for the same list of variables, excluding gestational age, gestational age squared, and sex, and models of preterm birth were adjusted for the same list of variables, excluding gestational age and gestational age squared.

[c]≥37 weeks gestation

After stratifying by sex of the baby, a significant effect on birth weight was only seen for girls (Figure 4.1), although an interaction between cadmium and sex was not significant (p=0.45). Similarly, living with a smoker, coal stove density, and intervention status were also not significant effect modifiers of the relationship between cadmium exposure and birth weight (Figure 4.1) or other outcomes (Tables D2-D5).

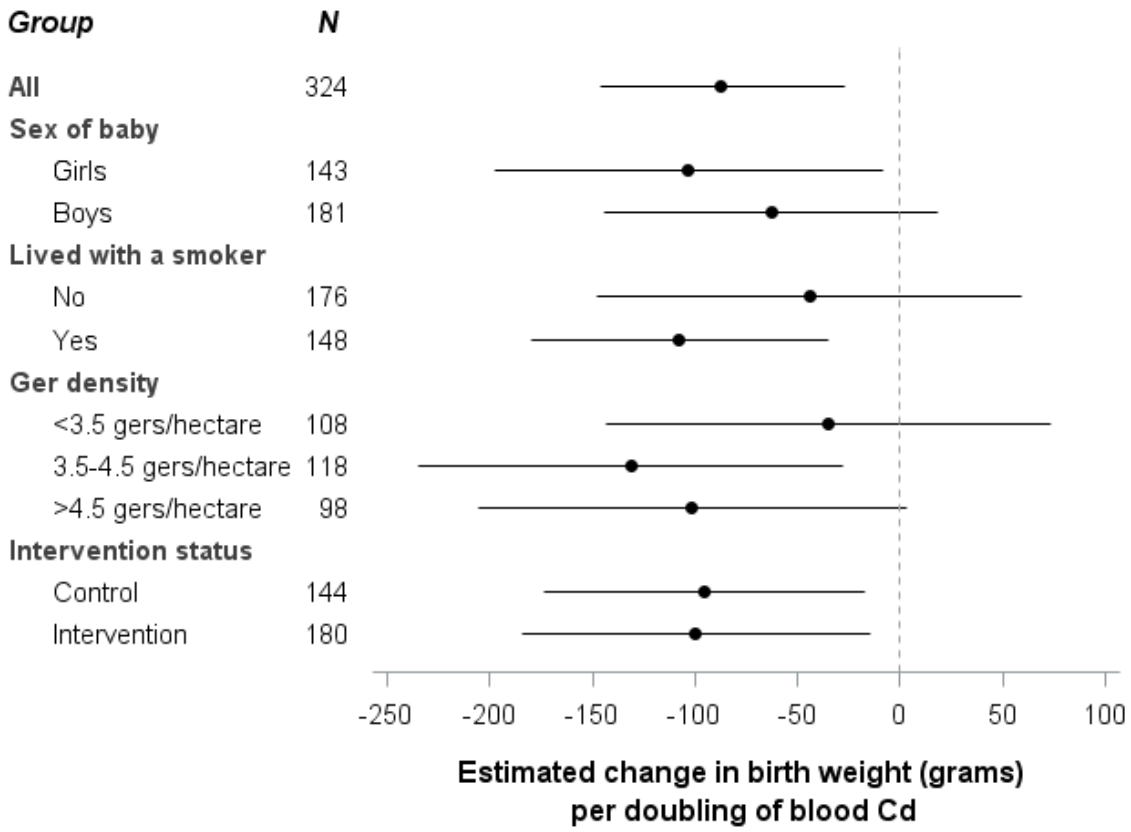


Figure 4.1 Estimated effects of a doubling of maternal blood cadmium (Cd) concentrations on birth weight in stratified analyses

After adjustment in a multiple linear regression model, an interquartile increase in coal stove density (from 3 to 5 gers/hectares) was associated with an 11% (95% CI: 0, 23%) increase in blood cadmium concentrations. Living with a smoker was associated with a 12% (95% CI: 0, 25%) increase in blood cadmium.

4.5. Discussion

This observational study was nested within the UGAAR randomized controlled trial of portable HEPA cleaners and early-life growth and development in Ulaanbaatar, Mongolia. We found that

cadmium exposure during pregnancy was associated with reductions in birth weight in adjusted models. We previously reported higher blood cadmium concentrations among participants who lived with a smoker as well as 14% (95% CI: 4, 23%) lower blood cadmium concentrations among intervention participants using HEPA cleaners during pregnancy, indicating an airborne source of exposure.[55] Here we found that the density of coal stoves surrounding participants' apartments was associated with blood cadmium concentrations.

Birth weight was reduced by 86 g (95% CI: 26, 145 g) per doubling of maternal blood cadmium concentrations in adjusted models, an exposure contrast that roughly corresponds with the blood cadmium interquartile range of 0.15-0.29 µg/L. Others have also reported decreases in birth weight with gestational cadmium exposure.[11-13,15,17,20,60,63,69] Taylor et al. (2016) reported a 63 g (95% CI: 18, 107 g) decrease in term birth weight per 1 µg/L increase in maternal blood cadmium concentrations among 4,191 pregnant women living in the United Kingdom.[13] Vidal et al. (2015) reported a 52 g decrease in birth weight with each log-unit increase in maternal blood cadmium concentrations (se=24.2, p=0.03) among 276 pregnant women in North Carolina, US.[19] Maternal urinary cadmium concentrations have also been linked to significant decreases in birth weight.[11,20,25,72] However, the evidence is not consistent, with others reporting no associations between maternal blood or urinary cadmium concentrations and birth weight.[16,24,67,71,173]

After stratifying by sex of the baby, maternal blood cadmium concentrations were associated with significant decreases in birth weight for girls only, but sex was not a significant effect modifier. Others have reported greater effects of cadmium exposure among girls,[11,13,17,20,22,25] and the lack of stratified analyses in some studies has been suggested as a potential explanation for the mixed findings of cadmium effects on fetal growth.[13] Taylor et al. (2016) reported significantly larger effects among girls than boys for birth weight, head circumference, and birth length.[174] Similarly, Cheng et al. (2016) reported that each log unit increase in maternal urinary cadmium (µg/g creatinine) was associated with a 117g (95% CI: 25, 209g) decrease in birth weight among girls, with no significant effects among boys.[11] The lack of a significant interaction effect seen in our study may be due, in part, to insufficient power to evaluate interactions.

There are multiple plausible pathways through which cadmium may affect fetal growth. Cadmium is absorbed into the body via inhalation or ingestion; roughly 10-50% of inhaled cadmium is absorbed compared with only 3-5% through ingested cadmium.[51,175] Cadmium is primarily stored in the kidneys and liver,[51] but during pregnancy it can also accumulate in the placenta and cross into the fetal environment.[82] Once in the placenta, cadmium can interfere with the transfer of zinc and other essential nutrients,[59,82] as well as with placental release of progesterone.[83] Cadmium may also induce oxidative stress, which can cause direct cellular damage and initiate secondary processes, including systemic inflammation, endothelial dysfunction, and increased blood pressure, ultimately decreasing utero-placental blood flow.[170,176] Cadmium has been linked to an increased risk of gestational hypertension in pregnant women, a risk factor for poor fetal growth.[29,177] Cadmium has also been shown to inhibit the release of the placental enzyme 1β-hydroxysteroid dehydrogenase type 2 (1β-HSD2), which is responsible for protecting the fetus from excess maternal cortisol.[77,178] Low enzymatic activity of 1β-HSD2 has been associated with increased risks of fetal growth restriction and preterm birth.[77] The sex-selective effects of cadmium may be, in part, due to differential responses in the methylation of growth-related genes, with hypomethylation in girls and hypermethylation in boys.[13]

Much of the research investigating air pollution effects on fetal growth has focussed on $PM_{2.5}$ as the main pollutant of interest. Studies have found relatively small but consistent effects of $PM_{2.5}$ on birth weight, LBW, SGA, and PTB.[4,7] In a recent meta-analysis of 17 studies, authors reported that each 10 $\mu g/m^3$ increase in outdoor $PM_{2.5}$ was associated with a 16 g (95% CI: 5, 27 g) decrease in birth weight.[4] Both the size and composition of $PM_{2.5}$ particles influence their toxicity, but few studies have attempted to understand how differences in composition may affect fetal growth.[4,179,180] In an investigation of $PM_{2.5}$ and LBW in 22 US counties, Hao et al. (2015) suggested that differences in nitrate and sulphate concentrations may in part explain differences in county-level effect estimates.[180] Similarly, Sun et al. (2016) reported that birth weight has been negatively associated with zinc, nickel, titanium, and vanadium particles, in their meta-analysis of outdoor $PM_{2.5}$ and fetal growth; none of the studies included in the analysis investigated cadmium.[4]

Differences in oxidative potential has been suggested to modify the relationship between $PM_{2.5}$ and fetal growth,[181] which in turn is attributed to its compositional differences in metals, polycyclic aromatic hydrocarbons (PAHs), and other components.[182,183] PAHs have been identified as particularly toxic components of coal-, tobacco-, and traffic-related $PM_{2.5}$ emissions that are linked to impaired fetal growth.[184,185] Cadmium may be another component of $PM_{2.5}$ mixtures that can explain, in part, the detrimental effects of $PM_{2.5}$ on fetal growth in some settings. Like cadmium, $PM_{2.5}$ has also been shown to induce oxidative stress, inflammation, and endothelial dysfunction[155] and these overlapping pathways may contribute to increased particle toxicity on fetal growth.

We interpret our finding of an association between coal stove density and blood cadmium as evidence that coal smoke is a source of cadmium among this population. We previously reported that the locations of ger neighbourhoods in Ulaanbaatar explained 66% of the variability in outdoor SO_2 concentrations, and that coal stove density was predictive of indoor $PM_{2.5}$ concentrations in the UGAAR cohort.[122] Notably, the impact of an interquartile range increase in coal stove density on blood cadmium (11%, 95% CI: 0, 23%) was similar to that of living with a smoker during pregnancy (12%, 95% CI: 0, 25%). SHS is an established source of cadmium.[17,186,187]

Source apportionment studies have linked industrial coal use to outdoor air cadmium concentrations in parts of China, New Zealand, and the US.[171,188-191] However, few studies have investigated industrial or residential coal emissions as a contributor to blood or urinary cadmium concentrations in communities that rely heavily on coal, particularly among pregnant women. Two studies reported that blood cadmium concentrations did not significantly differ in pregnant women who lived near a coal combustion factory or used coal as cooking fuel compared with those that were not exposed to coal, in China (n=215) and South Africa (n=641).[17,74] In contrast, Zhang et al. (2016) reported significantly higher airborne cadmium concentrations in homes using coal for cooking and heating (n=12) versus gas or electricity (n=83), as well as significantly higher cadmium concentrations during the heating (February to March) vs non-heating (April to January) season in Lanzhou, China.[75] Authors also reported a 3 g decrease in birth weight per 1 ng/m^3 increase in residential airborne cadmium concentration in the heating season only (p=0.05).[75] The

mixed study findings may in part be explained by differences in coal composition, which can depend on the type of coal as well as the geographic area from which it is mined.[192-194]

We cannot rule out the possibility that the association between coal stove density and cadmium exposure is confounded by diet. Diet is considered the most important source of cadmium among non-smokers,[50,51,53,195] but its relative importance to total exposures will depend on the population and setting. In general, diet-related exposures may be higher in areas where cadmium levels are naturally high, or where industrial or agricultural activities have contaminated surrounding soil. For example, diets high in fruits and vegetables are estimated to be a major contributor to cadmium exposure in Bangladesh due to widespread fertilizer-related soil contamination,[196] while diet has been found to be a relatively modest contributor to total exposures compared with active smoking among other populations, including among Norwegian women aged 28-40 years and the general Canadian population.[53,197] Limited information exists on the consumption of cadmium-rich foods in Ulaanbaatar, such as leafy green vegetables, shellfish, and organ meats. Some evidence suggests that women who migrated to Ulaanbaatar from the countryside may be more likely to eat a traditional diet consisting primarily of dairy and meat products.[198] Our questionnaires included questions about migration to Ulaanbaatar, but response rates for these questions were poor. Families who migrate from the country-side are more likely to be of lower income since most move in search of economic opportunities, and therefore, may be more likely to live in less expensive ger neighborhoods than apartments.[100] Ours was a relatively wealthy study population, and our models were adjusted for self-reported household income.

Blood cadmium concentrations measured in our study population were relatively low, with a median (25^{th}, 75^{th} percentile) concentration of 0.20 µg/L (0.15, 0.29 µg/L). In contrast, Wang et al. (2016) reported a median (25^{th}, 75^{th} percentile) blood cadmium of 0.80 µg/L (0.57, 1.06 µg/L) in 3,254 non-smoking pregnant women living in six Chinese cities. No specific source of cadmium was investigated in that study.[14] Similarly, in a review of 24 studies assessing blood cadmium concentrations among smoking and non-smoking pregnant women, Taylor et al. (2014) reported mean and median blood cadmium concentrations ranging from 0.09 to 2.26 µg/L among

populations residing in Poland, Russia, South Africa, Egypt, India, Norway, France, United States and China.[138]

Some limitations of our study should be noted. Our study sample was relatively small, which limited our ability to evaluate effect modifiers. The full UGAAR cohort consisted of 465 live births of which 374 non-smoking participants with an available cadmium blood measurement were included in this analysis. Diet may have potentially confounded the relationship seen between coal stove density and birth weight, but we were unable to assess consumption of typically cadmium-rich foods as a source of exposure in our study. However, we reasoned that airborne exposures were important, as evidenced by the reduction in blood cadmium concentrations among intervention participants who used HEPA cleaners. We did not assess micronutrient status, including levels of zinc and selenium, which can affect cadmium uptake and accumulation, while questionnaire data related to iron, folic acid, calcium, and multivitamin supplementation had poor response rates. Finally, we assessed blood cadmium concentrations only at one time in pregnancy, but previous studies have demonstrated that exposures do not change appreciably throughout pregnancy.[199]

4.6. Conclusions

Gestational cadmium exposure was associated with decreased birth weight, and neighborhood coal stove density, a proxy of residential coal smoke, was associated with higher maternal blood cadmium concentrations, in this cohort of non-smoking pregnant women. In some settings cadmium may play a role in the putative relationship between air pollution and impaired fetal growth.

Chapter 5.

Discussion

5.1. Summary

In our randomized controlled trial, we evaluated the impact of portable HEPA cleaner use during pregnancy on residential indoor $PM_{2.5}$ and maternal blood cadmium concentrations, as well as the effect of HEPA cleaner use during pregnancy and maternal cadmium exposure on fetal growth. The main findings from each chapter are summarized below.

5.1.1. Effect of portable HEPA cleaners on indoor $PM_{2.5}$ concentrations and SHS exposure (Chapter 2)

HEPA cleaner use was associated with a 29% (95% CI: 21, 37%) lower mean indoor $PM_{2.5}$ concentration. Effectiveness was highest in winter when the geometric mean indoor $PM_{2.5}$ concentrations were reduced from 45 to 29 $\mu g/m^3$. Effectiveness was greater when the HEPA cleaners were first deployed (40%, 95 % CI: 31, 48%) than after roughly five months of use (15%, 95 % CI: 0, 27%). We also observed greater reductions in $PM_{2.5}$ concentrations in homes with two HEPA cleaners (33%, 95% CI: 25, 41%) versus one cleaner (20%, 95% CI: 6, 32%). The density of air cleaners per area of the apartment was similar between the homes, so the difference in effectiveness may have been, in part, due to differences in use. For example, we heard anecdotal reports that some participants turned air cleaners off at night due to noise. For homes with two HEPA cleaners, participants may have turned off the unit in the main bedroom and allowed the second unit, which was located in the main living area, to run continuously. We found no evidence of effect modification by air cleaner density, self-reported air cleaner use, season, or window opening. Blood cadmium concentrations were, on average, 14% (95% CI: 4, 23%) lower among intervention participants. We reasoned that SHS was a source of airborne cadmium among our non-smoking population based on the following: (1) close to half of all study participants lived with smokers indicating SHS exposure was common, and (2) we found higher blood cadmium and hair nicotine concentrations as well as stronger correlations between the two measures among

participants who lived with a smoker. Overall, we concluded that HEPA cleaners are an effective intervention to reduce residential indoor $PM_{2.5}$ concentrations and SHS exposure among pregnant women living in a highly polluted community.

5.1.2. Effect of HEPA cleaner use on fetal growth (Chapter 3)

We found that HEPA cleaner use was not associated with fetal growth outcomes in our main analysis, but in a pre-specified subgroup analysis that was limited to 429 term births, we found that their use was associated with greater birth weight of 85 g (95% CI: 3, 167 g). Surprisingly, we found a lower risk of spontaneous abortions (OR=0.38; 95% CI: 0.18, 0.82) among the intervention group. In contrast, we also found a higher frequency of PTB (10% vs 4%; p=0.03) in the intervention group, and we reasoned that this could have offset the beneficial effect of the intervention among all births. We found a 100 g difference in median birth weight between the control (3450 g) and intervention (3550 g) participants, and when we adjusted for PTB we found that the estimated intervention effect on birth weight (84 g; 95% CI: -1, 170 g) was similar to that from the subgroup analysis on term births. We speculated that the higher risk of PTB and the lower risk of spontaneous abortion may have been explained by the intervention allowing for more fetuses to survive long enough to be born preterm. We found no evidence of effect modification by living with a smoker, average time spent indoors at home during pregnancy, sex of the baby, season of birth, self-reported air cleaner use, or household income. Overall, we concluded that use of HEPA cleaners during pregnancy was associated with greater term birth weight.

5.1.3. Effect of gestational cadmium exposure on fetal growth (Chapter 4)

We found that a doubling of maternal blood cadmium concentrations was associated with an 86 g (95% CI: 26, 145 g) and 84 g (95% CI: 2, 142 g) decrease in birth weight and term birth weight, respectively, in models adjusted for maternal age, monthly household income, pre-pregnancy BMI, anemia status, sex of the baby, gestational age and gestational age at birth squared, living with a smoker, coal stove density within 5000 m radius of the participant's apartment, and intervention

status. A doubling of blood cadmium concentrations was also associated with decreased ponderal index (-0.04 g/cm^3; 95% CI: -0.08, -0.01 g/cm^3) among term births only, in adjusted models. We found no evidence of effect modification by living with a smoker, coal stove density, intervention status, or sex of the baby. We also found that coal stove density, a proxy for coal smoke, contributed to maternal blood cadmium concentrations. An interquartile increase in coal stove density (from three to five gers/hectare) was associated with an 11% (95% CI: 0, 23%) increase in blood cadmium concentrations, after adjusting for age of mother, monthly household income, pre-pregnancy BMI, anemia status, living with a smoker, season in which blood sample was collected, and intervention status. Overall, we concluded that cadmium exposure during pregnancy is associated with decreased birth weight, and that in some settings, cadmium may play a role in the putative relationship between air pollution and impaired fetal growth.

5.2. Synthesis and significance of findings

We used HEPA cleaners as a tool to study the effects of residential indoor $PM_{2.5}$ on fetal growth. We showed that lowering indoor $PM_{2.5}$ concentrations during pregnancy led to higher term birth weight by an average of 85 g (95% CI: 3, 167 g). An 85 g effect may not be clinically relevant, but it can be meaningful on a population level since a rightward shift in the birth weight distribution of a population will result in fewer babies born at lower birth weights. Birth weight is an indicator of impaired fetal growth, a condition that can affect multiple systems in the body. Moreover, unfavorable intrauterine conditions are thought to force the fetus to make irreversible adaptions to ensure immediate survival. These adaptions are thought to have lasting effects on organ morphology, vasculature, physiology, and endocrine and metabolic functioning.[39,200] Evidence suggests that persons born growth restricted are at increased risks of poorer neurodevelopmental outcomes and obesity in childhood and of type-2 diabetes, hypertension and coronary heart disease in adulthood.[26,31-35]

Our finding of improvements in fetal growth with reductions in air pollution is consistent with the bulk of observational studies, which have found links between $PM_{2.5}$ concentrations during

pregnancy and decreased birth weight and other indicators of impaired fetal growth.[4-10,43-46] A recent meta-analysis of observational studies reported a 16 g (95% CI: 5, 27 g) reduction in birth weight and an OR of 1.09 (95% CI: 1.03, 1.15) for LBW per 10 μg/m^3 increase in $PM_{2.5}$ over full pregnancy.[4] The majority of studies included in the paper limited their analyses to term births to evaluate the effect of air pollution on "normal" fetal growth.[4,28]

A limited number of studies show detrimental effects of PM and other pollutants on fetal growth in LMICs.[47,201-204] Sources and $PM_{2.5}$ composition may differ between higher and lower income countries, which may in turn influence particle toxicity. Coal-related $PM_{2.5}$, which is more common in LMICs,[205] has been associated with increased risks of ischemic heart disease and mortality, with some evidence suggesting that coal smoke particles may be more toxic than those from other sources.[206-208] Our study was conducted in a community that relies heavily on residential coal use that contributes to 45-70% of total $PM_{2.5}$ concentrations in the city.[99,100] In addition to $PM_{2.5}$, coal smoke contains other pollutants that have been linked to impaired fetal growth, including cadmium, lead, mercury, and PAHs.[58,209-212] We showed that the density of coal stoves surrounding the apartments of pregnant women contributed to cadmium exposure and that cadmium was linked to decreased birth weight. Coal smoke has been linked to impaired fetal growth by others. A 2014 meta-analysis of 19 studies estimated that unprocessed solid fuel combustion in homes, including coal, reduced mean birth weight by 86 g (95% CI: 56, 117 g) and increased risks of LBW (OR=1.35; 95% CI: 1.23, 1.48).[213] Another study reported a 1.1% (95% CI: 0.2, 2.0%) increase in LBW for each 5-km closer that maternal residences were to coal and solid waste power plants in Florida, US.[214] $PM_{2.5}$ and cadmium share mechanistic pathways, including oxidative stress and inflammation, which could potentially increase the toxicity of coal-related $PM_{2.5}$ emissions.

Interventions are needed to address the air pollution-related burden of disease. In 2016, 95% of the world's population lived in areas where outdoor $PM_{2.5}$ concentrations exceeded the World Health Organization's annual average guideline of 10 μg/m^3, and concentrations are increasing in much of the world, particularly in LMICs.[2] Consequently, the burden of disease is likely to

continue to increase if actions are not taken to reduce exposures at community and household levels.

Previous research shows that HEPA cleaners can reduce residential indoor $PM_{2.5}$ concentrations by 25 to 79%, in relatively low pollution settings and over relatively short periods of time.[87,89-95] Our work adds to this literature by showing that HEPA cleaners can also lower residential indoor $PM_{2.5}$ concentrations in highly polluted communities over a period of several months. Other factors also make HEPA cleaners an effective intervention. HEPA cleaners are relatively inexpensive and easy to use, allowing individuals some control over reducing their air pollution exposures. HEPA cleaners address exposures in indoor settings where individuals spend a majority of their time, with exposure reduction benefits being available to all occupants in these settings. HEPA cleaners also lower concentrations of indoor-generated pollutants and those that infiltrate from outdoors. This intervention can be useful in multiple settings, including in LMICs where populations are overburdened by increasing air pollution concentrations and other environmental stressors,[215] in communities located near busy roadways, industry, or other sources,[95] as well as those experiencing temporary poor air quality events. The use of portable air cleaners is currently recommended to communities affected by wildfire smoke by several public health agencies, including the US Environmental Protection Agency and the BC Centre for Disease Control.[216-219]

However, HEPA cleaners are only a near-term solution to addressing air pollution exposures, and even then, are limited in the benefits they can provide. For example, HEPA cleaners operated in the home will have no impact on exposures experienced in other microenvironments, including during a commute, at work, or outdoors. Their effectiveness over the long term has not been well studied, with our study being the first to investigate longer term air cleaner use in a highly polluted setting. One of the biggest drawbacks of recommending HEPA cleaner use in homes is that it places the burden of exposure reduction on the individual or household even though the pollution may be mainly due to community sources over which individuals have little control. Lower income persons may not be able to access or may not benefit from HEPA cleaners for several reasons. HEPA cleaners have initial purchase, operating, and maintenance costs that may be prohibitive to

some households. Air cleaners also need a constant and reliable supply of electricity and should be used in homes that are relatively well constructed, since air cleaners are more effective at lower air exchange rates. In Ulaanbaatar, residents of ger households are the most highly exposed group,[100] but HEPA cleaners would probably have limited value in these homes due to a lack of electricity and higher air exchange rates in gers. Additionally, air cleaners may be less effective in warm climates if residents are unable to limit air exchange rates by keeping windows and doors closed.

Our findings suggest that HEPA cleaner use during pregnancy can benefit fetal growth. However, public health messaging on their use needs to be carefully crafted. Pregnant women and their fetuses are especially vulnerable to air pollution, but birth does not mark the end of the vulnerable period. Newborns, infants, and young children are also vulnerable,[220,221] and recommendations need to convey that extending the use of HEPA cleaners beyond pregnancy is likely most beneficial. Households should also be made aware that air cleaners are most effective when air exchange rates are limited in the home, as well as about potential risks from heat and indoor-generated pollutants when homes are kept tightly sealed. Finally, information also needs to be provided on appropriate sizing of HEPA cleaners in the rooms in which they are to be used, as well as on maintenance and timely replacement of filters.

The only way to effectively address air pollution exposures over the long term at the population level is to implement interventions that reduce air pollution emissions. Stricter emissions regulations, improvements in technology, and a shift toward cleaner fuels in high-income countries in recent decades have allowed for cost-effective decreases in air pollution and large public health benefits. In the US, programs implemented under the 1990 Clean Air Act are projected to lead to substantial long-term air quality improvements and reductions in premature death and illness.[222] The economic value of these improvements is estimated to reach $2 trillion by 2020, which far exceeds the costs of the program, which are estimated at $65 billion by 2020.[222] Reductions in $PM_{2.5}$ have also been associated with decreased mortality in other parts of the world, including Europe, Asia, and Australia.[223-226]

Multiple strategies have been proposed to curb increasing air pollution concentrations in Ulaanbaatar, including a shift to cleaner-burning fuels in ger households, improved emission controls for coal-fired power plants, and cleaner busses and cars.[97] Programs to disseminate cleaner-burning coal stoves in ger households have had modest success in reducing outdoor $PM_{2.5}$ concentrations.[227] Without aggressive actions, air pollution concentrations will likely increase as the city sees growth in the number of ger households and motor vehicles, and as the demands for energy from power plants increase.[100,101] Implementing long-term solutions to reduce air pollution emissions in any community will take several decades,[109] but such actions will lead to long-term exposure reduction benefits for all residents.

5.3. Strengths and limitations

The key strength of our study is the randomized study design. The bulk of the current research consists of observational studies, that while valuable, are limited in how much they can tell us about the relationship between air pollution and fetal growth, while randomized trials are scare. We minimized confounding by randomizing participants to control and intervention groups. We used the intervention as a tool to study the link between air pollution and fetal growth by introducing a concentration gradient in $PM_{2.5}$ concentrations between the groups. We assessed indoor $PM_{2.5}$ concentrations, collecting 447 measurements in homes, in contrast to observational studies which have largely focused on outdoor air pollution measurements. Our assessment was the first to evaluate the impact of HEPA cleaner use over a relatively long duration in a highly polluted community. As mentioned earlier, this is the second randomized trial of air pollution and fetal growth; our sample size of 463 live births was larger than the previous study which included 174 births.[144] Finally, we assessed coal smoke as a potential cadmium source among pregnant women, which has not been adequately investigated in the literature.

There are also several limitations of our study. First, participants were not blinded to their intervention status. Although our outcome measures were objective and therefore, unlikely to have been biased, the lack of blinding likely contributed to the greater loss to follow up among the control group (19 versus nine participants). Participants received air cleaners at a median of 11 weeks gestation so the intervention did not influence exposure during much of the first trimester. Our estimates of HEPA cleaner impacts on $PM_{2.5}$ concentrations were based on two one-week monitoring periods in early and later pregnancy, and it is possible that participants used the air cleaners more frequently during these periods, which would have caused us to overestimate the concentration reductions introduced by the intervention. Due to mechanical issues, our assessment of air cleaner effectiveness was limited because we were unable to objectively quantify air cleaner use; instead, we had to rely on self-reported use. However, neither measure allows for an assessment of changes in use since we were unable to assess whether HEPA cleaner use was different in earlier versus later stages of the study period, or whether use differed during day- and night-time periods. We did not systematically assess reasons that participants failed to use the intervention continuously throughout the study period, including issues around noise. There was a high frequency of missing data collected via questionnaires, including questions on parity, the number of smokers in the home, previous birth complications, and use of supplements. Finally, time activity data was crudely assessed; participants were asked to provide a daily breakdown for time spent in different microenvironments over a "typical" week in early and late pregnancy.

5.4. Future research directions

Several gaps remain in our understanding of the relationship between air pollution exposure and fetal growth that merit further investigation. The potential joint effects of multiple pollutants on fetal growth have been poorly studied, while we know little about the shape of the exposure-response relationship between $PM_{2.5}$ and fetal growth outcomes, whether a "threshold" or "safe" exposure level exists, how composition of $PM_{2.5}$ affects toxicity, and critical exposure windows. There is also a lack of studies investigating interventions aimed at reducing air pollution exposures during pregnancy.

Much of the available literature has relied on single pollutant models that do not consider potential joint effects of multiple pollutants. Pregnant women are exposed to multiple environmental contaminants[228] that together may impair fetal growth but few studies have attempted to investigate how multiple pollutants may influence fetal growth.[229,230] Similarly, few studies have investigated the effects of specific sources or particle composition on fetal growth.[4,180,214] We showed that both $PM_{2.5}$ and cadmium can impair fetal growth and reasoned that in some settings, cadmium may play a role in the putative relationship between air pollution and impaired fetal growth, in part due to overlapping mechanistic pathways. Others have linked living near industrial sources or busy roadways, as well as exposure to specific contaminants in $PM_{2.5}$ mixtures, such as zinc, vanadium, nitrates, and copper, to increased toxicity.[4,179,180,214,231]

Another important question that remains is the shape of the exposure-response relationship between $PM_{2.5}$ and fetal growth. Although non-linear functions have been identified for other $PM_{2.5}$-related health outcomes, including cardiovascular mortality and some respiratory effects,[232-234] analyses of $PM_{2.5}$ and fetal growth have mostly assumed linear functions. One of the main challenges in assessing the shape of the function is that most studies have been conducted in high-income countries where concentrations are relatively low. Understanding the shape of the exposure-response function is necessary to assess population-level impacts of air pollution on fetal growth as well as to understand the potential benefits of exposure reduction at different concentrations. A related issue is whether an effect threshold exists. $PM_{2.5}$-related effects on respiratory and cardiovascular morbidity and mortality appear to have no thresholds,[221] and it may be reasonable to assume that no threshold exists for fetal growth outcomes considering that effects have been reported even in settings where mean outdoor $PM_{2.5}$ concentrations were between 5-10 $\mu g/m^3$.[235]

Critical exposures windows are also not well understood. Some evidence suggests that exposures in the latter half of pregnancy are most detrimental.[4] Evidence linking air pollution exposures with repeated ultrasound measurements suggests that exposures may not alter growth trajectories until

late in the second trimester.[153,154] Another study reported that babies whose eighth month of gestation overlapped during the 2008 Beijing Olympics, when air pollution concentrations were substantially reduced, had a 23 g (95% CI: 5 g, 40 g) greater mean birth weight compared with babies born during the same calendar dates the year prior to and after the Olympics.[152] We were unable to investigate exposure windows. In Ulaanbaatar, air pollution concentrations are strongly associated with season, with the highest concentrations occurring in winter when coal use is greatest. However, season is also correlated with other factors that impact exposures, including air exchange in homes and behavior. We found that many participants visited the country-side for extended periods in the summer, which would have also reduced the impact of the intervention.

Finally, more intervention studies are needed to better understand how reductions in exposure translate to improvements in health and which interventions are most effective. This type of information is critical to guide decision making, particularly when interventions are costly and require commitment from various stakeholders and partners. We showed HEPA cleaners were effective at reducing indoor $PM_{2.5}$ and blood cadmium concentrations, but many questions remain about how to maximize exposure reduction and health benefits, including how factors such as noise and cost affect uptake and adherence to the intervention and how patterns of use throughout the day, in different climates, and in different housing types influence effectiveness.

Filling knowledge gaps is important to allow for a fuller understanding of how air pollution affects fetal growth. However, a lack of a complete understanding of this relationship should not preclude action since the available research collectively suggests that air pollution exposures are harmful. Interventions should be implemented to address exposures on community and household levels, and attention should be given to evaluating these interventions to ensure they are effective in reducing exposures and health effects, and that benefits are accessible to all community members.

5.5. Conclusions

The main aims of this research were to (1) investigate the causal role of $PM_{2.5}$ on fetal growth, (2) investigate the relationship between cadmium and fetal growth, and (3) evaluate portable HEPA cleaners as a household level intervention. Portable HEPA cleaner use during pregnancy is an effective household intervention to reduce indoor $PM_{2.5}$ concentrations and SHS exposures and to improve fetal growth. Our findings reinforce the evidence that reducing air pollution exposure can benefit health. Many questions still remain on the relationship between air pollution and fetal growth, including the role of multiple pollutants, how $PM_{2.5}$ composition affects toxicity, the shape of the exposure-response function, particularly at higher levels of exposure, and critical windows of exposure. However, enough evidence exists to warrant immediate actions to lower community-wide and household level air pollution exposures in the near- and long-term.

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Appendix A. Summary of studies investigating maternal cadmium exposure and fetal growth

Table A.1. Summary of studies investigating the relationships between maternal cadmium exposure and fetal growth

Reference	Study setting, sample size, timing of sample collection, and health outcomes of interest	Cadmium concentrations	Main findings
Blood			
Sabra et al. 2017[1]	Barcelona, Spain n=178 Samples collected on day of delivery IUGR[a], small for gestational age (SGA)	Median (IQR) values by type of growth restriction: AGA: 0.04 (0.009) ug/dL IUGR: 0.05 (0.005) ug/dL SGA: 0.05 (0.005) ug/dL.	Maternal serum cadmium (Cd) was significantly higher ($p<0.001$) in IUGR and SGA fetuses compared with AGA fetuses (appropriate for gestational age).
Cheng et al. 2017[2]	Wuhan, China n=282 Samples collected at 13, 24, and 35 weeks gestation Birth weight (BW), ponderal index (PI), birth length (BL)	GM (25^{th}, 75^{th} percentile) by trimester: 1^{st}: 0.51 (0.36, 0.77) ug/g creatinine; 2^{nd}: 0.59 (0.41, 0.79) ug/g creatinine; 3^{rd}: 0.61 (0.39, 0.92) ug/g creatinine	Each log unit increase in first trimester urinary Cd (ug/g creatinine) was associated with a mean decrease in BW of 117 g (95% CI: -209, -25 g) in girls. Cd levels in the first and second trimesters were also borderline associated with PI among girls. No significant effects were seen among boys.
Luo et al. 2017[3]	North Carolina, US n=275 Samples collected in the first trimester.	Mean or median concentrations were not provided for all participants, but authors provided median (IQR) concentrations by different	Regression models were run for tertiles of Cd exposure, and analyses were stratified by sex and smoking. Among boys, BW was significantly lower among the highest tertile group compared with the lowest (-812 g, SE =

	BW	characteristics (e.g. by maternal age, education, smoking status, baby's sex). Median concentrations ranged from 0.014 to 0.051 µg/dL.	346, p = 0.02). No significant effects seen among all births or girls. The relationship between Cd and BW was modified by select nutrient combinations (e.g. iron, folate, calcium).
Taylor et al. 2016[4]	Avon, UK n=4,191 Samples collected at ~11 weeks gestation. BW, BL, head circumference (HC), low birth weight (LBW)	Median (IQR) was 0.29 (0.14–0.68) µg/L	Cd concentrations were associated with decreased birthweight (unstandardized B coefficient -62.7 g, 95% CI: -107.0, -18.4) and crown–heel length (-0.28 cm, 95% CI: -0.48, -0.07) per 1 µg/L increase in Cd, in adjusted regression models. Adjustment variables were: maternal educational attainment, age, parity, pre-pregnancy BMI, height, and alcohol intake, and sex of baby. Stratification by sex showed adverse effect on birthweight (-87.1 g, 95% CI: -144.8, -29.4), head circumference (-0.22 cm, 95% CI: -0.39, -0.04), and crown–heel length (-0.44 cm, 95% CI: -0.71, -0.18) in girls only.
Wang et al. 2016[5]	6 cities, China n=3,254 Samples collected in first and second trimesters. SGA	Median (25^{th} and 75^{th} percentile) was 0.79 (0.57, 1.06) µg/L	Women with cd concentrations > 75^{th} percentile (1.06 µg/L) during pregnancy had increased odds of SGA [OR = 1.43 (95% CI: 1.09, 1.88), p = 0.009], compared to women with concentrations ≤ 75^{th} percentile, after adjusting for pre-pregnancy BMI, maternal age, time for collecting serum, monthly income, and gravidity. When stratified by trimester, a higher risk of SGA was reported for second trimester concentrations (OR = 1.57; 95% CI: 1.13, 2.19, p=0.007) for women in higher exposure vs low

			exposure group. No significant effects seen for first trimester concentrations.
Bloom et al. 2015[6]	Michigan & Texas, US N=235 Samples collect pre-conception BW, BL, HC, PI, gestational age (GA)	Mean (SD) was 0.24 (0.14) µg/L	Cd concentrations were associated with higher BW, with women in the third tertile having heavier babies (179g; 25, 332g) compared with women in the first tertile.
Hu et al. 2015[7]	4 cities, China N=81 Samples collected on day of delivery BW	Median (25^{th}, 75^{th} percentile) was 0.9 (0.7, 1.2) ng/g.	No associations were found between Cd and BW.
Rollin et al. 2015[8]	South Africa n=641 Samples collected on day of delivery BW, BL, HC, PI	Geometric mean (95% CI) was 0.25 µg/L (0.23, 0.27 µg/L)	An association between Cd concentrations and birth weight percentile was found in girls only (β = -0.13 for women in the third tertile versus first tertile of Cd concentration, p = 0.047).
Thomas et al. 2015[9]	10 cities, Canada n=1,835 Samples collected during first and third trimesters SGA	Median (IQR) blood cadmium level was 0.20 (0.13 – 0.30) µg/L.	Cd concentrations were not associated with risk of SGA.

Vidal et al. 2015[10]	North Carolina, US n=319 Samples collected at ≤ 12 weeks gestation BW	Mean or median concentrations were not presented for all participants, but authors provided means by different characteristics (e.g. by sex, age, BMI). Mean values ranged from 2.56 to 6.48 ng/L.	Cd concentrations were associated with birth weight (-52g for each log-unit increase; p = 0.03).
Al-Saleh et al. 2014[11]	Al-Kharj, Saudi Arabia n=1,578 Samples collected at delivery. BW, BL, HC, crown-heel length, Apgar 1-min score, Apgar 5-min score	Mean (SD) concentration was 0.99 (0.31) µg/L.	Cd concentrations were significantly higher for babies who were < 10th percentile for crown-heel length: OR (95%CI) was 1.644 (1.058, 2.555), p = 0.027.
Johnston et al. 2014[12]	Durham, North Carolina N=1,027 Samples collected at delivery. BW, SGA, LBW, preterm birth (PTB), GA, HC, BL	Median (IQR) was 0.40 (0.33) µg/L.	Women in the highest tertile (≥50 µg/L) had lower birth weight percentile by gestational age (-6 g, SE: 2.11, p = 0.007) and increased risk of SGA (OR =1.72, 95% CI: 1.1, 2.68, p = 0.001) compared with women the lowest tertile (≤0.28 µg/L).
Sun et al. 2014[13]	Eastern China n=209 Samples collected in third trimester BW, BL	Geometric mean (95% CI) concentration was 0.48 (0.43, 0.53) µg/L.	Cd was significantly correlated with BW (r=-0.41; p<0.05).

Ikeh-Tawari et al. 2013[14]	Nigeria n=125 Samples collected at various trimesters depending on when participant was recruited. BW, BL, HC, LBW	Mean (SD) concentrations by trimester: 1st: 0.20 (0.10) µmol/L 2nd: 0.21 (0.10) µmol/L 3rd: 0.25 (0.20) µmol/L	Third trimester Cd concentrations were significantly ($p<0.05$) correlated with BW (-0.708), BL (-0.499), and HC (-0.332). Cd concentrations were also significantly higher among women who delivered LBW [0.03 (0.10) µmol/L vs 0.02 (0.10) µmol/L; p=0.02; n=51).
Menai et al. 2012[15]	France n=901 Samples collected between 24-28 weeks gestation BW, SGA	Median (IQR) concentration was 0.8 (0.1-4.6) µg/L.	Cd concentrations were significantly correlated with BW in smokers ($r= -0.25$, $p<0.001$) but not in non-smokers ($r = 0,03$; p=0.398). A dose-response relationship was observed between exposure and BW among smokers only. BW was 204 g lower (p=0.007) among women in the highest tertile (>1.5 µg/L) compared with lowest tertile (<1 µg/L). Effects of Cd in the high exposure group and smoking in pregnancy had a similar effect on risk of SGA, with ORs of 1.41 (95% CI: 1.00, 1.99) and 1.89 (95% CI: 1.00, 3.58), respectively.
Lin et al. 2011[16]	Taiwan n=321 Samples collected at delivery. BL, HC, PTB	Median (IQR) concentration was 1.05 µg/L (0.98).	Cd concentrations were not significantly associated with any outcomes.
Nishijo et al., 2004[17]	Toyama, Japan N=55	Mean (range) concentration was 9.29 (1.43-39.6) nmol/L.	Cd concentrations were correlated with BL ($r = -0.337$, $p<0.01$). In regression analyses, a 1 nmol/L increase in Cd concentration was associated with a 0.59 cm decrease in BL (SE =

	Samples collected at 30-32 weeks gestation BL		0.277, p = 0.038), after adjusting for gestational age and maternal weight gain at 30-32 weeks.
Zhang et al. 2004[18]	Da-ye city, Hubei province, China n=44 Samples collected between 1 and 72 hours before delivery. PTB, BL	Concentrations ranged from 0.80 to 25.20 µg/L, with a median concentration of 1.72 µg/L.	No associations between blood cadmium and PTB or birth length were found.
Salpietro et al 2002[19]	Messina, Italy n=45 Samples collected during prenatal care (weeks gestation not reported) or at delivery BW	Mean (SD) concentration was 119 ng/L (75).	Cd concentrations were significantly correlated with BW (ρ= - 0.546; p=0.0003).
Odland et al., 1999[20]	Kola Peninsula of Russia and Norway n=262 Samples collected on day of delivery BW	Median (range) concentrations were 2.2 (0.5-35.2) nmol/L among women from Russia (n=148) and 1.8 (0.5-26.9) nmol/L among women from Norway (n=114)	No significant associations were found between Cd concentrations and BW.

Urine			
Zhang et al. 2018[21]	Guiyu (e-waste area) and Haojing, China n=237 (Guiyu), 212 (Hoajing) Samples collected on day of delivery BW, BL, HC, apgar score 1 min and 5 min	Median (25^{th}, 75^{th} percentiles) were reported by location and sex: Males: Haojiang and Guiyu: 0.67 (0.31 1.05) and 0.92 (0.55, 1.66) µg/g creatinine Females: Haojiang and Guiyu: 0.59 (0.29, 0.90) and 1.00 (0.69, 1.77) µg/g creatinine	Cd concentrations were significantly higher among women in Guiyu and higher among women giving birth to dgirls vs boys. For women in Guiyu, living in a house near e-waste site or highway was positively correlated with Cd concentrations. Among girls, an increase in 1 ug/g creatine Cd led to effects of -9 g (95% CI: -75, -2 g) in BW, -0.19 cm (95% CI: -0.36, -0.01 cm) in BL, and -0.09 (95% CI: -0.15, -0.03) in apgar 1-min score.
Guo et al. 2017[22]	Jiangsu Province, China n=1,073 Samples collected on day of delivery BW, BL, HC, PI	Median (25th, 75th percentile) concentration was 0.19 (0.08, 1.00) µg/g creatinine	No significant effects were found between Cd concentrations and outcomes.
Huang et al. 2017 [23]	Hubei province, China n=408 Samples collected on day of delivery Preterm LBW (PLBW)	Mean or median concentrations were not reported. Authors provide concentrations for l (<0.35 µg/g creatinine), medium (0.35-0.70 µg/g creatinine), high (>=0.70 µg/g creatinine) exposure groups.	Nested case-control study: controls were babies ≥37 weeks gestation, ≥2500g; cases were babies <37 weeks, <2500g An increased risk of PLBW was found for the highest exposure group (OR = 2.25; 95% CI: 1.21, 4.17). When stratified by sex, significant effects were only seen among girls OR= 5.90; 95% CI: 1.57, 22.23).
Wai et al. 2017[24]	Ayeyarwady Division, Myanmar n=419	Median (IQR) concentration was 0.86 (0.50-1.40) µg/g creatinine.	A 1-unit increase in Cd concentration was associated with an increased risk for LBW (OR = 1.10; 95% CI: 1.01, 1.21).

	Samples collected in the third trimester LBW, PTB		
Romano et al. 2016[25]	Seattle, Washington n=396 Samples collected at ~ 15 weeks gestation BW, BL, HC, PI	Overall mean or median concentrations were not reported. Authors reported concentrations by tertiles: low (<0.29 µg/g creatinine), medium (0.29–0.42 µg/g creatinine), and high (≥0.43 µg/g creatinine)	No significant effects seen among all births. When stratified by sex, each log unit increase in Cd concentration was associated with a 0.47 (95% CI: 0.2, 0.74) cm decrease in BL. Among boys, each log-unit decrease was associated with a 0.63 (95% CI: 0.24, 1.01) kg/m^3 decrease in PI.
Yang et al. 2016[26]	Wuhan, China n=5,364 Samples collected on day of delivery BW, BL, GA, PTB, LBW, SGA	GM (range) cd concentration was: 0.55 (0.01-2.85) µg/g creatinine.	A log-unit increase in Cd concentration was associated with a 0.77 day (95% CI: 0.39, 1.15 day) decrease in gestational age among all births. Each log-unit increase in Cd concentration was also associated with PTB (OR = 1.78; 95% CI: 1.45, 2.19). No significant effects seen for BW or BL. Interaction models of sex were not significant.
Kippler et al. 2012[27]	Rural Bangladesh n=1,616 Samples collected at ~8 weeks gestation BW, BL, HC, chest circumference (CC)	Median concentration was 0.63 µg/L.	Cd concentrations were associated with BW (–31.0 g; 95% CI: –59, –2.8 g) and HC (–0.15 cm; 95% CI: –0.27, –0.02 cm) per 1 µg/L increase. When stratified by sex, significant effects were only seen among girls: 1-µg/L increase in Cd was associated with a 0.26-cm (95% CI: –0.43, –0.088 cm) and 0.24-cm (95% CI: –0.44, –0.030 cm) decrease in girls' HC and CC, respectively, and a 45-g (95% CI: –82.5, 7.3 g) decrease in BW. No evidence of dose-response effect was seen in quantile regression analyses.
Shirai et al. 2010 [28]	Tokyo, Japan n=78	Mean (SD) concentration was 0.976 (0.891) µg/L.	A log-unit increase in Cd concentration was associated with a -135 g (p=0.021) decrease in BW.

	Samples collected at between 9 to 40 weeks BW, BL, HC		
Other media			
Everson et al. 2016[29]	Rhode Island, US n=242 Toenail clippings collected at a mean 2.8 months gestation SGA	Range was 0.00062 – 0.0846 µg/g.	A log-unit increase in Cd concentration was associated with an increased risk of SGA (OR = 2.44; 95% CI: 1.53, 3.89).

[a]Defined as estimated fetal weight <3rd or <10th percentile with cerebro-placental ratio <5th and/or mean uterine artery pulsatility index >95th percentile pathological Doppler.

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Appendix B. Supplemental material for chapter two

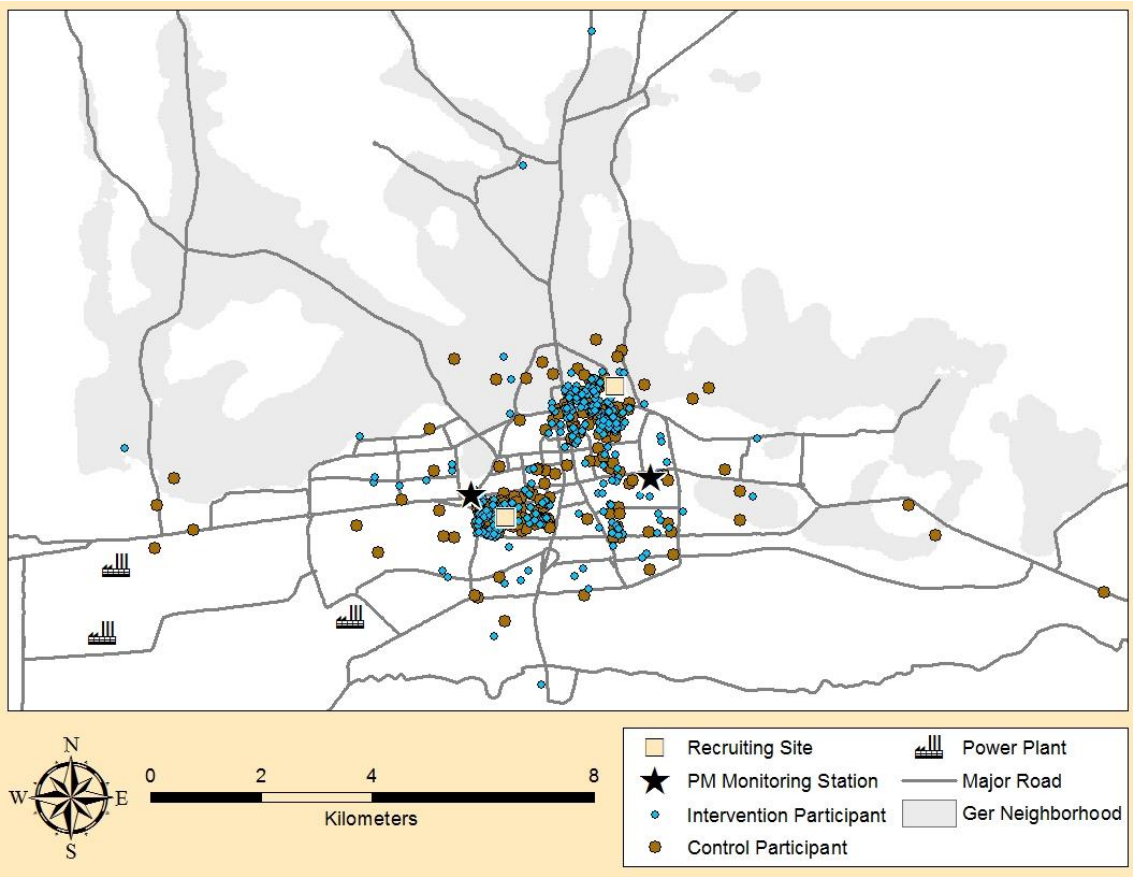

Figure B.1. Locations of control and intervention homes at time of at enrollment

*****Home locations have been randomly "jittered" to protect the confidentiality of participants.

Text B.1 Description of Dylos data preparation

We conducted 911 one-week sampling events using Dylos particle counters, representing over 1.7 million 5-minute averaged concentrations. We completed several quality control and data cleaning steps prior to data analysis. First, we removed measurements if more than 10% of the 5-minute concentrations were 0 particles/cm^3 for a given sampling event (n = 57). Next, we removed measurements made by faulty Dylos monitors, as identified by co-location tests (n = 342). We conducted co-location tests using all of our 42 Dylos monitors to identify faulty monitors. These tests were performed prior to data collection, and again in July 2014, February 2015, and March 2016. We operated monitors operated side by side for a minimum of 24-hours during which 5-min average particle counts were collected. The data were downloaded and the median concentration across all Dylos units was calculated for each 5-minute period. For each Dylos unit, we then regressed measured concentrations against the median concentrations. Since we expected measurements made with functional Dylos monitors to agree with the median concentration across all monitors (i.e., $R^2 \approx 1$; slope ≈ 1, and intercept ≈ 0), Dylos monitors with co-location regression results that met any of the following criteria were considered faulty: 1) $R^2 < 0.80$; 2) slope < 0.80 or > 1.20; or 3) intercept > 163,830 particles (equivalent of ~ 10 µg/m^3 $PM_{2.5}$). We identified 18 faulty monitors, and removed all field measurements made with those monitors from our dataset. In total, we removed data from 342 sampling events. Finally, we excluded 52 measurements where the Dylos monitors recorded a concentration for less than 50% of the one-week sampling event and five measurements with incorrect filenames that could not be matched to an UGAAR participant. We concluded that relative humidity (RH) did not influence Dylos particle counts based on (i) the low RH values measured in homes, and (ii) the weak relationship between RH and Dylos particle counts. In total, 175,467 5-min RH measurements were collected in 85 homes, with a geometric mean of 27.9 % (95 % CI: 27.9, 28.0 %). Regression analysis of 16,481 matched 5-minute RH and Dylos particle count measurements showed a weak relationship ($R^2 = 0.13$). Removal of data collected from participants who were lost to follow up left a total of 447 one-week Dylos measurements for analysis. We assessed baseline housing, personal, and behavioral characteristics among participants with no measurements and participants with one or two measurements using Fisher's exact tests and Mann-Whitney tests as appropriate. Participants with no measurements spent less time at home in early pregnancy (15.7 hours/day, 95% CI: 15.1, 16.2 hrs/day) compared with participants with one or two measurements (16.3 hours/day, 95% CI: 15.9, 16.8 hrs/day, p = 0.02). We found no other significant differences between these groups (Table

S2.1). We concluded participants and homes included in our analysis are representative of the full UGAAR cohort.

Table B.1. Summary of household, personal, behavioral, and intervention-related characteristics for participants with zero and one or two one-week Dylos measurements

	Participants with zero one-week Dylos measurements (n = 170)		Participants with one or two one-week Dylos measurements (n = 342)		
	GM (95 % CI) or N	**%**	**GM (95 % CI) or N**	**%**	**p-value**
Housing characteristics					
Total home area (m^2)	52.0 (48.1, 56.2)	91	54.0 (50.9, 57.3)	98	0.76
Not recorded		9		2	
Age of home (years)	10.6 (8.4, 13.4)	66	10.9 (9.3, 12.9)	71	0.74
Not recorded		34		29	
Window opening in winter					
Open < half the month	82	48	168	49	0.85
Open ≥ half the month	86	51	169	50	
Not recorded	2	1	5	1	
Window opening in summer					
Open < half the month	21	12	38	11	0.66
Open ≥ half the month	147	86	301	88	
Not recorded	2	1	3	1	
Used a non-UGAAR air cleaner					
No	160	94	319	93	0.63
Yes	5	3	15	5	
Not recorded	5	3	8	1	
Personal and behavioral characteristics					
Time spent indoors at home in early pregnancy (hours/day)	15.7 (15.1, 16.2)	74	16.3 (15.9, 16.8)	78	0.02
Not recorded		26		22	
Time spent indoors at home in late pregnancy (hours/day)	15.9 (15.3, 16.6)	50	15.6 (14.9, 16.3)	55	0.82
Not recorded		50		45	
Smoked at any point pregnancy					
No	157	92	309	90	0.30
Yes	10	6	30	9	
Not recorded	3	2	3	1	
Lived with a smoker in at any time in pregnancy					
No	81	48	168	49	0.98
Yes	81	48	169	50	
Not recorded	8	4	5	1	

Intervention-related characteristics					
Treatment group					
Control	89	52	164	48	0.40
Intervention	81	48	178	52	
Week of pregnancy at enrollment	9.8 (9.3, 10.2)	100	10.0 (9.7, 10.3)	100	0.35
Season of enrollment					
Winter (Dec-Feb)	63	37	104	30	0.43
Spring (Mar-May)	46	27	95	28	
Summer (Jun-Aug)	20	12	42	12	
Fall (Sep-Nov)	41	24	101	30	

Text B.2. Description of Dylos particle count conversion to $PM_{2.5}$ concentrations

Particle counts were converted to $PM_{2.5}$ concentrations using a conversion equation based on co-located Dylos and gravimetric $PM_{2.5}$ measurements. In total, 100 gravimetric filter samples were collected, of which 10 were field blanks, and two were duplicate samples collected side-by-side in the same home. The mean (standard deviation) of blanks filters was 0.01 (0.02) µg indicating minimal contamination of filters. The duplicate samples showed excellent agreement with respect to $PM_{2.5}$ concentrations, with values of 15.4 and 16.0 $\mu g/m^3$. Forty-one gravimetric samples were discarded due to incomplete data or differences of > 10 % in start and stop pump flow rates. The remaining 49 samples were matched with Dylos particle count data, resulting in 23 valid pairs of Dylos measurements and gravimetric $PM_{2.5}$ samples. To establish the conversion equation, Dylos particle counts were regressed on gravimetric $PM_{2.5}$ measurements, giving the following equation: $PM_{2.5}$ ($\mu g/m^3$) = 1.88 + 1.34*(Particle Count, particles/cm^3), R^2 = 0.94 (Figure S3.1). This equation was used to convert all one-week particle counts to $PM_{2.5}$ concentrations.

Table B.2. Summary of household, personal, behavioral, and intervention-related characteristics for participants who were lost to follow up and those who remained in the study

	Lost to follow up (n = 28)		Remained in study (n = 512)		
	GM (95 % CI) or N	%	GM (95 % CI) or N	%	p-value
Housing characteristics					
Total home area (m^2)	56.2 (44.8, 70.5)	64	53.4 (50.9, 55.9)	95	0.79
Not recorded		36		5	
Age of home (years)	14.2 (8.5, 23.7)	50	10.9 (9.5, 12.5)	69	0.71
Not recorded		50		31	
Window opening in winter					
Open < half the month	10	36	248	48	0.98
Open ≥ half the month	11	39	255	50	
Not recorded	7	25	9	2	
Window opening in summer					
Open < half the month	3	11	59	11	0.73
Open ≥ half the month	18	64	448	88	
Not recorded	7	25	5	1	
Used a non-UGAAR air cleaner					0.05
No	19	68	479	94	
Yes	2	7	20	4	
Not recorded	7	25	13	2	
Outdoor $PM_{2.5}$ ($\mu g/m^3$) at first home measurement	54.3 (50.5, 58.4)	68	55.0 (51.6, 58.6)	97	0.80
Not available		32		3	
Personal and behavioral characteristics					
Time spent indoors at home in early pregnancy (hours/day)	15.1 (13.4, 17.0)	54	16.1 (15.8, 16.4)	76	0.20
Not recorded		46		24	
Lived with a smoker in early pregnancy					
No	20	71	464	90	0.60
Yes	1	4	40	8	
Not recorded	7	25	8	2	
Smoking occurred in the home at early in pregnancy					
No	10	36	264	51	0.85
Yes	11	39	230	45	
Not recorded	7	25	18	4	
Intervention-related characteristics					
Treatment group					
Control	19	68	253	49	0.08

Intervention	9	32	259	51	
Week of pregnancy at enrollment	9.2 (8.2, 10.3)	100	9.9 (9.7, 10.2)	100	0.15
Season of enrollment					
Winter (Dec-Feb)	9	32	167	33	0.12
Spring (Mar-May)	13	46	142	28	
Summer (Jun-Aug)	1	4	62	12	
Fall (Sep-Nov)	5	18	141	28	

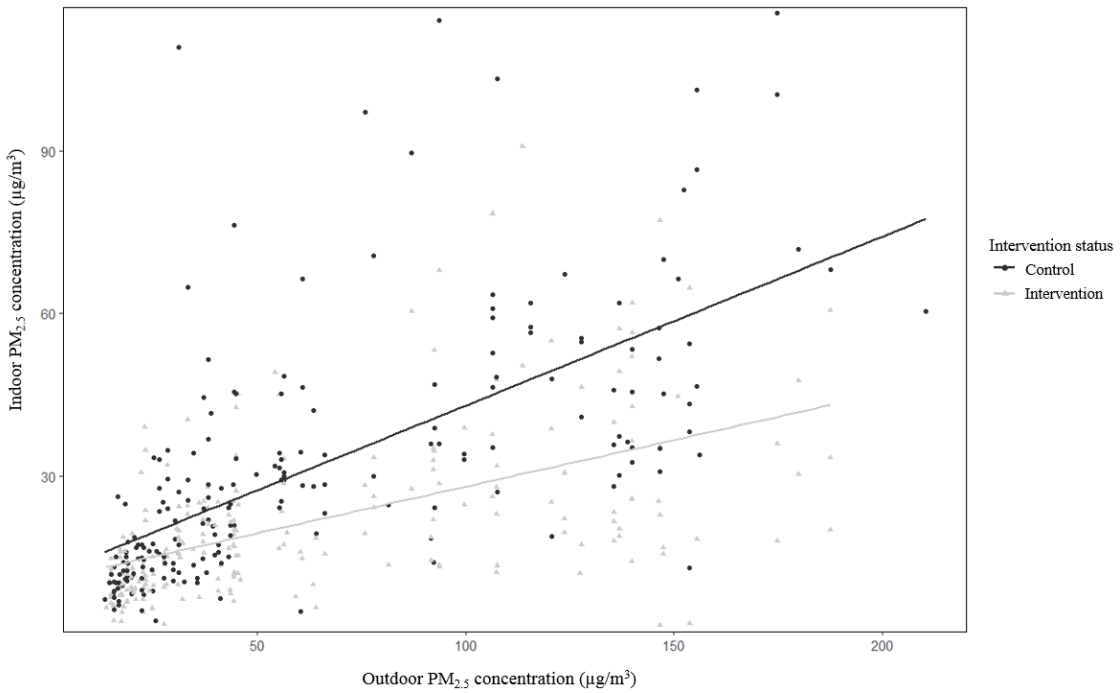

Figure B.2. Relationship between one-week outdoor and indoor PM2.5 concentrations for control and intervention homes

Table B.3. Summary of previous studies investigating air cleaner effectiveness in residences over periods of 6 to 12 months

Study	PM source of interest	Study design	Reduction in residential indoor particulate matter
McNamara et al. 2017 [1]	Wood smoke	Homes were randomized to one of two groups for 12 months: (i) the high efficiency filtration (mechanical filter with > 90% efficiency for capturing particles 1-3 µm; n = 25) group; or (ii) the low efficiency filtration (fiberglass filter; n = 23) group.	66 % Median (range) $PM_{2.5}$ concentrations were 22.0 µg/m^3 in low and 5.7 µg/m^3 in high efficiency filtration homes at the 12-month follow up period, respectively.
Batterman et al. 2012 [2]	No specific source	Homes were randomized to one of three groups for 3-4 consecutive seasons: (i) control (n=37); (ii) HEPA cleaner (n=47); or (iii) HEPA cleaner and air conditioner (n=42)	45 % Mean (sd) $PM_{2.5}$ concentrations were 21.4 (18.1) µg/m^3 at baseline and 11.8 (10.9) µg/m^3 over period when air cleaners were used over 3-4 consecutive seasons, in homes receiving HEPA cleaners.
Butz et al. 2011 [3]	Second hand smoke	Homes were randomized to one of three groups for 6 months: (i) control (n=44); (ii) 2 HEPA cleaners (n=41); or (iii) 2 HEPA cleaners plus home visits from a health coach (n=41)	47 % Mean (sd) $PM_{2.5}$ concentrations were 33.9 (26.4) µg/m^3 at baseline and 17.9 (15.2) µg/m^3 at the 6-month follow up period, in homes receiving HEPA cleaners.
Lanphear et al. 2011 [4]	Second hand smoke	Homes were randomized to one of two groups for 12 months: (i) 2 sham air cleaners (n=115); or (ii) 2 HEPA filter air cleaners (n=110)	25-38% Mean particle counts (> 0.3 um) were 4.0 x 10^6/ft^3, 2.5 x 10^6/ft^3, and 3.0 x 10^6/ft^3 at baseline, 6-month and 12-month follow up periods.

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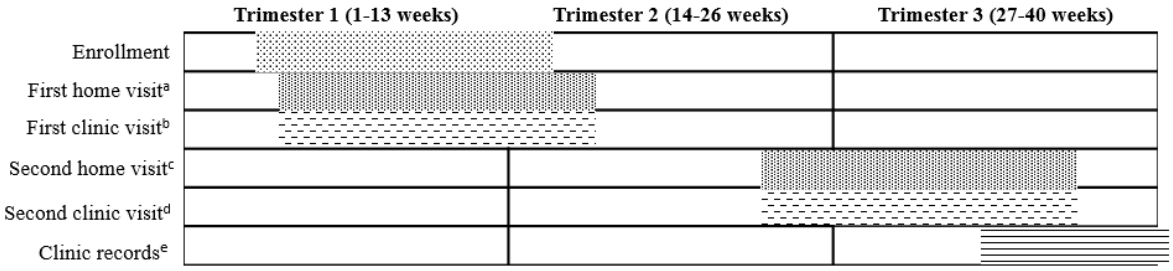
Appendix C. Supplemental material for chapter three



[a]In the first home visit: (i) air cleaners were deployed in homes of intervention participants, (ii) air pollution monitors were deployed for one week to measure particle number concentrations, (ii) gravimetric $PM_{2.5}$ monitors were deployed for one week in a subset of homes, (iii) a housing assessment was completed, and (iv) blood pressure was measured at beginning and end of the one-week visit.
[b]In the first clinic visit: (i) a questionnaire on health and lifestyle was administered, (ii) a dried blood spot sample was collected for determination of C-reactive protein (CRP), and (iii) a hair sample was collected for determination of nicotine.
[c]In the second home visit: (i) air pollution monitors were deployed for one week to measure particle counts, (ii) gravimetric $PM_{2.5}$ monitors were deployed for one week in a subset of homes, (iii) a second housing assessment was completed for participants who changed residences, and (iv) blood pressure was measured at beginning and end of the one-week visit.
[d]In the second clinic visit: (i) a questionnaire on health and lifestyle was administered, (ii) a dried blood spot sample was collected for determination of CRP, (iii) a whole blood sample was collected for determination of cadmium, lead, and mercury, and (iv) a hair sample was collected for determination of nicotine.
[e]Post delivery, the following data were extracted from clinic records: birth weight, length, head circumference, gestational age, sex, type of delivery, and health of participant during pregnancy (e.g. presence of infections, gestational diabetes and hypertension, preeclampsia).

Figure C.1. Summary of all data collected in the Ulaanbaatar Gestation and Air Pollution Research (UGAAR) study

Table C.1. Summary of baseline characteristics among those lost to follow up and those that remained in the study

	Lost to follow up (n=28)	Remained in study (n=512)	p-value[a]
	Median (25^{th}, 75^{th} percentile) or N (%)	**Median (25^{th}, 75^{th} percentile) or N (%)**	
Mother's age at enrollment, weeks	28.5 (25.0, 34.0)	29.5 (25.0, 33.0)	0.74
Gestational age at enrollment, weeks	10.0 (8.0,12.0)	10.0 (8.0,13.0)	0.17
Household income			
< 800,000 Tugriks[b]	6 (21)	170 (34)	0.20
≥ 800, 000 Tugriks	12 (43)	335 (65)	
Not reported, N (%)	10 (36)	7 (1)	
Mother's education			
Completed university	17 (61)	411 (80)	0.50
Did not complete university	4 (14)	61 (12)	
Not reported, N (%)	7 (25)	40 (8)	
Marital status			
Married/common-law	16 (57)	436 (85)	0.52
Not married/common-law	4 (14)	75 (15)	
Not reported, N (%)	8 (29)	1 (0)	
Worked/volunteered outside the home			
No	6 (21)	165 (33)	0.81
Yes	15 (54)	340 (66)	
Not reported, N (%)	7 (25)	7 (1)	
Parity			
0	2 (7)	46 (9)	0.78
1	6 (21)	192 (38)	
≥2	5 (18)	118 (23)	
Not reported, N (%)	15 (54)	156 (30)	
Time since last pregnancy, months	25 (11, 55)	31 (15, 60)	0.13
Not reported, N (%)	19 (68)	231 (45)	
Previous poor pregnancy outcome[c]			
No	6 (21)	104 (20)	0.16
Yes	2 (7)	114 (22)	
Not reported, N (%)	20 (72)	294 (58)	
Pre-pregnancy BMI, kg/m^2	21.2 (19.7, 24.0)	21.5 (19.8, 24.0)	0.48
Not reported, N (%)	7 (25)	35 (7)	

Time spent at home in early pregnancy, hrs/day	16.0 (14.0, 18.7)	16.1 (14.4, 18.8)	0.20
Not reported, N (%)	13 (46)	121 (24)	
Smoked at any time in pregnancy, N (%)			
No	20 (71)	464 (91)	0.95
Yes	1 (4)	40 (8)	
Not reported	7 (25)	8 (1)	
Lived with a smoker at any time in pregnancy, N (%)			
No	10 (36)	266 (52)	0.90
Yes	11 (39)	230 (45)	
Not reported	7 (25)	16 (3)	
Alcohol consumption at any time in pregnancy, N (%)			
No	13 (46)	320 (63)	0.90
Yes	7 (25)	165 (32)	
Not reported	8 (29)	27 (5)	
Drug use at any time in pregnancy, N (%)			
No	21 (75)	493 (96)	0.96
Yes	0 (0)	3 (1)	
Not reported	7 (25)	16 (3)	

[a]p-values were generated using non-parametric Wilcoxon rank tests for continuous outcomes and Fisher's exact tests for categorical outcomes.

[b]At the time of data collection 800,000 Tugriks was the equivalent of approximately $360 US.

[c]Previous poor outcome includes spontaneous abortion, still birth, low birthweight, macrosomia, ectopic pregnancy, birth defect, and intrauterine growth restriction.

Table C.2. Summary of sensitivity analyses conducted to investigate intervention effects on birth weight

Sensitivity Analysis	All births	Term births[a]
Participants analyzed according to the intervention they received (i.e. "per protocol")	-15 (-117, 87) n=463	69 (-13, 150) n=429
Excluding two observations identified as having potential errors in gestational age or birth weight (both observations were preterm)	15 (-88, 117) n=461	------
Excluding five neonatal deaths	37 (-63, 137) n=459	86 (4, 168) n=428
Excluding participants who reported smoking at any time during pregnancy	5 (-101, 112) n=424	76 (-10, 162) N=393
Model adjusted for anemia status	15 (-87, 118) n=463	85 (3, 167) n=429
Model adjusted for preterm birth	84 (-1, 170) n=463	------

[a]Births occurring ≥ 37 weeks gestation.
[b]Defined as observations that exceeded the WHO fetal growth chart 95th percentiles of birth weight for gestational age and sex by ≥20%

Appendix D. Supplemental material for chapter four

Table D.1. Summary of characteristics for UGAAR participants who had a live birth and (i) did not have a blood cadmium measure collected and (ii) had a blood cadmium measure collected.

	Participants with no blood cadmium measurement (n = 86)	Participants with a blood cadmium measurement (n=374)	p-value
	Median (25th, 75th percentile) Or N (%)	Median (25th, 75th percentile) Or N (%)	
MATERNAL			
Age at enrollment (yrs)	29 (25, 34)	29 (25, 33)	0.76
Gestational age at enrollment (weeks)	12 (10, 13)	10 (8, 12)	0.003
Season of enrollment			
Winter (December, January, February)	62 (72)	86 (23)	0.0001
Spring (March, April, May)	14 (16)	114 (30)	
Summer (June, July, August)	2 (2)	54 (14)	
Fall (September, October, November)	8 (9)	120 (32)	
Monthly household income			
< 600,000 Tugriks[a]	18 (21)	92 (25)	0.8
600,000 to <1,200,000 Tugriks	25 (29)	105 (28)	
≥ 1,200,000 Tugriks	39 (45)	163 (44)	
Missing	4 (5)	14 (4)	
Maternal education			
Completed university	67 (78)	302 (81)	0.22
Did not complete university	14 (16)	42 (11)	
Missing	5 (6)	30 (8)	
Marital status			
Married/common-law	68 (79)	320 (86)	0.14
Not married/common-law	18 (21)	54 (14)	
Missing	0 (0)	0 (0)	
Parity			
0	6 (7)	39 (10)	0.59
1	32 (37)	141 (38)	
≥2	21 (24)	82 (22)	
Missing	27 (31)	112 (30)	
Pre-preg BMI (GM, kg/m^2)	21.9 (20, 23.9)	21.5 (19.5, 24)	0.36
Missing	3 (3)	26 (7)	
Tobacco smoke exposures			
Smoked at any time in pregnancy			
No	76 (88)	344 (92)	0.31

Yes	9 (10)	27 (7)	
Missing	1 (1)	3 (1)	
Lived with a smoker at any time in pregnancy			
No	41 (48)	185 (49)	0.79
Yes	43 (50)	182 (49)	
Missing	2 (2)	7 (2)	
Health during current pregnancy			
Anemia			
No	69 (80)	304 (81)	0.83
Yes	17 (20)	70 (19)	
Diabetes			
No	86 (100)	374 (100)	NA
Yes	0 (0)	0 (0)	
Gestational diabetes			
No	86 (100)	374 (100)	NA
Yes	0 (0)	0 (0)	
Hypertension			
No	84 (98)	352 (94)	0.18
Yes	2 (2)	22 (6)	
Gestational hypertension			
No	63 (73)	327 (87)	0.01
Yes	0 (0)	32 (9)	
Missing			
TORCH infections			
No	71 (83)	367 (98)	0.78
Yes	1 (1)	7 (2)	
Missing	14 (16)	0 (0)	
NEWBORN			
Birth weight (g)	3450 (3000, 3900)	3500 (3200, 3800)	0.44
Gestational age at birth (weeks)	39.3 (38.5, 40)	39.5 (38.5, 40)	0.01
Birth length (cm)	50.5 (50, 52)	51 (50, 52)	0.15
Head circumference (cm)	35 (34, 36)	35 (34, 36)	0.13
Ponderal index (g/cm^3)	2.7 (2.5, 2.8)	2.6 (2.5, 2.8)	0.59
Low birth weight	8 (9)	15 (4)	0.04
Small for gestational age	6 (7)	27 (7)	0.94
Preterm birth	15 (17)	19 (5)	0.001

[a]At the time of data collection, 600,000 Tugriks was the equivalent of approximately $243 USD

Table D.2. Estimated effects of a doubling of maternal blood cadmium concentrations on fetal growth outcomes, stratified by sex

		Girls				Boys			
		Crude		Adjusted[a]		Crude		Adjusted[a]	
Outcome	**Type of effect estimate[b]**	**All births n = (169)**	**Term births n = (160)**	**All births n = (143)**	**Term births n = (136)**	**All births n = (205)**	**Term births n = (195)**	**All births n = (181)**	**Term births n = (175)**
Birth weight, g	Mean difference (95% CI)	-115 (-210, -19)	-116 (-200, -32)	-103 (-198, -8)	-116 (-205, -27)	-39 (-126, 47)	-62 (-139, 15)	-63 (-144, 18)	-58 (-138, 22)
Birth length, cm		-0.33 (-0.82, 0.16)	-0.17 (-0.55, 0.21)	-0.15 (-0.59, 0.28)	-0.18 (-0.60, 0.25)	-0.13 (-0.52, 0.26)	-0.23 (-0.57, 0.12)	-0.15 (-0.52, 0.22)	-0.17 (-0.54, 0.21)
Head circumference, cm		-0.24 (-0.57, 0.08)	-0.22 (-0.51, 0.07)	-0.27 (-0.59, 0.05)	-0.31 (-0.61, 0.00)	0.12 (-0.18, 0.42)	0.02 (-0.24, 0.27)	0.06 (-0.20, 0.31)	0.07 (-0.2, 0.33)
Ponderal index, g/cm^3		-0.03 (-0.09, 0.04)	-0.06 (-0.11, -0.02)	-0.06 (-0.13, 0.004)	-0.07 (-0.12, -0.02)	-0.01 (-0.05, 0.04)	-0.01 (-0.05, 0.04)	-0.03 (-0.08, 0.019)	-0.02 (-0.07, 0.03)
Low birthweight	Odds ratio (95% CI)	1.38 (0.59, 3.25)	2.06 (0.64, 6.61)	1.13 (0.39, 3.33)	1.16 (0.39, 3.49)	0.54 (0.2, 1.45)	1.95 (0.49, 7.79)	1.21 (0.46, 3.14)	1.00 (0.38, 2.64)
Small for gestational age		1.83 (0.95, 3.50)	2.30 (1.13, 4.66)	1.85 (0.90, 3.81)	2.03 (0.95, 4.33)	1.14 (0.58, 2.23)	0.82 (0.34, 1.96)	1.21 (0.6, 2.44)	0.84 (0.35, 2.00)
Preterm birth		0.63 (0.26, 1.50)		1.75 (0.70, 4.38)		0.70 (0.31, 1.58)		1.61 (0.68, 3.8)	

[a]Models of birth weight, birth length, head circumference, ponderal index and low birth weight were adjusted for maternal age, monthly household income, pre-pregnancy BMI, anemia status, gestational age and gestational age squared, living with a smoker in late pregnancy, ger density, and intervention status. Models of small for gestational age were adjusted for all same list of variables, except for gestational age, gestational age squared, and sex, and models of preterm birth were adjusted for the same list of variables, except for gestational age and gestational age squared.

[b]Per doubling of blood cadmium concentrations.

Table D.3. Estimated effects of a doubling of maternal blood cadmium concentrations on fetal growth outcomes, stratified by living with a smoker in late pregnancy.

		Did not live with a smoker in late pregnancy				Lived with a smoker in late pregnancy			
		Crude		Adjusted[a]		Crude		Adjusted[a]	
Outcome	**Type of effect estimate[b]**	**All births n = (193)**	**Term births n = (185)**	**All births n = (176)**	**Term births n = (169)**	**All births n = (160)**	**Term births n = (154)**	**All births n = (148)**	**Term births n = (142)**
Birth weight, g	Mean difference (95% CI)	-56 (-166, 54)	-76 (-181, 28)	-44 (-148, 59)	-33 (-134, 67)	-104 (-187, -22)	-89 (-160, -18)	-108 (-180, -35)	-108 (-179, -38)
Birth length, cm		-0.30 (-0.86, 0.25)	-0.18 (-0.65, 0.29)	-0.16 (-0.66, 0.34)	-0.05 (-0.53, 0.42)	-0.18 (-0.55, 0.19)	-0.15 (-0.46, 0.16)	-0.13 (-0.46, 0.2)	-0.15 (-0.48, 0.18)
Head circumference, cm		0.01 (-0.36, 0.37)	-0.01 (-0.34, 0.33)	0.04 (-0.28, 0.37)	0.07 (-0.25, 0.39)	-0.11 (-0.37, 0.15)	-0.08 (-0.31, 0.15)	-0.16 (-0.4, 0.08)	-0.16 (-0.40, 0.08)
Ponderal index, g/cm^3		0.03 (-0.04, 0.09)	-0.03 (-0.08, 0.02)	0.002 (-0.06, 0.069)	-0.01 (-0.07, 0.04)	-0.05 (-0.1, -0.01)	-0.05 (-0.09, -0.002)	-0.069 (-0.12, -0.023)	-0.06 (-0.11, -0.02)
Low birthweight	Odds ratio (95% CI)	0.43 (0.14, 1.35)	0.99 (0.15, 6.39)	1.13 (0.33, 3.91)	0.77 (0.20, 2.98)	1.78 (0.82, 3.87)	2.40 (0.79, 7.29)	1.32 (0.58, 3.05)	1.00 (0.43, 2.35)
Small for gestational age		1.09 (0.48, 2.45)	1.16 (0.49, 2.74)	0.92 (0.39, 2.18)	0.98 (0.40, 2.39)	2.19 (1.15, 4.17)	2.16 (1.04, 4.48)	1.91 (1.02, 3.55)	1.67 (0.84, 3.31)
Preterm birth		0.65 (0.23, 1.87)		1.47 (0.52, 4.11)		1.33 (0.59, 2.99)		1.41 (0.63, 3.15)	

[a]Models of birth weight, birth length, head circumference, ponderal index and low birth weight were adjusted for maternal age, monthly household income, pre-pregnancy BMI, anemia status, sex of the baby, gestational age and gestational age squared, ger density, and intervention status. Models of small for gestational age were adjusted for all same list of variables, except for gestational age and sex, and models of preterm birth were adjusted for the same list of variables, except for gestational age.
[b]Per doubling of blood cadmium concentrations.

Table D.4. Estimated effects of a doubling of maternal blood cadmium concentrations on fetal growth outcomes, stratified by ger density surrounding participants' apartments

				Birth weight, g	Birth length, cm	Head circumference, cm	Ponderal index, g/cm^3	Low birthweight[c]	Small for gestational age	Preterm birth
				Mean difference (95% CI)				Odds ratio (95% CI)		
< 3.5 gers per hectare	**Crude**	**All births**	n = 127	-43 (-164, 78)	0.05 (-0.48, 0.58)	0.02 (-0.39, 0.43)	-0.04 (-0.09, 0.02)	0.56 (0.16, 1.98)	1.18 (0.5, 2.75)	0.48 (0.17, 1.35)
		Term births	n = 118	-82 (-179, 14)	-0.06 (-0.48, 0.35)	-0.07 (-0.43, 0.28)	-0.05 (-0.1, 0.003)		1.49 (0.58, 3.82)	
	Adjusted[a]	**All births**	n = 108	-35 (-143, 73)	0.19 (-0.32, 0.69)	0.11 (-0.29, 0.51)	-0.05 (-0.11, 0.01)	1.02 (0.31, 3.32)	1.18 (0.89, 1.58)	1.75 (0.6, 5.13)
		Term births	n = 103	-52 (-154, 51)	0.13 (-0.37, 0.63)	0.07 (-0.32, 0.47)	-0.06 (-0.12, 0.01)		1.40 (0.99, 1.98)	
3.5 - 4.5 gers per hectare	**Crude**	**All births**	n = 130	-97 (-213, 18)	-0.24 (-0.75, 0.26)	-0.03 (-0.4, 0.33)	-0.04 (-0.1, 0.02)	2.69 (0.88, 8.25)	1.9 (0.92, 3.91)	2.37 (0.43, 13.13)
		Term births	n = 129	-87 (-199, 26)	-0.2 (-0.69, 0.3)	-0.001 (-0.36, 0.36)	-0.04 (-0.09, 0.019)	2.76 (0.8, 9.49)	1.85 (0.88, 3.87)	
	Adjusted[a]	**All births**	n = 118	-131 (-235, -28)	-0.32 (-0.76, 0.13)	-0.15 (-0.47, 0.17)	-0.07 (-0.13, -0.0001)	1.88 (0.66, 5.39)	1.85 (0.88, 3.89)	1.18 (0.42, 3.32)
		Term births	n = 117	-125 (-230, -21)	-0.30 (-0.75, 0.15)	-0.12 (-0.45, 0.2)	-0.06 (-0.13, 0.01)	1.49 (0.57, 3.91)	1.86 (0.86, 4.02)	
> 4.5 gers per hectare	**Crude**	**All births**	n = 115	-115 (-222, -8)	-0.56 (-1.18, 0.06)	-0.18 (-0.58, 0.23)	0.01 (-0.07, 0.09)	1.34 (0.51, 3.49)	1.22 (0.49, 3.05)	1.33 (0.6, 2.97)
		Term births	n = 107	-77 (-167, 14)	-0.33 (-0.77, 0.11)	-0.15 (-0.44, 0.13)	-0.003 (-0.05, 0.049)	0.32 (0.06, 1.62)	0.8 (0.25, 2.55)	
	Adjusted[a]	**All births**	n = 98	-102 (-206, 3)	-0.33 (-0.86, 0.21)	-0.22 (-0.55, 0.11)	-0.02 (-0.1, 0.06)	1.08 (0.44, 2.65)	1.22 (0.5, 3)	1.5 (0.63, 3.53)
		Term births	n = 91	-79 (-180, 22)	-0.21 (-0.69, 0.27)	-0.22 (-0.54, 0.1)	-0.02 (-0.08, 0.03)	1.00 (0.44, 2.26)	0.57 (0.16, 2.05)	

[a]Models of birth weight, birth length, head circumference, ponderal index and low birth weight were adjusted for maternal age, monthly household income, pre-pregnancy BMI, anemia status, sex of the baby, gestational age and gestational age squared, living with a smoker in late pregnancy, and intervention status. Models of small for gestational age were adjusted for all same list of variables, except for gestational age and sex, and models of preterm birth were adjusted for the same list of variables, except for gestational age.
[b]Per doubling of blood cadmium concentrations.
[c]There were no cases of low birth weight among term births in the intervention group

Table D.5. Estimated effects of a doubling of maternal blood cadmium concentrations on fetal growth outcomes, stratified by intervention status

		Control group				Intervention group			
		Crude		Adjusted[a]		Crude		Adjusted[a]	
Outcome	**Type of effect estimate[b]**	**All births n = (173)**	**Term births n = (169)**	**All births n = (144)**	**Term births n = (142)**	**All births n = (201)**	**Term births n = (186)**	**All births n = (180)**	**Term births n = (169)**
Birth weight, g	Mean difference (95% CI)	-51 (-142, 39)	-70 (-156, 16)	-95 (-174, -17)	-98 (-190, -6)	-88 (-182, 6)	-89 (-167, -11)	-100 (-184, -15)	-95 (-174, -17)
Birth length, cm		-0.08 (-0.47, 0.31)	-0.16 (-0.54, 0.21)	-0.05 (-0.46, 0.36)	-0.08 (-0.49, 0.33)	-0.34 (-0.82, 0.14)	-0.18 (-0.54, 0.18)	-0.29 (-0.7, 0.12)	-0.23 (-0.62, 0.16)
Head circumference, cm		0.05 (-0.24, 0.33)	-0.01 (-0.29, 0.26)	-0.06 (-0.36, 0.25)	-0.06 (-0.37, 0.25)	-0.13 (-0.47, 0.21)	-0.14 (-0.42, 0.13)	-0.12 (-0.39, 0.15)	-0.13 (-0.39, 0.14)
Ponderal index, g/cm^3		-0.02 (-0.07, 0.02)	-0.03 (-0.07, 0.02)	-0.06 (-0.11, -0.01)	-0.06 (-0.12, -0.01)	-0.004 (-0.06, 0.05)	-0.04 (-0.08, 0.01)	-0.03 (-0.09, 0.03)	-0.04 (-0.09, 0.01)
Low birthweight[c]	Odds ratio (95% CI)	1.03 (0.41, 2.64)	1.55 (0.60, 4.04)	1.34 (0.48, 3.77)	1.57 (0.53, 4.69)	0.87 (0.37, 2.04)	-----	1.19 (0.40, 3.49)	-----
Small for gestational age		1.22 (0.67, 2.21)	1.21 (0.66, 2.22)	1.18 (0.89, 1.58)	1.40 (0.99, 1.98)	1.70 (0.81, 3.57)	1.85 (0.71, 4.84)	1.49 (0.72, 3.11)	1.51 (0.62, 3.65)
Preterm birth		0.60 (0.16, 2.23)		1.21 (0.40, 3.67)		0.77 (0.39, 1.54)		1.72 (0.82, 3.64)	

[a]Models of birth weight, birth length, head circumference, ponderal index and low birth weight were adjusted for maternal age, monthly household income, pre-pregnancy BMI, anemia status, sex of the baby, gestational age and gestational age squared, living with a smoker in late pregnancy, and ger density. Models of small for gestational age were adjusted for all same list of variables, except for gestational age and sex, and models of preterm birth were adjusted for the same list of variables, except for gestational age.
[b]Per doubling of blood cadmium concentrations.
[c]There were no cases of low birth weight among term births in the intervention group.