A Randomized Air Cleaner Intervention Study of Social and Behavioral Impairment in Childhood: The Ulaanbaatar Gestation and Air Pollution Research (UGAAR) study

by

Undarmaa Enkhbat

MSPH, Johns Hopkins University, 2015

BSc, Medical University of Ciego de Avila, Cuba, 2010

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

Summer 2023

Declaration of Committee

Name:	**Undarmaa Enkhbat**
Degree:	**Doctor of Philosophy**
Title:	**A Randomized Air Cleaner Intervention Study of Social and Behavioral Impairment in Childhood: The Ulaanbaatar Gestation and Air Pollution Research (UGAAR) study**
Committee:	**Chair: Chris G. Buse** Assistant Professor, Health Sciences
	Ryan W. Allen Supervisor Professor, Health Sciences
	Bruce P. Lanphear Committee member Professor, Health Sciences
	Lawrence C. McCandless Committee member Professor, Health Sciences
	David C. Bellinger Committee member Professor, Harvard School of Public Health Harvard University
	Nicole Catherine Examiner Assistant Professor, Health Sciences
	Zhanghua Chen External Examiner Assistant Professor Population and Public Health Science University of Southern California

Ethics Statement

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

a. human research ethics approval from the Simon Fraser University Office of Research Ethics

or

b. advance approval of the animal care protocol from the University Animal Care Committee of Simon Fraser University

or has conducted the research

c. as a co-investigator, collaborator, or research assistant in a research project approved in advance.

A copy of the approval letter has been filed with the Theses Office of the University Library at the time of submission of this thesis or project.

The original application for approval and letter of approval are filed with the relevant offices. Inquiries may be directed to those authorities.

Simon Fraser University Library
Burnaby, British Columbia, Canada

Update Spring 2016

Abstract

Background: Maternal exposure to particulate matter (PM) air pollution during pregnancy may impair children's social and behavioral development. My objectives were to assess (1) the impact of reducing indoor PM using portable HEPA cleaners during pregnancy on behavioral problems at ages 2 and 4 (2) the impact of reducing indoor PM using portable HEPA cleaners during pregnancy on the autistic traits at age 4 and, (3) the influence of prenatal maternal stress on the relationship between the intervention and children's social and behavioral outcomes at age 4. ***Methods:*** This research used data collected in the Ulaanbaatar Gestation and Air Pollution Research (UGAAR) randomized controlled trial. A total of 540 non-smoking pregnant women were randomly assigned to receive 1 to 2 HEPA filter air cleaners or no air cleaners. The HEPA air cleaners were deployed at median of 11 weeks of pregnancy. UGAAR staff collected exposure data through home visits and health, demographic data, and hair and blood samples through clinic visits during pregnancy. Staff also administered the Behavior Assessment System for Children, 3rd Edition (BASC-3) when children were two and four years old and the Social Responsiveness Scale, Second Edition (SRS-2) at four years old. Blood samples were also collected from children at age two. I imputed missing data using multiple imputation with chained equations and assessed the effect of the intervention on mean BASC-3 and SRS-2 scores. I also evaluated adjusted associations between trimester-specific $PM_{2.5}$ concentrations inside residences and behaviour scores. Finally, I tested modification of the intervention's effect on behaviour by maternal stress hormone concentrations and perceived stress in early pregnancy. ***Results*:** No differences in the mean BASC-3 and SRS-2 scores between treatment groups were observed. An interquartile range (20.1 $\mu g/m^3$) increase in first trimester $PM_{2.5}$ concentration was associated with higher externalizing problem scores (2.4 units, 95% CI: 0.7, 4.1), higher internalizing problem scores (2.4 units, 95% CI: 0.7, 4.0), lower adaptive skills scores (-1.5 units, 95% CI: -3.0, 0.0), and higher behavior symptoms index scores (2.3 units, 95% CI: 0.7, 3.9) when children were 4 years old. I found evidence of interactions between the intervention and maternal stress, with generally greater benefits of the intervention on behavior scores among children whose mothers had higher levels of stress in early pregnancy. ***Conclusion:*** This work provides further evidence that $PM_{2.5}$ exposure during pregnancy increases the risk of social and behavioral problems in children. It may be necessary to intervene early in pregnancy to protect children.

Keywords: $PM_{2.5}$, RCT, portable HEPA cleaner, behavior, autistic traits, stress, Mongolia

Dedication

This thesis is dedicated to my mom and dad for their love, support, and encouragement throughout my pursuit of education.

Acknowledgements

First and foremost, I would like to express my sincere gratitude to my supervisor, Dr. Ryan Allen, for his unwavering attention and support throughout every step of the process. Without his guidance, this experience would been entirely different. I am deeply grateful to have been supervised by Drs. David Bellinger, Bruce Lanphear, and Lawrence McCandless, whose expertise and input have been invaluable to this work.

I also want to extend my heartful thanks for my UGAAR team at SFU: Battsetseg, Prabjit, Sukhpreet, Tanner, and Weiran. A special mention goes to Weiran Yuchi for her exceptional work on exposure modeling of UGAAR participant homes, which formed a significant component of this thesis.

Acknowledgments are due to the UGAAR team in Mongolia, where this project would not have been possible without the dedication and passion of many individuals, particularly Drs. Enkhjargal, Chimeglkham, Gerel, and Buyantushig, Sarangerel, Enkhtuul. Their commitment to this endeavor has been truly inspiring.

Lastly, I would like to express my heartful appreciation to my husband, children and the Enkhbat clan for being my steady support system from the very beginning.

Table of Contents

List of Tables

List of Figures

List of Acronyms

ADHD	Attention Deficit Hyperactivity Disorder
ASD	Autism Spectrum Disorder
BASC-3	Behavioral Assessment System for Children
BDI-II	Beck Depression Inventory
DHEA	Dehydroepiandrosterone
FSIQ	Full Scale Intelligence Quotient
HEI	Health Effects Institute
HEPA	High efficiency particulate air
HOME	Home Observation Measurement of the Environment
HPA	Hypothalamic-pituitary-adrenal
ICP-MS	Inductively coupled plasma-mass spectrometry
IQR	Interquartile range
LMIC	Low- and middle-income countries
PM	Particulate matter
$PM_{2.5}$	Fine particulate matter
PSS-4	Perceived stress scale
PTB	Preterm birth
RCT	Randomized controlled trial
SFU	Simon Fraser University
SRS-2	Social Responsiveness Scale
UGAAR	Ulaanbaatar Gestation and Air Pollution Research
UNDP	United Nations Development Programme
WASI	Wechsler Abbreviated Scale Intelligence

Preface

This document is formatted in accordance with the manuscript-based thesis guidelines provided by the Faculty of Health Sciences at Simon Fraser University. This thesis is based on three peer-reviewed manuscripts. Chapter one is an introductory chapter that provides background on the topic and hypotheses evaluated in this work. 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.

Chapter two was published in *Environmental Health* in 2021:

> Undarmaa Enkhbat, Enkhjargal Gombojav, Chimeglkham Banzrai, Sarangerel Batsukh, Buyantushig Boldbaatar, Enkhtuul Enkhtuya, Chimedsuren Ochir, David C. Bellinger, Bruce P. Lanphear, Lawrence C. McCandless and Ryan W. Allen. Portable HEPA Filter Air Cleaner Use During Pregnancy and Children's Behavior Problem Scores: A Secondary Analysis of the UGAAR Randomized Controlled Trial. *Environmental Health*. 2021 Jul 5; 20(1):78.

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

Chapter three was published in *Environment International* in 2022:

> Undarmaa Enkhbat, Enkhjargal Gombojav, Chimeglkham Banzrai, Sarangerel Batsukh, Buyantushig Boldbaatar, Enkhtuul Enkhtuya, David C. Bellinger, Bruce P. Lanphear, Lawrence C. McCandless and Ryan W. Allen. Portable HEPA Filter Air Cleaner Use During Pregnancy and Children's Autistic Behaviors at Four Years of Age: The UGAAR Randomized Controlled Trial. *Environment International*. 2022 Jul 25; 168:107432.

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

Chapter four has been prepared for submission to *Environment International*. Co-authors have provided feedback on the version included in this thesis. I developed the data analysis plan with input from my supervisory committee. I conducted all statistical analyses and drafted the manuscript.

> Undarmaa Enkhbat, Enkhjargal Gombojav, Chimeglkham Banzrai, Sarangerel Batsukh, Buyantushig Boldbaatar, Enkhtuul Enkhtuya, David C. Bellinger, Bruce P. Lanphear, Lawrence C. McCandless, Sukhpreet Tamana, Pablo Nepomnaschy, Katrina Salvante, Joanne Weinberg and Ryan W. Allen. The Influence of Stress During Pregnancy on the Association between an Air Cleaner Intervention and Children's Social and Behavioral Development at Four-years of Age: The UGAAR Randomized Controlled Trial

Chapter 1.

Introduction

Air pollution is a leading contributor to death and disease globally (1). More than 90% of the world's population is exposed to fine particulate matter ($PM_{2.5}$) concentrations above the World Health Organization's annual average guideline of 5 $\mu g/m^3$ (1,2).

Exposure to $PM_{2.5}$ during pregnancy has been linked to impaired fetal growth (3), which may, in turn, cause developmental programming that adversely affects health in childhood and beyond. This is consistent with the "Barker Hypothesis" (4–7), which posits that unfavorable intrauterine conditions lead to irreversible fetal adaptions that increase the likelihood of survival but have lasting effects on the morphology, vasculature, physiology, and endocrine and metabolic functioning of organs (5–7).

Air pollution exposure during pregnancy may affect brain development. The temporal process of brain development makes the brain particularly vulnerable to external stressors at different periods in pregnancy (8). Although the biological mechanisms underlying the brain effects from prenatal air pollution exposure have not yet been established, there are several plausible hypotheses, including placental impairments, the movement of particles across the blood-brain barrier, and/or maternal systematic inflammation and oxidative stress (9).

Attention Deficit Hyperactive Disorder (ADHD) and Autism Spectrum Disorder (ASD) are the most common neurodevelopmental disorders among children, and the prevalence of these disorders has been increasing (10,11). ADHD is defined as a persistent pattern of inattention and hyperactive or impulsive behavior, while ASD is characterized by repetitive behaviors and impairment in communication and social skills (12). There are several possible explanations for the increasing prevalence of neurodevelopmental disorders, including changes to diagnostic criteria and increased awareness. Genes and environmental influences both contribute to the development of neurodevelopmental disorders, but genes do not change at a rate that can account for the rapid increase in the

prevalence of these disorders (13,14). The twin studies of ASD provided evidence that shared environmental factors play a large role in the development of ASD (15).

Air pollution continues to increase in many low- and middle-income countries (13,16). The relationship between air pollution and neurodevelopmental disorders remains unclear as previous studies of the effects of prenatal exposure to air pollution on social and behavioral development relied on either animal experiments or observational designs (17). Thus, it is crucial to understand the role of air pollution exposure in the rising prevalence of neurodevelopmental disorders (18).

The Ulaanbaatar Gestation and Air Pollution (UGAAR) study is a single-blind randomized controlled trial (RCT) designed to assess the impacts of high efficiency particulate air (HEPA) filter air cleaners ("HEPA cleaners") use during pregnancy on fetal growth and childhood development. I joined the UGAAR study group in 2017, and as part of the study group I translated the social and behavioral assessments from English to Mongolian. Additionally, I collected questionnaire data from the participants. Using the data collected on social and behavioral outcomes from the UGAAR study, I conducted this research to investigate the impact of HEPA cleaners during pregnancy on social and behavioral development at ages 2 and 4.

1.1. Background

1.1.1. Neurodevelopmental disorders and their public health implications

Neurodevelopmental disorders are cognitive and behavioral conditions that are associated with the functioning of the neurological system and the brain (11,19). According to the Diagnostic and Statistical Manual for Mental Disorders, 5th edition (DSM-5) these disorders are categorized as developmental deficits in a variety of domains including social, cognitive, motor, and language (13). Genetic factors contribute neurodevelopmental disorders such as ASD, however, environmental risk factors also play an important role (15,16,20).

Behavioral impairments are categorized into internalizing or externalizing problems. Internalizing problems include anxiety, depression, withdrawal, and somatization while externalizing problems include aggression, hyperactivity, and attention problems. Though behaviors such as "tantrums" and aggression can be a normal part of development, atypical behavioral development is characterized by a pattern of behavior that is outside the expected norm for age and level of development (19). According to the US Centers for Disease Control (CDC), Attention Deficit Hyperactivity Disorder (ADHD) is estimated to affect 9.4% of children and adolescents in the US, while 7.1% of children ages 3-17 are diagnosed with anxiety and 3.2% with depression (21). This statistic was slightly lower in the Canadian population as according to Canadian ADHD Resource Alliance (CADDRA), the estimated prevalence of ADHD among children and adolescents is 5-7% (22).

The prevalence of ASD in low- and middle-income countries varies from 0.09 to 1.2 % (23). The lower prevalence in these countries, relative to high-income countries, may be due to lack of ASD knowledge, awareness, and a lack of diagnostic tools in these countries (23). In Mongolia, ASD was not officially classified as a disorder until 2015 and there are no official data on the prevalence of ASD or ADHD. Unofficial sources have indicated that in 2019 there were 763 children registered with an ASD diagnosis nationwide (24).

Atypical behaviors and their underlying morbidities can impair learning, restrict access to normal activities and social opportunities, and require a considerable amount of both human and financial resources to manage (19,25). Furthermore, many of the neurodevelopmental disorders in childhood increase the risk of negative outcomes in adulthood, such as substance abuse and suicide (13,19).

1.1.2. Biological mechanisms of brain effects from particulate matter exposure

The mechanisms underlying the neurodevelopment effects from air pollution exposure are not yet fully understood. Investigators have identified multiple possible mechanisms through which exposure to $PM_{2.5}$ during pregnancy can negatively affect the

developing brain (9,26). Findings from experimental studies have suggested that oxidative stress, chronic neuroinflammation, mitochondrial dysfunction, DNA methylation may be involved (26). These biological mechanisms may overlap making it challenging to understand the role of single mechanistic pathways (27). The chemical constituents of the air pollutant maybe play an important role in the effects (27).

Exposure to PM causes localized oxidative stress and inflammation in the respiratory system, which can lead to systemic oxidative stress and an inflammatory response throughout the body (27). During pregnancy, these responses alter the development and functioning of the placenta, ultimately decreasing the transfer of oxygen and nutrients to the fetus (9,27). Placental impairment also increases the risk of fetal growth restriction and preterm birth. These outcomes have been associated with neuroinflammation, neuron damage, and oxidative stress in the child's brain (28,29).

There is evidence to suggest that PM exposure during pregnancy can lead to direct damage to the fetal brain. This may occur through the transport of PM particles into the maternal bloodstream, through the placental barrier, and across the fetal blood-brain barrier (9). Black carbon particles have been found on both the fetal and maternal sides of the placenta. The amount of black carbon found in the placenta has been shown to be correlated with the mother's residential black carbon exposure (30).

PM exposure may also cause epigenetic changes, which may alter gene expression without changing DNA sequence. Epigenetic mechanisms play a crucial role in fetal development by regulating important cellular processes such as apoptosis, cell growth, and cell differentiation (31). Studies have reported that PM exposure during pregnancy is associated with altered mitochondrial function in the placenta as indicated by changes in mitochondrial DNA methylation (32,33).

1.1.3. Epidemiological studies of air pollution on social and behavior impairment in childhood

There is growing epidemiologic evidence that air pollution in pregnancy negatively impacts children's social and behavior development. Several studies reported that higher

exposure to $PM_{2.5}$ in utero was associated with a reduced corpus callosum volume which has implications for processing speed, attention, ADHD symptoms, and externalizing problems in young children (8,34,35). An analysis of 186 children from the European Study of Cohorts for Air Pollution Effects (ESCAPE) indicated that a 7 $\mu g/m^3$ increase in prenatal exposure to $PM_{2.5}$ was associated with a -57.2 (-117.7, 3.4) mm^3 reduction in the mean corpus callosum volume quantified by magnetic resonance imaging (MRI) (34). Such structural changes in the corpus callosum may link early life exposure to $PM_{2.5}$ with childhood behavioral problems (8,34). However the study used modelled $PM_{2.5}$ estimates at participants' current residential addresses to assess prenatal exposure, which may have introduced non-differential exposure misclassification (34).

Several epidemiologic studies also implicate specific particle constituents. For example, prenatal exposure to polycyclic aromatic hydrocarbons (PAHs) has been associated with attention problems and symptoms of anxiety and depression in children (36–38). Black carbon from diesel exhaust has been linked with atypical behaviors in children (39,40).

Other observational studies have reported weaker relationships between gestational exposure to air pollution and behavior. An analysis of 8 European population-based birth cohorts indicated that prenatal $PM_{2.5}$ exposure was not associated with increases in depressive and anxiety symptoms among children 7-11 years old. The investigators suggested that the lack of association was possibly due to the young age of participants, whose emotional and behavioral problems were not fully developed (41). A study conducted in Mexico city, in which behavior of children aged 4 to 6 years was assessed using the Behavior Assessment System for Children, 2nd Edition (BASC-2), observed that prenatal exposure to $PM_{2.5}$ averaged over the full pregnancy was not associated with externalizing or internalizing problem scores (42). The Conditions Affecting Neurocognitive Development and Learning in Early Childhood (CANDLE) cohort observed no association between prenatal PM_{10} and externalizing and internalizing raw scores when children were 1.5 to 5 years old (43).

There is growing evidence of an association between prenatal exposure to $PM_{2.5}$ and ASD. However, the effect estimates vary considerably between studies (17,44–46). A recent meta-analysis of 13 observational studies reported that five studies observed significant associations between prenatal $PM_{2.5}$ and ASD, while 8 studies did not report an association (46). The latest findings from a pooled analysis of 23 studies have reported that 10 $\mu g/m^3$ increment in $PM_{2.5}$ exposure during pregnancy could increase the risk of ASD by 1.34 times (OR=1.34, 95% CI: 1.11, 1.60) (47).

Existing studies of air pollution exposure and social and behavioral development in childhood have important limitations. To date all existing studies have been observational, so residual confounding cannot be ruled out. Another challenge with understanding these association is cultural differences in the interpretation of social and behavior norms. Behaviors may be accepted differently in different settings, so use of an instrument designed for children in one setting may not fully capture behavior problems elsewhere. It is possible that the timing of exposure to air pollution during pregnancy may modify the relationship between exposure and neurodevelopment. 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 low- and middle-income countries (LMIC). Finally, use of outdoor $PM_{2.5}$ concentrations as a proxy for personal exposure to outdoor-generated $PM_{2.5}$ may introduce exposure misclassification as given that people spend the majority of their time indoors (48).

1.1.4. Timing of exposure in pregnancy

Given the speed, complexity and pattern of brain development in early life, the impact of air pollution exposure may depend on timing (8,49). Studies have examined the association between trimester-specific exposure and social and behavioral outcomes (46,50–52). In a nested case-control within the Nurse's Health Study II, outdoor $PM_{2.5}$ concentrations during each trimester were associated with an increased risk of ASD. The strongest association was observed for exposure in the third trimester (OR =1.49; 95% CI: 1.20, 1.85 per 4.4 $\mu g/m^3$ contrast) (53). A similar result was observed in a case control study in California, which reported that exposure to traffic-related $PM_{2.5}$ in each trimester

was associated with ASD, with the strongest association observed for the second trimester (OR=1.48; 95% CI: 1.40, 1.57 per 8.7 $\mu g/m^3$ contrast) (54). In the BREATH cohort, researchers observed that prenatal exposure to $PM_{2.5}$ during third trimester of pregnancy was associated with a 5% reduction in volume of the body corpus callosum (34). A study conducted in Changsha, China used the Neonatal Behavioral Neurological Assessment (NBNA) to assess children's behavioral impairments at 48-72 hours after birth. Prenatal $PM_{2.5}$ was not associated with total NBNA score during any of the trimesters of pregnancy but associations with behavioral subscale scores were strongest for exposure during the second trimester (55).

Other studies suggest that exposure during early pregnancy might be most important. In a recent birth cohort study in California, the investigators used a weekly exposure model to examine the association between $PM_{2.5}$ and ASD. The exposure models were mutually adjusted for all other weeks of exposure to isolate associations to specific time periods. The researchers reported that outdoor $PM_{2.5}$ in 1-27 weeks of pregnancy was associated with risk of developing ASD in children (cumulative HR = 1.14; 95% CI: 1.06, 1.23 per 7.4 $\mu g/m^3$ contrast) and the association decreased over the course of pregnancy (52). In a study conducted in Mexico City using the BASC-2, a 5 $\mu g/m^3$ increase in outdoor $PM_{2.5}$ concentration during the first trimester was associated with a 1.1-unit (95% CI: -0.2, 2.4) increase in mean Behavioral Symptom Index (BSI) T-score and a decrease of 1.5 units (95% CI: -2.6, -0.3) in mean adaptive skills T-score. $PM_{2.5}$ concentrations in other trimesters were not associated with behavior scores. In the Upstate KIDS study, a 10 $\mu g/m^3$ increase in outdoor $PM_{2.5}$ exposure during the first and third trimesters was associated with increases of 1.6% (95% CI: 0.1%, 3.2%) and 2.7% (95% CI: 0.6%, 4.9%) respectively, in the risk of a failed developmental screening between 8 and 36 months of age. The effect estimated for exposure during the second trimester was smaller (29).

Several other studies did not observe an association with exposure to $PM_{2.5}$ in any of the trimester of pregnancy (56–59). Thus, the evidence regarding the critical window of exposure to $PM_{2.5}$ during pregnancy and its impacts on social and behavioral impairment is inconclusive and not well understood.

1.1.5. Potential effect modifiers

Epidemiologic studies often focus on the average effect of air pollution in a population, but there may be heterogeneity in the effects across a population. Previous studies have identified several plausible effect modifiers in the association between air pollution and social and behavioral outcomes in children.

Sex

Biological differences in the male and female fetus may play a role in the association between air pollution during pregnancy and neurodevelopmental outcomes in children. The National Institutes of Health (NIH) recommends that biomedical studies of humans and animals address the potential modifying effects of sex (60), suggesting that there may be important biological differences between sexes in developmental outcomes.

Animal experimental studies have indicated that both antioxidant and anti-inflammatory factors are lower in male rat fetuses (61,62). Toxicological studies have shown that microglial cells induced by neuro inflammation may lead to synapse dysfunction linked to ASD (63,64). Male fetus have more microglia than females during gestation, potentially leading males to be more sensitive to PM or other inflammatory insults (65).

Child's sex has been the most commonly examined effect modifier in epidemiologic studies of early life air pollution exposure and autistic and behavioral outcomes (66). Five studies of ASD and three studies of behavioral outcomes have evaluated sex as an effect modifier and reported results from interaction models. A consistent pattern of greater effect estimates of prenatal exposure to $PM_{2.5}$ on ASD among males was observed. However, significant interaction by sex was only observed in two analyses from the Kaiser Permanente Southern California (KPSC) cohort (52,67). In an analysis of 246,420 mother-child pairs born in the KPSC hospitals between 1999 to 2009, investigators reported that the effect of a 6.5 $\mu g/m^3$ contrast in early life $PM_{2.5}$ exposure on ASD was stronger among males (cumulative HR =1.23; 95% CI: 1.10, 1.40) than females (HR = 1.02; 95% CI: 0.79, 1.37). The sex difference was most pronounced for exposure in the first trimester (cumulative HR for males = 1.18; 95% CI: 1.08 – 1.27; HR for females

= 0.90; 95% CI: 0.76 –1.07, interaction p-value = 0.03) (67). In a subsequent analysis, the investigators observed a similar trend on 294,937 mother-child pairs born in the KPSC hospitals between 2001-2014. The effect of a 7.4 $\mu g/m^3$ contrast in early life $PM_{2.5}$ exposure on ASD was stronger among males (cumulative HR =1.19; 95% CI: 1.09 – 1.31) than females (HR = 1.06; 95% CI: 0.86 –1.29, interaction P-value = 0.01) (52).

Prenatal maternal stress

Prenatal maternal anxiety and depression are linked to fetal growth restriction and impaired cognitive, psychomotor, behavioral, and emotional development in childhood (68). The hypothalamic-pituitary-adrenal (HPA) axis produces glucocorticoids in response to stress (69). Some scientists have hypothesized that increased fetal exposure to glucocorticoids causes abnormalities in the structure and function of neurons and glial cells (70). The influence of glucocorticoids is partly mediated by the enzyme 11 β-hydroxysteriod dehydrogenase type 2 (11β-HSD2), which protects the fetus from exposure to high levels of glucocorticoids (71). Air pollution may alter the activity of 11β-HSD2 in the placenta, resulting in higher exposure of the fetus to maternal glucocortoids (69,72). This biological process suggests that both prenatal maternal stress and air pollution share a common biological pathway (73).

Epidemiologists have observed that maternal stress during pregnancy increased the risk of neurodevelopmental outcomes in children when mothers were also exposed to higher levels of air pollution (74,75). A longitudinal birth cohort study in Krakow, Poland, observed that the effect of demoralizing experiences during pregnancy on children's externalizing and internalizing problems were greater among children whose mothers were also exposed to higher levels of prenatal airborne PAHs (75). Similar results were observed in a birth cohort in New York City, where the effect of material hardship during pregnancy on children's ADHD symptoms was greater among children whose mothers were also exposed to high levels of prenatal PAHs (74).

Socioeconomic status

Lower socioeconomic status (SES) is a known risk factor for neurodevelopmental outcomes in children (43). It is possible that maternal SES characteristics and air pollution

share common pathways (73). Mothers with lower socioeconomic status may also experience other risk factors such as lack of resources or lower intelligence. Studies conducted in the United States reported that lower SES also predicted higher prenatal exposure to air pollution (39,40,43). Therefore, in addition to potentially modifying the association between air pollution and behaviour, SES likely also confounds the relationship between prenatal air pollution and behavior and ASD outcomes in many settings (76,77).

Researchers have used several indicators of SES (78). Some studies defined SES as a structural variable (e.g., household income, employment status, parental educational level) while other studies defined SES by material indicators (e.g., material of walls, roof and floor of the housing, age of the housing, material goods) (66,79). When examining SES as a potential modifier in the relationship between air pollution exposure and social and behavior outcomes, some studies used composite SES indices (59,80), while many studies used household income, maternal education or maternal hardship to indicate SES (43,58,59,74,75,81). The CANDLE cohort investigators conducted a study to investigate the association between prenatal exposure to NO_2 and PM_{10} on childhood behavioral disorders using the Child Behavior Checklist (CBCL) as a measure of outcome. The investigators also examined whether the association differed based on household income, maternal education, which were used as individual-level indicators of SES. The investigators reported that higher levels of postnatal exposure to PM_{10} were associated with more externalizing behavioral problems in children from lower income families, but not those in higher incomes. Specifically, there was an 11% increase (95% CI: 0, 25%) in externalizing behavioral problems per 2 $\mu g/m^3$ increase in PM_{10} exposure among children from lower-income families, compared to a 10% decrease (95% CI: -1, 19%) among children from higher-income families. A statistically significant interaction (p=0.01) was observed with postnatal exposure but no interaction was observed between prenatal PM_{10} exposure and any of the behavioral outcomes (43). The SEED cohort used neighborhood deprivation index (NDI) to characterize SES. An interaction between $PM_{2.5}$ and SES on ASD was observed for $PM_{2.5}$ exposure in the first year of life, but no interaction was observed between prenatal $PM_{2.5}$ exposure and ASD (80). In the Stockholm Youth Cohort, neighborhood deprivation did not modify the association between prenatal traffic-related PM_{10} exposure and ASD (59).

Maternal diet and vitamin intake during pregnancy

Prenatal folic acid and multivitamin supplements intake is linked to increased survival rate and reduced risk of fetal growth restriction and impaired cognitive, psychomotor, behavioral, and emotional development in childhood (82,83). Some scientists have hypothesized that folic acid,-which is critical nutrient in the methylation process for gene regulation (84), may modify air pollution's effect on DNA methylation (85). This suggests that folic acid intake and air pollution share a common biological pathway and that folate may offset some of the neurodevelopmental effects of air pollution (73,86).

Several epidemiological studies observed that folate intake during pregnancy modified the effect of multiple air pollutants on neurodevelopmental outcomes (77,86,87). Two of these studies investigated folic acid and vitamin intake as effect modifiers in the association between either prenatal PM exposure and ASD or cognitive outcomes (77,86). Investigators in the CANDLE cohort study reported that maternal plasma folate levels modified the association between prenatal air pollution and full-scale IQ (FSIQ). Among mothers with low levels of plasma folate, a 5 $\mu g/m^3$ increase in prenatal PM_{10} exposure was associated with a 6.8-point (95% CI: 1.4, 12.3) reduction in mean FSIQ while no association was observed in mothers with higher levels of plasma folate (interaction p=0.07) (77). In the CHARGE study researchers reported that increased folate intake early in pregnancy reduced the effect of prenatal NO_2 on ASD (interaction p=0.04). However, there was not a significant interaction between folate and PM_{10} or $PM_{2.5}$ (86).

Maternal age

The fetus is more exposed and vulnerable to oxidative stress as maternal age increases due to accumulated oxidative damage in somatic cells from biological aging (88,89). This increased oxidative stress may share common pathways with those linking air pollution exposure and neurodevelopment outcomes in children (89). A study conducted in Wuxi, China, indicated that maternal age modifies the association between maternal PM_{10} exposure and preterm birth, which is a risk factor for neurodevelopment outcomes in children. The investigators reported that among mothers exposed to the lowest

quartile of PM_{10} levels compared to highest quartile of PM_{10} exposure, the risk of preterm birth in women aged 35 years or older was (OR: 2.0; 95% CI: 1.0, 3.9; interaction p=0.03) (90).

1.1.6. HEPA filter air cleaner as an environmental exposure intervention

HEPA cleaners lower $PM_{2.5}$ concentrations through mechanical filtration. By definition, HEPA filters remove 99.7% of particles sized 0.3 um, with higher efficiency for larger and smaller particles (91). The effectiveness of HEPA cleaners to reduce indoor particles concentrations is a function of the volume of air that can be cleaned by the unit relative to the volume and air exchange rate of the room (92,93). Given that people spend the majority of their time indoors, HEPA filter air cleaners can be an effective intervention for reducing PM exposure and, potentially, improving health (92–95).

Environmental exposure studies can be challenging to conduct due to ethical considerations, However, RCTs are helpful in evaluating causality between environmental exposures and health outcomes (96). Previous studies have shown that HEPA air cleaner can reduced indoor $PM_{2.5}$ concentrations ranging between 30%-80% (92). Numerous studies also evaluated the effects of using HEPA filter air cleaners on respiratory and cardiovascular intermediate outcomes including blood pressure level, heart rate variability, lung function, inflammation and oxidative stress (92,93,95). While some of these studies have reported beneficial results, only few studies have examined the long term effects of using HEPA air cleaners (93). The effects of HEPA filter air cleaners during pregnancy on children's neurodevelopment has not been studied, but their use has been associated to improvements in cardiovascular intermediate outcomes which may have benefits to better neurodevelopmental outcomes in children (92,93,95).

1.1.7. The Ulaanbaatar Gestation and Air Pollution Research (UGAAR) Study

Study setting

The UGAAR study is being conducted in Ulaanbaatar, the capital city of Mongolia and home to approximately half of the country's 3.2 million people. Ulaanbaatar's annual

average $PM_{2.5}$ concentration in 2019 was 62 $\mu g/m^3$ (97). The main source of particulate pollution in Ulaanbaatar is the combustion of coal heating and cooking in neighborhoods comprised of traditional Mongolian felt-lined yurts (gers) and poorly constructed one or two-story wood and brick homes. Coal emissions from home heating stoves are responsible for 45–70% of total outdoor $PM_{2.5}$ concentrations in the city (98–101). Three coal-fired power plants supply electricity and heat to apartments and other buildings in the city (98–100). It has been estimated that 10% to 25% of the mortality in Ulaanbaatar can be attributed to ambient air pollution (101).

Study population

We recruited participants at two perinatal health clinics in the centrally located Sukhbaatar district of Ulaanbaatar. A total of 540 non-smoking women who met the following criteria: ≥ 18 years of age, ≤ 18 weeks into a single gestation pregnancy, Non-smoker, living in an apartment, not using portable air cleaner(s) at enrollment, and planning to give birth in a medical facility in Ulaanbaatar consented to participate in the study.

Randomization

Randomization was carried out using sealed opaque envelopes containing randomly generated "filter" or "control" allocations and labeled with participant identification numbers running from 1 to 600. Once an individual who met the eligibility criteria and consent to participate, a sealed envelope was drawn in sequential order and opened by a project coordinator who then informed the participant of the allocation. Only one envelope was opened per participant. In case if the participant did not agree to their allocation, they were not enrolled in the study. The envelope was then discarded and a new one was opened at the time of enrollment of the next participant. Participants were not blinded to their intervention status.

Intervention

Participants were assigned to the intervention or control group at a 1:1 ratio. Participants in the intervention group received one or two HEPA filter air cleaners (Coway AP-1009CH) to use from enrolment to delivery. In smaller apartments (<40 m2) we placed an air cleaner in the main living area of the home and in larger apartments (≥40 m2), we

placed the second unit in the participant's bedroom. We deployed the HEPA cleaners in intervention homes shortly after enrollment into the study. The control group received no HEPA cleaners. We did not replace the HEPA filter(s) during the study and we collected the HEPA cleaner(s) after pregnancy ended.

Informed consent

The informed consent was obtained from all participants before randomization. At median of 15.4 months of childbirth (range: 7.7 to 28.9 months) we contacted the participants for follow-up study to investigate child's developmental outcomes from prenatal HEPA air cleaner intervention. Participants again provided written informed consent. The consent form outlines the study objectives, inclusion, and exclusion criteria for participation. We compensated participants up to 65,000 Mongolian tugriks (approximately $30 USD) during prenatal follow-up and up to 260,000 tugriks (approximately $100 USD) during the four years of post-natal follow-up. Compensation was pro-rated based on the specific activities that participants completed.

Data collection

Data collection for the UGAAR study started in January 2014 and was completed in December 2015, during which mothers were enrolled, and intervention took place in the prenatal period. The follow-up study (UGAARII) started in January 2016 through December 2017, during which the child's 24-month assessments were conducted and again in September 2018 to September 2019 for the child's 48-month assessment. Data were collected at home and the UGAAR study office in Ulaanbaatar (figure 1.1).

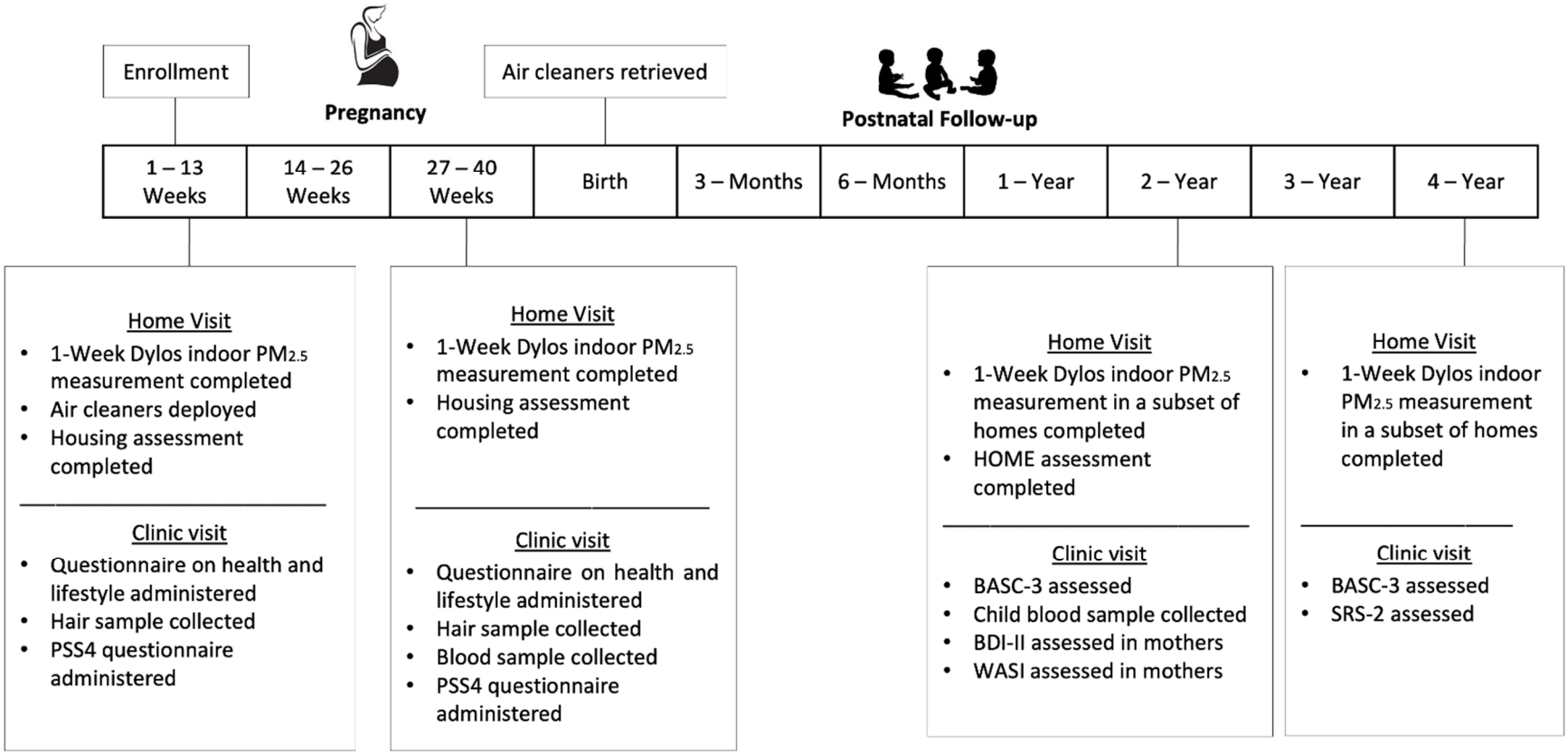


Figure 1.1. Data collection timeline

1.2. Rationale

The purpose of this research was to evaluate the impact of reducing exposure to PM with HEPA air cleaners during pregnancy on social and behavioral impairment in childhood. In addition, I aimed to test for potential modifiers of the air cleaner benefits on social and behavioral impairment in children. I made use of data collected in the Ulaanbaatar Gestation and Air Pollution Research (UGAAR) study, a randomized controlled trial designed to assess the impact of portable HEPA filter air cleaner use during pregnancy on fetal growth and early childhood development (ClinicalTrials.gov: NCT01741051).

My dissertation includes three manuscripts for publication, with each manuscript focused on testing a specific hypothesis:

1. Children born to mothers who used portable air cleaners during pregnancy will have lower behavioral problems scores at ages 2 and 4 than children born to mothers who did not use portable air cleaners during pregnancy.

2. Children born to mothers who used portable air cleaners during pregnancy will have lower autistic traits scores at age 4 than children born to mothers who did not use portable air cleaners during pregnancy.

3. Maternal cortisol and dehydroepiandrosterone (DHEA) in early pregnancy modify the effects of the HEPA air cleaner intervention on children's social and behavioral outcomes at age 4.

Chapter 2. Portable HEPA filter air cleaner use during pregnancy and children's behavior problem scores

2.1. Abstract

Background: Developmental exposure to particulate matter (PM) air pollution may impair children's behaviors. Our objectives were to quantify the impact of reducing indoor PM using portable HEPA filter air cleaners during pregnancy on behavioral problems in children and to assess associations between indoor fine PM ($PM_{2.5}$) concentrations during pregnancy and children's behavior.

Methods: In this single-blind parallel-group randomized controlled trial, we randomly assigned 540 non-smoking pregnant women to receive 1 to 2 HEPA filter air cleaners or no air cleaners. We administered the Behavior Assessment System for Children (BASC-3) to caregivers when children were a mean age of 23 months, and again at a mean age of 48 months. Primary outcomes were the four BASC-3 composite scales: externalizing problems, internalizing problems, adaptive skills, and the behavioral symptoms index. We imputed missing data using multiple imputation with chained equations. The primary analysis was by intention-to-treat. In a secondary analysis, we evaluated associations between BASC-3 composite indices and trimester-specific $PM_{2.5}$ concentrations inside residences.

Results: We enrolled participants at a median of 11 weeks' gestation. After excluding miscarriages, still births and neonatal deaths, our analysis included 478 children (233 control and 245 intervention). We observed no differences in the mean BASC-3 scores between treatment groups. An interquartile increase (20.1 $\mu g/m^3$) in first trimester $PM_{2.5}$ concentration was associated with higher externalizing problem scores (2.4 units, 95% CI: 0.7, 4.1), higher internalizing problem scores (2.4 units, 95% CI: 0.7, 4.0), lower adaptive skills scores (-1.5 units, 95% CI: -3.0, 0.0), and higher behavior symptoms index scores (2.3 units, 95% CI: 0.7, 3.9). Third trimester $PM_{2.5}$ concentrations were also associated with some behavioral indices at age 4, but effect estimates were smaller. No significant

associations were observed with $PM_{2.5}$ concentrations during the second trimester or for any of the BASC indices when children were 2 years old.

Conclusion: We found no benefit of reducing indoor particulate air pollution during pregnancy on parent-reported behaviors in children. Associations between $PM_{2.5}$ concentrations in the first trimester and behavioral scores among 4-year-old children suggest that interventions in early pregnancy may be necessary to protect children, but these exploratory findings should be interpreted cautiously.

2.2. Introduction

Exposure to fine particulate matter air pollution ($PM_{2.5}$) during pregnancy is linked to impaired fetal growth (3,102), which may in turn cause developmental programming that adversely affects health in childhood and beyond (4). Evidence from animal and epidemiologic studies suggests that prenatal exposure to air pollution may adversely affect brain development (37,103,104). Results from birth cohort studies of prenatal exposure and children's behaviors have been inconsistent (29,34,36,41–43,105,106).

Given the speed and complexity of brain development, the impact of an exposure may depend on timing (8,42,49). Two studies of PM exposure and behavior problems in childhood have evaluated the impacts of exposure during specific stages of pregnancy and suggested that exposures in the first and third trimesters may be most important (29,42).

Investigators have not definitively identified the biological mechanism(s) through which air pollution exposure in pregnancy could impact brain development in childhood, but such a link is biologically plausible. Systematic inflammation may play a role (107). Animal experiments have suggested that prenatal exposure to airborne particles induces inflammation in mothers followed by changes in brain morphology in the offspring (103,108).

Portable high efficiency particulate air (HEPA) filter air cleaners ("HEPA cleaners") are a promising intervention to reduce indoor $PM_{2.5}$ exposure. HEPA cleaners reduce average indoor $PM_{2.5}$ concentrations by 29-82% (92,109). Because outdoor air

pollution infiltrates into buildings, indoor air contains pollution emitted from both outdoor and indoor sources. As a result, a substantial portion of the health impacts from outdoor pollution sources stem from exposure that occurs indoors. For example, indoor exposures account for 61% and 81% of the deaths attributed to outdoor-generated $PM_{2.5}$ in the US and China, respectively (110,111). Thus, reducing particle concentrations indoors may mitigate the health impacts of outdoor pollution sources.

2.3. Objective

To quantify the impact of reducing $PM_{2.5}$ using HEPA cleaners during pregnancy on behavioral problems in children at two and four years of age. In addition, we sought to explore associations between indoor $PM_{2.5}$ during different periods of pregnancy and behavior in these children.

2.4. Methods

2.4.1. Prenatal Data Collection

Participants visited our study office shortly after enrollment, between 5 and 19 weeks gestation, and again at 24-37 weeks' gestation (112). At both visits we administered questionnaires on demographics, lifestyle, housing, and health. Participants completed the 4-question perceived stress scale (PSS-4) as part of both prenatal questionnaires (113). During the second visit, we also collected a venous whole blood sample, which was analyzed within six weeks of collection for lead, mercury, and cadmium concentrations using quadrupole-based inductively coupled plasma-mass spectrometry (ICP-MS), with matrix-matched calibration (114).

We measured indoor $PM_{2.5}$ in participants' apartments over seven days shortly after enrollment and again at a median of 30 weeks using Dylos DC 1700 laser particle counters. As described elsewhere, these measurements were used to develop a blended multiple linear regression random forest regression prediction model that provides estimates of $PM_{2.5}$ concentrations during each week of pregnancy for each UGAAR participant (115).

We obtained birth weight, length, head circumference, gestational age, sex, and mode of delivery from medical records. We also collected information from medical records on stillbirths, pregnancy complications and co-morbidities (116). Participants self-reported the occurrence and timing of spontaneous abortions.

2.4.2. Postnatal Data Collection

Between February 2016 and January 2017, all living UGAAR mother-child dyads were invited to continue in a follow-up study of health and development in childhood. We re-enrolled dyads when the children were a median of 15.4 months of age (range: 7.7 to 28.9). Participants again provided written informed consent.

We made annual visits to participants' homes, roughly corresponding with the child's birthdays. During the first of these home visits we also assessed nurturing and stimulation of the child using the Home Observation Measurement of the Environment (HOME) inventory (117). We again measured $PM_{2.5}$ concentrations over seven days in a subsample of participants' homes based on availability of Dylos laser particle counters. Shortly after re-enrollment and at 6-month intervals thereafter, we asked participants to complete questionnaires about family characteristics and the child's home environment, diet, activities, and health.

Mothers and children were invited to our study office when the children were approximately two and four years of age. At the two-year visit, we obtained a venous whole blood sample from children for analysis of lead, mercury, and cadmium concentrations (114). At the two-year visit, trained assessors also administered the matrix reasoning and vocabulary subtests of the Wechsler Abbreviated Scale of Intelligence (WASI) and the Beck Depression Inventory-II (BDI) to the mothers (118).

2.4.3. Assessment of Behavioral Outcomes

We administered the Behavior Assessment System for Children (BASC-3) to caregivers during the two-year visits (February 2016 to January 2017) and four-year visits (September 2018 to December 2019) to our study office. We obtained BASC-3 data for a

total of 407 children including 391 children (214 intervention, 177 control) at age 2 and 388 children (205 intervention, 183 control) at age 4. The BASC-3 asks caregivers how frequently their child demonstrated 139 specific behaviors or activities over the past several months. All English BASC-3 materials were translated by native Mongolian speakers. The translations were then back translated to English. We piloted the BASC-3 on Mongolian children, updated the translations, and piloted with additional children prior to finalizing the translation to assess the UGAAR children. Research staff who administered and scored the BASC-3 were blinded to intervention status.

Our primary outcomes were the four BASC-3 composite scales: externalizing problems, internalizing problems, adaptive skills, and the behavioral symptoms index (BSI). For externalizing problems, internalizing problems, and the BSI higher scores indicate more behavioral problems. For adaptive skills, lower scores indicate poorer functioning.

2.4.4. Sample Size

The UGAAR study was originally designed to evaluate the effects of HEPA cleaners on fetal growth, so our sample size calculations were based on term birth weight. Assuming 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 the treatment and control groups, were needed. We targeted a population of 540 participants assuming 18% attrition due to withdrawal and pregnancy loss.

2.4.5. Data Analysis

To evaluate the influence of the intervention on indoor $PM_{2.5}$ concentrations, we compared 7-day measurements of indoor residential $PM_{2.5}$ between intervention and control participants during pregnancy and after birth. To account for temporal variations in outdoor $PM_{2.5}$ concentrations and lack of independence in repeated measurements in some homes, we regressed measured $PM_{2.5}$ concentrations on intervention status in a mixed model with random participant intercept while adjusting for month of measurement.

To our knowledge, this was the first use of the BASC-3 in Mongolia. Calculation of composite indices from BASC-3 responses requires the conversion of raw scores into sex-specific T scores based on the distribution of scores in a reference population. Since there was no Mongolian reference population with which to normalize BASC-3 scores, we transformed the UGAAR raw scores to have the same mean and variance as the US reference population. This allowed us to then estimate sex-specific T-scores according to the BASC-3 protocol.

Our primary analysis was by intention-to-treat (ITT) and included 478 children. The complete-case analyses included 407 children whose caregivers completed the BASC-3 on at least one-time point (391 at age two and 388 children at age four). The 478 children in the ITT analysis represent the full study population except those who withdrew prior to baseline data collection (N=8), known pregnancy losses and neonatal deaths (N=51), and three children with conditions unrelated to air pollution that could affect behavior or our ability to reliably impute BASC-3 scores (one child with Down's syndrome, one with cerebral palsy, and one with a hearing and speech impairment).

We used multiple imputation with chained equations (MICE) to impute outcome and covariate data for 71 children. We created 20 imputed data sets stratified by treatment group (SAS Proc MI and PROC Mianalyze). Variables used for imputation included those that met one of two criteria: 1) variables associated ($p<0.20$) with the outcome and with < 15% missing observations, 2) variables associated ($p<0.05$) with missingness and with < 15% missing observations. Variables that met these criteria included maternal age at baseline, marital status at baseline, maternal smoking at baseline, and maternal self-reported stress level at baseline, vitamin use at baseline, pre-pregnancy BMI, and living with a smoker early in pregnancy. In addition, to improve precision in our estimates we also adjusted for variables that, while unlikely to be confounders, contribute to variability in parent-reported behavior and are unlikely to be on the causal pathway between PM2.5 and behavior: mother's self-reported depression score on the BDI and maternal matrix reasoning and vocabulary subtest scores on the WASI. Trimester-specific models were also adjusted for PM2.5 concentrations in other trimesters. We did not adjust for sex because BASC T-scores were derived from sex-specific distributions for the reference population.

To allow for comparisons of effect estimates from the full pregnancy and different trimesters of exposure we scaled our effect estimates to the interquartile ranges (IQR) of PM2.5 concentrations.

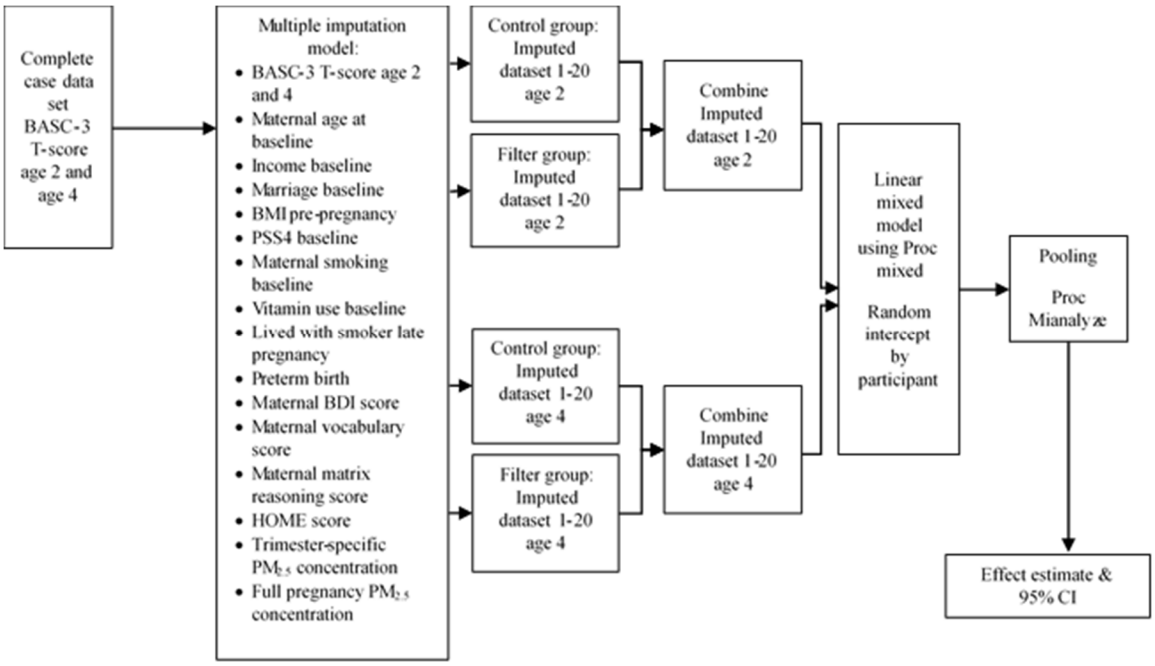


Figure 2.1. Data analysis scheme of the linear mixed effect model with 20 imputations.

In both our primary and secondary analyses, we analyzed data collected when children were two years old and four years old separately and with the two time points combined. We used multiple linear regression for the age-specific models, and in the analysis combining 2- and 4-year data we used linear mixed models with random participant intercepts to account for repeated measurements of behavioral outcomes (Figure 2.1). We used variance inflation factors (VIF) to evaluate multicollinearity in the multiple linear regression models. All analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC USA).

2.5. Results

2.5.1. Baseline characteristics

We recruited 540 participants (272 control and 268 intervention) from January 9, 2014 to May 1, 2015. Participants were enrolled at a median (25^{th}, 75^{th} percentile) gestational age of 11 (9, 13) weeks. There were 532 participants enrolled at the start of data collection, 468 known live births, and five neonatal deaths (Figure 2.2). At baseline, control and intervention participants had similar characteristics (Table 2.1). For example, mothers' median (25^{th}, 75^{th} percentile) ages at enrollment were 28 (25, 33) years in the control group and 29 (25, 33) years in the intervention groups. In both groups, 80% of participants reported completing university.

2.5.2. Pregnancy and postnatal characteristics

During pregnancy, the HEPA cleaners reduced mean indoor $PM_{2.5}$ concentrations by 29% (95% CI: 21%, 37%) (112). The post-natal $PM_{2.5}$ concentrations were similar between groups (3% lower in the intervention group, 95% CI: -14%, 7%).

The characteristics of mother-child dyads in the intervention and control groups were generally similar during pregnancy and during postnatal follow-up (Table 2.2). The median maternal blood lead concentration late in pregnancy was 1.5 (1.2, 1.8) μg/dL in the control group and 1.4 (1.2, 1.9) μg/dL in the intervention group. As previously reported, there were more preterm births in the intervention group (10%) than in the control group (5%). In both groups, approximately 5% of mothers reported moderate to severe depression during the 2-year visit (Table 2.2).

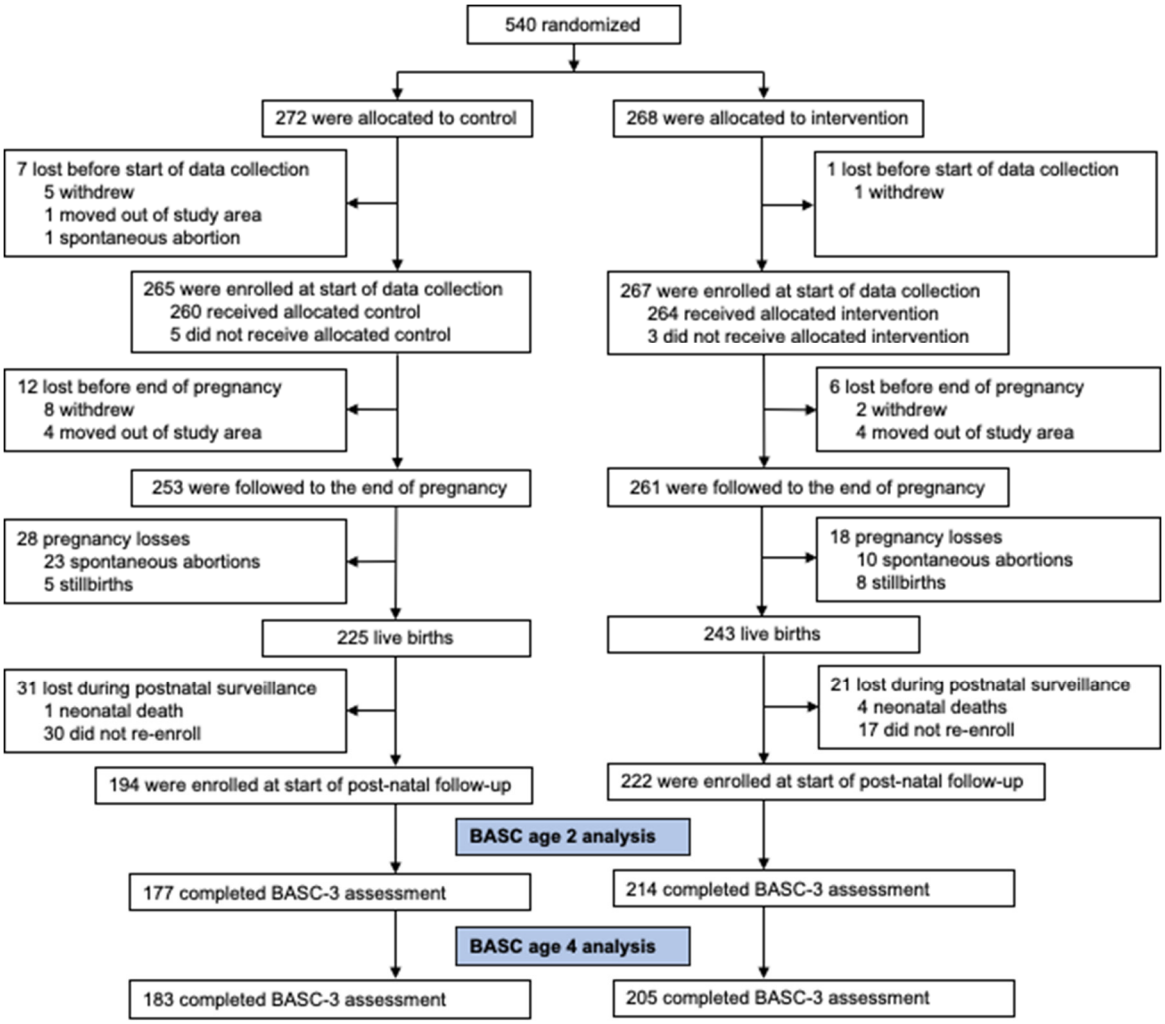


Figure 2.2. Trial profile

Table 2.1. Comparison of baseline characteristics for control and intervention participants included in the intention-to-treat analysis.

Characteristic	n	Control (n=233) Median (25th, 75th percentile) or n (%)	Intervention (n=245) Median (25th, 75th percentile) or n (%)
Season of enrollment			
Winter (Dec, Jan, Feb)	151 (32)	77 (33)	74 (30)
Spring (Mar, Apr, May)	138 (29)	73 (31)	65 (27)
Summer (Jun, July, Aug)	56 (12)	24 (11)	32 (13)
Fall (Sep, Oct, Nov)	133 (28)	59 (25)	74 (30)
Gestational age, wk	478 (100)	10 (9, 12)	11 (9, 13)
Maternal age, yr	478 (100)	28 (25, 33)	29 (25, 33)
Monthly household income, Tugriks			
≥ 800,000	376 (79)	182 (78)	194 (79)
< 800,000	93 (19)	46 (20)	47 (19)
Not reported, n (%)	9 (2)	5 (2)	4 (2)
Maternal marital status			
Married	282 (59)	135 (58)	147 (60)
Engaged/Common-law	180 (38)	88 (38)	92 (38)
Single	10 (2)	7 (3)	3 (1)
Not reported, n (%)	6 (1)	3 (1)	3 (1)
Maternal education			
Completed university	383 (80)	187 (80)	196 (80)
Less than university	60 (13)	31 (13)	29 (12)
Not reported, n (%)	35 (7)	15 (6)	20 (8)
Lived with a smoker baseline			
No	248 (52)	120 (52)	128 (52)
Yes	218 (46)	107 (46)	111 (45)
Not reported, n (%)	12 (3)	6 (3)	6 (2)
Maternal pre-pregnancy BMI, kg/m2	449 (94)	21.7 (19.6, 23.9)	21.4 (19.7, 24.0)
Not reported, n (%)	29 (6)	21 (9)	8 (3)
Paternal age, yr	453 (95)	31 (26, 35)	30 (26, 35)
Not reported, n (%)	25 (5)	9 (4)	16 (7)
Paternal education			
Completed university	364 (76)	179 (77)	185 (76)
Less than university	85 (18)	45 (19)	40 (16)
Not reported, n (%)	29 (6)	9 (4)	20 (8)

Table 2.2. Comparison of pregnancy and post-natal characteristics for control and intervention participants included in the intention-to-treat analysis.

Characteristic	n	Control (n=233) Median (25th, 75th percentile) or n (%)	Intervention (n=245) Median (25th, 75th percentile) or n (%)
Maternal blood lead concentration in late pregnancy ug/dL	375 (78)	1.5 (1.2, 1.8)	1.4 (1.2, 1.9)
Missing, n (%)	103 (22)	61 (26)	42 (17)
Type of birth			
Cesarean	174 (36)	86 (37)	88 (36)
Vaginal	285 (60)	134 (57)	151 (62)
Missing, n (%)	19 (4)	13 (6)	6 (2)
Preterm birth			
Preterm (<37 weeks)	31 (7)	10 (4)	21 (9)
Full tern (≥ 37 weeks)	428 (89)	210 (90)	218 (88)
Missing, n (%)	19 (4)	13 (6)	6 (3)
Birth weight, grams	458 (96)	3450 (3125, 3800)	3550 (3200, 3800)
Missing, n (%)	19 (4)	13 (6)	6 (2)
Child's sex			
Female	220 (46)	110 (47)	110 (45)
Male	239 (50)	111 (48)	128 (52)
Missing, n (%)	19 (4)	13 (5)	6 (3)
Child's blood lead concentration at age 2, ug/dL	328 (69)	2.6 (1.9, 3.6)	2.5 (1.7, 3.5)
Missing, n (%)	150 (31)	80 (46)	70 (45)
Maternal depression level (BDI) at 2-year visit			
Mild	369 (77)	168 (72)	201 (82)
Moderate to severe	31 (6)	8 (4)	13 (5)
Missing, n (%)	88 (18)	57 (24)	31 (13)
Maternal WASI matrix reasoning raw score	387 (81)	16 (12, 19)	17 (13, 19)
Missing, n (%)	91 (19)	58 (25)	33 (13)
Maternal WASI vocabulary raw score	387 (81)	36 (32, 40)	36 (32, 40)
Missing, n (%)	91 (19)	58 (25)	33 (13)

BDI = Beck Depression Inventory-II; WASI = Wechsler Abbreviated Scale of Intelligence

2.5.3. Intervention effects

We found no significant difference in the mean BASC-3 scores by treatment group in our ITT analysis of 478 participants (Table 2.3). Results were not sensitive to adjustment for PTB (Table 2.3). Children's behavior T scores measured 2 and 4 years of age were moderately correlated, ranging from r = 0.39 (adaptive skills) to 0.46 (behavioral symptoms index).

Table 2.3. Estimated effects of the intervention on BASC composite scores in an intention-to-treat analysis.

	Unadjusted		Adjusted for preterm birth	
Composite score	Change in mean T score (95%CI)	p-value	Change in mean T score (95%CI)	p-value
Age 2				
Externalizing	0.21 (-1.69, 2.12)	0.83	0.21 (-1.70, 2.12)	0.83
Internalizing	-0.84 (-2.84, 1.16)	0.41	-0.84 (-2.84, 1.16)	0.41
Adaptive skills	-0.06 (-1.77, 1.64)	0.94	-0.01 (-1.73, 1.71)	0.99
Behavioral Symptoms Index	-0.28 (-1.98, 1.42)	0.75	-0.29 (-1.99, 1.40)	0.73
Age 4				
Externalizing	0.09 (-1.98, 2.17)	0.93	0.09 (-1.98, 2.17)	0.93
Internalizing	-0.48 (-2.51, 1.54)	0.64	-0.47 (-2.50, 1.55)	0.65
Adaptive skills	-0.29 (-2.12, 1.55)	0.76	-0.17 (-1.99, 1.66)	0.86
Behavioral Symptoms Index	-0.21 (-2.17, 1.76)	0.84	-0.20 (-2.17, 1.76)	0.84
Ages 2 and 4 combined[1]				
Externalizing problems	0.15 (-1.54, 1.85)	0.86	0.13 (-1.55, 1.82)	0.88
Internalizing problems	-0.66 (-2.36, 1.04)	0.44	-0.60 (-2.29, 1.10)	0.49
Adaptive skills	-0.18 (-1.65, 1.30)	0.82	-0.09 (-1.56, 1.38)	0.91
Behavioral symptoms index	-0.24 (-1.81, 1.32)	0.76	-0.28 (-1.84, 1.28)	0.72

[1]Age 2 and 4 BASC scores modeled together in a linear mixed effects model.

In our secondary observational analysis, we did not observe any associations between $PM_{2.5}$ concentrations and behavior scores at age 2 (Figure 2.3). We did, however, find that indoor $PM_{2.5}$ during the first trimester of pregnancy was consistently associated with worse behavior scores at age 4 (Figure 2.3). Specifically, an IQR increase (20.1 $\mu g/m^3$) in $PM_{2.5}$ was associated with difference of 2.4 units (95% CI: 0.7, 4.1), 2.4 units (95% CI: 0.7, 4.0), 2.3 units (95% CI: 0.7, 3.9), and -1.5 units (95% CI: -3.0, 0.0) in mean externalizing problems, internalizing problems, behavioral symptoms index, and adaptive skills T scores, respectively. Third trimester $PM_{2.5}$ concentrations were associated with some behavioral indices, but effect estimates were smaller. We did not observe associations between $PM_{2.5}$ exposure in the second trimester and any of the BASC indices when children were 2 years old (Figure 2.3). Variance inflation factors were <1.7 for all variables.

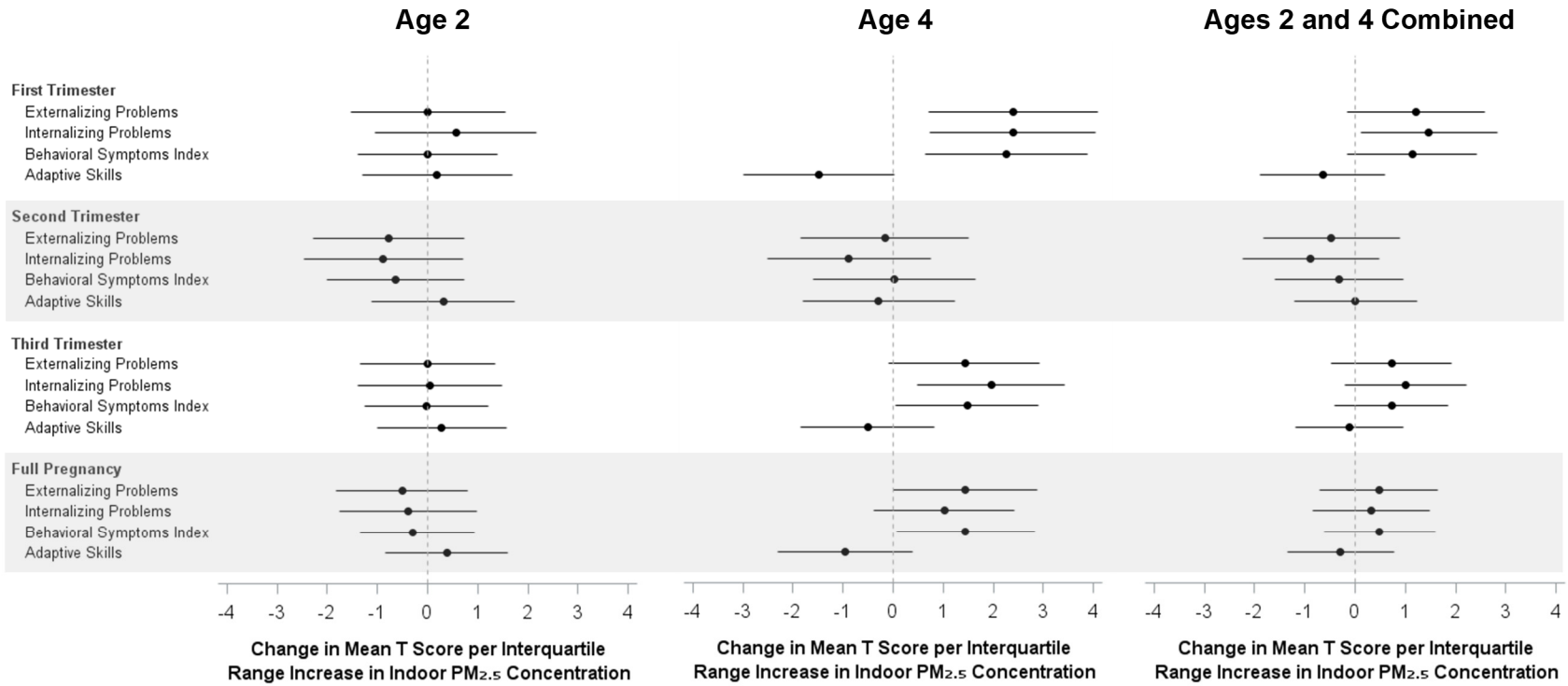


Figure 2.3. Associations between indoor $PM_{2.5}$ concentrations during pregnancy and BASC composite scores at age 2, age 4, and combined[1]

[1]Age 2 and 4 BASC scores modeled together in a linear mixed effects model. 1st trimester IQR = 20.1 µg/m^3, 2nd trimester IQR = 21.6 µg/m^3, 3rd trimester IQR = 13.5 µg/m^3, full pregnancy IQR = 9.63 µg/m^3.Models adjusted for intervention status, maternal age at baseline, monthly family income at baseline, living with a smoker at any time during pregnancy, mother's depression score at the 2-year visit, and maternal WASI matrix reasoning and vocabulary scores at the 2-year visit. Trimester-specific models were also adjusted for $PM_{2.5}$ concentrations in other trimesters.

2.6. Discussion

In this cohort of women living in a heavily polluted community we found no evidence in the intent to treat analysis that reducing indoor air pollutants using HEPA air cleaners starting late in the first trimester of pregnancy improved parent-reported behavioral problems. In a secondary observational analysis, we found no associations between $PM_{2.5}$ concentration during pregnancy and behavior at age 2. We did, however, find that first trimester $PM_{2.5}$ concentrations were consistently associated with behavioral problem scores when children were 4 years old. Third trimester $PM_{2.5}$ concentration was also associated with some behavioral indices at age 4, but effects were smaller. $PM_{2.5}$ concentrations during the second trimester were not associated with behavior at any age. These results suggest that behavior scores in childhood may be particularly sensitive to air pollution exposure early in pregnancy, but these are exploratory findings and should be interpreted cautiously.

Brain development is a rapid, complex and patterned process and the timing of exposure to neurotoxicants may be an important determinant of adverse impacts (49,119,120). Our finding of consistent associations with exposure in the first trimester is similar to a recent analysis of 4 to 6-year-old children in Mexico City (42). In that study, which assessed behavior using the BASC (BASC-2), a 5 $\mu g/m^3$ increase in outdoor $PM_{2.5}$ concentration during the first trimester was associated with a 1.1 unit (95% CI: -0.2, 2.4) increase in mean BSI T score and a decrease of 1.5 units (95% CI: -2.6, -0.3) in mean adaptive skills T score. $PM_{2.5}$ concentrations in other trimesters were not associated with behavior scores. In the Upstate KIDS study, a 10 $\mu g/m^3$ increase in $PM_{2.5}$ exposure during the first and third trimesters was associated with increases of 1.6% (95% CI: 0.1%, 3.2%) and 2.7% (95% CI: 0.6%, 4.9%), respectively, in the risk of a failed developmental screening between 8 and 36 months of age. The association was smaller in second trimester exposure to $PM_{2.5}$ and failed developmental domains in those children (29).

For individual children, a change in behavioral symptoms T scores of 1-3 units would generally not be problematic. However, at a population level, these impacts could

be important given that 90% of the world's population is exposed to $PM_{2.5}$ above the World Health Organization guideline concentration (121,122).

As with many birth cohort studies, our results may have been influenced by the live birth bias (123). We previously reported a decreased risk of spontaneous abortion and an increased risk of preterm birth in the intervention group. We speculated that the intervention enabled fetuses who otherwise might have died *in utero* to instead be born preterm. This difference in pregnancy losses would have most likely have caused an underestimation of the intervention's effect on behavioral problems. If air pollution increases the risk of fetal loss preferentially among fetuses susceptible to the impacts of air pollution on brain development, the control group would have fewer susceptible children and the intervention effect estimate would be attenuated (123).

This study had several limitations. Staff who administered and scored the BASC-3 were blinded, but participants were not blinded to their treatment group, which may have contributed to information bias in this analysis of parent-reported outcomes. The lack of blinding could also partly explanation for the greater loss of control participants. This may have introduced some selection bias, which we tried to address through an ITT analysis using multiple imputation. To our knowledge, this was the first use of the BASC-3 in Mongolia. We translated the BASC-3 using an iterative process that included back-translation and extensive pilot testing in Mongolian children before collecting data from UGAAR participants. However, even careful translation may not account for important cultural differences in the way behaviors are described and interpreted (124). Behaviors may be accepted differently in different settings, so use of an instrument designed for North American children may not have fully captured behavior problems in this cohort of Mongolian children. This would likely have introduced non-differential errors leading to underestimated effects. In addition, because there was no Mongolian reference population, we scaled the raw scores to match those of the Canadian reference population before calculating scaled scores and composite indices. While this may have introduced some error in the BASC-3 scores, these errors were also likely non-differential. Although we demonstrated that the intervention reduced $PM_{2.5}$ in participants' homes, we did not measure personal exposure to $PM_{2.5}$ and the impacts of this residential intervention would

be attenuated by time spent outside of the home. In our secondary exploratory analysis, we ran numerous models involving many combinations of exposure periods, behavioral indices, and children's ages.

2.7. Conclusion

In this randomized controlled trial, we found no benefit of reducing indoor air pollution during pregnancy on parent-reported behaviors in children at 2-4 years of age. In secondary analyses, however, we found that first trimester residential $PM_{2.5}$ concentrations were associated with worse behavior scores at 4 years of age, suggesting that it may be necessary to intervene early in pregnancy to protect children. However, these exploratory findings should be interpreted cautiously and require replication.

Chapter 3. Portable HEPA filter air cleaner use during pregnancy and childhood autistic traits at four years of age

3.1. Abstract

Background: Developmental exposure to airborne particulate matter (PM) air pollution may increase children's risk of developing autism spectrum disorder. Our objective was to quantify the impact of reducing PM exposure during pregnancy using portable air cleaners on the development of autistic traits in children. We also sought to assess associations between indoor fine PM ($PM_{2.5}$) concentrations during pregnancy and autistic traits.

Methods: In this parallel-group randomized controlled trial, we randomly assigned 540 non-smoking pregnant women to receive HEPA filter air cleaners or to a control group, which did not receive air cleaners. We administered the Social Responsiveness Scale, Second Edition (SRS-2) to caregivers when children were a median of 48 months (range: 48 to 51 months). Participants were not blinded to intervention status but staff responsible for administering and scoring the SRS-2 were blinded. Our primary outcome was the SRS-2 total T-score. We imputed missing data using multiple imputation with chained equations and our primary analysis was by intention to treat (ITT). In secondary analyses, we estimated adjusted associations between full pregnancy and trimester-specific $PM_{2.5}$ concentrations inside residences and SRS-2 T-scores. In a *post hoc* analysis, we used quantile regression to estimate intervention and $PM_{2.5}$ effects across the SRS-2 T-score distribution.

Results: We enrolled participants at a median of 11 weeks' gestation. After excluding miscarriages, still births, and neonatal deaths, our analysis included 478 children (233 control and 245 intervention). We previously reported that the intervention reduced average indoor $PM_{2.5}$ concentrations by 29% (95% CI: 21, 37%). The mean SRS-2 total T-score was 0.5 units lower (95% CI: -2.5, 1.5) among intervention participants, but quantile regression results indicated larger benefits for children at the high end of the T-score distribution. An interquartile range (9.6 $\mu g/m^3$) increase in indoor $PM_{2.5}$ during pregnancy was associated with 1.8-unit (95% CI: 0.3, 3.2) increase in mean SRS-2 total T-score.

Effect estimates for $PM_{2.5}$ concentrations in each trimester were smaller and confidence intervals spanned no effect.

Conclusion: We found limited evidence that reducing indoor PM during pregnancy with air cleaners reduced parent-reported autistic traits in children. In secondary analyses, however, indoor $PM_{2.5}$ concentrations during pregnancy were associated with higher autism trait scores among 4-year-old children. These findings suggest that exposure to particulate matter during pregnancy may influence the development of autistic traits in childhood.

3.2. Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition characterized by repetitive behaviors and impaired communication and social skills (44). While the etiology of ASD is poorly understood, environmental exposures may play a role (15). Structural and functional brain development peaks early life (49), which makes the brain particularly vulnerable to external stressors during gestation and early childhood (26,49).

Exposure to fine particulate matter air pollution ($PM_{2.5}$) during pregnancy is linked to impaired fetal growth, which may result in irreversible structural and functional modifications (125–127). Epidemiological studies suggest that $PM_{2.5}$ exposure during pregnancy may impair neurodevelopment (17). Prenatal exposure to $PM_{2.5}$ has been associated with an increased risk of ASD in several studies, but the size and precision of effect estimates has varied widely (17,52,128).

Portable high-efficiency particulate air (HEPA) filter air cleaners ("HEPA cleaners") have been shown to reduce indoor $PM_{2.5}$ by 29-82% (92,93). The Ulaanbaatar Gestation and Air Pollution (UGAAR) study is a parallel group RCT designed to assess the impacts of HEPA cleaners use during pregnancy on fetal growth and childhood development (112,116,129,130). We previously reported that the HEPA cleaner intervention was associated with increases in mean term birth weight and full-scale IQ at age 4, but not with children's behavioral scores at ages 2 and 4 (116,129,131).

In this analysis we sought to extend our previous work and evaluate the effects of the HEPA cleaner intervention on autistic traits among 4-year-old children in the UGAAR cohort. In secondary analyses, we assessed the associations between modeled indoor $PM_{2.5}$ concentrations during different periods of pregnancy and autistic traits in these children.

3.3. Methods

3.3.1. Assessment of Autistic Traits

We obtained data on autistic behaviors for a total of 387 children (205 intervention, 182 control) by administering the school-age (4-18 years) form of the Social Responsiveness Scale, Second Edition (SRS-2) to caregivers during the four-year visit (September 2018 to January 2020) when children were a median of 48 months (range: 48 to 51 months). Respondents indicated the frequency of 65 behaviors on a Likert scale from 0 (not true) to 3 (almost always true) (132,133). The 65 items are organized into social awareness, social cognition, social communication, social motivation and restricted interests and repetitive behavior subscales. Our primary outcome was the sex-specific total SRS-2 T-score, which is associated with clinical diagnoses of ASD (134). Secondary outcomes included T-scores for the five SRS-2 subscales. Higher T-scores indicate more social impairment.

All English SRS-2 materials were translated from English to Mongolian by native Mongolian speakers, then independently back-translated to English. We then piloted the translated SRS-2 on Mongolian parents and refined the translations based on their feedback before administering the SRS-2 to UGAAR participants. In this trial participants were not blinded to intervention status but staff who administered and scored the SRS-2 were blinded to intervention status.

3.3.2. Statistical analysis

To our knowledge, this was the first use of the SRS-2 in Mongolia. Calculation of composite indices from SRS-2 responses requires the conversion of raw scores into sex-specific T scores based on the distribution of scores in a reference population. Since there

was no Mongolian reference population with which to normalize SRS-2 scores, we transformed the UGAAR raw scores to have the same mean and variance as the US reference population. This allowed us to then estimate sex-specific T-scores according to the SRS-2 protocol.

To address validity of our outcome, we examined the correlation between SRS and the Behavior Assessment System for Children 3rd edition (BASC-3) composite scores which was conducted on same day, as described elsewhere (129). We also examined the total SRS T-scores to specific domains of BASC-3 that are most indicative of ASD related behaviors (atypicality, withdrawal, attention problem, social skills, functional communication) by evaluating contribution of each domain on overall BASC-3 composite scores. This both validates that SRS total score, and BASC-3 composite scores are consistent and also confirms that these two assessments measured different aspects of neurodevelopment of the children in this cohort.

Our primary analysis was by intention-to-treat (ITT) and included 478 children. The complete-case analyses included 387 children whose caregivers completed the SRS-2 at child's four-year assessment. The 478 children in the ITT analysis represent the full study population except those who withdrew prior to baseline data collection (N=8), known pregnancy losses and neonatal deaths (N=51), and three children with conditions unrelated to air pollution that could affect social impairment or our ability to reliably impute SRS-2 scores (one child with Down's syndrome, one with cerebral palsy, and one with a hearing and speech impairment).

We used multiple imputation with chained equations (MICE) to impute outcome and covariate data for 91 children without SRS-2 data. We created 20 imputed data sets stratified by treatment group (SAS Proc MI and PROC Mianalyze). We considered for inclusion in our imputation model predictor variables with < 15% of observations missing. Of these, we included variables that were associated ($p<0.05$) with a child having missing SRS-2 data (Table B.2) and/or associated ($p<0.20$) with the SRS-2 total T-score (Table B.3). Variables that met one or both criteria were maternal age at baseline (continuous), marital status at baseline (married/common-law or single/engaged), maternal self-reported

stress level (PSS-4 score <8 or ≥8) at baseline and during late pregnancy, prior pregnancy (yes or no), and season of enrollment. We also included in the imputation model the outcome variable and adjustment variables for our primary and secondary analyses (described below).

In our primary ITT analysis, we regressed outcomes on a binary intervention variable in both unadjusted models and models adjusting for preterm birth (PTB), which is defined as a birth at <37 weeks' gestation. We previously reported that the HEPA cleaner intervention was associated with a decreased risk of spontaneous abortion but an increased risk of preterm birth in this cohort (116). We hypothesized that the intervention may have enabled fetuses who might have otherwise died *in utero* to be born preterm. In a *post hoc* analysis, we also evaluated the effect of the intervention in models stratified by child's sex.

In a secondary analysis, we used multiple linear regression to evaluate the associations between the SRS-2 T-scores and trimester-specific and full-pregnancy averaged indoor $PM_{2.5}$ concentrations estimated from the blended multiple linear regression / random forest model predictions of weekly concentrations (115). We used a directed acyclic graph to select adjustment variables in our analysis of $PM_{2.5}$ concentrations and social impairments. We identified five variables as potential confounders: intervention status (intervention or control), maternal age at baseline (continuous), monthly family income at baseline (≥ 800,000 Tugriks or < 800,000 Tugriks), maternal matrix reasoning and vocabulary subtest scores on the WASI (continuous), and living with a smoker during early pregnancy (yes or no). In addition, to improve precision in our estimates we also adjusted for mother's self-reported depression score on the BDI-II (0-16 or >16), which is probably not a confounder, but contributes to variability in parent-reported SRS-2 scores and is unlikely to be on the causal pathway between $PM_{2.5}$ and social impairment. Trimester-specific models were also adjusted for $PM_{2.5}$ concentrations in other trimesters. We did not adjust for sex because SRS-2 T-scores were derived from sex-specific distributions for the reference population.

In addition, we evaluated the sensitivity of our results to the removal of maternal depression and intelligence from the analysis models and to the inclusion of additional

variables in the imputation model and analysis models: season of enrollment, perceived stress (PSS-4) in early and late pregnancy, maternal blood lead level, and maternal pre-pregnancy body mass index (BMI) (76).

To allow for comparisons of effect estimates from full pregnancy and trimester-specific indoor $PM_{2.5}$ we scaled our effect estimates to the interquartile ranges (IQR) of $PM_{2.5}$ concentrations. The distributions of SRS-2 T-scores were slightly skewed to the right, so we conducted a sensitivity analysis to assess the influence of skewness by log-transforming the SRS-2 T-scores and we report effect estimates as percent changes.

In complete case analyses, we also evaluated the sensitivity of our intervention and $PM_{2.5}$ results to the scaling of UGAAR participants' SRS-2 scores to match the mean and standard deviation of the U.S. reference population. As alternatives, we converted the UGAAR scores directly to sex-specific T-scores (i.e., internal scaling) and we analyzed raw scores in regression models adjusted for sex.

Additionally, for both our primary and secondary analyses, we ran *post hoc* quantile regression analysis among complete cases to evaluate the associations between both the intervention effects and the $PM_{2.5}$ concentrations at different parts of the SRS-2 total T-score distribution. All analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC USA).

3.4. Results

3.4.1. Baseline characteristics

We recruited 540 participants (272 control and 268 intervention) from January 9, 2014 to May 1, 2015. Participants were enrolled at a median (25^{th}, 75^{th} percentile) gestational age of 11 (9, 13) weeks. There were 532 participants enrolled at the start of data collection, 468 known live births, and five neonatal deaths (Figure 3.1). At baseline, control and intervention participants had similar characteristics (Table 3.1). For example, mothers' median (25^{th}, 75^{th} percentile) ages at enrollment were 28 (25, 33) years in the control group and 29 (25, 33) years in the intervention groups (Table 3.1). In both groups, 80% of

participants reported completing university. The 387 mothers who completed the SRS-2 were older and more likely to have had a prior pregnancy than the 91 mothers who did not complete the SRS-2 (Table B.2).

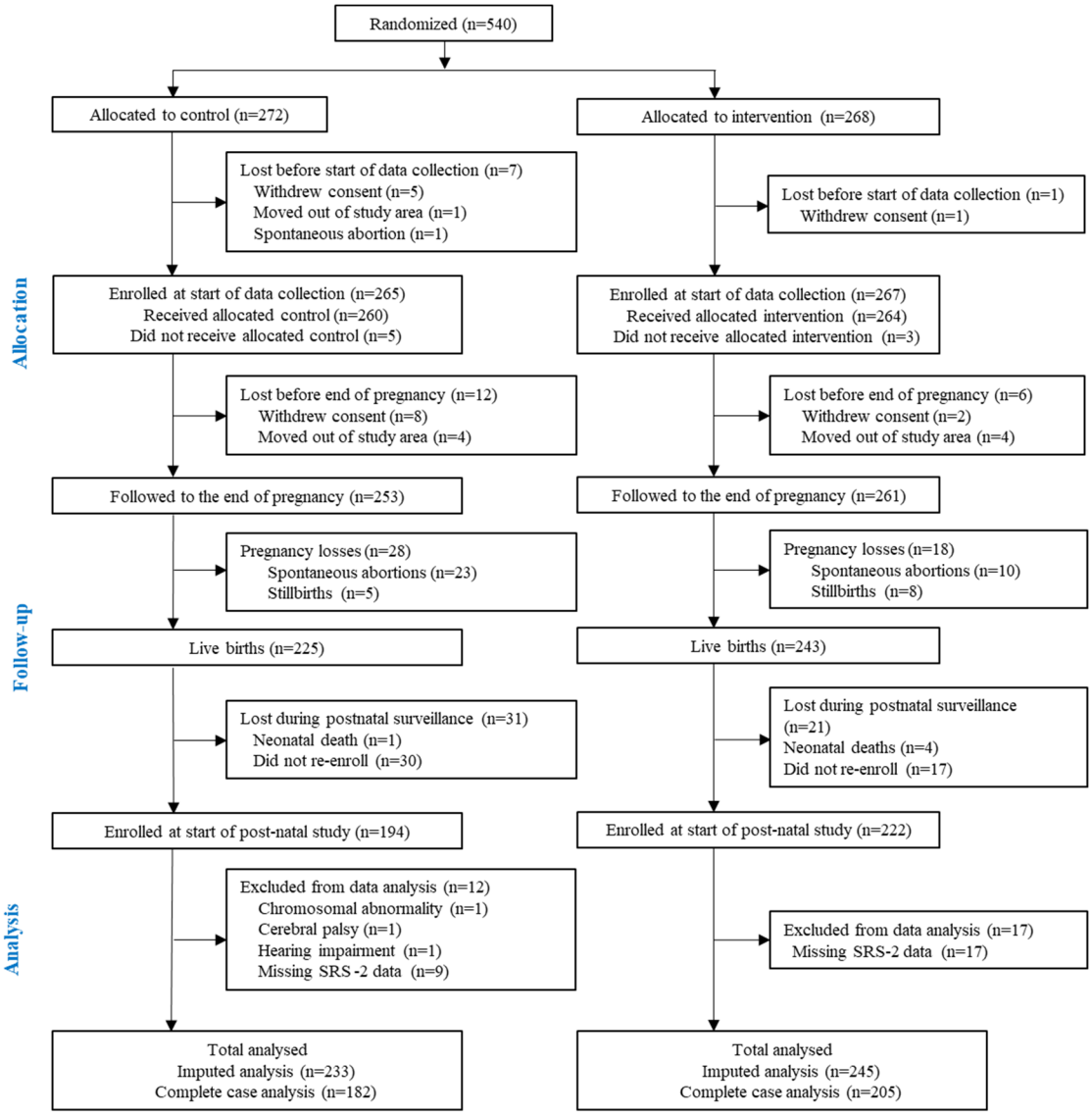


Figure 3.1. Trial profile

Table 3.1. Baseline characteristics for control and intervention participants included in the intention-to-treat analysis.

Characteristic	Full sample (n = 478)	Control (n=233)	Intervention (n=245)
	Median (25^{th}, 75^{th} percentile) or n (%)	Median (25^{th}, 75^{th} percentile) or n (%)	Median (25^{th}, 75^{th} percentile) or n (%)
Season of enrollment			
Winter (Dec, Jan, Feb)	151 (32)	77 (33)	74 (30)
Spring (Mar, Apr, May)	138 (29)	73 (31)	65 (27)
Summer (Jun, July, Aug)	56 (12)	24 (11)	32 (13)
Fall (Sep, Oct, Nov)	133 (28)	59 (25)	74 (30)
Gestational age, wk	478 (100)	10 (9, 12)	11 (9, 13)
Maternal age, yr	478 (100)	28 (25, 33)	29 (25, 33)
Monthly household income, Tugriks			
≥ 800,000	376 (79)	182 (78)	194 (79)
< 800,000	93 (19)	46 (20)	47 (19)
Not reported, n (%)	9 (2)	5 (2)	4 (2)
Maternal marital status			
Married	282 (59)	135 (58)	147 (60)
Engaged/Common-law	180 (38)	88 (38)	92 (38)
Single	10 (2)	7 (3)	3 (1)
Not reported, n (%)	6 (1)	3 (1)	3 (1)
Maternal education			
Completed university	383 (80)	187 (80)	196 (80)
Less than university	60 (13)	31 (13)	29 (12)
Not reported, n (%)	35 (7)	15 (6)	20 (8)
Lived with a smoker baseline			
No	248 (52)	120 (52)	128 (52)
Yes	218 (46)	107 (46)	111 (45)
Not reported, n (%)	12 (3)	6 (3)	6 (2)
Maternal pre-pregnancy BMI, kg/m2	449 (94)	21.7 (19.6, 23.9)	21.4 (19.7, 24.0)
Not reported, n (%)	29 (6)	21 (9)	8 (3)
Vitamin use early pregnancy			
No	224 (48.6)	61(26)	52 (21)
Yes	237 (51.4)	163 (70)	185(76)
Not reported, n (%)	17 (4)	9(4)	8(3)
Early prenatal perceived stress PSS-4)	472	5 (4,7)	6 (4, 7)
Not reported, n (%)	6 (1)	3 (1)	3(1)

Prior pregnancy			
No	121 (26)	60 (26)	61 (25)
Yes	352 (74)	169 (73)	183 (75)
Not reported, n (%)	5(1)	4(2)	1(0)
Paternal age, yr	453 (95)	31 (26, 35)	30 (26, 35)
Not reported, n (%)	25 (5)	9 (4)	16 (7)
Paternal education			
Completed university	364 (76)	179 (77)	185 (76)
Less than university	85 (18)	45 (19)	40 (16)
Not reported, n (%)	29 (6)	9 (4)	20 (8)

3.4.2. Pregnancy and postnatal characteristics

We previously reported that during pregnancy the HEPA cleaners reduced mean indoor $PM_{2.5}$ concentrations by 29% (95% CI: 21%, 37%) from a geometric mean of 24.5 $\mu g/m^3$ in control homes to 17.3 $\mu g/m^3$ in intervention homes (112). The post-natal $PM_{2.5}$ concentrations were similar between groups (3% lower in the intervention group, 95% CI: -14%, 7%) (129).

The characteristics of mother-child dyads in the intervention and control groups were generally similar during pregnancy and during postnatal follow-up (Table 3.2). The median maternal blood lead concentration late in pregnancy was 1.5 (1.2, 1.8) ug/dL in the control group and 1.4 (1.2, 1.9) ug/dL in the intervention group. As previously reported, there were more preterm births in the intervention group (10%) than in the control group (5%) (Table 3.2).

Table 3.2. Comparison of pregnancy and post-natal characteristics for control and intervention participants included in the intention-to-treat analysis.

Characteristic	n	Control (n=233)	Intervention (n=245)
		Median (25^{th}, 75^{th} percentile) or n (%)	Median (25^{th}, 75^{th} percentile) or n (%)
Maternal blood lead concentration in late pregnancy ug/dL	375 (78)	1.5 (1.2, 1.8)	1.4 (1.2, 1.9)
Missing, n (%)	103 (22)	61 (26)	42 (17)
Type of birth			
Cesarean	174 (36)	86 (37)	88 (36)
Vaginal	285 (60)	134 (57)	151 (62)
Missing, n (%)	19 (4)	13 (6)	6 (2)
Preterm birth			
Preterm (<37 weeks)	31 (7)	10 (4)	21 (9)
Full term (≥ 37 weeks)	428 (89)	210 (90)	218 (88)
Missing, n (%)	19 (4)	13 (6)	6 (3)
Birth weight, grams	458 (96)	3450 (3125, 3800)	3550 (3200, 3800)
Missing, n (%)	19 (4)	13 (6)	6 (2)
Child's sex			
Female	220 (46)	110 (47)	110 (45)
Male	239 (50)	111 (48)	128 (52)
Missing, n (%)	19 (4)	13 (5)	6 (3)
Child's blood lead concentration at age 2, µg/dL	328 (69)	2.6 (1.9, 3.6)	2.5 (1.7, 3.5)
Missing, n (%)	150 (31)	80 (46)	70 (45)
Maternal depression level (BDI) at 2-year visit			
Minimum to mild (Score 0-16)	369 (77)	168 (72)	201 (82)
Moderate to severe (Score >16)	31 (6)	8 (4)	13 (5)
Missing, n (%)	88 (18)	57 (24)	31 (13)
Maternal WASI matrix reasoning raw score	387 (81)	16 (12, 19)	17 (13, 19)
Missing, n (%)	91 (19)	58 (25)	33 (13)
Maternal WASI vocabulary raw score	387 (81)	36 (32, 40)	36 (32, 40)
Missing, n (%)	91 (19)	58 (25)	33 (13)
Total T-score	387 (81)	48 (43, 57)	49 (43, 54)
Missing, n (%)	91 (19)	51 (22)	40 (16)

Social awareness T-score	387 (81)	50 (45, 57)	50 (43, 56)
Missing, n (%)	91 (19)	51 (22)	40 (16)
Social cognition T-score	387 (81)	49 (42, 55)	49 (44, 55)
Missing, n (%)	91 (19)	51 (22)	40 (16)
Social communication T-score	387 (81)	49 (43, 57)	49 (42, 56)
Missing, n (%)	91 (19)	51 (22)	40 (16)
Social motivation T-score	387 (81)	49 (44, 56)	50 (43, 56)
Missing, n (%)	91 (19)	51 (22)	40 (16)
Restricted interests and repetitive behavior T-score	387 (81)	48 (42, 56)	50 (43, 54)
Missing, n (%)	91 (19)	51 (22)	40 (16)

BDI = Beck Depression Inventory-II; WASI = Wechsler Abbreviated Scale of Intelligence

There were small differences in the SRS raw score distribution between the Mongolian and the US reference. Though the % difference in the means were higher, SD generally agreed. For example, the restricted interest and repetitive behavior the mean raw scores were 46% and 61% higher in the UGAAR population compared to the reference population for males and females respectively while the SD for males were 12.3 points lowers in the UGAAR population but no difference in the SD were observed in the females. The highest difference was observed on social cognition were the mean raw score were 69% and 85% higher in the UGAAR population compared to the reference population for males and females respectively. The SD was 22% and 23.5% lower in males and females respectively in the UGAAR population compared to the reference population.

The Pearson correlation between the SRS total T-score and the BASC individual domains ranged between r=0.11 for anxiety and r=0.67 for withdrawal.

3.4.3. Intervention effects

The mean SRS-2 total T-score was 0.5 units lower (95% CI: -2.5, 1.5) among intervention participants in our ITT analysis of 478 participants (Table 3.3). Results did not change appreciably after adjustment for PTB, when the analysis was restricted to complete cases, when using the UGAAR population for internal scaling of scores, or after log transforming the SRS-2 scores.

Table 3.3. Estimated effects of the intervention on mean SRS T-scores (*n*=478).

	Mean (SD)		Estimated effect of the intervention on mean SRS-2 T-score (95% CI)	
SRS-2 Scale	Control	Intervention	Crude	Adjusted for preterm birth
Total T-score	50.5 (9.9)	50.0 (9.8)	-0.5 (-2.5, 1.5)	-0.5 (-2.5, 1.5)
Social awareness T-score	50.4(10.2)	49.8 (10.0)	-0.5 (-2.6, 1.5)	-0.5 (-2.5, 1.5)
Social cognition T-score	50.1 (9.1)	50.7 (9.7)	0.6 (-1.2, 2.5)	0.6 (-1.2, 2.5)
Social communication T-score	51.0 (9.8)	49.8 (9.5)	-1.2 (-3.2, 0.9)	-1.2 (-3.2, 0.9)
Social motivation T-score	50.7 (9.8)	50.5 (9.8)	-0.2 (-2.3, 1.9)	-0.2 (-2.3, 1.9)
Restricted interests and repetitive behavior T-score	51.1(10.0)	50.7 (9.5)	-0.4 (-2.4, 1.6)	-0.4 (-2.4, 1.6)

In our secondary analysis, an interquartile range (9.6 μg/m^3) increase in indoor $PM_{2.5}$ concentration over the full pregnancy was associated with a 1.8-unit (95% CI: 0.3, 3.2) increase in mean SRS-2 T-score (Table 5). For trimester-specific concentrations, we observed larger estimates for the first (1.4-unit increase; 95% CI: -0.3, 3.1) and second (1.3-unit increase; 95% CI: -0.4, 2.9) trimesters than for the third trimester (0.8-unit increase; 95% CI: -0.6, 2.2), but confidence intervals for all estimates spanned to no effect (Table 3.4). Inclusion of additional variables in the imputation and analysis models generally increased the first trimester effect estimate and decreased second trimester estimates. In our secondary analysis of SRS-2 subscales, effects were most pronounced for $PM_{2.5}$ concentrations over the full pregnancy, with the largest effect estimates for social cognition (1.4 points; 95% CI: 0.0, 2.8), social communication (1.7 points; 95% CI: 0.2, 3.1), and restricted interests and repetitive behavior (2.0 points; 95% CI: 0.6, 3.4). The

estimate was smaller for social awareness (0.2 points; 95% CI: -1.3, 1.7). The use of internal scaling had little effect on the estimates.

Table 3.4. Estimated changes in mean SRS-2 total T-scores per interquartile range (IQR) increase in indoor PM 2.5 concentration during pregnancy (n=478).

	Unadjusted effect estimates (95%CI)	Adjusted effect estimates (95%CI)
1st trimester (IQR = 20.1 μg/m^3)	0.9 (-0.5, 2.3)	1.4 (-0.3, 3.1)
2nd trimester (IQR = 21.6 μg/m^3)	1.6 (-0.1, 3.2)	1.3 (-0.4, 2.9)
3rd trimester (IQR = 13.5 μg/m^3)	0.1 (-1.0, 1.2)	0.8 (-0.6, 2.2)
Full pregnancy (IQR = 9.6 μg/m^3)	1.8 (0.4, 3.2)	1.8 (0.3, 3.2)

Adjusted models include intervention status, maternal age at baseline, family income, living with a smoker early in pregnancy, maternal matrix reasoning and vocabulary subtest scores on the WASI, and mother's self-reported depression score on the BDI. Trimester-specific models were also adjusted for $PM_{2.5}$ concentrations in other trimesters.

A post hoc quantile regression analysis among complete cases suggested larger benefits of the intervention among children at the high end of the SRS total T-score distribution (Figure 3.2). For PM2.5 concentrations over the full pregnancy, there was a consistent trend of larger effect estimates at the higher end of the SRS-2 total T-score distribution(Figure3.3).

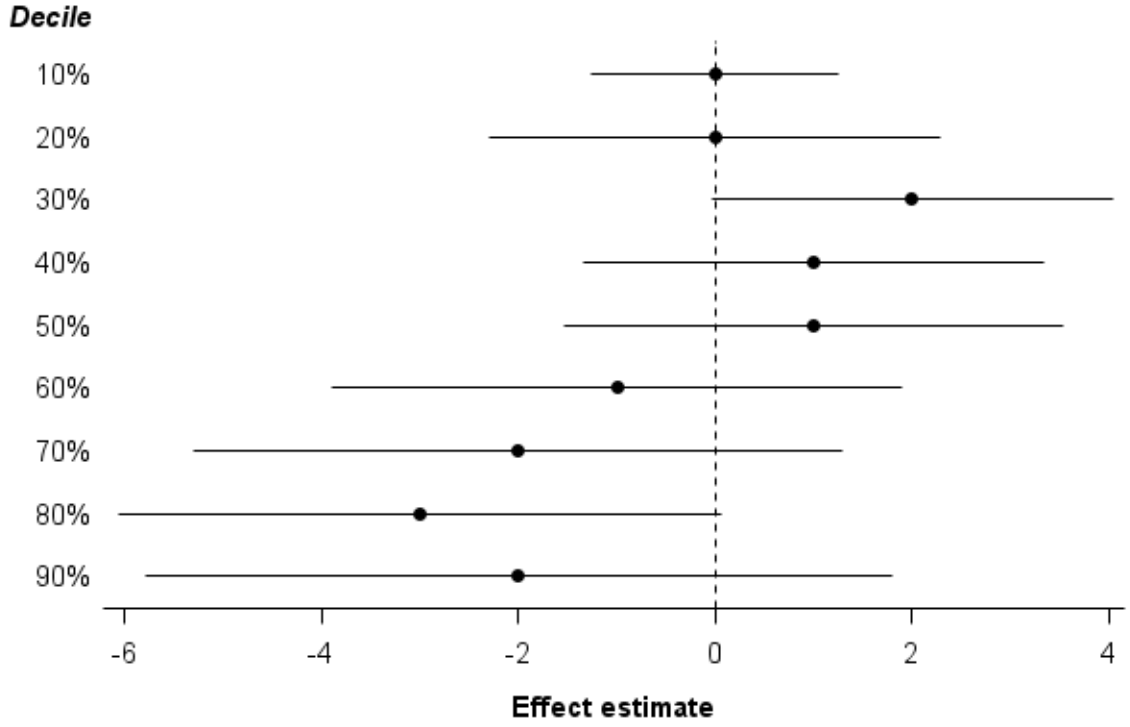


Figure 3.2. Intervention effects on SRS total T-scores estimated from a quantile regression analysis among complete cases (*n*=387)

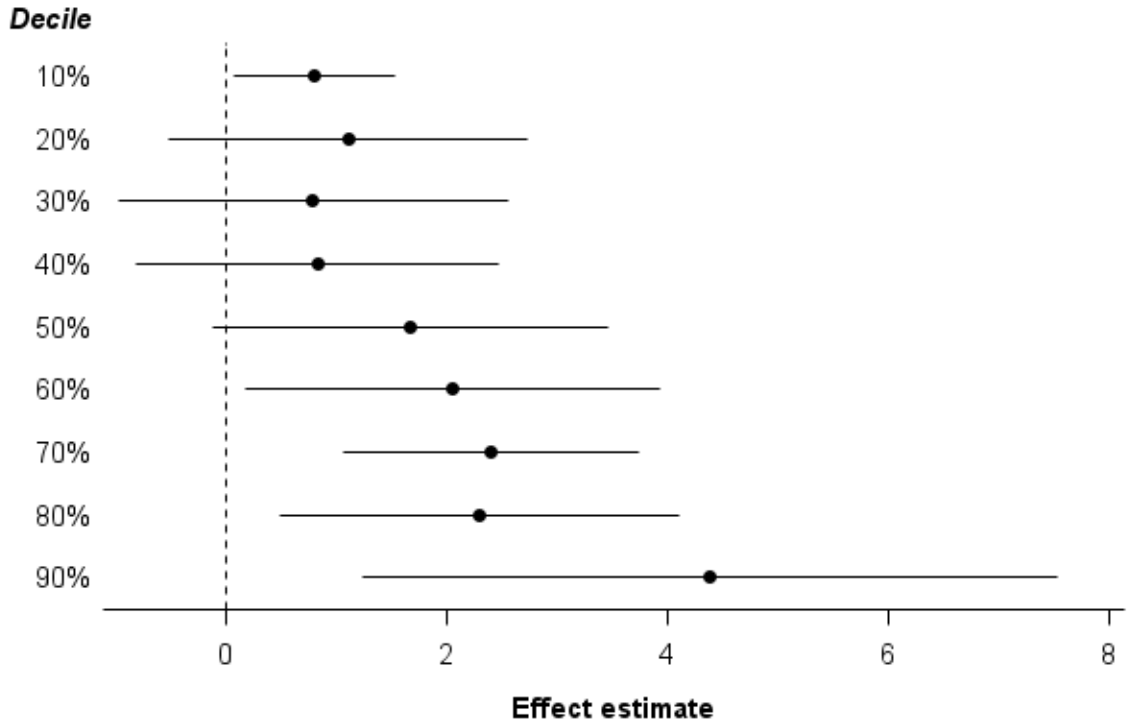


Figure 3.3. Estimated effects of an interquartile range (IQR) increase in indoor $PM_{2.5}$ over the full pregnancy on SRS total T-scores estimated from a quantile regression analysis among complete cases (*n*=353).

Full pregnancy IQR = 9.6 μg/m^3, Models adjusted for intervention status, maternal age at baseline, family income, living with a smoker early in pregnancy, maternal matrix reasoning and vocabulary subtest scores on the WASI, and mother's self-reported depression score on the BDI-II.

3.5. Discussion

In this cohort of women living in a heavily polluted city, we found modest evidence that reducing indoor particulate matter with HEPA cleaners from late in the first trimester until the end of pregnancy improved parent-reported autism scores in 4-year-old children. However, the intervention may have had larger benefits for children with higher scores. We also observed that increases in indoor $PM_{2.5}$ concentrations during pregnancy were associated with higher mean SRS-2 T-scores, social communication and restricted interests and repetitive behavior in children.

To our knowledge, this is the first study to use an RCT design to evaluate the relationship between prenatal exposure to PM and autism-related behaviors in children. Several possible explanations exist for our observation that the intervention had only modest effects on parent-reported autism behaviors. Despite observational evidence of an association between $PM_{2.5}$ and ASD (52,53,135–139), it is possible that air pollution is not a causal risk factor for autism. In addition, it is possible that exposure early in pregnancy is most important and by deploying the air cleaners at a median of 11 weeks we missed some of the crucial exposure period. Another plausible explanation for the discrepancy between our RCT and observational results is exposure misclassification caused by using a binary treatment group indicator in the ITT analysis. When developing the indoor $PM_{2.5}$ prediction model used in this analysis, we found that intervention status alone explained only 6% of the variance in weekly indoor $PM_{2.5}$ concentrations (115). Although we adjusted for several important variables, we cannot rule out the possibility of residual confounding in the analysis of $PM_{2.5}$ concentrations and SRS-2 scores. It is also possible that the 29% reduction in $PM_{2.5}$ concentrations (from a geometric mean of 24.5 $\mu g/m^3$ in the control group to 17.3 $\mu g/m^3$ in intervention group) introduced by the intervention was insufficient. Finally, the benefits of the intervention may have been masked by effect heterogeneity across the cohort. From our quantile regression analysis, we observed that effects of the intervention were not consistent across SRS-2 score distribution.

The associations between $PM_{2.5}$ concentrations and autistic traits, with larger effect estimates earlier in pregnancy, is consistent with results from our previous publication on

children's behaviors assessed with the Behavior Assessment System for Children, Third Edition (BASC-3) in this cohort (129). Several previous studies compared the SRS-2 with behavioral assessment tools to evaluate their discriminant validity, a measure of the extent to which these tools capture different behavioral impairments (133,134,140–142). A comparison of the Child Behavior Checklist (CBCL), a behavior assessment tool similar to the BASC, and the SRS-2 conducted among German children suggested that the two provided independent information, with moderate correlations ranging from r=0.48 to r=0.64 (143). In an another study of 219 pairs of male twins, investigators found that only 43% of the variance in SRS-2 scores could be predicted from CBCL scores (133). These findings suggest that the SRS-2 distinguishes autism-related behaviors from other behavioral problems (134).

Previous birth cohort studies of prenatal exposure to $PM_{2.5}$ and ASD risk have produced a wide range of effect estimates (17,128). In our secondary observational analysis, we observed that a 9.6 $\mu g/m^3$ contrast in indoor $PM_{2.5}$ over the full pregnancy was associated with a 1.8-unit (95% CI: 0.3, 3.2) increase in the mean SRS-2 total T-score. Our effect estimates are not directly comparable with those of previous studies because we analyzed a continuous measure of ASD-related behaviors and used indoor $PM_{2.5}$ concentrations as a proxy for exposure.

Our observation that $PM_{2.5}$ exposures earlier in pregnancy may be most important for autistic traits is consistent with a study in southern California, which reported that the $PM_{2.5}$-associated risk of ASD decreased over the course of pregnancy (52). In contrast, several birth cohorts have suggested that second and the third trimesters of exposure are most important (17,53,128). For example, the Nurses' Health Study analysis found an association with ASD for all three trimesters of exposure, but the strongest association was observed for exposure in the third trimester (53). Results from the CHARGE cohort also indicated that exposure to $PM_{2.5}$ in second and third trimesters were more strongly linked with ASD development (136).

As with many birth cohort studies, our results may have been influenced by the live birth bias, a form of selection bias (123). In a case control study in Israel, Raz and

colleagues reported that prenatal exposure to nitrogen dioxide was associated with lower risk of ASD (135), a finding that they speculated may have been due to selection bias caused by fetal loss (123). We previously reported a decreased risk of spontaneous abortion and an increased risk of preterm birth in the intervention group (116). We speculated that the intervention enabled fetuses who otherwise might have died *in utero* to instead be born preterm. If air pollution increases the risk of fetal loss preferentially among fetuses susceptible to the impacts of air pollution on brain development, the control group would have fewer susceptible children and the intervention effect estimate would be attenuated (123).

Our study had several limitations. Staff who administered and scored the SRS-2 were blinded to the participants' group assignments, but the participants were not blinded, and their awareness of their intervention status could have influenced the way that they perceived and reported their child's behaviors. The lack of blinding could also partly explain the greater loss of control participants. This may have introduced some selection bias, which we tried to address through an ITT analysis using multiple imputation. Although we demonstrated that the intervention reduced $PM_{2.5}$ in participants' homes, we did not measure personal exposure to $PM_{2.5}$ and the impacts of this residential intervention would be attenuated by exposure encountered outside of the home. This study may have been underpowered for this outcome as the sample size calculation was based on term birth weight, the original outcome of this trial. We gained power by using a continuous outcome, but SRS-2 scores do not represent clinical ASD diagnoses, which have been used in some previous studies of air pollution and autistic behaviors. With no Mongolian reference population, we explored multiple approaches to scaling scores, which produced similar results. Finally, even careful translation may not account for important cultural differences in the interpretation of social behaviors. Therefore, use of an assessment tool designed for North American children may not have fully captured autism-related behavior problems in this cohort of Mongolian children.

Our study also had several strengths. This is the first study to use a randomized study design to evaluate the causal association between PM and autistic behavior in children. In addition, a limited number of studies on ASD have been conducted in low and

middle income countries (144). Finally, most air pollution studies used outdoor $PM_{2.5}$ concentration as a proxy for exposure to outdoor-generated PM. We used modeled indoor $PM_{2.5}$ concentrations to capture exposure in location where the majority of time is spent (48).

3.6. Conclusions

In this randomized controlled trial, we found little benefit of reducing indoor particulate matter air pollution during pregnancy on parent-reported autistic traits in children at age 4. However, the intervention may have been more beneficial for children with more autistic traits. In a secondary analysis, however, we found increases in indoor $PM_{2.5}$ concentrations over the entire pregnancy were associated with increases in autism-related behaviors. These findings suggest that exposure to air pollution during pregnancy may influence the development of these behaviors in childhood and interventions early in pregnancy may be most beneficial.

Chapter 4. The influence of stress during pregnancy on the association between an air cleaner intervention and children's social and behavioral development at four years of age

4.1. Abstract

Background: Maternal exposure to fine particulate matter ($PM_{2.5}$) air pollution has been linked to fetal growth impairments and children's social and behavioral developmental trajectories. The objective of the study is to test if maternal stress during pregnancy may modify these associations.

Methods: We enrolled 540 non-smoking pregnant women and randomly assigned them either to an intervention group (n=268), which received HEPA air cleaners to use from enrollment to the end of pregnancy, or a control group (n=272), which did not receive air cleaners. At a median of 11 weeks gestation (range: 5 to 19 weeks), we collected hair samples and analyzed them for cortisol and dehydroepiandrosterone (DHEA). When children were a median of 48 months (range: 48 to 51 months), we collected maternal reports of children's behavioral and social development using the Behavioral Assessment Systems for Children, Third Edition (BASC-3) and the Social Responsiveness Scale, Second Edition (SRS-2). To evaluate modification of intervention-behavior relationships by maternal stress, we ran linear regression models with interactions between the intervention and tertiles of stress variables. Our analysis included 297 mother-child dyads (153 intervention and 144 control) who provided hair samples for cortisol and DHEA analysis and completed the BASC-3 and SRS-2 assessments.

Results: The intervention was not associated with changes in mean BASC-3 or SRS-2 scores. We found, however, several statistically significant interactions between the intervention and maternal stress, with generally greater benefits on BASC-3 or SRS-2 scores among children whose mothers had lower hair DHEA concentrations or higher hair cortisol:DHEA ratios.

Conclusion: Benefits of a prenatal air cleaner intervention on children's social and behavioral problem scores in our sample differed by markers of maternal stress in

pregnancy. These findings suggest that benefits from air pollution reductions in pregnancy on children's behavior may be greatest for children whose mothers experience HPA-axis dysregulation in early pregnancy.

4.2. Introduction

Prenatal maternal exposure to fine particulate matter ($PM_{2.5}$) air pollution has been linked to impairments in fetal growth and neurodevelopment (3,102,145). Observational studies have identified associations between gestational exposure to $PM_{2.5}$ and anxiety, depression, attention-deficit/hyperactivity disorder (ADHD), and autism spectrum disorder (145–148) in children. The mechanisms underlying the neurodevelopmental effects of air pollution are not fully understood, but experimental studies suggest that oxidative stress, inflammation, mitochondrial dysfunction, and epigenetic changes may be involved (33,149,150).

Maternal exposure to physical, immunologic and energetic challenges often referred to as stress may have lasting effects on fetal brain development (68,69,151,152). These stressors affect hypothalamic-pituitary-adrenal (HPA) axis activity in terms of the production of cortisol and other glucocorticoids (69). Increased fetal exposure to glucocorticoids may cause abnormalities in the structure and function of neurons and glial cells (70) which may lead to changes in brain structure and function, potentially increasing the risk for social and behavioural impairments (153,154). The influence of maternal glucocorticoids on the fetus is partly mediated by the enzyme 11 β-hydroxysteriod dehydrogenase type 2 (11β-HSD2), which protects the fetus from exposure to high levels of glucocorticoids (71,155). Air pollution may alter the activity of 11β-HSD2 in the placenta, resulting in higher exposure of the fetus to maternal glucocorticoids (69,72).

Adrenal dehydroepiandrosterone (DHEA), a steroid that acts as a glucocorticoid antagonist is another critical modulator of individual responses to stress. Indeed, quantification of the cortisol:DHEA ratio may provide a better indicator of HPA axis activity and regulation than either cortisol or DHEA alone (20–23). For example, individuals who experienced long-term stress had significantly lower serum DHEA

concentrations and higher cortisol:DHEA ratios than those who reported low stress (156). Stress hormones are commonly measured in blood and saliva (157), but interpretation of these measurements is complicated by diurnal variation (157); as cortisol levels are highest in the morning upon awakening and lowest in the evening before bedtime. Therefore, time of day when samples are collected must be tightly controlled, which is not always possible in human studies. Moreover, even if time of day can be controlled, a single measurement only reflects the individual's state at that moment in time, and therefore multiple samples would need to be collected to assess long-term HPA function (153). The measurement of stress hormones in hair provides a non-invasive and useful measure of longer-term concentration, over an interval of approximately 3 months (158–160).

Investigators have explored interactions between various air pollutants and psychosocial stress in pregnancy on health in childhood using both, animals and human models (161). Bolton and colleagues report that in a mice model, stress late in pregnancy exacerbated the effects of prenatal diesel exhaust exposure on anxiety in offspring, with more pronounced effects among males offspring (162). In humans, Perera and colleagues reported that exposure to polycyclic aromatic hydrocarbons (PAHs) during pregnancy had greater effects on externalizing and internalizing problems among children who mothers reported higher material hardship or demoralization (74,163). Importantly, studies examining interactions between exposure to air pollution and maternal stress on behavioral outcomes have all been observational and relied on self-reported stress.

Using data from the Ulaanbaatar Gestation and Air Pollution (UGAAR) randomized controlled trial (RCT), we previously reported that use of high efficiency particulate air (HEPA) filter air cleaners ("HEPA cleaners") during pregnancy had little effect on parent-reported behavior problem scores of children at age four years (129,164). However, results from a *post hoc* quantile regression analysis indicated that the benefits of the intervention were more pronounced among children with more autism-related behaviors (164), suggesting that the benefits of the intervention may have been masked by effect heterogeneity across the cohort. In the present analysis, we sought to extend our previous work from the UGAAR trial to evaluate heterogeneity in the effect of the HEPA cleaner intervention on behavioral outcomes assessed at age four. Specifically, we

hypothesize that the greater intervention effect on children with higher SRS score was because of greater maternal stress during pregnancy.

4.3. Objective

To investigate whether biomarkers of prenatal maternal HPA axis function, cortisol and dehydroepiandrosterone (DHEA) concentrations in hair and the cortisol/DHEA ratio, modified the effects of the HEPA filter air cleaner intervention on parent-reported behaviour at age four.

4.4. Methods

4.4.1. Participants

Our analysis is based on UGAAR study's data, an RCT that assess the impacts of HEPA cleaners use during pregnancy on fetal growth and childhood development (ClinicalTrials.gov: NCT01741051) (116,129,130,165). The trial was conducted in Ulaanbaatar, Mongolia's capital. In this polluted city the primary source of $PM_{2.5}$ is coal combustion in home heating stoves (98–101). We enrolled 540 women who met our inclusion criteria: ≥ 18 years of age, ≤ 18 weeks into a single gestation pregnancy, non-smoker, living in an apartment, not using portable air cleaner(s) at enrollment, and planning to give birth in a medical facility in Ulaanbaatar. The UGAAR study protocol was approved by the Simon Fraser University Office of Research Ethics, the Research Ethics Committee of Mongolian National University of Medical Sciences, and the Mongolian Ministry of Heath Medical Ethics Approval Committee.

4.4.2. Intervention

The intervention group received one or two HEPA cleaners (Coway AP-1009CH) depending on the size of the home. In smaller apartments (<40 m^2) we placed an air cleaner in the main living area of the home; in larger apartments (≥40 m^2), we placed a second air cleaner in the participant's bedroom. We deployed the HEPA cleaners in intervention homes shortly after enrollment into the study at median of 11 weeks (range: 5 to 19 weeks).

The control group received no HEPA cleaners. Participants were encouraged to use the air cleaner continuously throughout pregnancy. We did not replace the HEPA filter(s) during the study, and we collected the HEPA cleaner(s) after pregnancy ended.

4.4.3. Data collection

Participants visited our study office shortly after enrollment, between 5- and 19-weeks' gestation, and again at 24-37 weeks' gestation. We collected data on sociodemographic factors during pregnancy via questionnaire administered at a median of 11 weeks of gestation (range: 5 to 19 weeks), and again at a median of 30 weeks (range: 24 to 37 weeks). At approximately the same times, we also assessed prenatal maternal stress in two ways. First, participants completed the four-question perceived stress scale (PSS-4), which prompts respondents to describe their feelings and thoughts over the previous month (113). Second, to evaluate the mothers' physiologic stress levels, we collected hair samples from the mothers in which we could quantify cortisol and dehydroepiandrosterone (DHEA).

At approximately the same times that the questionnaires were administered, we also collected hair samples from the mothers. We collected hair samples from 485 participants in early pregnancy (range: 5 to 19 weeks) and from 451 participants in late pregnancy (range: 24-37 weeks). Each sample consisted of approximately 30-50 strands (~ 30 mg) of hair but close to the scalp from the occipital area. Some hair samples, particularly those collected late in pregnancy, were previously used for cotinine analysis with a destructive assay (166). This left us with 319 hair samples from early pregnancy and 72 samples from late pregnancy for analysis of stress hormones (166).

We analyzed four cm of hair to quantify cortisol and DHEA concentrations over approximately three months prior to sample collection. To remove contaminants such as oil and residue, we washed the samples twice in 10 ml isopropanol using a Bio-Tek ELx50 washer. Following each wash, we air-dried the samples for 48 hours. Next, we pulverized the samples into fine powder with a Retsch MM301 Grinder, at 2.5 Hz for 2.5 min, and extracted twice for 24 hours with methanol. The solvent was then dried down using a Savant Speed Vac Plus and dried samples were reconstituted with 250 µl buffer. We used

commercially available high sensitivity enzyme immunoassay kits (Salimetrics LLC, State College, PA) to analyze the samples for cortisol (assay #1-3002) and DHEA (assay #1-1202). We standardized the hormone concentrations by the weight of the hair. In this analysis we focused on the early pregnancy hair samples because they were available for more participants.

We obtained birth weight, length, head circumference, gestational age, sex, and mode of delivery from medical records. We also collected information from medical records on stillbirths, pregnancy complications and co-morbidities (116). When children were two years of age, their mothers were asked to report depression symptoms and, severity over the two weeks prior to the interview, using the Beck Depression Inventory (BDI-2).

4.4.4. Assessment of outcomes

To assess children's behavior and emotional functioning, we administered the preschool version of the Behavioral Assessment System for Children, 3rd Edition (BASC-3) to the child's primary caregiver when the children were a median of 48 months (range: 48 to 51 months) old (167). The BASC-3 asks caregivers how frequently their child demonstrated 139 specific behaviors or activities over the past several months. The responses are categorized into four composite scales: externalizing problems (hyperactivity and aggression), internalizing problems (anxiety, depression, and somatization), behavioral symptoms index (BSI) (attention problems, atypicality and withdrawal), and adaptive skills (adaptability, social skills, activities of daily living and functional communication). We obtained BASC-3 data for 388 children (205 intervention, 183 control).

Our primary outcomes from the BASC-3 were the T-scores for the four composite scales. For externalizing problems, internalizing problems, and the BSI higher scores indicate more behavioral problems. For adaptive skills, lower scores indicate poorer functioning.

At the same time, we also obtained data on social impairments typical of children with an autism spectrum disorder for a total of 387 children (205 intervention, 182 control)

by administering to caregivers the school-age (4-18 years) form of the Social Responsiveness Scale, Second Edition (SRS-2). Respondents indicated the frequency of 65 behaviors on a Likert scale from 0 (not true) to 3 (almost always true) (132).

Our primary outcome from the SRS-2 was the total T-score, which is derived from the sum of five subscales: social awareness, social cognition, social communication, social motivation and restricted interest and repetitive behaviors scores. Higher scores are associated with a greater degree of social impairment.

All BASC-3 and SRS-2 materials were translated from English to Mongolian by native Mongolian speakers, then independently back-translated to English. We then piloted the translated SRS-2 and BASC-3 assessments on Mongolian parents and refined the translations before administering them to UGAAR participants.

4.4.5. Statistical analysis

In this *post hoc* analysis of potential effect modification by maternal stress, we restricted our analysis to 297, complete cases of mother-child dyads with maternal hair cortisol and DHEA concentrations and the BASC-3 and SRS-2 assessments of behavior in childhood (153 intervention and 144 control). We used the Kruskall-Wallis test to investigate differences in median hair cortisol and DHEA concentrations across categories of several maternal and newborn characteristics.

To evaluate intervention effect heterogeneity due to maternal stress, we stratified the population by tertiles of hair cortisol, hair DHEA, the cortisol/DHEA ratio, and the PSS-4 score (168). Next, for each indicator of stress, we tested for differences in the effect of the intervention on behaviour across tertiles of the indicator using stratified analysis. To evaluate effect modification, we used SAS (v9.4) PROC PLM with an “estimate” statement, we regressed behaviour scores on intervention status, a categorical variable of stress tertiles, and intervention x stress tertile interaction terms. We summarized these results graphically and report differences in intervention effect estimates between stress tertiles when the interaction $p<0.10$.

Finally, we conducted a sensitivity analysis to evaluate the influence of baseline imbalances between intervention and control participants and to evaluate whether the observed effect heterogeneity was due to stress and not other variables correlated with stress. Specifically, we re-ran the models after also including 1) variables that were associated with intervention group (marital status and preterm birth), 2) variables that were associated with stress (season of enrollment and maternal age at enrollment), and 3) interactions between the intervention and those variables (intervention x season of enrollment and intervention x maternal age at enrollment). The presence of an association was assessed using a Kruskal Wallace test.

4.5. Results

4.5.1. Characteristics of the participants

We recruited 540 pregnant women from January 9, 2014, to May 1, 2015. The participants were enrolled at a median (25^{th}, 75^{th} percentile) gestational age of 11 (9, 13) weeks. We followed 514 participants to the end of pregnancy. There were 51 pregnancy losses or neonatal deaths, and 416 participants re-enrolled in the follow-up study of childhood development (129,164).

The intervention and control participants included in this analysis were broadly similar (Table 4.1). Control participants were less likely to be married or common-law and had a lower median hair cortisol concentration than intervention participants (Table 4.1). As previously reported, preterm birth was more common in the intervention group (10%) than the control group (4%) (Table 4.1) (129,164), presumably due to differences in pregnancy losses and the live-birth bias (169).

The maternal hair cortisol and DHEA concentrations were similar across maternal and child characteristics (Table 4.2). However, we observed that median cortisol and DHEA concentrations were higher in mothers enrolled in winter months (Table 4.2). Additionally, we observed that median cortisol concentrations were higher for older mothers, which is expected (170).

The stress hormone measured at early and late pregnancy were moderately correlated with cortisol levels ($r=0.63$, $p<0.01$), DHEA levels ($r=0.66$ $p<0.01$) and cortisol/DHEA ratio ($r=0.52$, $p<0.01$) (Table C.1). Of the 297 children included in this analysis, 261 had their behavior reported on the BASC-3 and SRS-2 by their mothers, while for 36 children behavior was evaluated by the father or another caregiver. The PSS-4 scores were not correlated with cortisol ($r=-0.10$, $p=0.07$) or DHEA ($r=-0.02$, $p=0.76$) concentrations, or with the cortisol/DHEA ratio ($r=0.01$, $p=0.90$) (Table C.2).

The baseline, pregnancy, and postnatal characteristics for the 297 participants included in the analysis and the 181 participants excluded from the analysis were generally similar (Table C.3). However, the participants included in the analysis enrolled earlier in pregnancy and were more likely to have enrolled during the fall season than participants who were not included.

Table 4.1. Pregnancy and post-natal characteristics for control and intervention dyads included in the analysis (n=297)

Characteristic	Participants in the control group (n=144) Median (25^{th}, 75^{th} percentile) or n (%)	Participants in the intervention group (n=153) Median (25^{th}, 75^{th} percentile) or n (%)	p-value
Season of enrollment			
Winter (Dec, Jan, Feb)	47 (33)	45 (29)	
Spring (Mar, Apr, May)	37 (26)	28 (18)	0.26
Summer (Jun, July, Aug)	15 (10)	18 (12)	
Fall (Sep, Oct, Nov)	45 (31)	62 (41)	
Gestational age at enrollment, wk	10 (8, 12)	10 (8, 12)	0.59
Maternal age at enrollment, yr	28 (25, 32)	30 (26, 33)	0.15
Not reported, n (%)	2 (1)	4 (3)	
Monthly household income, Tugriks			
< 800,000	27 (19)	25 (16)	
≥ 800,000	114 (79)	127 (83)	0.55
Not reported, n (%)	3 (2)	1 (1)	
Maternal marital status			
Married/Common-law	114 (79)	134 (88)	0.05
Single/engaged	30 (21)	19 (12)	
Maternal education			
Less than university	18 (13)	16 (10)	
Completed university	116 (81)	125 (82)	0.60
Not reported, n (%)	10 (6)	12 (8)	
Lived with a smoker during pregnancy			
No	73 (51)	82 (54)	
Yes	66 (46)	67 (44)	0.67
Not reported, n (%)	5 (3)	4 (1)	
Maternal pre-pregnancy BMI, kg/m2	21.5 (19.6, 24.5)	21.8 (19.7, 24.2)	0.82
Not reported, n (%)	16 (11)	4 (3)	
Paternal age, yr	31 (26, 35)	31 (27, 35)	0.48
Not reported, n (%)	8 (6)	15 (9)	
PSS-4 score in early pregnancy			
Minimal	112 (78)	125 (82)	0.34

Moderate to severe	32 (22)	27 (18)	
Not reported, n (%)		1 (0)	
Hair cortisol concentration in early pregnancy (pg/mg)	5.2 (4.0, 6.9)	5.6 (4.5, 7.2)	0.09
Hair DHEA concentration in early pregnancy (pg/mg)	13.4 (9.2, 19.0)	13.8 (9.9, 18.8)	0.95
Hair colored in early pregnancy			
No	107 (75)	121 (79)	0.45
Yes	35 (25)	32 (21)	
Hair chemically treated in early pregnancy			
No	138 (98)	150 (98)	0.92
Yes	3 (2)	3 (2)	
Preterm birth			
Preterm (<37 weeks)	6 (4)	16 (10)	0.04
Full term (≥ 37 weeks)	138 (96)	137 (90)	
Sex of the child			
Boy	76 (53)	75 (49)	0.52
Girl	68 (47)	78 (51)	
Maternal depression level (BDI) at 2-year visit			
Minimum to mild (Score 0-16)	129 (90)	146 (95)	
Moderate to severe (Score >16)	8 (5)	7 (5)	0.63
Not reported, n (%)	7 (5)		
SRS-2 total T score	48 (43, 57)	50 (44, 55)	0.93
BASC-3 externalizing T-score	49 (43, 56)	49 (43, 57)	0.69
BASC-3 internalizing T-score	50 (45, 56)	49 (42, 55)	0.36
BASC-3 behavior symptoms index T-score	49.5 (44, 55)	50 (44, 57)	0.80
BASC-3 adaptive skills T-score	50 (44.5, 57)	49 (43, 56)	0.36

P-values were calculated using the Chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables. Missing observations were not included in p-value calculations.

Table 4.2. Maternal hair cortisol and DHEA concentrations (pg/mg) by maternal and child characteristics (n=297)

		Cortisol		DHEA	
Characteristic	N (%)	Median (25^{th}, 75^{th} percentile)	p-value	Median (25^{th}, 75^{th} percentile)	p-value
Season of enrollment					
Winter (Dec, Jan, Feb)	92 (31)	6.4 (5.1, 8.0)		15.2 (10.8, 21.5)	
Spring (Mar, Apr, May)	65 (22)	4.8 (3.6, 5.9)		14.2 (11.3, 19.9)	
Summer (Jun, July, Aug)	33 (11)	4.7 (4.0, 6.2)	<0.01	15.5 (12.6, 19.7)	<0.01
Fall (Sep, Oct, Nov)	107 (36)	5.3 (4.1, 6.9)		11.1 (8.6, 15.2)	
Gestational age at enrollment, wk.					
<11 weeks	155 (52)	5.6 (4.0, 7.4)	0.23	13.5 (10.1, 18.5)	0.88
≥11 weeks	142 (48)	5.3 (4.1, 6.7)		13.9 (9.3, 20.4)	
Maternal age at enrollment, yr					
<30 years	156 (53)	5.3 (4.0, 6.6)	0.04	14.4 (9.9, 19.6)	0.15
≥30 years	141 (47)	5.8 (4.3, 7.4)		12.6 (9.3, 17.9)	
Monthly household income, Tugriks					
< 800,000	52 (17)	5.5 (4.3, 6.8)	0.91	14.3 (9.4, 18.9)	0.79
≥ 800,000	241 (82)	5.4 (4.1, 7.2)		13.5 (9.6, 19.2)	
Not reported, n (%)	4 (1)				
Maternal marital status					
Married/Common-law	248 (84)	5.4 (4.2, 7.2)	0.43	13.9 (9.5, 19.0)	0.79
Single/engaged	49 (16)	5.2 (3.7, 6.7)		13.0 (9.9, 18.3)	
Maternal education					
Less than university	34 (12)	5.6 (4.8, 7.0)	0.61	16.7 (11.2, 20.8)	0.08
Completed university	241 (81)	5.4 (4.1, 7.0)		13.1 (9.4, 18.8)	
Not reported, n (%)	22 (7)				
Lived with a smoker during pregnancy					
No	155 (52)	5.2 (4.2, 6.8)	0.54	13.0 (9.3, 18.3)	0.15
Yes	133 (45)	5.7 (4.0, 7.3)		14.2 (10.1, 19.8)	
Not reported, n (%)	9 (3)				
PSS-4 in early pregnancy					
Minimal	237 (80)	5.4 (4.3, 7.1)	0.26	13.7 (9.8, 18.8)	0.71
Moderate to severe	59 (20)	5.0 (4.0, 6.7)		13.4 (8.3, 19.2)	
Not reported, n (%)	1 (0)				

Sex of the child					
Boy	151 (49)	5.2 (4.2, 7.0)	0.41	14.0 (9.9, 17.9)	0.94
Girl	146 (51)	5.7 (4.0, 7.2)		12.9 (9.3, 19.7)	

P-values were calculated using the Kruskal-Wallis test. Missing observations were not included in p-value calculations.

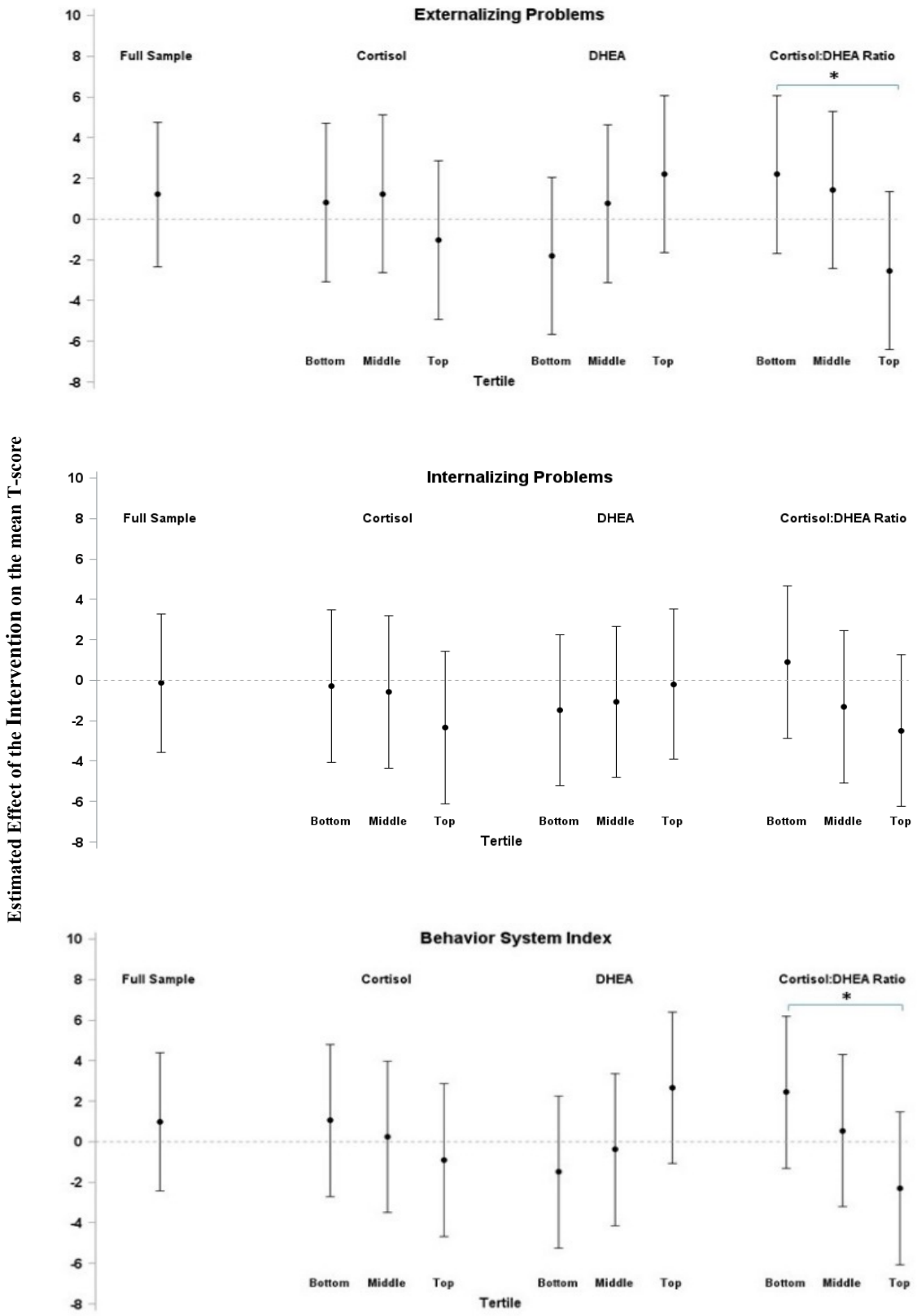
4.5.2. Effectiveness of the intervention

We previously reported that the HEPA air cleaners reduced mean indoor $PM_{2.5}$ concentrations by 29% (95% CI: 21%, 37%) during pregnancy, from a geometric mean (GM) of 24.5 $\mu g/m^3$ in control homes to 17.3 $\mu g/m^3$ in intervention homes (112). The post-natal $PM_{2.5}$ concentrations were similar between groups (3% lower in the intervention group, 95% CI: -14%, 7%) (129). Consistent with our previous intention-to-treat analyses, the intervention had little effect on behavior problem scores in the sample as a whole (Figure 4.1).

4.5.3. Effect modification by stress markers

We generally observed larger benefits of the intervention among children whose mothers were in the lowest DHEA tertile or the highest cortisol:DHEA ratio tertile (Figure 4.1). However, intervention effect estimates within stress hormone tertiles had wide confidence intervals that consistently spanned the null. For DHEA, only adaptive skills scores had intervention effect estimates that differed (p=0.02) between the lowest and highest hair concentration tertiles. For the cortisol:DHEA ratio, the intervention effect estimates differed between the lowest and highest tertiles for externalizing problems (p=0.09), behavior symptom index (p=0.08), and adaptive skills (p=0.02), with larger benefits in children whose mothers were in the top cortisol:DHEA ratio tertile. Results were similar after including additional variables in our models (Figure C.1).

For perceived stress, we observed differences in the intervention effect estimates between the bottom and top tertiles only for externalizing problems scores (Figure 4.2). Results were not sensitive to the inclusion of additional variables in the model (Figure C.2).


Externalizing Problems
Full Sample
Cortisol
DHEA
Cortisol:DHEA Ratio
*
10
8
6
4
2
0
-2
-4
-6
-8
Bottom
Middle
Top
Tertile
Internalizing Problems
Behavior System Index
Estimated Effect of the Intervention on the mean T-score

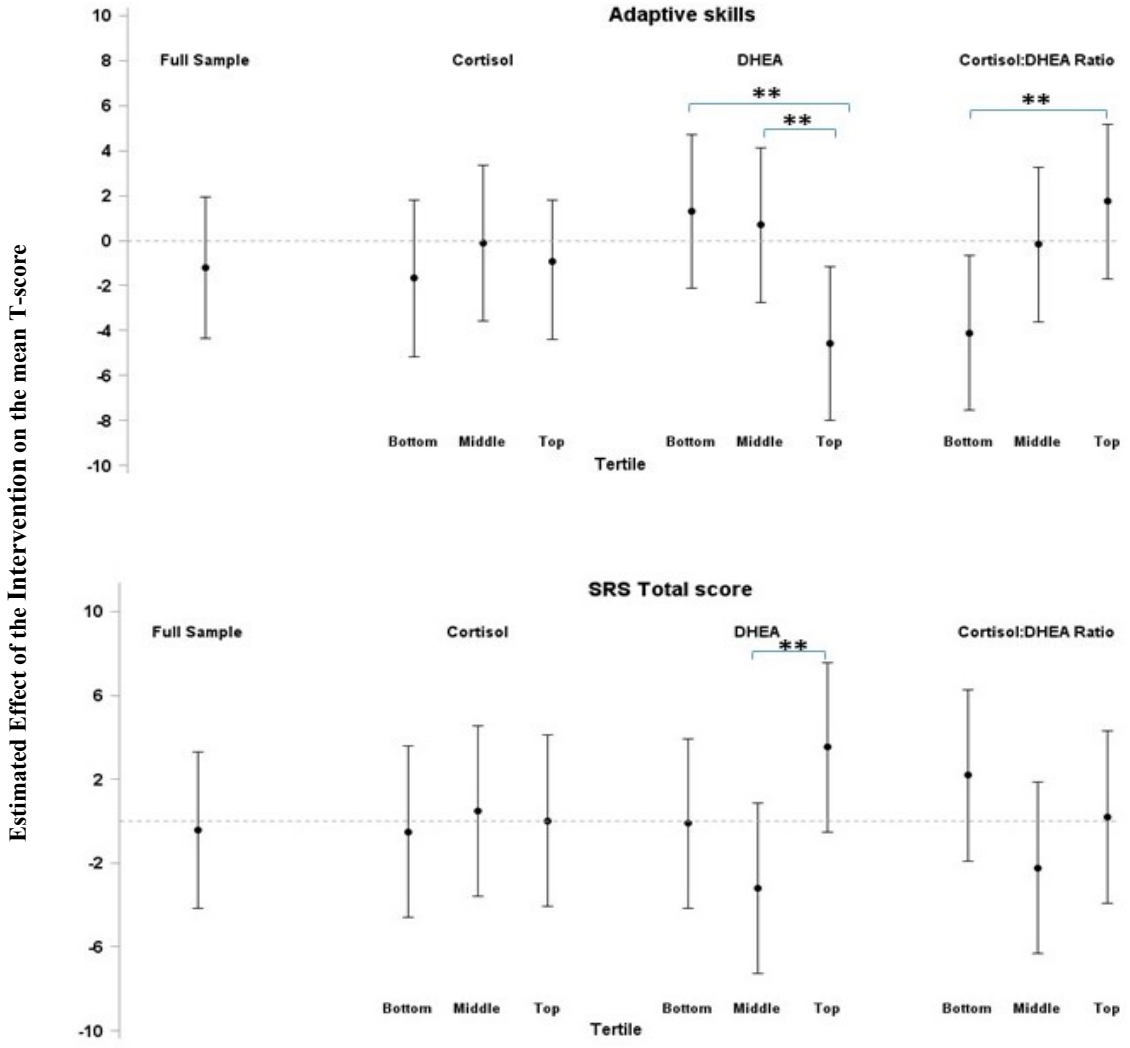


Figure 4.1. Estimated effects of the intervention on mean BASC-3 and SRS-2 scores stratified by maternal stress tertiles during pregnancy (n=297).

The figure illustrates estimated effects of the intervention on externalizing problems composite T-score, internalizing problems composite T-score, behavioral system index (BSI) T-score, adaptive skills composite T-score, and SRS total T-score. For externalizing, internalizing, BSI and SRS total T-scores, a higher score indicates more social and behavioral problems. For adaptive skills scores, a lower score indicates more social and behavioral problems.

*Interaction $p<0.10$
**Interaction $p<0.05$

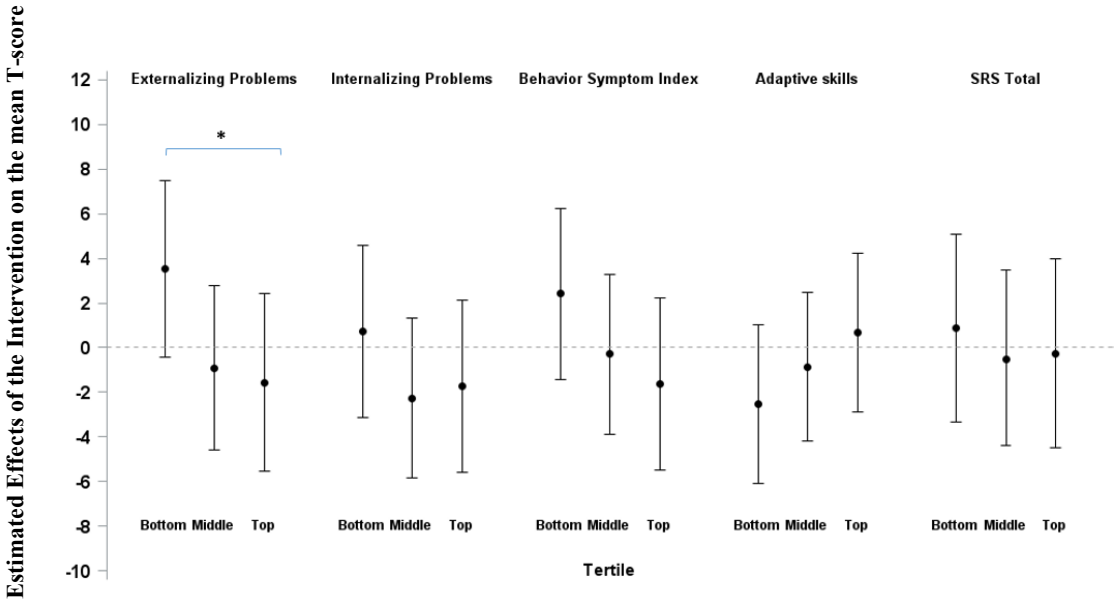


Figure 4.2. Estimated effects of the intervention on BASC-3 and SRS-2 scores stratified by maternal perceived stress scores during pregnancy (n=296).

The figure illustrates estimated effects of the intervention on externalizing problems composite T-score, internalizing problems composite T-score, behavioral system index (BSI) T-score, adaptive skills composite T-score, and SRS total T-score. For externalizing, internalizing, BSI and SRS total T-scores, a higher score indicates more social and behavioral problems. For adaptive skills scores, a lower score indicates more social and behavioral problems.

*Interaction $p<0.10$

4.6. Discussion

In this cohort of women living in a relatively polluted city, children whose mothers had lower hair DHEA concentrations and higher cortisol:DHEA ratios tended to experience larger benefits from the air cleaner intervention than children from mothers in other hormone tertiles. These findings suggest that maternal HPA axis activity during early pregnancy may influence the benefits of air pollution exposure reductions on children's social and behavioral development. However, as the confidence intervals were imprecise, caution is warranted in interpreting our findings.

Cortisol is the primary stress hormone secreted by the HPA axis, involved in body's responding to challenges (171). In the short term, cortisol released following an acute challenge enables the organism to respond both behaviorally and physiologically after which cortisol tends to return to basal levels. However, prolonged challenges can lead to cortisol being consistently secreted at high levels which can have negative consequences for the health of both mother and the fetus (172,173). Animal studies have demonstrated that fetal exposure to high levels of glucocorticoid hormones alters neural development in monkeys and rats (174,175). In humans, too high maternal cortisol levels can overwhelm protective mechanisms by crossing the placenta and reach the fetus, impacting its development. It is hypothesized that prenatal exposure to air pollution, may affect one of those protective mechanism by altering the activity of 11β-HSD2 in the placenta, which catalyzes the dehydrogenase conversion of cortisol to cortisone reducing fetal exposure to maternal cortisol (69,72). DHEA may be involved in another protective mechanism as it has anti-glucocorticoid, antioxidative, anti-inflammatory, and neuroprotective effects (176). Therefore, it has been hypothesized that higher levels of DHEA and hence, a lower cortisol/DHEA ratio, may also be protective against the adverse effects of high cortisol levels (159).

To our knowledge, this is the first study to use biomarkers of HPA axis function to evaluate interactions between air pollution and maternal stress during pregnancy and their effect on children's postnatal behavior. The results from previous studies, which relied on self-reported measures of stress, are broadly consistent with our findings. In a study of 248

mother-child dyads in Poland, researchers observed significant interactions between PAH exposure and maternal distress during gestation on children's internalizing and externalizing problem scores (163). Another study conducted in New York City reported significant interactions between PAH exposure and maternal hardship during gestation on ADHD-related symptoms in children (74). Our results show significant interactions between air pollution and maternal stress during gestation on children's behavior, suggesting the potential value of addressing both environmental and psychosocial stressors in efforts to promote children's healthy neurodevelopment.

We did not observe significant differences in the intervention-behavior relationships by tertiles of maternal cortisol. In a previous analysis from this cohort, Ulzikhuu and colleagues found a "U-shaped" pattern in which the HEPA cleaners increased full-scale IQ (FSIQ) among children whose mothers were in the lowest and highest cortisol tertiles, but not among those whose mothers were in the middle tertile (177). There are several possible explanations for the differences between our results and those of Ulzikhuu et al. Maternal stress may affect children's behavior through changes in maternal behavior and parenting practices, while the relationship between maternal stress and children's FSIQ may act through some other pathway (154). Because we relied on parent-reported behavior, it is also possible that the effect heterogeneity we observed is actually due to stress-related differences in mothers' interpretations and reporting of their children's behaviors.

Hair hormone concentrations were not correlated with self–reported perceived stress in this cohort. Our results align with previous studies that reported low correlations between hair cortisol concentration and self-reported stress (154,178,179). Hair hormone concentrations and perceived stress may capture different time periods (180). The correlations may be influenced the fact that perceived stress only captures how mother is feeling within the last one month which may not be reflective of long-term stress. Finally, the relationship between hair cortisol concentrations and perceived stress may be nonlinear because chronic stress can lead to blunted cortisol (180).

This study had several strengths. We used biological samples to quantify chronic stress in mothers. Previous studies to date all have evaluated self-reported questionnaire as an effect modifier in studies that is evaluating interaction between air pollution exposure and social and behavioral developmental outcomes (36,74,163). We measured both cortisol and DHEA as an integrated index of hormone concentrations to indicate long-term HPA axis functioning. Finally, both use of cortisol and DHEA led us to use the cortisol:DHEA ratio as an additional index of HPA axis function (159).

This study had some limitations. Staff who administered and scored the BASC-3 and SRS-2 were blinded to the participants' intervention assignments, but the participants were not. Participants' awareness of their intervention status may have introduced bias by influencing how they interpreted and reported their children's behavior. Another limitation is that we relied on cortisol and DHEA quantified from hair samples collected in the first trimester of pregnancy, which may not capture stress over the full pregnancy. However, moderate correlations between samples collected in early and late pregnancy suggest that our first trimester samples provide a reasonable proxy for stress over the full pregnancy. We also did not measure maternal stress after pregnancy ended, so we were unable to disentangle the impacts of prenatal and postnatal stress. The sample size in UGAAR was calculated based on term birth weight, the original outcome of this trial, and we were likely underpowered to detect interactions with stress. Finally, the large number of multiple comparisons made in the p-value calculation increases the risk of false positive results. Therefore, caution is warranted in interpreting the results.

4.7. Conclusion

These findings suggest that reducing exposure to particulate matter air pollution during pregnancy can have the greatest benefits on the social and behavioral development of children, especially for pregnant women who are most physiologically stressed. Therefore, targeted interventions addressing maternal physiological stress may maximize the benefits of reducing air pollution during pregnancy for the social and behavioral development of children in early childhood.

Chapter 5. Discussion

5.1. Summary of results

Using data from the UGAAR randomized controlled trial, I examined the impact of a HEPA filter air cleaner intervention during pregnancy on children's social and behavioral development. I also evaluated the influence of prenatal maternal stress on the relationship between HEPA filter air cleaner use and children's social and behavioral development at four years of age.

5.1.1. Portable HEPA filter air cleaner use during pregnancy and children's behavior problems scores (Chapter 2)

I found that HEPA filter air cleaner use was not associated with mean externalizing, internalizing, behavioral symptom index, or adaptive skills scores at two or four years of age in an intention-to-treat analysis. The results were not sensitive to adjustment for preterm birth. In the secondary analysis of modelled indoor $PM_{2.5}$ concentrations during pregnancy, I observed that an IQR (20.1 $\mu g/m^3$) increase in $PM_{2.5}$ during the first trimester was associated with changes of 2.4 units (95% CI: 0.7, 4.1), 2.4 units (95% CI: 0.7, 4.1), 2.3 units (95% CI: 0.7, 3.9), and -1.5 units (95% CI: -3.0, 0.0) in mean externalizing problems, internalizing problems, behavioral symptoms index, and adaptive skills T-score, respectively, at age 4. $PM_{2.5}$ concentrations during the third trimester were associated with some behavioral indices, but effect estimates were smaller. I did not observe associations between $PM_{2.5}$ exposure in the second trimester and any of the BASC indices at 2 and 4 years old. Overall, the larger effect estimates during the first trimester suggest that it may be necessary to intervene early in pregnancy to protect children from the impacts of air pollution on behavior.

5.1.2. Portable HEPA filter air cleaner use during pregnancy and childhood autistic traits at four years of age (Chapter 3)

HEPA filter air cleaner use during pregnancy was not associated with mean SRS-2 total T-score (-0.5 units; 95% CI: -2.5, 1.5) in 4-year old children. The results were not

sensitive to adjustment for preterm birth. Results from a *post hoc* quantile regression analysis among complete cases suggested larger benefits of the intervention among children at the higher end of the SRS total T-score distribution. In the secondary analysis, I observed that an IQR (9.6 $\mu g/m^3$) increase in modelled indoor $PM_{2.5}$ during the full pregnancy was associated with 1.8-unit (95% CI: 0.3, 3.2) increase in mean SRS-2 total T-score. Effect estimates for $PM_{2.5}$ concentrations in each trimester were smaller and confidence intervals spanned no effect. Overall, the findings suggest that exposure to air pollution during pregnancy may influence the development of autistic behaviors in children.

5.1.3. The influence of stress during pregnancy on the association between an air cleaner intervention and children's social and behavioral development at four years of age (Chapter 4)

In a subgroup analysis of 297 mother-child dyads with maternal hair cortisol and DHEA measures, I observed greater benefits from the intervention among children whose mothers were in the lowest DHEA tertile or the highest cortisol:DHEA ratio tertile. However, intervention effect estimates within stress tertiles had wide confidence intervals that consistently spanned the null. For DHEA, only adaptive skills scores had intervention effect estimates that differed (p=0.02) between the lowest and highest hair concentration tertiles. For the cortisol:DHEA ratio, the intervention effect estimates differed between the lowest and highest tertiles for externalizing problems (p=0.09), behavioral system index (p=0.08), and adaptive skills (p=0.02), with larger benefits for children whose mothers were in the top cortisol:DHEA ratio tertile. Results were similar after including additional variables in the models. For perceived stress, I observed differences in the intervention effect estimates between the bottom and top tertiles only for externalizing problems scores. Results were not sensitive to the inclusion of additional variables in the models. Overall, the findings suggest that the benefits of reducing exposure to PM air pollution during pregnancy on children's social and behavioral development may be influenced by maternal stress.

5.2. Synthesis and significance of findings

The UGAAR study used HEPA air cleaners in the homes of pregnant mothers to examine the effects of reducing indoor PM on social and behavioral problems in a highly polluted environment. To the best of my knowledge, this is the first study to utilize an RCT design to assess the relationship between prenatal exposure to PM and social and behavioral problems in children. The results showed that lowering indoor PM concentrations during pregnancy did not provide benefits for social and behavioral development in children. However, I observed that indoor $PM_{2.5}$ concentrations during pregnancy were associated with increases in average BASC and SRS scores in children.

The results from the observational component of the analysis differed from the ITT results of this study. It is not uncommon for an intention-to-treat analyses in an RCT to produce different results than a corresponding exposure-response analysis (181,182). For example, the RESPIRE trial of improved indoor cookstoves observed that physician-diagnosed pneumonia for children younger than 18 months was lower among children in the treatment group (RR 0.84, 0.63-1.13), but failed to reach statistical significance. However, a 50% reduction in carbon monoxide exposure was associated with lower risk of pneumonia (RR = 0.82; 95% CI: 0.70, 0.98). The investigators attributed the discrepancy in results to greater exposure misclassification in the intention-to-treat analysis (183).

There are several possible explanations for observation that HEPA air cleaners did not improve social and behavioral outcomes in the UGAAR trial. One possibility is that there may be no causal link between *in utero* exposure to PM and social and behavioral aspects of neurodevelopment in children. Although I found associations between indoor $PM_{2.5}$ and behavior scores, the broader observational evidence on this relationship remains mixed. Another possible explanation is that the crucial exposure periods for social and behavioral aspects of neurodevelopment may have been missed by deploying the air cleaners at a median of 11 weeks. As seen from the observational component of the study, exposure to $PM_{2.5}$ during the first trimester was associated with increases in mean externalizing, internalizing, BSI, and adaptive skills scores. Additionally, like in the RESPIRE trial, the use of a binary intervention group variable in the ITT analysis may

have introduced exposure misclassification. When developing the indoor $PM_{2.5}$ prediction model used in this analysis, Yuchi and colleges reported that intervention status alone explained only 6% of the variance in weekly indoor $PM_{2.5}$ concentrations, while outdoor $PM_{2.5}$ concentrations from government-run measurement stations explained 9% of the variance (115). Lastly, it is possible that the 29% reduction in $PM_{2.5}$ concentrations (from a geometric mean of 24.5 $\mu g/m^3$ in the control group to 17.3 $\mu g/m^3$ in the intervention group) produced by the intervention was insufficient to produce meaningful differences in the social and behavioral problems scores.

Because outdoor-generated $PM_{2.5}$ infiltrates indoors, indoor $PM_{2.5}$ concentrations are a mixture of indoor- and outdoor-generated pollution. Therefore, portable air cleaners potentially reduce the impacts of pollution from both outdoor sources and indoor sources (184). A study conducted in China reported that exposure indoors accounted for 81% of the deaths attributable to outdoor $PM_{2.5}$ (184). In the US indoor exposures are estimated to account for 61% of the deaths attributable to outdoor-generated $PM_{2.5}$ (110).

Brain development is a rapid and complex process, and the timing of exposure to neurotoxicants may be a crucial factor in determining adverse impacts (27,49,120). My findings suggest that increased exposure to $PM_{2.5}$ in early pregnancy may have the greatest impact on social and behavioral impairments in children. However, the results from observational studies are inconsistent on the critical window(s) of exposure to PM on social and behavioral outcomes. While some studies have found that increased PM exposure in the third trimester was linked with lower social and behavior scores, others indicated that exposure during the first trimester has the greatest impact on these outcomes (29,42,52). One possible biological mechanism that may explain the significance of early pregnancy exposures involves the activation of microglia, the brain's innate immune cells. Microglia start to develop from the fourth week of gestation through mid-gestation and may become activated by maternal exposure to $PM_{2.5}$ during this period, leading to oxidative stress in the mothers and subsequent neuroinflammation in the fetal brain (49,185).

At present, there is no objective measure of social and behavioral problems in children. However, in recent years magnetic resonance imaging (MRI) has been used to

measure structural and functional changes in the brain and, in combination with psychometric tools, to understand biological mechanisms linking air pollution with social behavioral impairments (34,38,107,186,187). These studies using neuroimaging suggests that prenatal air pollution exposure is associated with smaller white matter volume (34,38), white matter lesion (107) and decrease of pre-frontal cortical thickness (187).

In this study I was unable to identify the specific $PM_{2.5}$ components or sources that are driving associations with children's social and behavioral development. Previous UGAAR work reported that mean maternal blood cadmium was 14% (95% CI: 4, 23%) lower in the intervention group than in the control group. Participants living with smokers in their homes and those living in areas with higher coal stove density both had higher mean blood cadmium concentrations (188), suggesting that cadmium may be a marker for both cigarette smoke and coal emissions. Furthermore, cadmium exposure was associated with lower birth weight in UGAAR participants, which suggests that cadmium exposure may play a role in the associations between $PM_{2.5}$ and social and behavioral development (188–190). However, adjustment for maternal blood cadmium had little effect on the estimated effect of $PM_{2.5}$ on SRS T-scores (Table B.7), suggesting that the association with $PM_{2.5}$ is not primarily acting through cadmium exposure.

My findings with SRS T-scores are not directly comparable with those of previous studies because I analyzed a continuous measure of ASD-related behaviors while other studies of similar outcomes reported binary ASD diagnosis. There is an important implication to using a continuous measure for ASD-related outcomes. At present the diagnosis of ASD is based on developmental screenings and clinical evaluation of psychometric assessments (191,192). The clinical relevance of a 1.8-unit increase in the mean SRS T-score may not be meaningful to an individual child, but an upward "shift" in the population distribution of autistic traits scores could potentially result in more children meeting the ASD diagnosis criteria, given that more than 90% of the world's population is breathing air with $PM_{2.5}$ concentrations that exceed the World Health Organization guidelines.

There is strong evidence suggesting that prenatal air pollution exposure increases the risk of social and behavioral problems in males in previous studies (52,56,193). My findings from the stratified analysis of the intervention on SRS-2 scores did not provide evidence of effect modification by sex (Table B.6).

The findings from this study revealed that the maternal HPA axis may have influenced the impact of the air cleaner intervention on children's social and behavioral development. It is observed that the benefits of HEPA air cleaner intervention were greatest for women who experienced HPA-axis dysregulation in early pregnancy. This is important because HPA-axis plays a critical role in stress regulation. Previous studies, which relied on self-reported measures of stress, are broadly consistent with my findings (36,194). The results indicate that addressing both maternal stress and reducing air pollution exposure during pregnancy may promote children's neurodevelopment.

To the best of my knowledge, UGAAR is the first to use of both the BASC and SRS assessments tools in the Mongolian population. As a result, I had no Mongolian reference population with which to standardize scores. I explored multiple approaches to scaling scores. I transformed the BASC and SRS raw score to have the same mean and variance as the US reference population, and then used the US reference distribution for the T-score conversion. I also scaled scores using the UGAAR distributions (i.e., used the UGAAR population as its own reference population), and the results from the two approaches were similar (Table B.4). The distribution of BASC and SRS scores from this study can potentially be useful for future studies of behavior in the Mongolian population.

I found a significant association between indoor $PM_{2.5}$ during pregnancy and BASC-3 scores when children were four years old. However, such an association was not observed for behavior scores at age two. The BASC was originally developed to assess behaviors that were challenging and disruptive in children aged 4-18 years, so it is possible that the assessment may have been less sensitive to the developmental changes that occurred at younger ages (195). Additionally, internalizing behaviors can be hard to assess in younger children compared to externalizing behaviors. Therefore in-home observational assessments may be more reliable for younger children (196,197).

Previous research studies have shown that HEPA filter air cleaners can reduce indoor PM (92,93,95). Many HEPA air cleaner interventions have shown improvements in blood pressure, markers of inflammation, oxidative stress (92,95). However, as noted in a systematic review, improvement in these intermediate health outcomes were more pronounced in studies conducted in Asian cities with relatively higher air pollution concentrations, where substantial absolute reductions in PM from the intervention were followed by improved health benefits (92). Most RCTs of HEPA air cleaners were conducted over a few hours to weeks to understand effects on health, but less is known about the long-term use of HEPA air filtration (92,93,95). Additionally, most RCTs of HEPA air cleaner interventions were conducted to evaluate changes in intermediate health outcomes, such as blood pressure and biomarkers, which are usually direct precursors of the clinical outcomes of interest (198). However, these indicators would not detect the changes in clinical health outcomes (95,198). Therefore, less is known on the HEPA air cleaner use on clinical outcomes.

While I did not observe a benefit of the intervention on social and behavioral outcomes, previous results from UGAAR indicate that the intervention was associated with a decreased risk of spontaneous abortion and an increased risk of PTB (116). The researchers speculated that "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." (116) The reduction in spontaneous abortion, and the increase in mean term birth weight, suggest that the HEPA cleaner intervention provided benefits in this population.

Air cleaners, such as HEPA filter air cleaners installed at heating, ventilation and air conditioning (HVAC) system, or portable HEPA cleaners can be a short-term cost-effective intervention for high risk population exposed to high levels of air pollution such as schools and senior homes (92,199–201). A meta-analysis that examined cost and the economic benefits found that the economic benefits of using air cleaners exceeded costs mainly due to mortality reductions associated with indoor PM exposure (92). For example, a modeling study indicated for elders who were exposed to wildfire smoke in Southern

California, the health benefits from installing enhanced filtration in central HVAC systems outweighed the costs (200). Another study estimates that using filters in the HVAC systems in homes of 22 US cities would reduce premature death between 0.002-2.5% which equal to annual economic benefits from $1 to $1348 per person (92). Therefore, in highly polluted settings, air cleaners can be a useful harm reduction strategy for reducing exposure to indoor air pollutants, especially for vulnerable populations such as the elderly, young children, pregnant women and people with chronic health problems. Governments and local health agencies should promote the use of air cleaners as a short-term measure to improve air quality (201–203). However, air cleaners should not replace the role of governments in reducing emissions at their sources (203,204).

The government of Mongolia and international organizations have attempted to mitigate air pollution in Ulaanbaatar through various initiatives, such as replacing traditional heating stoves with advanced models, reducing electricity costs, shifting to centralized heating stations, launching affordable housing projects, modernizing road and intersection designs, and substituting raw coal with processed briquettes (98,205,206). These efforts have had limited benefits. The stove replacement measure showed little success because many of the households sold the improved stoves to earn money rather than using them (207). Additionally, in contrast to traditional stoves, the improved stoves have smaller cook-top openings which is not convenient for cooking. In the initial preliminary testing of improved stoves conducted in 1997 through the World Bank's Energy Sector Management Assistance Programme, only 19 out of 40 households who were distributed the improved stoves were found to be using them two years after deployment (208). The city of Ulaanbaatar recently eliminated electricity fees at night (9 pm – 6 am) during the heating season to reduce coal use, but many residents in ger districts still used stoves for cooking and heating (209). The National Program for Reducing Air and Environmental Pollution (NPRAEP) established a goal of moving 20,000 ger households into apartments by 2019 through a special mortgage system. Only 10,287 households were moved into apartments between 2013-2020 (205). The United Nations Development Programme (UNDP) concluded that many of these air pollution reduction initiatives were not successful in substantially reducing air pollution in the city. This was

mainly due to failed political will to cooperate on air quality improvement policies between ministries, and a lack of accountability of sectors for these projects (210).

Recently, the city of Ulaanbaatar banned the use of raw coal in the city. Effective May 2019, Ulaanbaatar residents were permitted only to burn processed coal briquettes (206). There is anecdotal evidence that $PM_{2.5}$ concentrations were lower in 2020 and 2021, which the government attributed to the use of processed coal briquettes. However, these observations cannot disentangle the influence of SARS-CoV-2 pandemic-related behavior changes on pollution emissions (211,212).

5.3. Strengths and limitations

This research had several strengths. Despite a reasonably large environmental epidemiology literature on prenatal air pollution exposure and children's social and behavioral impairments, this study is the first to use an RCT design to evaluate the benefits of PM reductions on social and behavioral aspects of children's neurodevelopment.

In this study, I used a modeled indoor $PM_{2.5}$ exposure developed based on two-time 7-day indoor $PM_{2.5}$ measurements in each participant's home. The modeled $PM_{2.5}$ concentrations allowed me to assess participants' exposure to $PM_{2.5}$ in their homes. In contrast, most air pollution studies used outdoor $PM_{2.5}$ concentration as a proxy for exposure to PM. Furthermore, the observational analysis using the modeled indoor $PM_{2.5}$ concentration provided valuable insight in this trial.

Most previous RCTs of HEPA air cleaners were conducted over short durations to understand health effects. In contrast, the UGAAR trial was conducted over an extended period to assess the potential benefits for fetal growth and early childhood development of reducing exposure to PM throughout most of pregnancy. Therefore, this study advances our understanding of the health benefits from long-term use of HEPA air filter filtration.

Additionally, the study used a hair sample during pregnancy to quantify cortisol, DHEA, and cortisol/DHEA ratio as indicators of HPA axis functioning over a relatively

long time period. This objective measure of biological stress is a relatively novel approach in the field of environmental epidemiology.

This study also had several limitations that should be taken into consideration when interpreting the results. A key limitation was that, although the staff who administered and scored the BASC-3 and SRS-2 were blinded to the participants' group assignments, the participants were not blinded to their intervention status. This lack of blinding may have influenced the study in two ways. First, participants' awareness of their intervention status may have introduced information bias by influencing how they interpreted and reported their children's behavior. A meta-analysis of 1,346 trials revealed that estimates of intervention effects were exaggerated by ratio of odds ratios 0.75 (95% CI: 0.61, 0.93). This implies that non-blinded trials with subjective outcomes exaggerate intervention benefits as indicated by a ratio of odds ratios of less than one. However, the same meta-analysis found little evidence of bias in trials with objective outcomes, with ratios of odds ratios 1.01 (95% CI: 0.92, 1.10) (213). Secondly, the lack of blinding may have also led to selection bias. More participants from the control group dropped out from the study during pregnancy (12 vs 6) and during postnatal surveillance (31 vs 21). The differential loss to follow-up can introduce selection bias depending on the type of missing data. Missing not at random (MNAR) occurs when participants who completed the study differ on unobserved data from those who dropped out. On the other hand, missing at random (MAR) refers to missing data that is related to measured variables and this type of missing data can be accounted for during analysis. To account for missing data, I conducting ITT analysis using multiple imputation with chained equations. However, this approach assumes that missing data are MAR. It is not possible to distinguish between MAR and MNAR empirically for differential lost to follow-up because identifying MNAR data would require testing for systematic differences across unmeasured values (214,215).

These results may also have been influenced by the live birth bias, which is a challenge in studies of prenatal exposures and childhood health outcomes. In the UGAAR trial, PTB was more frequent in the intervention group compared to the control group. I crudely accounted for the live birth bias by adjusting for PTB. This adjustment accounts

for differences in PTB between groups but also blocks any effect of the intervention that is mediated by PTB. This adjustment had little influence on my effect estimates.

A recent publication from UGAAR investigators assessed the effects of live birth bias on birthweight and full-scale IQ (FSIQ) (169). Using multiple imputation methods, the authors simulated alternative scenarios in which pregnancy losses were instead born alive. The analysis suggested that if, for example, 100% of the pregnancy losses had instead been born alive but preterm, the estimated effects of the intervention on mean birth weight and FSIQ would have increased by 219% (from 26 grams to 83 grams) and 19% (from 2.7 points to 3.2 points), respectively (169). Birthweight was more sensitive to live birth bias than FSIQ because PTB is a stronger predictor of birth weight than FSIQ (169).

Although I demonstrated that the intervention reduced $PM_{2.5}$ in participants' homes, personal exposure to $PM_{2.5}$ was not measured in the UGAAR study. The impacts of this residential intervention would be attenuated by exposure encountered outside of the home such a workplace etc. Studies on HEPA air cleaner interventions have shown that a reduction in indoor $PM_{2.5}$ levels does not necessarily result in a corresponding reduction in personal $PM_{2.5}$ exposure (216,217). The UGAAR trials collected data on the average amount of time each participant spent at home during pregnancy. Stratified analysis of time spent at home did not show any evidence of effect modification on the relationship (116). However, the time activity data was self-reported and crudely assessed.

The indoor $PM_{2.5}$ prediction model was based on only two 7-day measurements per home. The model predictions may have introduced nondifferential exposure errors, which would likely bias effect estimates towards the null.

This study may have been underpowered to detect social and behavioral impairment outcomes due to its sample size, which was based on term birth weight. Furthermore, I ran many models and results were not corrected for multiple comparisons, so some associations between$PM_{2.5}$ and behaviors may be due to chance. Although the use of continuous outcome measures increased power, both BASC-3 and SRS-2 scores do not represent clinical diagnoses of specific behavioral impairments or ASD. These continuous social and behavioral outcome measurements have been used in some previous studies evaluating

prenatal PM exposure air pollution and autistic or behavioral impairments particularly looking at prenatal endocrine disrupting chemical exposures (42,47,53,56,218,219). The BASC-3 and SRS-2 assessment tools used in this study have several advantages over other psychometric tools used in research on early life exposure to air pollution and social and behavioral problems in childhood. For example, compared to the commonly used Child Behavior Checklist (CBCL), the BASC-3 includes adaptive skills ratings that encompass social communication and adaptability domains (167). However, one limitation to using the BASC-3 is its length; there are 134 questions in this version, which can be burdensome for participants. The SRS, on the other hand, has advantages compared to other tools in terms of its brevity and focus on autism spectrum traits (220).

Control participants may have benefitted from their participation in the study. These benefits would decrease the differences between treatment groups and cause an underestimation of the intervention's benefits (221,222). Future RCTs like UGAAR would benefit from a 3-arm design to evaluate intervention efficacy while testing for inclusion benefits among the placebo ("sham" filtration) group (222).

The results from UGAAR may not be generalizable to other populations and settings. This trial was conducted in a heavily polluted city where the primary source of $PM_{2.5}$ pollution is raw coal combustion. In addition, the study population was relatively racially and economically homogeneous. Therefore, the results from this study may not be directly extrapolated to other populations with different sources of $PM_{2.5}$ exposure with more diverse population.

Finally, potential challenges of using not clinical assessments designed for one cultural context in another cultural context may represent another important limitation to this study. It is possible that careful translations of the BASC and SRS assessments from English into Mongolian may not have fully accounted for all the cultural nuances and differences in language used to describe behaviors. For example, we observed the mean and variance of hyperactivity, aggression, anxiety and depression raw scores to be similar between UGAAR and the reference population, while the mean and variance of functional

communication, social skills and atypicality raw scores were different (Table A.1). Therefore, these results should be interpreted with caution.

5.4. Future research needs

Several gaps remain in our understanding of the relationship between prenatal air pollution exposure and children's social and behavioral impairments.

The disagreement between the ITT results and the $PM_{2.5}$ effect estimates suggest that the results from the ITT analysis may have been biased. Therefore, future RCTs should address some of the limitations of UGAAR. For example, a three-arm RCT would allow for quantification of the "inclusion benefit," which may lead to an underestimate of an intervention's effect (223).

Blinding both the assessors and the participants to group assignment is particularly important with subjective health measures such as self-reported symptoms or parent rating scales (224). In pharmaceutical trials, blinding is usually achieved by placebo. Environmental intervention trials of HEPA filter air cleaners sometimes use "sham filters" as a placebo (225,226). However, in trials evaluating other environmental interventions blinding can be difficult or impossible. Out of the 27 environmental health RCTs that I have reviewed, only eight studies were double blinded (Table D.2).

An important question that remains is the role of folate consumption during pregnancy in the relationship between $PM_{2.5}$ and social and behavioral outcomes. An increasing amount of evidence suggests that the effect of prenatal air pollution exposure on children's neurodevelopment is modified by maternal folate consumption during pregnancy (77,86). In future studies, quantifying the folate level in maternal blood samples would be valuable.

It would also be useful for future intervention studies to measure both residential and personal $PM_{2.5}$ exposure to assess the impact of the intervention on exposure more precisely. This would provide a clearer understanding of the effect of the intervention on

actual $PM_{2.5}$ exposure and the potential health benefits that could result from such exposure reductions.

Despite the cost, it is important to design a 3-arm trial to measure inclusion benefits in the placebo group. This is useful for estimating the true intervention effects from the trial. Additionally, objective measurement of HEPA air cleaner use would also be useful. Logging the time that the air cleaners are used would provide additional information for evaluating and interpreting effectiveness. In the UGAAR trial, air cleaners were set with an internal timer that counted total hours of use, however the timer only logged after the user pressed specific buttons when starting the air cleaners. The complexity of this procedure resulted in incomplete logged data (112). In the UGAAR study, HEPA air cleaner effectiveness decreased over time, potentially due to the filters becoming overloaded (112). Therefore, for optimum effectiveness of HEPA filters air cleaners, studies should consider periodic maintenance of the air cleaners and filter replacement.

Finally, it is important to situate any future air cleaners studies in the broader literature on accountability research (227). In this study, I evaluated how a household-level intervention would benefit social and behavioral outcomes. However, there is also tremendous need to evaluate the impacts of regulatory policies implemented during last twenty years and the corresponding health improvement in children in Ulaanbaatar. It is essential to assess and ensure that past and future regulatory policies achieve the intended public health benefits (228). The coal banning in Irish cities provides an example of assessing the temporary regulatory intervention on mortality outcomes. This accountability study would be very useful in Ulaanbaatar. Researcher took advantage of the many years of longitudinal data to evaluate whether coal banning regulatory policies implemented at the national or state level between 1990 to 1996 in Dublin reduced outdoor air pollution and reduced death rates in the city (229). The findings provided evidence that decreases in $PM_{2.5}$ and other pollutants were associated with reduced mortality rate. Developing similar accountability studies in Ulaanbaatar would be very useful in quantifying the benefits of air quality policy changes.

5.5. Conclusions

The main objectives of this research were to investigate the causal association of PM exposure during pregnancy with children's behavioral problems and autistic traits, as well as the influence of maternal stress on PM-behavior relationships. While the results indicate that reducing indoor PM during pregnancy had little effect on children's social and behavioral development, I observed a significant increase in the mean SRS-2 total T-score and the mean BASC-3 scores in the observational analysis. Although the changes in these scores may be small at the individual level, they can have important implications at the population level, given the ubiquity of air pollution. My findings also revealed that the maternal HPA axis may have influenced the relationship between the air cleaner intervention and children's social and behavioral development, emphasizing the importance of addressing both environmental and psychosocial stress in efforts to promote children's neurodevelopment.

Many questions remain regarding the relationship between air pollution and children social and behavioral development. Given that the observational component revealed stronger associations than the primary ITT analysis, future RCTs should address some of the shortcomings of UGAAR.

HEPA filter air cleaners may be useful for reducing air pollution and its health impacts, but air cleaners are not a long-term solution. Rather, air cleaners should be used as a complementary measure alongside efforts to reduce air pollution at the source. Mitigating air pollution will require a comprehensive approach, which involves multiple strategies and interventions at different levels, such as policy and regulation, technology improvements, and behavior change.

References

1. Health Effects Institute. State of Global Air 2020 [Internet]. [cited 2023 Mar 28]. Available from: https://www.stateofglobalair.org/

2. World Health Organization [Internet]. 2021 [cited 2022 Jan 3]. Ambient air pollution. Available from: https://www.who.int/news-room/fact-sheets/detail/ambient-(outdoor)-air-quality-and-health

3. Sun X, Luo X, Zhao C, Zhang B, Tao J, Yang Z, et al. The associations between birth weight and exposure to fine particulate matter (PM2.5) and its chemical constituents during pregnancy: A meta-analysis. Environmental Pollution. 2016 Apr;211:38–47.

4. Gluckman PD. Living with the Past: Evolution, Development, and Patterns of Disease. Science. 2004 Sep 17;305(5691):1733–6.

5. Hall JG. Review and hypothesis: Syndromes with severe intrauterine growth restriction and very short stature-Are they related to the epigenetic mechanism(s) of fetal survival involved in the developmental origins of adult health and disease? Am J Med Genet. 2010 Feb;152A(2):512–27.

6. Eriksson JG. The fetal origins hypothesis—10 years on. BMJ. 2005 May 14;330(7500):1096–7.

7. Barn P. 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 [Internet]. Simon Fraser University; 2018. Available from: https://theses.lib.sfu.ca/file/thesis/4981

8. Sunyer J, Dadvand P. Pre-natal brain development as a target for urban air pollution. Basic Clin Pharmacol Toxicol. 2019 Aug;125(S3):81–8.

9. Ha S. Air pollution and neurological development in children. Dev Med Child Neurol. 2021 Apr;63(4):374–81.

10. Centers for Disease Control and Prevention (CDC). Increasing prevalence of parent-reported attention-deficit/hyperactivity disorder among children --- United States, 2003 and 2007. MMWR Morb Mortal Wkly Rep. 2010 Nov 12;59(44):1439–43.

11. U.S. Environmental Protection Agency. America's Children and the Environment. In: 3rd ed. Available from: https://www.epa.gov/sites/default/files/2015-10/documents/ace3_neurodevelopmental.pdf

12. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders [Internet]. Fifth Edition. American Psychiatric Association; 2013 [cited

2022 May 14]. Available from: https://psychiatryonline.org/doi/book/10.1176/appi.books.9780890425596

13. Feigin VL, Nichols E, Alam T, Bannick MS, Beghi E, Blake N, et al. Global, regional, and national burden of neurological disorders, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet Neurology. 2019 May;18(5):459–80.

14. Lein PJ. Overview of the Role of Environmental Factors in Neurodevelopmental Disorders. In: Environmental Factors in Neurodevelopmental and Neurodegenerative Disorders [Internet]. Elsevier; 2015 [cited 2021 Sep 21]. p. 3–20. Available from: https://linkinghub.elsevier.com/retrieve/pii/B9780128002285000017

15. Hallmayer J. Genetic Heritability and Shared Environmental Factors Among Twin Pairs With Autism. Arch Gen Psychiatry. 2011 Nov 1;68(11):1095.

16. Cohen AJ, Brauer M, Burnett R, Anderson HR, Frostad J, Estep K, et al. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. The Lancet. 2017 May;389(10082):1907–18.

17. Fordyce TA, Leonhard MJ, Chang ET. A critical review of developmental exposure to particulate matter, autism spectrum disorder, and attention deficit hyperactivity disorder. Journal of Environmental Science and Health, Part A. 2018 Jan 28;53(2):174–204.

18. Myhre O, Låg M, Villanger GD, Oftedal B, Øvrevik J, Holme JA, et al. Early life exposure to air pollution particulate matter (PM) as risk factor for attention deficit/hyperactivity disorder (ADHD): Need for novel strategies for mechanisms and causalities. Toxicology and Applied Pharmacology. 2018 Sep;354:196–214.

19. Ogundele MO. Behavioural and emotional disorders in childhood: A brief overview for paediatricians. World Journal of Clinical Pediatrics. 2018 Feb 8;7(1):9–26.

20. American's children and the Environment. epa.gov. Neurodevelopment disorders. Available from: https://www.epa.gov/sites/default/files/2015-10/documents/ace3_neurodevelopmental.pdf

21. Center for Disease Control and Prevention. Attention-Deficit/Hyperactivity Disorder (ADHD). prevelance of ADHD. Available from: https://www.cdc.gov/ncbddd/adhd/features/national-prevalence-adhd-and-treatment.html

22. CADDAC. Centre for ADHD Awareness, Canada. About ADHD. Available from: https://caddac.ca/about-adhd/#:~:text=Attention%20Deficit%20Hyperactivity%20Disorder%20(ADHD,the%20country%20has%20the%20disorder.

23. Matos MB, Bara TS, Cordeiro ML. Autism Spectrum Disorder Diagnoses: A Comparison of Countries with Different Income Levels. CLEP. 2022 Aug;Volume 14:959–69.

24. Zindaa. news.zindaa.mn. Registered number of children with Autistm has increased 9 folds. Available from: https://news.zindaa.mn/2oel

25. Church JS, Tijerina PB, Emerson FJ, Coburn MA, Blum JL, Zelikoff JT, et al. Perinatal exposure to concentrated ambient particulates results in autism-like behavioral deficits in adult mice. NeuroToxicology. 2018 Mar;65:231–40.

26. Block ML, Elder A, Auten RL, Bilbo SD, Chen H, Chen JC, et al. The outdoor air pollution and brain health workshop. NeuroToxicology. 2012 Oct;33(5):972–84.

27. Block ML, Calderón-Garcidueñas L. Air pollution: mechanisms of neuroinflammation and CNS disease. Trends in Neurosciences. 2009 Sep;32(9):506–16.

28. Weitekamp CA, Hofmann HA. Effects of air pollution exposure on social behavior: a synthesis and call for research. Environ Health. 2021 Dec;20(1):72.

29. Ha S, Yeung E, Bell E, Insaf T, Ghassabian A, Bell G, et al. Prenatal and early life exposures to ambient air pollution and development. Environmental Research. 2019 Jul;174:170–5.

30. Bové H, Bongaerts E, Slenders E, Bijnens EM, Saenen ND, Gyselaers W, et al. Ambient black carbon particles reach the fetal side of human placenta. Nat Commun. 2019 Dec;10(1):3866.

31. Kundakovic M, Jaric I. The Epigenetic Link between Prenatal Adverse Environments and Neurodevelopmental Disorders. Genes. 2017 Mar 18;8(3):104.

32. Janssen BG, Byun HM, Gyselaers W, Lefebvre W, Baccarelli AA, Nawrot TS. Placental mitochondrial methylation and exposure to airborne particulate matter in the early life environment: An ENVIR *ON* AGE birth cohort study. Epigenetics. 2015 Jun 3;10(6):536–44.

33. Saenen ND, Martens DS, Neven KY, Alfano R, Bové H, Janssen BG, et al. Air pollution-induced placental alterations: an interplay of oxidative stress, epigenetics, and the aging phenotype? Clin Epigenet. 2019 Dec;11(1):124.

34. Mortamais M, Pujol J, Martínez-Vilavella G, Fenoll R, Reynes C, Sabatier R, et al. Effects of prenatal exposure to particulate matter air pollution on corpus callosum and behavioral problems in children. Environmental Research. 2019 Nov;178:108734.

35. Luders E, Kurth F, Das D, Oyarce DE, Shaw ME, Sachdev P, et al. Associations between corpus callosum size and ADHD symptoms in older adults: The PATH through life study. Psychiatry Research: Neuroimaging. 2016 Oct;256:8–14.

36. Perera FP, Tang D, Wang S, Vishnevetsky J, Zhang B, Diaz D, et al. Prenatal Polycyclic Aromatic Hydrocarbon (PAH) Exposure and Child Behavior at Age 6–7 Years. Environmental Health Perspectives. 2012 Jun;120(6):921–6.

37. Rauh VA, Margolis AE. Research Review: Environmental exposures, neurodevelopment, and child mental health - new paradigms for the study of brain and behavioral effects. J Child Psychol Psychiatr. 2016 Jul;57(7):775–93.

38. Peterson BS, Rauh VA, Bansal R, Hao X, Toth Z, Nati G, et al. Effects of Prenatal Exposure to Air Pollutants (Polycyclic Aromatic Hydrocarbons) on the Development of Brain White Matter, Cognition, and Behavior in Later Childhood. JAMA Psychiatry. 2015 Jun 1;72(6):531.

39. Newman NC, Ryan P, LeMasters G, Levin L, Bernstein D, Hershey GKK, et al. Traffic-Related Air Pollution Exposure in the First Year of Life and Behavioral Scores at 7 Years of Age. Environmental Health Perspectives. 2013 Jun;121(6):731–6.

40. Harris MH, Gold DR, Rifas-Shiman SL, Melly SJ, Zanobetti A, Coull BA, et al. Prenatal and childhood traffic-related air pollution exposure and childhood executive function and behavior. Neurotoxicology and Teratology. 2016 Sep;57:60–70.

41. Jorcano A, Lubczyńska MJ, Pierotti L, Altug H, Ballester F, Cesaroni G, et al. Prenatal and postnatal exposure to air pollution and emotional and aggressive symptoms in children from 8 European birth cohorts. Environment International. 2019 Oct;131:104927.

42. McGuinn LA, Bellinger DC, Colicino E, Coull BA, Just AC, Kloog I, et al. Prenatal PM2.5 exposure and behavioral development in children from Mexico City. NeuroToxicology. 2020 Dec;81:109–15.

43. Loftus CT, Ni Y, Szpiro AA, Hazlehurst MF, Tylavsky FA, Bush NR, et al. Exposure to ambient air pollution and early childhood behavior: A longitudinal cohort study. Environmental Research. 2020 Apr;183:109075.

44. Morales-Suárez-Varela M, Peraita-Costa I, Llopis- González A. Systematic review of the association between particulate matter exposure and autism spectrum disorders. Environmental Research. 2017 Feb;153:150–60.

45. Imbriani G, Panico A, Grassi T, Idolo A, Serio F, Bagordo F, et al. Early-Life Exposure to Environmental Air Pollution and Autism Spectrum Disorder: A Review of Available Evidence. IJERPH. 2021 Jan 29;18(3):1204.

46. Chun H, Leung C, Wen SW, McDonald J, Shin HH. Maternal exposure to air pollution and risk of autism in children: A systematic review and meta-analysis. Environmental Pollution. 2020 Jan;256:113307.

47. Liu H, Ding L, Qu G, Guo X, Liang M, Ma S, et al. Particulate matter exposure during pregnancy and infancy and risks of autism spectrum disorder in children: A systematic review and meta-analysis. Science of The Total Environment. 2023 Jan;855:158830.

48. U.S. Environmental Protection Agency. The total exposure assessment methodology (TEAM) study: Summary and analysis [Internet]. Washingto, DC; 1987. Available from: EPA/600/6-87/002a

49. Rice D, Barone S. Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. Environmental Health Perspectives. 2000 Jun;108(suppl 3):511–33.

50. Suades-González E, Gascon M, Guxens M, Sunyer J. Air Pollution and Neuropsychological Development: A Review of the Latest Evidence. Endocrinology. 2015 Oct 1;156(10):3473–82.

51. Flores-Pajot MC, Ofner M, Do MT, Lavigne E, Villeneuve PJ. Childhood autism spectrum disorders and exposure to nitrogen dioxide, and particulate matter air pollution: A review and meta-analysis. Environmental Research. 2016 Nov;151:763–76.

52. Rahman MM, Shu YH, Chow T, Lurmann FW, Yu X, Martinez MP, et al. Prenatal Exposure to Air Pollution and Autism Spectrum Disorder: Sensitive Windows of Exposure and Sex Differences. Environ Health Perspect. 2022 Jan;130(1):017008.

53. Raz R, Roberts AL, Lyall K, Hart JE, Just AC, Laden F, et al. Autism Spectrum Disorder and Particulate Matter Air Pollution before, during, and after Pregnancy: A Nested Case–Control Analysis within the Nurses' Health Study II Cohort. Environmental Health Perspectives. 2015 Mar;123(3):264–70.

54. Volk HE, Lurmann F, Penfold B, Hertz-Picciotto I, McConnell R. Traffic-Related Air Pollution, Particulate Matter, and Autism. JAMA Psychiatry. 2013 Jan 1;70(1):71.

55. Chen B, Huang S, He J, He Q, Chen S, Liu X, et al. Sex-specific influence of prenatal air pollutant exposure on neonatal neurobehavioral development and the sensitive window. Chemosphere. 2020 Sep;254:126824.

56. Guxens M, Ghassabian A, Gong T, Garcia-Esteban R, Porta D, Giorgis-Allemand L, et al. Air Pollution Exposure during Pregnancy and Childhood Autistic Traits in Four European Population-Based Cohort Studies: The ESCAPE Project. Environ Health Perspect. 2016 Jan;124(1):133–40.

57. Talbott EO, Arena VC, Rager JR, Clougherty JE, Michanowicz DR, Sharma RK, et al. Fine particulate matter and the risk of autism spectrum disorder. Environmental Research. 2015 Jul;140:414–20.

58. Becerra TA, Wilhelm M, Olsen J, Cockburn M, Ritz B. Ambient Air Pollution and Autism in Los Angeles County, California. Environmental Health Perspectives. 2013 Mar;121(3):380–6.

59. Gong T, Dalman C, Wicks S, Dal H, Magnusson C, Lundholm C, et al. Perinatal Exposure to Traffic-Related Air Pollution and Autism Spectrum Disorders. Environmental Health Perspectives. 2017 Jan;125(1):119–26.

60. Clayton JA, Collins FS. Policy: NIH to balance sex in cell and animal studies. Nature. 2014 May 15;509(7500):282–3.

61. Cole TB, Coburn J, Dao K, Roqué P, Chang YC, Kalia V, et al. Sex and genetic differences in the effects of acute diesel exhaust exposure on inflammation and oxidative stress in mouse brain. Toxicology. 2016 Dec;374:1–9.

62. Roqué PJ, Dao K, Costa LG. Microglia mediate diesel exhaust particle-induced cerebellar neuronal toxicity through neuroinflammatory mechanisms. NeuroToxicology. 2016 Sep;56:204–14.

63. Bolton JL, Marinero S, Hassanzadeh T, Natesan D, Le D, Belliveau C, et al. Gestational Exposure to Air Pollution Alters Cortical Volume, Microglial Morphology, and Microglia-Neuron Interactions in a Sex-Specific Manner. Front Synaptic Neurosci. 2017 May 31;9:10.

64. Hammond TR, Robinton D, Stevens B. Microglia and the Brain: Complementary Partners in Development and Disease. Annu Rev Cell Dev Biol. 2018 Oct 6;34(1):523–44.

65. Lenz KM, McCarthy MM. A Starring Role for Microglia in Brain Sex Differences. Neuroscientist. 2015 Jun;21(3):306–21.

66. Yu X, Rahman MM, Wang Z, Carter SA, Schwartz J, Chen Z, et al. Evidence of susceptibility to autism risks associated with early life ambient air pollution: A systematic review. Environmental Research. 2022 May;208:112590.

67. Jo H, Eckel SP, Wang X, Chen JC, Cockburn M, Martinez MP, et al. Sex-specific associations of autism spectrum disorder with residential air pollution exposure in a large Southern California pregnancy cohort. Environmental Pollution. 2019 Nov;254:113010.

68. Madigan S, Oatley H, Racine N, Fearon RMP, Schumacher L, Akbari E, et al. A Meta-Analysis of Maternal Prenatal Depression and Anxiety on Child Socioemotional Development. Journal of the American Academy of Child & Adolescent Psychiatry. 2018 Sep;57(9):645-657.e8.

69. Entringer S, Buss C, Wadhwa PD. Prenatal stress, development, health and disease risk: A psychobiological perspective—2015 Curt Richter Award Paper. Psychoneuroendocrinology. 2015 Dec;62:366–75.

70. Vänskä M, Punamäki RL, Tolvanen A, Lindblom J, Flykt M, Unkila-Kallio L, et al. Maternal pre- and postnatal mental health trajectories and child mental health and development: Prospective study in a normative and formerly infertile sample. International Journal of Behavioral Development. 2011 Nov;35(6):517–31.

71. Shallie PD, Naicker T. The placenta as a window to the brain: A review on the role of placental markers in prenatal programming of neurodevelopment. Int j dev neurosci. 2019 Apr;73(1):41–9.

72. Erickson NL, Gartstein MA, Dotson JAW. Review of Prenatal Maternal Mental Health and the Development of Infant Temperament. Journal of Obstetric, Gynecologic & Neonatal Nursing. 2017 Jul;46(4):588–600.

73. Cowell WJ, Bellinger DC, Coull BA, Gennings C, Wright RO, Wright RJ. Associations between Prenatal Exposure to Black Carbon and Memory Domains in Urban Children: Modification by Sex and Prenatal Stress. Chen A, editor. PLoS ONE. 2015 Nov 6;10(11):e0142492.

74. Perera FP, Wheelock K, Wang Y, Tang D, Margolis AE, Badia G, et al. Combined effects of prenatal exposure to polycyclic aromatic hydrocarbons and material hardship on child ADHD behavior problems. Environmental Research. 2018 Jan;160:506–13.

75. Perera FP, Wang S, Rauh V, Zhou H, Stigter L, Camann D, et al. Prenatal Exposure to Air Pollution, Maternal Psychological Distress, and Child Behavior. Pediatrics. 2013 Nov;132(5):e1284–94.

76. Weisskopf MG, Kioumourtzoglou MA, Roberts AL. Air Pollution and Autism Spectrum Disorders: Causal or Confounded? Curr Envir Health Rpt. 2015 Dec;2(4):430–9.

77. Loftus CT, Hazlehurst MF, Szpiro AA, Ni Y, Tylavsky FA, Bush NR, et al. Prenatal air pollution and childhood IQ: Preliminary evidence of effect modification by folate. Environmental Research. 2019 Sep;176:108505.

78. Munoz-Pizza DM, Villada-Canela M, Reyna MA, Texcalac-Sangrador JL, Osornio-Vargas ÁR. Air pollution and children's respiratory health: a scoping review of socioeconomic status as an effect modifier. Int J Public Health. 2020 Jun;65(5):649–60.

79. Lynch JW. Income inequality and mortality: importance to health of individual income, psychosocial environment, or material conditions. BMJ. 2000 Apr 29;320(7243):1200–4.

80. McGuinn LA, Windham GC, Messer LC, Di Q, Schwartz J, Croen LA, et al. Air pollution, neighborhood deprivation, and autism spectrum disorder in the Study to Explore Early Development. Environmental Epidemiology. 2019 Oct;3(5):e067.

81. Dickerson AS, Rahbar MH, Bakian AV, Bilder DA, Harrington RA, Pettygrove S, et al. Autism spectrum disorder prevalence and associations with air concentrations of lead, mercury, and arsenic. Environ Monit Assess. 2016 Jul;188(7):407.

82. Gao Y, Sheng C, Xie R hua, Sun W, Asztalos E, Moddemann D, et al. New Perspective on Impact of Folic Acid Supplementation during Pregnancy on Neurodevelopment/Autism in the Offspring Children – A Systematic Review. Rosenfeld CS, editor. PLoS ONE. 2016 Nov 22;11(11):e0165626.

83. Keats EC, Oh C, Chau T, Khalifa DS, Imdad A, Bhutta ZA. Effects of vitamin and mineral supplementation during pregnancy on maternal, birth, child health and development outcomes in low- and middle-income countries: A systematic review. Campbell Systematic Reviews [Internet]. 2021 Jun [cited 2023 Mar 28];17(2). Available from: https://onlinelibrary.wiley.com/doi/10.1002/cl2.1127

84. Gardiki-Kouidou P, Seller MJ. Amniotic fluid folate, vitamin B12 and transcobalamins in neural tube defects. Clinical Genetics. 2008 Jun 28;33(6):441–8.

85. Baccarelli A, Wright RO, Bollati V, Tarantini L, Litonjua AA, Suh HH, et al. Rapid DNA Methylation Changes after Exposure to Traffic Particles. Am J Respir Crit Care Med. 2009 Apr;179(7):572–8.

86. Goodrich AJ, Volk HE, Tancredi DJ, McConnell R, Lurmann FW, Hansen RL, et al. Joint effects of prenatal air pollutant exposure and maternal folic acid supplementation on risk of autism spectrum disorder: Prenatal folic acid, air pollution, and ASD. Autism Research. 2018 Jan;11(1):69–80.

87. Bragg M, Chavarro JE, Hamra GB, Hart JE, Tabb LP, Weisskopf MG, et al. Prenatal Diet as a Modifier of Environmental Risk Factors for Autism and Related Neurodevelopmental Outcomes. Curr Envir Health Rpt [Internet]. 2022 Mar 19 [cited 2022 Mar 28]; Available from: https://link.springer.com/10.1007/s40572-022-00347-7

88. Finkel T, Holbrook NJ. Oxidants, oxidative stress and the biology of ageing. Nature. 2000 Nov;408(6809):239–47.

89. Sasaki H, Hamatani T, Kamijo S, Iwai M, Kobanawa M, Ogawa S, et al. Impact of Oxidative Stress on Age-Associated Decline in Oocyte Developmental Competence. Front Endocrinol. 2019 Nov 22;10:811.

90. Han Y, Jiang P, Dong T, Ding X, Chen T, Villanger GD, et al. Maternal air pollution exposure and preterm birth in Wuxi, China: Effect modification by maternal age. Ecotoxicology and Environmental Safety. 2018 Aug;157:457–62.

91. United States Environmental Protection Agency. Indoor Air Quality. [cited 2023 Mar 30]. What is a HEPA filter? Available from: https://www.epa.gov/indoor-air-quality-iaq/what-hepa-filter

92. Kelly FJ, Fussell JC. Improving indoor air quality, health and performance within environments where people live, travel, learn and work. Atmospheric Environment. 2019 Mar;200:90–109.

93. Allen RW, Barn P. Individual- and Household-Level Interventions to Reduce Air Pollution Exposures and Health Risks: a Review of the Recent Literature. Curr Envir Health Rpt. 2020 Dec;7(4):424–40.

94. Leech JA, Nelson WC, Burnett RT, Aaron S, Raizenne ME. It's about time: A comparison of Canadian and American time–activity patterns. J Expo Sci Environ Epidemiol. 2002 Nov 1;12(6):427–32.

95. Liu S, Wu R, Zhu Y, Wang T, Fang J, Xie Y, et al. The effect of using personal-level indoor air cleaners and respirators on biomarkers of cardiorespiratory health: a systematic review. Environment International. 2022 Jan;158:106981.

96. Allen RW, Barn PK, Lanphear BP. Randomized Controlled Trials in Environmental Health Research: Unethical or Underutilized? PLoS Medicine. 2015 Jan 6;12(1):e1001775.

97. IqAir. air quality [Internet]. Available from: https://www.iqair.com/us/mongolia

98. Hill LD, Edwards R, Turner JR, Argo YD, Olkhanud PB, Odsuren M, et al. Health assessment of future PM2.5 exposures from indoor, outdoor, and secondhand tobacco smoke concentrations under alternative policy pathways in Ulaanbaatar, Mongolia. Coulombe RA, editor. PLOS ONE. 2017 Oct 31;12(10):e0186834.

99. Guttikunda SK, Lodoysamba S, Bulgansaikhan B, Dashdondog B. Particulate pollution in Ulaanbaatar, Mongolia. Air Quality, Atmosphere & Health. 2013 Sep;6(3):589–601.

100. World Bank. Air Quality Analysis of Ulaanbaatar: Improving Air Quality to Reduce Health Impacts [Internet]. World Bank; 2011 [cited 2020 Nov 23]. Available from: http://elibrary.worldbank.org/doi/book/10.1596/26802

101. Allen RW, Gombojav E, Barkhasragchaa B, Byambaa T, Lkhasuren O, Amram O, et al. An assessment of air pollution and its attributable mortality in Ulaanbaatar, Mongolia. Air Quality, Atmosphere & Health. 2013 Mar;6(1):137–50.

102. Li C, Yang M, Zhu Z, Sun S, Zhang Q, Cao J, et al. Maternal exposure to air pollution and the risk of low birth weight: A meta-analysis of cohort studies. Environmental Research. 2020 Nov;190:109970.

103. Klocke C, Allen JL, Sobolewski M, Mayer-Pröschel M, Blum JL, Lauterstein D, et al. Neuropathological Consequences of Gestational Exposure to Concentrated Ambient Fine and Ultrafine Particles in the Mouse. Toxicological Sciences. 2017 Jan 13;kfx010.

104. Suades-González E, Gascon M, Guxens M, Sunyer J. Air Pollution and Neuropsychological Development: A Review of the Latest Evidence. Endocrinology. 2015 Oct 1;156(10):3473–82.

105. Harris MH, Gold DR, Rifas-Shiman SL, Melly SJ, Zanobetti A, Coull BA, et al. Prenatal and childhood traffic-related air pollution exposure and childhood executive function and behavior. Neurotoxicology and Teratology. 2016 Sep;57:60–70.

106. Yorifuji T, Kashima S, Diez MH, Kado Y, Sanada S, Doi H. Prenatal exposure to outdoor air pollution and child behavioral problems at school age in Japan. Environment International. 2017 Feb;99:192–8.

107. Calderón-Garcidueñas L, Engle R, Mora-Tiscareño A, Styner M, Gómez-Garza G, Zhu H, et al. Exposure to severe urban air pollution influences cognitive outcomes, brain volume and systemic inflammation in clinically healthy children. Brain and Cognition. 2011 Dec;77(3):345–55.

108. Chang YC, Cole TB, Costa LG. Prenatal and early-life diesel exhaust exposure causes autism-like behavioral changes in mice. Particle and Fibre Toxicology [Internet]. 2018 Dec [cited 2020 Oct 16];15(1). Available from: https://particleandfibretoxicology.biomedcentral.com/articles/10.1186/s12989-018-0254-4

109. Allen RW, Barn P. Individual- and Household-Level Interventions to Reduce Air Pollution Exposures and Health Risks: a Review of the Recent Literature. Curr Envir Health Rpt. 2020 Dec;7(4):424–40.

110. Azimi P, Stephens B. A framework for estimating the US mortality burden of fine particulate matter exposure attributable to indoor and outdoor microenvironments. J Expo Sci Environ Epidemiol. 2020 Mar;30(2):271–84.

111. Yun X, Shen G, Shen H, Meng W, Chen Y, Xu H, et al. Residential solid fuel emissions contribute significantly to air pollution and associated health impacts in China. Sci Adv. 2020 Oct;6(44):eaba7621.

112. Barn P, Gombojav E, Ochir C, Laagan B, Beejin B, Naidan G, et al. The effect of portable HEPA filter air cleaners on indoor PM2.5 concentrations and second hand tobacco smoke exposure among pregnant women in Ulaanbaatar, Mongolia: The UGAAR randomized controlled trial. Science of The Total Environment. 2018 Feb;615:1379–89.

113. Cohen S, Kamarck T, Mermelstein R. A Global Measure of Perceived Stress. Journal of Health and Social Behavior. 1983 Dec;24(4):385.

114. Palmer CD, Lewis ME, Geraghty CM, Barbosa F, Parsons PJ. Determination of lead, cadmium and mercury in blood for assessment of environmental exposure: A comparison between inductively coupled plasma–mass spectrometry and atomic absorption spectrometry. Spectrochimica Acta Part B: Atomic Spectroscopy. 2006 Aug;61(8):980–90.

115. Yuchi W, Gombojav E, Boldbaatar B, Galsuren J, Enkhmaa S, Beejin B, et al. Evaluation of random forest regression and multiple linear regression for predicting indoor fine particulate matter concentrations in a highly polluted city. Environmental Pollution. 2019 Feb 1;245:746–53.

116. Barn P, Gombojav E, Ochir C, Boldbaatar B, Beejin B, Naidan G, et al. The effect of portable HEPA filter air cleaner use during pregnancy on fetal growth: The UGAAR randomized controlled trial. Environment International. 2018 Dec;121:981–9.

117. Bradley RH. The Home Inventory: Review and Reflections. In: Advances in Child Development and Behavior [Internet]. Elsevier; 1994 [cited 2020 Nov 14]. p. 241–88. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0065240708600543

118. Beck AT, Steer RA, Brown G. Beck Depression Inventory–II [Internet]. American Psychological Association; 2011 [cited 2021 Jan 21]. Available from: http://doi.apa.org/getdoi.cfm?doi=10.1037/t00742-000

119. Adams J, Barone S, LaMantia A, Philen R, Rice DC, Spear L, et al. Workshop to identify critical windows of exposure for children's health: neurobehavioral work group summary. Environmental Health Perspectives. 2000 Jun;108(suppl 3):535–44.

120. Chiu YHM, Hsu HHL, Coull BA, Bellinger DC, Kloog I, Schwartz J, et al. Prenatal particulate air pollution and neurodevelopment in urban children: Examining sensitive windows and sex-specific associations. Environment International. 2016 Feb;87:56–65.

121. State of Global Air 2020. Health Effects Institute. 2020;28.

122. Bellinger DC. A Strategy for Comparing the Contributions of Environmental Chemicals and Other Risk Factors to Neurodevelopment of Children. Environmental Health Perspectives. 2012 Apr;120(4):501–7.

123. Raz R, Kioumourtzoglou MA, Weisskopf MG. Live-Birth Bias and Observed Associations Between Air Pollution and Autism. American Journal of Epidemiology. 2018 Nov 1;187(11):2292–6.

124. Tan TX, Yi Z, Li Z, Cheng K, Li J. Comparing Chinese youth with American youth on adjustment: An illustration of measurement issues in CROSS-CULTURAL research. Int J Psychol. 2020 Jun 14;ijop.12693.

125. Klocke C, Allen JL, Sobolewski M, Mayer-Pröschel M, Blum JL, Lauterstein D, et al. Neuropathological Consequences of Gestational Exposure to Concentrated Ambient Fine and Ultrafine Particles in the Mouse. Toxicological Sciences. 2017 Jan 13;kfx010.

126. Li C, Yang M, Zhu Z, Sun S, Zhang Q, Cao J, et al. Maternal exposure to air pollution and the risk of low birth weight: A meta-analysis of cohort studies. Environmental Research. 2020 Nov;190:109970.

127. Sun X, Luo X, Zhao C, Zhang B, Tao J, Yang Z, et al. The associations between birth weight and exposure to fine particulate matter (PM2.5) and its chemical constituents during pregnancy: A meta-analysis. Environmental Pollution. 2016 Apr;211:38–47.

128. Imbriani G, Panico A, Grassi T, Idolo A, Serio F, Bagordo F, et al. Early-Life Exposure to Environmental Air Pollution and Autism Spectrum Disorder: A Review of Available Evidence. IJERPH. 2021 Jan 29;18(3):1204.

129. Enkhbat U, Gombojav E, Banzrai C, Batsukh S, Boldbaatar B, Enkhtuya E, et al. Portable HEPA filter air cleaner use during pregnancy and children's behavior problem scores: a secondary analysis of the UGAAR randomized controlled trial. Environ Health. 2021 Dec;20(1):78.

130. Tamana SK, Gombojav E, Kanlic A, Banzrai C, Batsukh S, Enkhtuya E, et al. Portable HEPA filter air cleaner use during pregnancy and children's body mass index at two years of age: The UGAAR randomized controlled trial. Environment International. 2021 Nov;156:106728.

131. Ulziikhuu B, Gombojav E, Banzrai C, Batsukh S, Boldbaatar B, Lanphear BP, et al. The impact of reducing air pollution during pregnancy on cognitive abilities at fours years of age: The UGAAR randomized controlled trial of HEPA air cleaners. ISEE Conference Abstracts [Internet]. 2020(1). Available from: https://ehp.niehs.nih.gov/doi/10.1289/isee.2020.virtual.P-0218

132. Constantino JN. Social Responsiveness Scale. In: Volkmar FR, editor. Encyclopedia of Autism Spectrum Disorders [Internet]. New York, NY: Springer New York; 2013 [cited 2021 Oct 13]. p. 2919–29. Available from: http://link.springer.com/10.1007/978-1-4419-1698-3_296

133. Constantino JN, Hudziak JJ, Todd RD. Deficits in Reciprocal Social Behavior in Male Twins: Evidence for a Genetically Independent Domain of Psychopathology. Journal of the American Academy of Child & Adolescent Psychiatry. 2003 Apr;42(4):458–67.

134. Constantino JN, Gruber C. Socia Responsiveness Scale SRS-2 Manual. Second (SRS-2). Torrance, CA: Western Psychological Services; 2012.

135. Raz R, Levine H, Pinto O, Broday DM, Yuval, Weisskopf MG. Traffic-Related Air Pollution and Autism Spectrum Disorder: A Population-Based Nested Case-Control Study in Israel. American Journal of Epidemiology. 2018 Apr 1;187(4):717–25.

136. Volk HE, Lurmann F, Penfold B, Hertz-Picciotto I, McConnell R. Traffic-Related Air Pollution, Particulate Matter, and Autism. JAMA Psychiatry. 2013 Jan 1;70(1):71.

137. Ritz B, Liew Z, Yan Q, Cuia X, Virk J, Ketzel M, et al. Air pollution and autism in Denmark. Environmental Epidemiology. 2018 Dec;2(4):e028.

138. Talbott EO, Arena VC, Rager JR, Clougherty JE, Michanowicz DR, Sharma RK, et al. Fine particulate matter and the risk of autism spectrum disorder. Environmental Research. 2015 Jul;140:414–20.

139. Becerra TA, Wilhelm M, Olsen J, Cockburn M, Ritz B. Ambient Air Pollution and Autism in Los Angeles County, California. Environmental Health Perspectives. 2013 Mar;121(3):380–6.

140. Constantino JN, Przybeck T, Friesen D, Todd RD. Reciprocal Social Behavior in Children With and Without Pervasive Developmental Disorders: Journal of Developmental & Behavioral Pediatrics. 2000 Feb;21(1):2–11.

141. Hus V, Bishop S, Gotham K, Huerta M, Lord C. Factors influencing scores on the social responsiveness scale: Factors influencing the SRS. Journal of Child Psychology and Psychiatry. 2013 Feb;54(2):216–24.

142. Ooi YP, Rescorla L, Ang RP, Woo B, Fung DSS. Identification of Autism Spectrum Disorders Using the Child Behavior Checklist in Singapore. J Autism Dev Disord. 2011 Sep;41(9):1147–56.

143. Bölte S, Poustka F, Constantino JN. Assessing autistic traits: cross-cultural validation of the social responsiveness scale (SRS). Autism Res. 2008 Dec;1(6):354–63.

144. Chen G, Jin Z, Li S, Jin X, Tong S, Liu S, et al. Early life exposure to particulate matter air pollution (PM1, PM2.5 and PM10) and autism in Shanghai, China: A case-control study. Environment International. 2018 Dec;121:1121–7.

145. Suades-González E, Gascon M, Guxens M, Sunyer J. Air Pollution and Neuropsychological Development: A Review of the Latest Evidence. Endocrinology. 2015 Oct 1;156(10):3473–82.

146. Ha S. Air pollution and neurological development in children. Dev Med Child Neurol. 2021 Apr;63(4):374–81.

147. Jorcano A, Lubczyńska MJ, Pierotti L, Altug H, Ballester F, Cesaroni G, et al. Prenatal and postnatal exposure to air pollution and emotional and aggressive symptoms in children from 8 European birth cohorts. Environment International. 2019 Oct;131:104927.

148. McGuinn LA, Bellinger DC, Colicino E, Coull BA, Just AC, Kloog I, et al. Prenatal PM2.5 exposure and behavioral development in children from Mexico City. NeuroToxicology. 2020 Dec;81:109–15.

149. Johnson NM, Hoffmann AR, Behlen JC, Lau C, Pendleton D, Harvey N, et al. Air pollution and children's health—a review of adverse effects associated with prenatal exposure from fine to ultrafine particulate matter. Environ Health Prev Med. 2021 Dec;26(1):72.

150. Yan Q, Liew Z, Uppal K, Cui X, Ling C, Heck JE, et al. Maternal serum metabolome and traffic-related air pollution exposure in pregnancy. Environment International. 2019 Sep;130:104872.

151. McGuinn LA, Tamayo-Ortiz M, Rosa MJ, Harari H, Osorio-Valencia E, Schnaas L, et al. The influence of maternal anxiety and cortisol during pregnancy on childhood anxiety symptoms. Psychoneuroendocrinology. 2022 May;139:105704.

152. Buss C, Entringer S, Wadhwa PD. Fetal Programming of Brain Development: Intrauterine Stress and Susceptibility to PsychopathologyA Presentation from the European Society for Paediatric Endocrinology (ESPE) New Inroads to Child Health (NICHe) Conference on Stress Response and Child Health in Heraklion, Crete, Greece, 18 to 20 May 2012. Sci Signal [Internet]. 2012 Oct 9 [cited 2023 Jan 19];5(245). Available from: https://www.science.org/doi/10.1126/scisignal.2003406

153. Sarkar P, Bergman K, O'Connor TG, Glover V. Maternal Antenatal Anxiety and Amniotic Fluid Cortisol and Testosterone: Possible Implications for Foetal Programming. J Neuroendocrinol. 2008 Apr;20(4):489–96.

154. Mclean MA, Scoten OC, Yu W, Ye XY, Petrie J, Church PT, et al. Lower Maternal Chronic Physiological Stress and Better Child Behavior at 18 Months: Follow-Up of a Cluster Randomized Trial of Neonatal Intensive Care Unit Family Integrated Care. The Journal of Pediatrics. 2022 Apr;243:107-115.e4.

155. Salvante KG, Milano K, Kliman HJ, Nepomnaschy PA. Placental 11 β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) expression very early during human pregnancy. J Dev Orig Health Dis. 2017 Apr;8(2):149–54.

156. Lennartsson AK, Theorell T, Kushnir MM, Bergquist J, Jonsdottir IH. Perceived stress at work is associated with attenuated DHEA-S response during acute psychosocial stress. Psychoneuroendocrinology. 2013 Sep;38(9):1650–7.

157. Wester VL, van Rossum EFC. Clinical applications of cortisol measurements in hair. European Journal of Endocrinology. 2015 Oct;173(4):M1–10.

158. Qiao S, Li X, Zilioli S, Chen Z, Deng H, Pan J, et al. Hair Measurements of Cortisol, DHEA, and DHEA to Cortisol Ratio as Biomarkers of Chronic Stress among People Living with HIV in China: Known-Group Validation. Nater UM, editor. PLoS ONE. 2017 Jan 17;12(1):e0169827.

159. Kamin HS, Kertes DA. Cortisol and DHEA in development and psychopathology. Hormones and Behavior. 2017 Mar;89:69–85.

160. Greff MJE, Levine JM, Abuzgaia AM, Elzagallaai AA, Rieder MJ, van Uum SHM. Hair cortisol analysis: An update on methodological considerations and clinical applications. Clinical Biochemistry. 2019 Jan;63:1–9.

161. Padula AM, Rivera-Núñez Z, Barrett ES. Combined Impacts of Prenatal Environmental Exposures and Psychosocial Stress on Offspring Health: Air Pollution and Metals. Current Environmental Health Reports. 2020 Jun;7(2):89–100.

162. Bolton JL, Huff NC, Smith SH, Mason SN, Foster WM, Auten RL, et al. Maternal Stress and Effects of Prenatal Air Pollution on Offspring Mental Health Outcomes in Mice. Environmental Health Perspectives. 2013 Sep;121(9):1075–82.

163. Perera FP, Wang S, Rauh V, Zhou H, Stigter L, Camann D, et al. Prenatal Exposure to Air Pollution, Maternal Psychological Distress, and Child Behavior. Pediatrics. 2013 Nov;132(5):e1284–94.

164. Enkhbat U, Gombojav E, Banzrai C, Batsukh S, Boldbaatar B, Enkhtuya E, et al. Portable HEPA filter air cleaner use during pregnancy and children's autistic behaviors at four years of age: The UGAAR randomized controlled trial. Environment International. 2022 Oct;168:107432.

165. Ulziikhuu B, Gombojav E, Banzrai C, Batsukh S, Enkhtuya E, Boldbaatar B, et al. Portable HEPA Filter Air Cleaner Use during Pregnancy and Children's Cognitive Performance at Four Years of Age: The UGAAR Randomized Controlled Trial. Environ Health Perspect. 2022 Jun;130(6):067006.

166. Barn P, Gombojav E, Ochir C, Laagan B, Beejin B, Naidan G, et al. The effect of portable HEPA filter air cleaners on indoor PM2.5 concentrations and second hand tobacco smoke exposure among pregnant women in Ulaanbaatar, Mongolia: The UGAAR randomized controlled trial. Science of The Total Environment. 2018 Feb;615:1379–89.

167. Reynolds CR. Behavior Assessment System for Children, Third Edition (BASC™-3) [Internet]. 2019 [cited 2019 Aug 13]. Available from: https://www.pearsonclinical.ca/en/products/product-master.html/item-33

168. Gelman A, Park DK. Splitting a Predictor at the Upper Quarter or Third and the Lower Quarter or Third. The American Statistician. 2009 Feb;63(1):1–8.

169. McCandless LC, Gombojav E, Allen RW. Sensitivity analysis for live birth bias in the Ulaanbaatar Gestation and Air Pollution Research study. Environmental Epidemiology. 2022 Dec;6(6):e229.

170. Moffat SD, An Y, Resnick SM, Diamond MP, Ferrucci L. Longitudinal Change in Cortisol Levels Across the Adult Life Span. Newman A, editor. The Journals of Gerontology: Series A. 2020 Jan 20;75(2):394–400.

171. Zijlmans MAC, Riksen-Walraven JM, de Weerth C. Associations between maternal prenatal cortisol concentrations and child outcomes: A systematic review. Neuroscience & Biobehavioral Reviews. 2015 Jun;53:1–24.

172. Fries E, Hesse J, Hellhammer J, Hellhammer DH. A new view on hypocortisolism. Psychoneuroendocrinology. 2005 Nov;30(10):1010–6.

173. Basson R, O'Loughlin JI, Weinberg J, Young AH, Bodnar T, Brotto LA. Dehydroepiandrosterone and cortisol as markers of HPA axis dysregulation in women with low sexual desire. Psychoneuroendocrinology. 2019 Jun;104:259–68.

174. Coe CL, Kramer M, Czéh B, Gould E, Reeves AJ, Kirschbaum C, et al. Prenatal stress diminishes neurogenesis in the dentate gyrus of juvenile Rhesus monkeys. Biological Psychiatry. 2003 Nov;54(10):1025–34.

175. Schmitz C, Rhodes ME, Bludau M, Kaplan S, Ong P, Ueffing I, et al. Depression: reduced number of granule cells in the hippocampus of female, but not male, rats due to prenatal restraint stress. Mol Psychiatry. 2002 Aug 1;7(7):810–3.

176. Maninger N, Wolkowitz OM, Reus VI, Epel ES, Mellon SH. Neurobiological and neuropsychiatric effects of dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS). Frontiers in Neuroendocrinology. 2009 Jan;30(1):65–91.

177. Ulziikhuu B, Gombojav E, Banzrai C, Batsukh S, Enkhtuya E, Boldbaatar B, et al. Who benefits most from a prenatal HEPA filter air cleaner intervention on childhood cognitive development? The UGAAR randomized controlled trial. Environmental research. (under review).

178. Stalder T, Kirschbaum C, Heinze K, Steudte S, Foley P, Tietze A, et al. Use of hair cortisol analysis to detect hypercortisolism during active drinking phases in alcohol-dependent individuals☆. Biological Psychology. 2010 Dec;85(3):357–60.

179. Dowlati Y, Herrmann N, Swardfager W, Thomson S, Oh PI, Van Uum S, et al. Relationship between hair cortisol concentrations and depressive symptoms in patients with coronary artery disease. Neuropsychiatric Disease and Treatment. 2010 Dec 31;6:393–400.

180. Wells S, Tremblay PF, Flynn A, Russell E, Kennedy J, Rehm J, et al. Associations of hair cortisol concentration with self-reported measures of stress and mental

health-related factors in a pooled database of diverse community samples. Stress. 2014 Jul;17(4):334–42.

181. Smith KR, McCracken JP, Weber MW, Hubbard A, Jenny A, Thompson LM, et al. Effect of reduction in household air pollution on childhood pneumonia in Guatemala (RESPIRE): a randomised controlled trial. The Lancet. 2011 Nov;378(9804):1717–26.

182. Chillrud SN, Ae-Ngibise KA, Gould CF, Owusu-Agyei S, Mujtaba M, Manu G, et al. The effect of clean cooking interventions on mother and child personal exposure to air pollution: results from the Ghana Randomized Air Pollution and Health Study (GRAPHS). J Expo Sci Environ Epidemiol. 2021 Jul;31(4):683–98.

183. Smith KR, McCracken JP, Weber MW, Hubbard A, Jenny A, Thompson LM, et al. Effect of reduction in household air pollution on childhood pneumonia in Guatemala (RESPIRE): a randomised controlled trial. The Lancet. 2011 Nov;378(9804):1717–26.

184. Xiang J, Weschler CJ, Wang Q, Zhang L, Mo J, Ma R, et al. Reducing Indoor Levels of "Outdoor PM $_{2.5}$ " in Urban China: Impact on Mortalities. Environ Sci Technol. 2019 Mar 19;53(6):3119–27.

185. Menassa DA, Gomez-Nicola D. Microglial Dynamics During Human Brain Development. Front Immunol. 2018 May 24;9:1014.

186. Pujol J, Martínez-Vilavella G, Macià D, Fenoll R, Alvarez-Pedrerol M, Rivas I, et al. Traffic pollution exposure is associated with altered brain connectivity in school children. NeuroImage. 2016 Apr;129:175–84.

187. Guxens M, Lubczyńska MJ, Muetzel RL, Dalmau-Bueno A, Jaddoe VWV, Hoek G, et al. Air Pollution Exposure During Fetal Life, Brain Morphology, and Cognitive Function in School-Age Children. Biological Psychiatry. 2018 Aug;84(4):295–303.

188. Barn P, Gombojav E, Ochir C, Boldbaatar B, Beejin B, Naidan G, et al. Coal smoke, gestational cadmium exposure, and fetal growth. Environmental Research. 2019 Dec;179:108830.

189. Lin Q, Hou XY, Yin XN, Wen GM, Sun D, Xian DX, et al. Prenatal Exposure to Environmental Tobacco Smoke and Hyperactivity Behavior in Chinese Young Children. IJERPH. 2017 Sep 27;14(10):1132.

190. Tanaka K, Miyake Y, Furukawa S, Arakawa M. Perinatal smoking exposure and behavioral problems in Japanese children aged 5 years: The Kyushu Okinawa Maternal and Child Health Study. Environmental Research. 2016 Nov;151:383–8.

191. CDC. Centers for Disease Control and Prevention. [cited 2023 Jan 5]. Autism Spectrum Disorder (ASD). Available from:

https://www.cdc.gov/ncbddd/autism/screening.html#:~:text=Diagnosing%20autism%20spectrum%20disorder%20(ASD,months%20of%20age%20or%20younger.

192. American Psychiatric Association, American Psychiatric Association, editors. Diagnostic and statistical manual of mental disorders: DSM-5. 5th ed. Washington, D.C: American Psychiatric Association; 2013. 947 p.

193. Pagalan L, Bickford C, Weikum W, Lanphear B, Brauer M, Lanphear N, et al. Association of Prenatal Exposure to Air Pollution With Autism Spectrum Disorder. JAMA Pediatr. 2019 Jan 1;173(1):86.

194. Perera FP, Wheelock K, Wang Y, Tang D, Margolis AE, Badia G, et al. Combined effects of prenatal exposure to polycyclic aromatic hydrocarbons and material hardship on child ADHD behavior problems. Environmental Research. 2018 Jan;160:506–13.

195. Altmann RA, Reynolds CR, Kamphaus RW, Vannest KJ. BASC-3. In: Kreutzer J, DeLuca J, Caplan B, editors. Encyclopedia of Clinical Neuropsychology [Internet]. Cham: Springer International Publishing; 2018 [cited 2023 Feb 14]. p. 1–7. Available from: http://link.springer.com/10.1007/978-3-319-56782-2_1524-2

196. For the British Columbia Healthy Connections Project Scientific Team, Catherine NLA, Lever R, Sheehan D, Zheng Y, Boyle MH, et al. The British Columbia Healthy Connections Project: findings on socioeconomic disadvantage in early pregnancy. BMC Public Health. 2019 Dec;19(1):1161.

197. Glennon B, Weisz JR. An observational approach to the assessment of anxiety in young children. Journal of Consulting and Clinical Psychology. 1978;46(6):1246–57.

198. Walzer D, Gordon T, Thorpe L, Thurston G, Xia Y, Zhong H, et al. Effects of Home Particulate Air Filtration on Blood Pressure: A Systematic Review. Hypertension. 2020 Jul;76(1):44–50.

199. Martenies SE, Batterman SA. Effectiveness of Using Enhanced Filters in Schools and Homes to Reduce Indoor Exposures to $PM_{2.5}$ from Outdoor Sources and Subsequent Health Benefits for Children with Asthma. Environ Sci Technol. 2018 Sep 18;52(18):10767–76.

200. Fisk WJ, Chan WR. Health benefits and costs of filtration interventions that reduce indoor exposure to PM 2.5 during wildfires. Indoor Air. 2017 Jan;27(1):191–204.

201. Liu Y, Zhou B, Wang J, Zhao B. Health benefits and cost of using air purifiers to reduce exposure to ambient fine particulate pollution in China. Journal of Hazardous Materials. 2021 Jul;414:125540.

202. Huang G, Zhou W, Qian Y, Fisher B. Breathing the same air? Socioeconomic disparities in PM2.5 exposure and the potential benefits from air filtration. Science of The Total Environment. 2019 Mar;657:619–26.

203. Laumbach RJ, Cromar KR. Personal Interventions to Reduce Exposure to Outdoor Air Pollution. Annu Rev Public Health. 2022 Apr 5;43(1):293–309.

204. Frumkin H, editor. Environmental health: from global to local. Third edition. San Francisco, CA: Jossey-Bass, A Wiley Brand; 2016. 1 p.

205. Ariunsaikhan A, Batbaatar B, Dorjsuren B, Chonokhuu S. Air pollution levels and PM2.5 concentrations in Khovd and Ulaanbaatar cities of Mongolia. Int J Environ Sci Technol [Internet]. 2022 Sep 5 [cited 2022 Dec 27]; Available from: https://link.springer.com/10.1007/s13762-022-04493-1

206. WHO. Air pollution in Mongolia. Bull World Health Organ. 2019 Feb 1;97(2):79–80.

207. Braham WW, Hakkarainen M, Buyan M, Janjindorj G, Turner J, Erdenekhuyag S. Cooking, Heating, Insulating Products and Services (CHIPS) for Mongolian ger: Reducing energy, cost, and indoor air pollution. Energy for Sustainable Development. 2022 Dec;71:462–79.

208. World bank. Open knowledge repository beta. 2005 [cited 2023 Mar 30]. Impact of Improved Stoves on Indoor Air Quality in Ulaanbaatar, Mongolia. Available from: http://documents.worldbank.org/curated/en/2005/11/6743802/impact-improved-stoves-indoor-air-quality-ulaanbaatar-mongolia

209. Koo B, Na JI, Thorsteinsson T, Cruz AM. Participatory Approach to Gap Analysis between Policy and Practice Regarding Air Pollution in Ger Areas of Ulaanbaatar, Mongolia. Sustainability. 2020 Apr 18;12(8):3309.

210. UNDP. UNDP, AARC Consultancy, “Air pollution in Mongolia: Oppertunities for further actions, Public expenditure review.” 2019.

211. ADB. Imprving Air Quality in Ulaanbaatar [Internet]. Asian Development Bank; 2022. Available from: https://www.adb.org/sites/default/files/publication/842651/adb-brief-229-improving-air-quality-ulaanbaatar.pdf

212. Jun S. Princeton University Journal of Public & International Affairs. 2021. Is the raw coal ban a siver bullet to solving air pollution in Mongolia?: A study of the Mongolian Government’s air pollution reduction policies and recommendations in the context of COVID-19. Available from: https://jpia.princeton.edu/news/raw-coal-ban-silver-bullet-solving-air-pollution-mongolia-study-mongolian-governments-air

213. Wood L, Egger M, Gluud LL, Schulz KF, Jüni P, Altman DG, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different

interventions and outcomes: meta-epidemiological study. BMJ. 2008 Mar 15;336(7644):601–5.

214. Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials – a practical guide with flowcharts. BMC Medical Research Methodology [Internet]. 2017 Dec [cited 2020 Mar 11];17(1). Available from: https://bmcmedresmethodol.biomedcentral.com/articles/10.1186/s12874-017-0442-1

215. Dong Y, Peng CYJ. Principled missing data methods for researchers. SpringerPlus [Internet]. 2013 Dec [cited 2020 Mar 11];2(1). Available from: https://springerplus.springeropen.com/articles/10.1186/2193-1801-2-222

216. Morishita M, Adar SD, D'Souza J, Ziemba RA, Bard RL, Spino C, et al. Effect of Portable Air Filtration Systems on Personal Exposure to Fine Particulate Matter and Blood Pressure Among Residents in a Low-Income Senior Facility: A Randomized Clinical Trial. JAMA Intern Med. 2018 Oct 1;178(10):1350.

217. Zhan Y, Johnson K, Norris C, Shafer MM, Bergin MH, Zhang Y, et al. The influence of air cleaners on indoor particulate matter components and oxidative potential in residential households in Beijing. Science of The Total Environment. 2018 Jun;626:507–18.

218. Miodovnik A, Engel SM, Zhu C, Ye X, Soorya LV, Silva MJ, et al. Endocrine disruptors and childhood social impairment. NeuroToxicology. 2011 Mar;32(2):261–7.

219. Engel SM, Miodovnik A, Canfield RL, Zhu C, Silva MJ, Calafat AM, et al. Prenatal Phthalate Exposure Is Associated with Childhood Behavior and Executive Functioning. Environmental Health Perspectives. 2010 Apr;118(4):565–71.

220. Constantino JN, Frazier TW. Commentary: The observed association between autistic severity measured by the Social Responsiveness Scale (SRS) and general psychopathology - a response to Hus et al.(). J Child Psychol Psychiatry. 2013 Jun;54(6):695–7.

221. Lantos JD. The "inclusion benefit" in clinical trials. The Journal of Pediatrics. 1999 Feb;134(2):130–1.

222. Carter MC, Perzanowski MS, Raymond A, Platts-Mills TAE. Home intervention in the treatment of asthma among inner-city children. Journal of Allergy and Clinical Immunology. 2001 Nov;108(5):732–7.

223. Carter MC, Perzanowski MS, Raymond A, Platts-Mills TAE. Home intervention in the treatment of asthma among inner-city children. Journal of Allergy and Clinical Immunology. 2001 Nov;108(5):732–7.

224. Jadad AR. Randomised controlled trials: a user's guide. Reprint. London: BMJ Books; 2002. 123 p.

225. Lanphear BP, Hornung RW, Khoury J, Yolton K, Lierl M, Kalkbrenner A. Effects of HEPA Air Cleaners on Unscheduled Asthma Visits and Asthma Symptoms for Children Exposed to Secondhand Tobacco Smoke. PEDIATRICS. 2011 Jan 1;127(1):93–101.

226. Bennett DH, Moran RE, Krakowiak P, Tancredi DJ, Kenyon NJ, Williams J, et al. Reductions in particulate matter concentrations resulting from air filtration: A randomized sham-controlled crossover study. Indoor Air [Internet]. 2022 Feb [cited 2023 Mar 27];32(2). Available from: https://onlinelibrary.wiley.com/doi/10.1111/ina.12982

227. Boogaard H, van Erp AM, Walker KD, Shaikh R. Accountability Studies on Air Pollution and Health: the HEI Experience. Curr Envir Health Rpt. 2017 Dec;4(4):514–22.

228. HEI Accountability Working Group. HEI communication. 2003. Assessing health impact of air quality regulations: concepts and methods for accountability research. Available from: chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.healtheffects.org/system/files/Comm11ExecSumm.pdf

229. Dockery DW, Rich DQ, Goodman PG, Clancy L, Ohman-Strickland P, George P, et al. Effect of air pollution control on mortality and hospital admissions in Ireland. Res Rep Health Eff Inst. 2013 Jul;(176):3–109.

Appendix A. Supplemental material for chapter two

Table A.1. Comparison of BASC score distributions between the UGAAR population and the reference population.

Domain	UGAAR raw score Mean (SD)		Reference raw score Mean (SD)	
	Males (n=201)	Females (n=190)	Males	Females
Hyperactivity	12.26 (4.10)	12.14 (4.72)	11.72 (5.20)	10.43 (5.23)
Aggression	4.23 (2.86)	4.07 (3.01)	3.61 (2.93)	3.32 (3.06)
Anxiety	4.80 (3.54)	5.04 (4.09)	4.62 (4.37)	4.45 (4.20)
Depression	7.72 (3.06)	7.88 (4.01)	7.89 (4.12)	7.64 (4.43)
Somatization	7.16 (3.66)	6.98 (3.90)	5.27 (3.66)	5.71 (4.86)
Attention Problems	8.94 (3.11)	8.61 (3.03)	8.11 (3.69)	7.38 (3.35)
Atypicality	6.26 (3.44)	6.59 (3.86)	3.76 (3.56)	3.20 (3.93)
Withdrawal	10.39 (4.41)	10.34 (4.59)	9.69 (4.85)	10.43 (5.13)
Adaptability	14.75 (3.86)	14.79 (4.30)	16.15 (4.84)	16.60 (4.58)
Social Skills	10.74 (4.66)	11.97 (5.61)	13.91 (5.92)	15.99 (5.42)
Activities of Daily Living	8.33 (4.32)	9.39 (4.25)	8.82 (4.33)	10.13 (3.84)
Functional Communication	11.13 (3.96)	12.68 (4.60)	16.84 (6.77)	18.40 (6.33)

Table A.2. Effects of the air cleaner intervention on BASC composite scores at ages 2 and 4 estimated from a mixed effects model among complete cases.

Composite score	Unadjusted model			Adjusted for preterm birth		
	N	Change in mean T score (95%CI)	p-value	N	Change in mean T score (95%CI)	p-value
Externalizing	407	0.34 (-1.27, 1.94)	0.68	406	0.33 (-1.28, 1.94)	0.69
Internalizing	407	-0.59 (-2.21, 1.02)	0.47	406	-0.57 (-2.19, 1.05)	0.49
Adaptive	407	-0.07 (-1.49, 1.35)	0.93	406	0.03 (-1.39, 1.45)	0.96
Behavior Symptom Index	407	-0.07 (-1.58, 1.43)	0.92	406	-0.12 (-1.63, 1.39)	0.88

Table A.3. Summary on comparison of baseline characteristics for complete cases and imputed population

Baseline characteristic	Completed BASC-3 Median (25th, 75th percentile) or n (%)	Did not complete BASC-3 Median (25th, 75th percentile) or n (%)	p-value
Season of enrollment			
Winter (Dec, Jan, Feb)	124 (31)	27 (38)	
Spring (Mar, Apr, May)	115 (28)	23 (32)	0.25
Summer (Jun, July, Aug)	54 (13)	2 (3)	
Fall (Sep, Oct, Nov)	113 (28)	20 (27)	
Gestational age, wk	11 (8, 13)	11 (9, 13)	0.11
Maternal age, yr	29 (25, 33)	27 (24.5, 32)	0.17
Monthly household income, Tugriks			
< 800,000	79 (20)	14 (19)	
≥ 800,000	322 (79)	54 (75)	0.87
Not reported, n (%)	5 (1)	4 (6)	
Maternal marital status			
Married/ Common-law	339 (83)	56 (78)	
Single/engaged	67 (17)	16 (22)	0.24
Not reported, n (%)			
Maternal education			
Less than university	50 (12)	10 (14)	
Completed university	328 (81)	55 (76)	0.64
Not reported, n (%)	28 (7)	7 (10)	
Lived with a smoker during pregnancy			
No	211 (52)	37 (51)	
Yes	185 (46)	33 (46)	0.95
Not reported, n (%)	10 (2)	2 (3)	
Maternal pre-pregnancy BMI, kg/m2	21.6 (19.6, 24.2)	21.3 (19.6, 23.1)	0.37
Not reported, n (%)	28 (7)	1 (1)	
Paternal age, yr	31 (26, 35)	29 (25, 34)	0.25
Not reported, n (%)	24 (6)	1 (1)	
Paternal education			
Less than university	71 (17)	14 (19)	
Completed university	308 (76)	56 (78)	0.80
Not reported, n (%)	27 (7)	2 (3)	

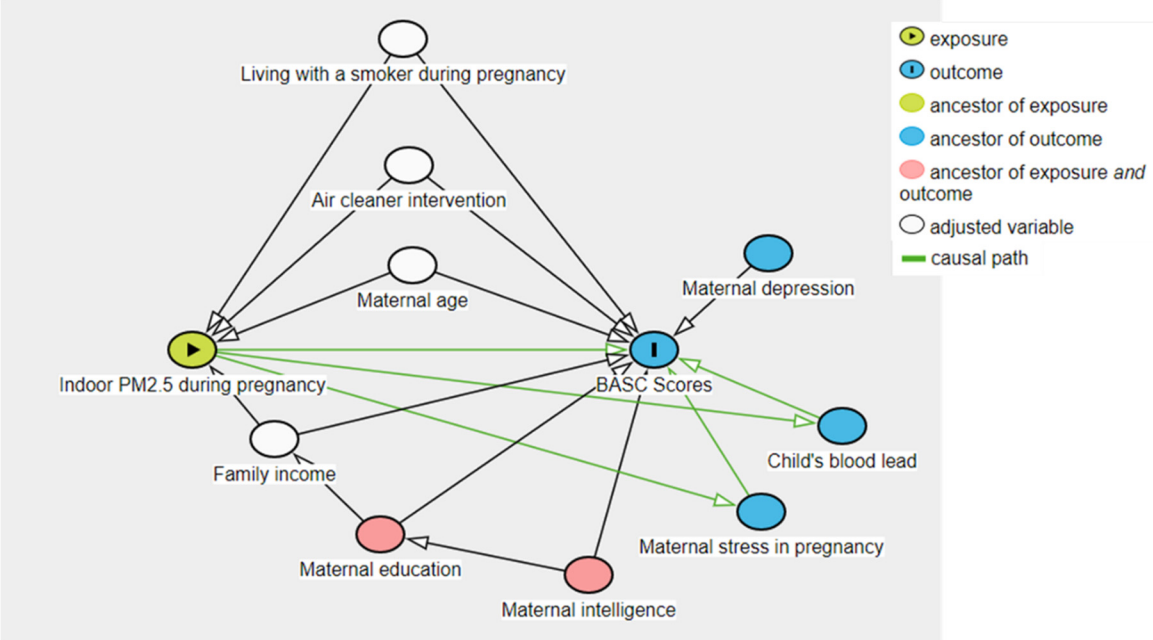


Figure A.1. Directed acyclic graph used to identify adjustment variables in models of the association between $PM_{2.5}$ and BASC scores.

Appendix B. Supplemental material for chapter three

Table B.1. Summary statistics of raw SRS-2 scores for UGAAR participants and the SRS-2 reference population.

SRS subscale	UGAAR mean (SD)		Reference mean (SD)[a]		% difference from the reference mean (% difference from reference SD)	
	Males	Females	Females	Females	Males	Females
Social awareness	6.9 (2.9)	6.8 (2.6)	5.7 (3.2)	5.1 (3.2)	21 (-9.4)	33 (-18.8)
Social cognition	10.5 (4.2)	10.0 (3.9)	6.2 (5.4)	5.4 (5.1)	69 (-22.0)	85 (-23.5)
Social Communication	16.1 (7.3)	14.8 (7.1)	10.8	9.0 (8.7)	49 (-19.8)	64 (-18.4)
Social motivation	8.0 (4.4)	7.7 (4.6)	6.0 (4.9)	5.4 (4.6)	33 (-10.2)	43 (0)
Restricted interest and repetitive	7.3 (5.0)	6.6 (4.9)	5.0 (5.7)	4.1 (4.9)	46 (-12.3)	61 (0)

[a]Based on sample of 1,012 children aged 4-18 years in the United States.

Table B.2. Baseline characteristics for parents who did and did not complete the SRS-2 when their child was 4 years old.

Baseline characteristic	Completed SRS-2 Median (25^{th}, 75^{th} percentile) or n (%)	Did not complete SRS-2 Median (25^{th}, 75^{th} percentile) or n (%)	p-value
Season of enrollment			
Winter (Dec, Jan, Feb)	115 (30)	36 (40)	
Spring (Mar, Apr, May)	111 (29)	27 (30)	0.07
Summer (Jun, July, Aug)	50 (13)	6 (7)	
Fall (Sep, Oct, Nov)	111 (29)	22 (24)	
Gestational age, wk	11 (8, 12.5)	11 (9, 13)	0.12
Maternal age, yr	29 (25, 33)	27 (24, 32)	0.06
Monthly household income, Tugriks			
< 800,000	74 (19)	19 (21)	
≥ 800,000	308 (80)	68 (75)	0.60
Not reported, n (%)	5 (1)	4 (4)	
Maternal marital status			
Married/ Common-law	322 (83)	73 (80)	0.50
Single/engaged	65 (17)	18 (20)	
Maternal education			
Less than university	47 (12)	13 (14)	
Completed university	314 (81)	69 (76)	0.50
Not reported, n (%)	26 (7)	9 (10)	
Prior pregnancy			
No	90 (23)	31 (34)	0.03
Yes	293 (76)	59(65)	
Not reported, n (%)	4 (1)	1 (1)	
Lived with a smoker in early pregnancy			
No	204 (53)	44 (48)	0.50
Yes	174 (45)	44 (48)	
Not reported, n (%)	9 (2)	3 (3)	
Maternal pre-pregnancy BMI, kg/m2	21.6 (19.7, 24.2)	21.5 (19.6, 23.1)	0.32
Not reported, n (%)	26 (7)	3 (1)	
Paternal age, yr	31 (26, 35)	29 (25, 34)	0.25
Not reported, n (%)	24 (6)	1 (1)	
Paternal education			

Less than university	69 (18)	16 (18)	
Completed university	293 (76)	71 (78)	0.89
Not reported, n (%)	25 (6)	4 (4)	

Table B.3. Unadjusted associations between potential imputation model variables and SRS-2 total T-scores among complete cases (*n* = 387)

Variable	Changes in mean SRS-2 total T-score (95% CI)	p-value
Gestational weeks at enrollment	-0.02 (-0.40, 0.35)	0.90
Maternal age at enrollment	-0.22 (-0.39, -0.04)	0.02
Season of enrollment		
Winter (Dec, Jan, Feb)	Reference	
Spring	-1.60 (-3.97, 0.77)	0.19
Summer	-1.90 (-5.01, 1.21)	0.23
Fall	-0.06 (-2.81, 2.70)	0.97
Monthly household income		
≥ 800,000 Tugriks	Reference	0.53
< 800,000 Tugriks	-0.79 (-3.30, 1.71)	
Marital status		
Married/common-law	Reference	0.08
Single/Engaged	1.07 (-0.14, 2.27)	
Maternal education		
Completed university	Reference	
Less than university	0.35 (-3.35, 2.66)	0.82
Maternal pre-pregnancy BMI, kg/m2	0.14 (-0.14, 0.42)	0.33
Prior pregnancy	0.39 (-1.94, 2.72)	0.74
Early pregnancy prenatal perceived stress		
Less stressed (<8)	Reference	0.11
More stressed (≥8)	1.98 (-0.47, 4.43)	
Late pregnancy prenatal perceived stress		
Less stressed (<8)	Reference	0.06
More stressed (≥8)	3.12 (-0.12, 6.37)	
Vitamin use in early pregnancy		
No	Reference	0.42
Yes	0.96 (-1.37, 3.29)	
Lived with a smoker in early pregnancy		
No	Reference	0.34
Yes	0.96 (-1.02, 2.94)	
Preterm birth		
No	Reference	0.46
Yes	1.36 (-2.25, 4.97)	
Sex of child		
Female	Reference	0.99
Male	-0.01 (-1.97, 1.96)	
Maternal depression score (BDI-II)		
Minimal to mild (0-16)	Reference	0.18
Moderate to severe (>16)	2.21 (-1.00, 5.43)	

BMI= Body Mass Index; BDI-II = Beck Depression Inventory-II

Table B.4. Estimated effects of the air cleaner intervention on mean SRS T-scores among complete cases (*n*=387) using different methods for scaling scores.

	Scores scaled using reference population				**Scores scaled using UGAAR population**				**Raw scores (no scaling)**			
	Mean (SD)		Effect Estimate		Mean (SD)		Effect Estimate		Mean (SD)		Effect Estimate	
SRS-2 Scale	Control	Intervention	Crude	Adjusted for PTB	Control	Intervention	Crude	Adjusted for PTB	Control	Intervention	Adjusted for sex	Adjusted for sex & PTB
Total T-score	50.3 (9.9)	50.0 (9.8)	-0.3 (-2.3, 1.7)	-0.3 (-2.3, 1.6)	50.2 (10.0)	49.9 (10.0)	-0.3 (-2.3, 1.7)	-0.3 (-2.3, 1.7)	47.6 (19.2)	47.0 (19.0)	-0.6 (-4.4, 3.2)	-0.7 (-4.5, 3.1)
Social awareness T-score	50.5 (9.9)	49.7 (9.9)	-0.8 (-2.8, 1.2)	-0.8 (-2.8, 1.2)	50.3 (10.1)	49.7 (9.9)	-0.6 (-2.6, 1.4)	-0.6 (-2.6, 1.4)	6.9 (2.8)	6.8 (2.7)	-0.2 (-0.7, 0.4)	-0.2 (-0.7, 0.4)
Social cognition T-score	50.0 (8.9)	50.6 (9.6)	0.7 (-1.2, 2.5)	0.6 (-1.3, 2.5)	49.5 (9.8)	50.5 (10.1)	1.0 (-1.0, 3.0)	0.9 (-1.1, 2.9)	10.0 (4.0)	10.5 (4.1)	0.4 (-0.4, 1.2)	0.4 (-0.4, 1.2)
Social communication T-score	50.9 (9.8)	49.8 (9.5)	-1.1 (-3.0, 0.8)	-1.1 (-3.1, 0.8)	50.6 (10.1)	49.5 (9.9)	-1.1 (-3.1, 0.9)	-1.2 (-3.2, 0.8)	15.8 (7.3)	15.0 (7.1)	-0.8 (-2.2, 0.6)	-0.8 (-2.3, 0.6)
Social motivation T-score	50.6 (9.7)	50.6 (9.6)	0.0 (-1.9, 1.9)	0.0 (-1.9, 1.9)	50.0 (9.9)	50.0 (10.1)	0.0 (-2.0, 2,0)	0.0 (-2.0, 2.0)	7.8 (4.4)	7.8 (4.5)	0.0 (-0.9, 0.9)	0.0 (-0.9, 0.9)
Restricted interests and repetitive behavior T-score	50.7 (9.8)	50.8 (9.5)	0.1 (-1.8, 2.1)	0.1 (-1.8, 2.1)	50.0 (10.1)	50.0 (9.9)	0.0 (-2.0, 2,0)	0.0 (-2.0, 2,0)	6.9 (5.0)	6.9 (4.9)	0.0 (-1.0, 1.0)	0.0 (-1.0, 1.0)

Table B.5. Estimated effects of the intervention on mean SRS T-scores from an intention-to-treat analysis after log-transforming (*n*=478).

	Estimated % difference in mean SRS T-score between the intervention and control groups (95% CI)	
SRS-2 Scale	Crude	Adjusted for preterm birth
Total T-score	-0.8 (-4.5, 3.0)	-0.8 (-4.6, 3.0)
Social awareness T-score	-1.0 (-5.1, 3.1)	-1.0 (-5.1, 3.1)
Social cognition T-score	1.1 (-2.7, 4.9)	1.1 (-2.7, 4.9)
Social communication T-score	-2.2 (-5.9, 1.5)	-2.2 (-6.0, 1.5)
Social motivation T-score	-0.2 (-4.1, 3.6)	-0.2 (-4.1, 3.7)
Restricted interests and repetitive behavior T-score	-0.5 (-4.1, 3.0)	-0.5 (-4.1, 3.0)

Table B.6. Estimated effects of the intervention on mean SRS T-scores stratified by child sex (*n*=387).

	Mean (95%CI) SRS-2 total T-score		Estimated effects of the intervention on mean SRS-2 T-score		
Stratum	Control (n=182)	Intervention (n=205)	Difference in means (95% CI)	p-value	Interaction Sex X Filter
All	50.3 (48.9, 51.7)	50.0 (48.7, 51.4)	-0.3 (-1.68, 2.25)	0.77	
Females	49.8 (47.6, 52.1) (n=88)	50.4 (48.6, 52.3) (n=97)	0.6 (-2.29, 3.42)	0.69	0.41
Males	50.7 (48.8, 52.6) (n=94)	49.6 (47.7, 51.6) (n=108)	-1.1 (-1.67, 3.81)	0.44	

Table B.7. Estimated effects of an interquartile range increase in indoor $PM_{2.5}$ concentrations on mean SRS-2 total T-score after inclusion of different variables in the imputation and analysis models (*n*=478).

Sensitivity Analysis	1st trimester	2nd trimester	3rd trimester	Full pregnancy
	Changes in mean SRS total T-score (95% CI)			
Core imputation model, adjustment model includes core variables	1.4 (-0.3, 3.1)	1.3 (-0.4, 2.9)	0.8 (-0.6, 2.2)	1.8 (0.3, 3.2)
Core imputation model, adjustment model includes core variables – maternal depression (BDI-II)	1.5 (-0.2, 3.1)	1.2 (-0.5, 2.8)	1.0 (-0.5, 2.4)	1.8 (0.3, 3.2)
Expanded imputation model, adjustment model includes core variables	1.7 (-0.0, 3.3)	1.2 (-0.4, 2.8)	1.0 (-0.5, 2.5)	1.8 (0.4, 3.2)
Expanded imputation model, adjustment model includes core variables + season of enrollment	2.0 (-0.1, 4.1)	1.0 (-0.8, 2.7)	0.9 (-0.7, 2.4)	1.8 (0.4, 3.2)
Expanded imputation model, adjustment model includes core variables + maternal blood cadmium concentration	1.6 (-0.1, 3.3)	1.2 (-0.4, 2.8)	0.9 (-0.6, 2.5)	1.8 (0.4, 3.2)
Expanded imputation model, adjustment model includes core variables + maternal blood lead concentration	1.7 (-0.0, 3.3)	1.2 (-0.4, 2.8)	1.0 (-0.5, 2.5)	1.8 (0.4, 3.2)
Expanded imputation model, adjustment model includes core variables + PSS-4 early in pregnancy	1.7 (0.0, 3.4)	1.2 (-0.4, 2.8)	1.1 (-0.5, 2.6)	1.9 (0.5, 3.4)
Expanded imputation model, adjustment model includes core variables + PSS-4 late in pregnancy	1.9 (0.2, 3.6)	1.0 (-0.6, 2.6)	1.2 (-0.4, 2.8)	1.9 (0.5, 3.3)
Expanded imputation model, adjustment model includes core variables + maternal pre-pregnancy BMI	1.7 (0.0, 3.4)	1.0 (-0.6, 2.6)	1.0 (-0.5, 2.6)	1.8 (0.4, 3.2)

Expanded imputation model variables: SRS-2 total score, SRS-2 subscale scores, maternal age at baseline, marital status at baseline, maternal self-reported stress level at baseline and during late pregnancy, prior pregnancy, maternal BDI-II score, maternal WASI matrix reasoning and vocabulary subset scores, preterm birth, season of enrollment, trimester specific PM2.5 concentration and full pregnancy PM2.5 concentration, maternal lead level, maternal cadmium level, pre-pregnancy BMI. Core adjustment variables: Intervention status, maternal age at baseline, monthly family income, living with a smoker early in pregnancy, maternal matrix reasoning and vocabulary subtest scores on the WASI, and mother's self-reported depression score on the BDI-II. Trimester-specific models were also adjusted for PM2.5 concentrations in other trimesters.1st trimester interquartile range (IQR) = 20.1 ug/m3, 2nd trimester IQR = 21.6 ug/m3, 3rd trimester IQR = 13.5 ug/m3 full pregnancy IQR = 9.6 ug/m3

Table B.8. Estimated changes in mean SRS T-scores per interquartile range increase in indoor $PM_{2.5}$ concentration during pregnancy (*n*=478).

	Estimated changes in mean SRS T-scores (95% CI) per interquartile range contrast in $PM_{2.5}$ concentration			
SRS-2 Scale	**1st trimester**	**2nd trimester**	**3rd trimester**	**Full pregnancy**
Total T-score	1.4 (-0.3, 3.1)	1.3 (-0.4, 2.9)	0.8 (-0.6, 2.2)	1.8 (0.3, 3.2)
Social awareness T-score	0.8 (-1.2, 2.7)	-0.2 (-1.9, 1.5)	-0.4 (-1.2, 1.9)	0.2 (-1.3, 1.7)
Social cognition T-score	1.1 (-0.5, 2.8)	1.1 (-0.5, 2.6)	0.5 (-0.9, 1.8)	1.4 (0.0, 2.8)
Social communication T-score	1.1 (-0.6, 2.7)	1.5 (-0.2, 3.1)	0.6 (-0.9, 2.0)	1.7 (0.2, 3.1)
Social motivation T-score	0.9 (-0.8, 2.5)	1.2 (-0.6, 2.9)	-0.1 (-1.5, 1.4)	1.1 (-0.4, 2.6)
Restricted interests and repetitive behavior T-score	1.4 (-0.3, 3.1)	1.3 (-0.4, 3.1)	1.3 (-0.2, 2.8)	2.0 (0.6, 3.4)

Models adjusted for intervention status, maternal age at baseline, family income, living with a smoker in early pregnancy, maternal matrix reasoning and vocabulary subtest scores on the Wechsler Abbreviated Scale of Intelligence (WASI), and mother's self-reported depression score on the Beck Depression Inventory (BDI-II). Trimester-specific models were also adjusted for $PM_{2.5}$ concentrations in other trimesters. 1st trimester interquartile range (IQR) = 20.1 ug/m^3, 2nd trimester IQR = 21.6 ug/m^3, 3rd trimester IQR = 13.5 ug/m^3 full pregnancy IQR = 9.6 ug/m^3

Table B.9. Estimated effects of an interquartile range increase (9.6 ug/m^3) in full pregnancy average indoor $PM_{2.5}$ on mean SRS T-scores among complete cases (*n*=387) using different methods for scaling scores.

	Scores scaled using reference population		Scores scaled using UGAAR population		Raw scores (no scaling)	
	Effect Estimate (95% CI)		Effect Estimate (95% CI)		Effect Estimate (95% CI)	
SRS-2 Scale	Crude	Adjusted[a]	Crude	Adjusted[a]	Crude	Adjusted[b]
Total T-score	2.1 (0.6, 3.5)	2.0 (0.6, 3.4)	2.1 (0.6, 3.5)	2.0 (0.5, 3.4)	3.9 (1.2, 6.7)	3.8 (1.0, 6.5)
Social awareness T-score	0.6 (-0.9, 2.0)	0.5 (-1.0, 2.1)	0.5 (-1.0, 1.9)	0.4 (-1.1, 1.8)	0.1 (-0.3, 0.5)	0.1 (-0.3, 0.5)
Social cognition T-score	1.8 (0.5, 3.2)	1.6 (0.3, 3.0)	1.9 (0.4, 3.3)	1.6 (0.2, 3.1)	0.7 (0.2, 1.3)	0.7 (0.1, 1.2)
Social communication T-score	1.9 (0.5, 3.3)	1.8 (0.5, 3.2)	1.9 (0.4, 3.3)	1.9 (0.4, 3.3)	1.4 (0.3, 2.4)	1.4 (0.3, 2.4)
Social motivation T-score	1.3 (-0.1, 2.7)	1.2 (-0.2, 2.6)	1.4 (-0.1, 2.8)	1.3 (-0.1, 2.8)	0.6 (0.0, 1.3)	0.6 (-0.1, 1.2)
Restricted interests and repetitive behavior T-score	2.2 (0.8, 3.6)	2.1 (0.8, 3.5)	2.2 (0.7, 3.6)	2.1 (0.7, 3.5)	1.1 (0.4, 1.8)	1.0 (0.3, 1.8)

[a]Adjusted for intervention status, maternal age at baseline, monthly family income, living with a smoker early in pregnancy, maternal matrix reasoning and vocabulary subtest scores on the WASI, and mother's self-reported depression score on the BDI-II.

[b]Adjusted for intervention status, maternal age at baseline, monthly family income, living with a smoker early in pregnancy, maternal matrix reasoning and vocabulary subtest scores on the WASI, mother's self-reported depression score on the BDI-II, and child's sex.

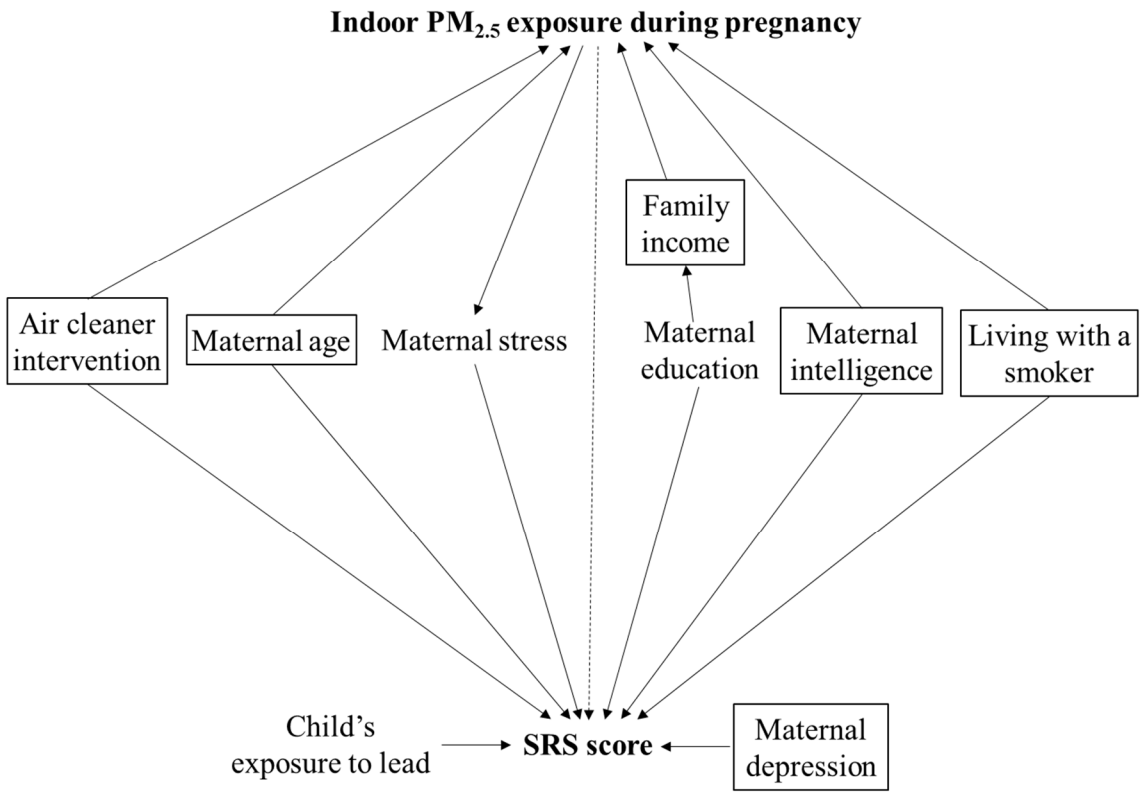
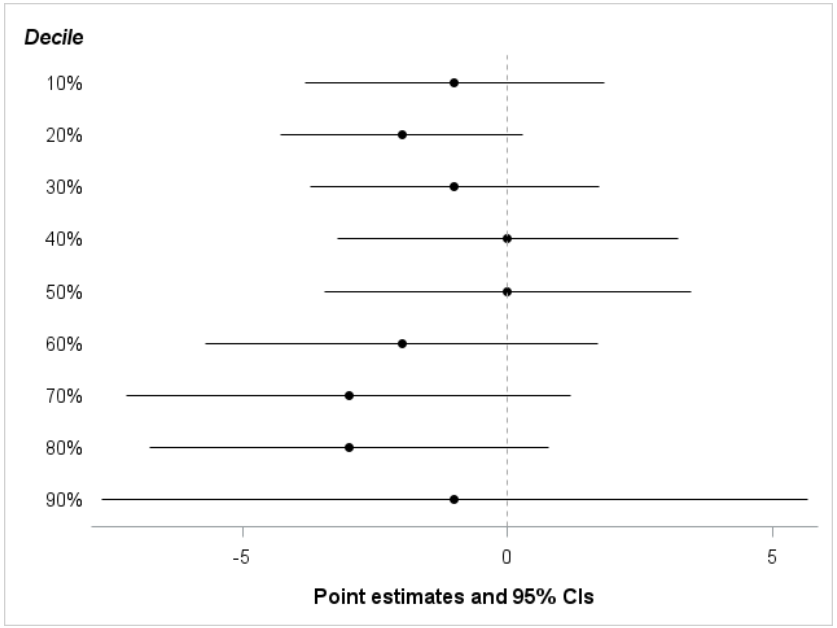


Figure B.1. Directed acyclic graph used to identify adjustment variables in models of the association between $PM_{2.5}$ and SRS-2 scores.

Note: Adjustment variables are shown in boxes. Arrows are not shown if they are on a path that is already blocked by an adjustment variable.

a)



b)

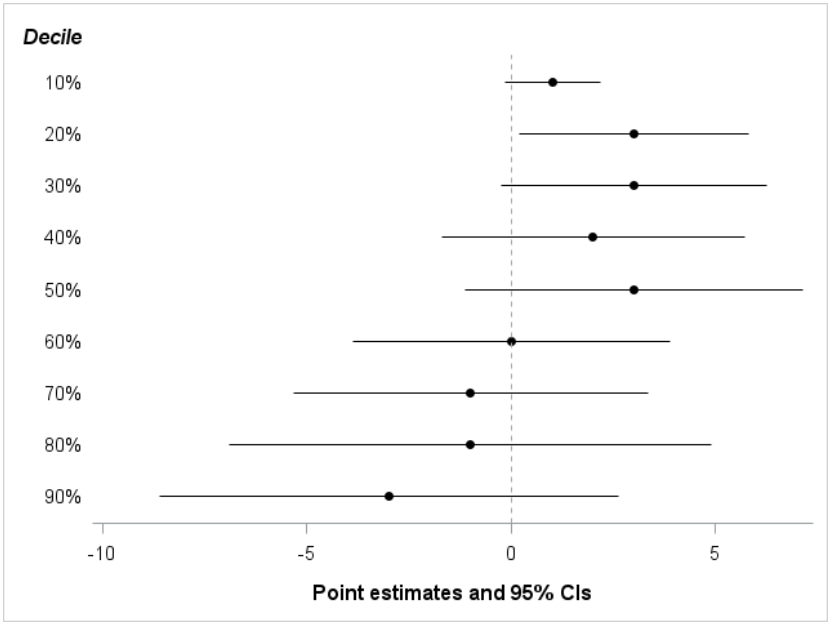


Figure B.2. Intervention effects on SRS total T-scores estimated from a quantile regression analysis for a) males *n*=202 and b) females *n*=185 adjusted for PTB

Appendix C. Supplemental material for chapter four

Table C.1. Spearman's correlation coefficients between biomarker from samples collected in early pregnancy and late pregnancy (n=74)

Biomarker	Correlation	P-value
Cortisol	0.63	<0.01
DHEA	0.66	<0.01
Ratio	0.52	<0.01

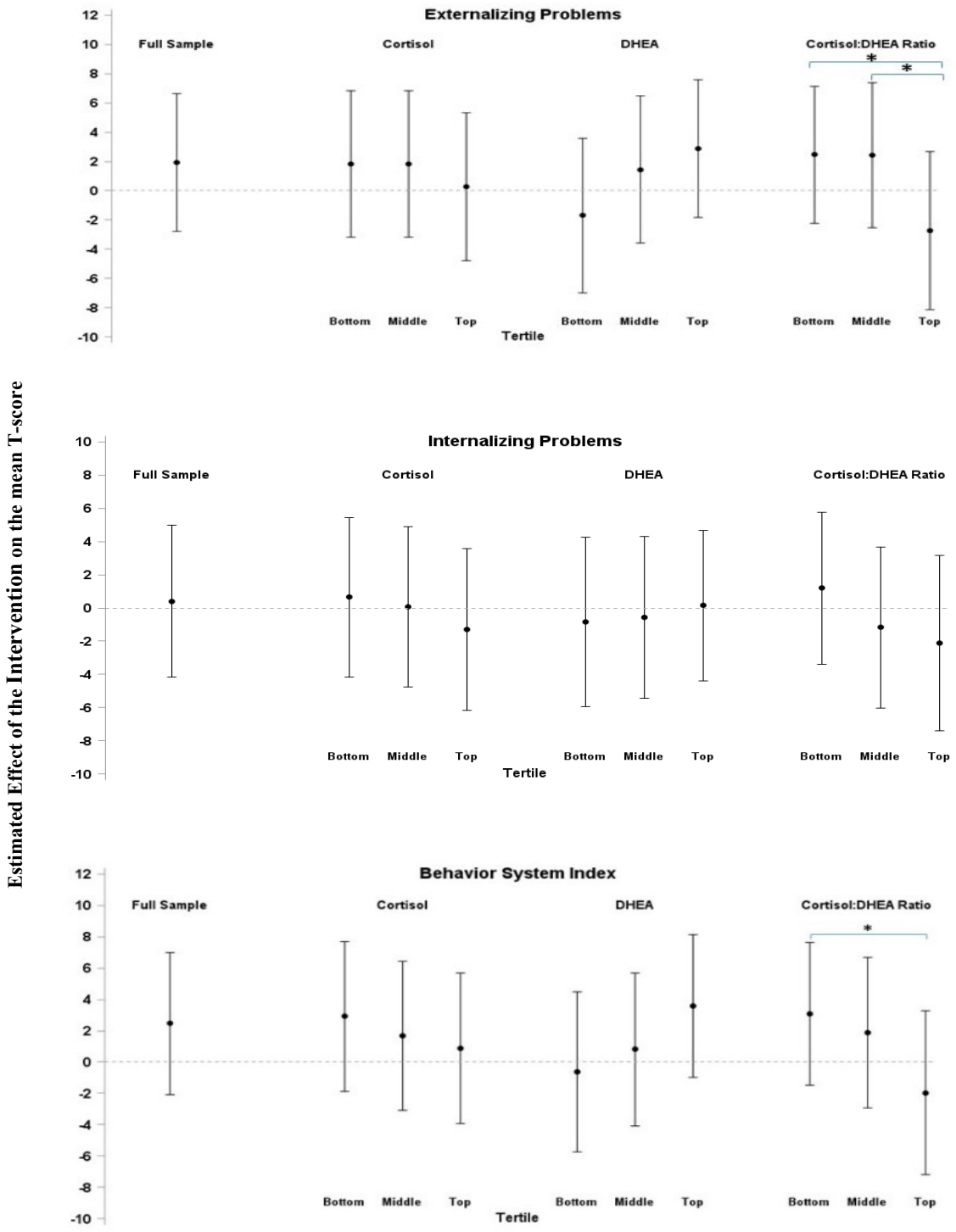
Table C.2. Spearman's correlation coefficients between cortisol, DHEA, the cortisol/DHEA ratio, and perceived stress (PSS-4) (n=297).

	Cortisol	DHEA	C/D	PSS-4
Cortisol	-			
DHEA	0.19 P<0.01	-		
Cortisol/DHEA	0.27 P<0.01	-0.27 P<0.01	-	
PSS-4	-0.10 P=0.07	-0.02 P=0.76	0.01 P=0.90	-

Table C.3. Pregnancy and post-natal characteristics for participants included and not included in the analysis.

Characteristic	Participants included in the analysis (n=297) Median (25^{th}, 75^{th} percentile) or n (%)	Participants not included in the analysis (n=181) Median (25^{th}, 75^{th} percentile) or n (%)	p-value
Season of enrollment			
Winter (Dec, Jan, Feb)	92 (31)	59 (33)	
Spring (Mar, Apr, May)	65 (22)	73 (40)	<0.01
Summer (Jun, July, Aug)	33 (11)	23 (13)	
Fall (Sep, Oct, Nov)	107 (36)	26 (14)	
Gestational age at enrollment, wk	10 (8, 12)	11 (9, 13)	<0.01
Maternal age at enrollment, yr	29 (25, 33)	28 (25, 3)	0.45
Not reported, n (%)	6 (2)	4 (4)	
Monthly household income, Tugriks			
< 800,000	52 (17)	41 (23)	
≥ 800,000	241 (82)	135 (76)	0.14
Not reported, n (%)	4 (1)	5 (1)	
Maternal marital status			
Married/ Common-law	248 (84)	147 (81)	0.52
Single/engaged	49 (16)	34 (19)	
Maternal education			
Less than university	34 (12)	26 (14)	
Completed university	241 (81)	142 (78)	0.35
Not reported, n (%)	22 (7)	13 (7)	
Lived with a smoker during pregnancy			
No	155 (52)	93 (51)	
Yes	133 (45)	85 (47)	0.74
Not reported, n (%)	9 (3)	3 (2)	
Maternal pre-pregnancy BMI, kg/m2	21.6 (19.6, 24.2)	21.5 (19.8, 23.7)	0.48
Not reported, n (%)	20 (7)	9 (5)	
Paternal age at enrollment, yr.	31 (26, 35)	30 (26, 35)	0.47
Not reported, n (%)	23 (8)	2 (1)	
PSS-4 score in early pregnancy			
Minimal	237 (80)	122 (67)	
Moderate to severe	59 (20)	34 (19)	0.58
Not reported, n (%)	1 (0)	25 (14)	
Sex of the child			
Boy	146 (49)	74 (41)	
Girl	151 (51)	88 (49)	0.48
Not reported, n (%)		19 (10)	

P-values were calculated using Chi-square test for categorical variables and Kruskal-Wallis test for continuous variables.


Externalizing Problems
Full Sample
Cortisol
DHEA
Cortisol:DHEA Ratio
Internalizing Problems
Full Sample
Cortisol
DHEA
Cortisol:DHEA Ratio
Behavior System Index
Full Sample
Cortisol
DHEA
Cortisol:DHEA Ratio
Bottom
Middle
Top
Tertile
Estimated Effect of the Intervention on the mean T-score

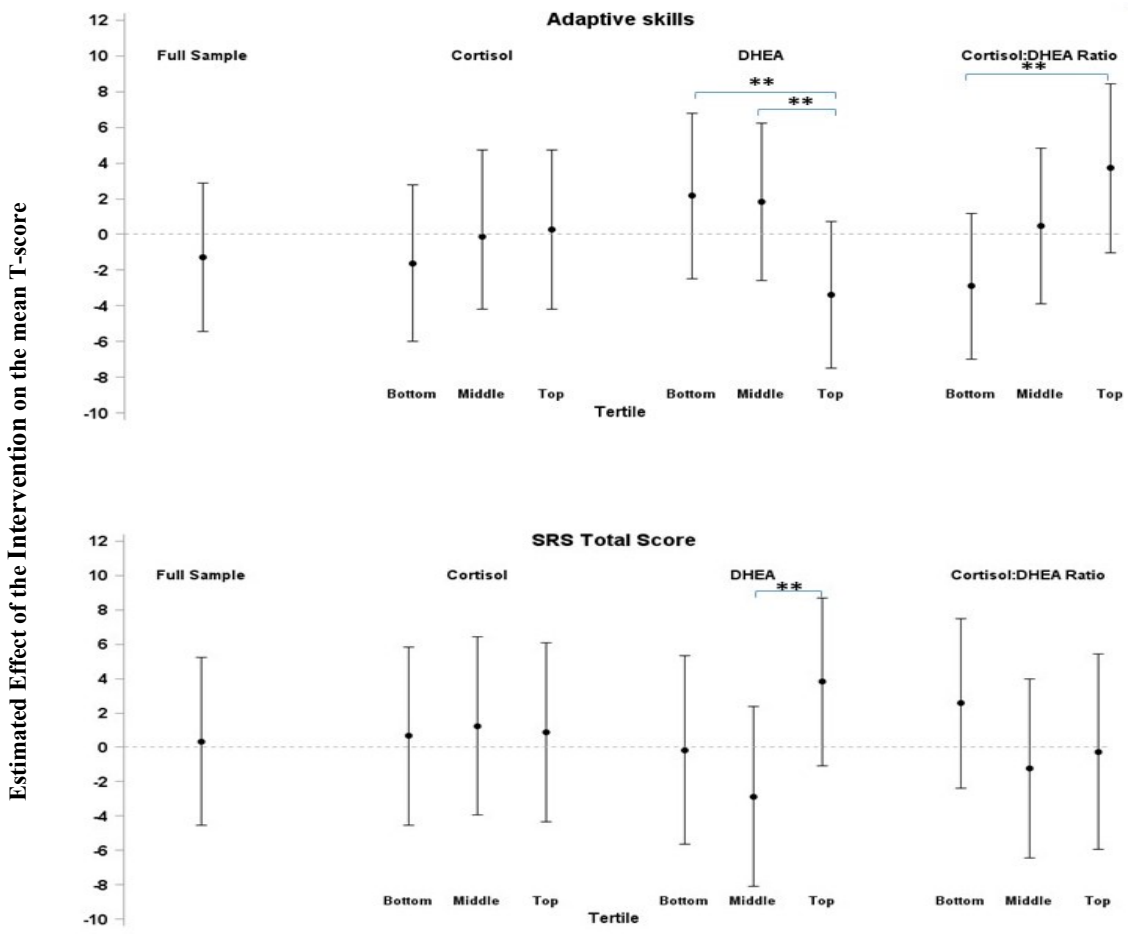


Figure C.1. Estimated effects of the intervention on BASC-3 and SRS-2 scores stratified by maternal stress levels during pregnancy (n=297).

Note:
After inclusion of additional terms the model: season of enrollment, maternal age at enrollment, marital status, preterm birth, intervention x season of enrollment, intervention x maternal age at enrollment. The figure illustrates estimated effects of the intervention on externalizing problems composite T-score, internalizing problems composite T-score, behavioral system index (BSI) T-score, adaptive skills composite T-score, SRS total T-score. For externalizing, internalizing, BSI and SRS total T-scores, a higher score indicates more social and behavioral problems. For adaptive skills scores, a lower score indicates more social and behavioral problems.

*Interaction $p<0.10$

**Interaction $p<0.05$

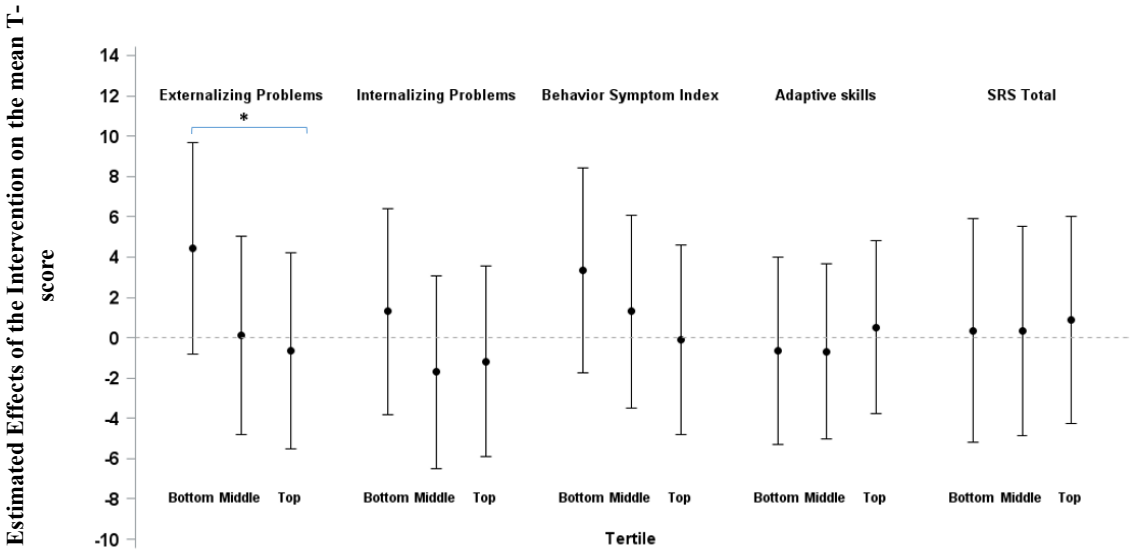


Figure C.2. Estimated effects of the intervention BASC-3 and SRS-2 scores stratified by maternal perceived stress scores during pregnancy (n=296).

After inclusion of additional terms, the model: season of enrollment, maternal age at enrollment, marital status, preterm birth, intervention x season of enrollment, intervention x maternal age at enrollment.

*Interaction $p<0.10$

Appendix D. Supplemental material for chapter five

Table D.1. Association between doubling of maternal blood cadmium concentrations on BASC and SRS outcomes at age 4 (n=319).

Outcomes	Crude		Adjusted*	
	Effect estimate	p-value	Effect estimate	p-value
SRS	3.04 (-0.75, 6.83)	0.12	2.64 (-1.25, 6.53)	0.18
Externalizing T	2.17 (-1.38, 5.72)	0.23	1.20 (-2.69, 5.09)	0.54
Internalizing	1.93 (-1.84, 5.70)	0.32	1.36 (-2.45, 5.18)	0.48
BSI	1.46 (-2.26, 5.18)	0.44	1.11 (-2.66, 4.88)	0.56
adaptive	-3.30 (-6.79, 0.19)	0.06	-2.70 (-6.31, 0.90)	0.14

*adjustment variables: BDI, mother's age, living with smoker late pregnancy, intervention status, child sex

Table D.2. Review of environmental inervention trials.

Author	Publication	Publication date	Study population/Intervention	Allocation concealment reported?	Types of blinding	Imbalance in baseline covariates?	Analysis used ITT or per-protocol?	Approaches on handling missing data	Covariate adjustment?	Comments
Alexander et al.,	Pregnancy outcomes and ethanol cook stove intervention: A randomized-controlled trial in Ibadan, Nigeria	2017	324 pregnant women randomized. 162 women into intervention (ethanol stove) and 162 to control group. The primary outcome is birth weight. Randomization was stratified by parity and the presence or absence of diabetes.	Not reported	Not reported	Baseline imbalance exist on marital status and BMI	ITT	Missing outcomes were excluded from the analysis	Yes. Adjustment is made on marital status and BMI because these variables differed at baseline.	Limitations: Primary outcome is subgroup of 3 different groups which lead loss of power in sample size.
Arbes et al.,	Abatement of Cockroach Allergen (Bla G 1) in Low-Income, Urban Housing: A Randomized Controlled Trial	2003	Total of 22 intervention homes and 17 control homes were randomized. Occupant education, insecticide and professional cleaning as intervention to abate cockroach allergy.	Not reported	Not blinded	2 Groups are similar in prognostic baseline covariates after randomization.	not reported	Missing outcomes were excluded from the analysis	Yes. Adjusted for one covariate (baseline allergen level)	Limitations: small sample size,6/22 homes in intervention and 2/17 homes in control groups withdrawn from the study.
Aung et al.,	Effect on blood pressure and eye health symptoms I a climate-financed randomized cookstove intervention study in rural Idea.	2018	111 women in intervention stove group and 111 women in control group were randomized. The primary outcome is the adjusted before and after mean difference in blood pressure	Not reported	Not reported	Imbalance in baseline blood pressure and eye health in the randomized groups.	ITT and pre-protocol analysis	Missing outcomes were excluded from the analysis	Yes. Adjustment made on imbalance in the baseline measurement of BP and eye symptoms.	Limitations: presence of differential dropout rate in the intervention and control groups (4 vs 19) and was not address in the analysis.

Barn et al.,	The Effects of portable HEPA filter air cleaner use during pregnancy on fetal growth	2018	540 pregnant women randomized into intervention (HEPA filter) and control group. Primary outcome is birth weight.	Yes	Single blinded. Assessors are blinded	2 Groups are similar in prognostic baseline covariates after randomization.	ITT and pre-protocol	Missing outcomes were excluded from the analysis	Yes. Adjustment made on preterm birth	Limitations: differential loss to follow up due to lack of blinding on participants. Strength: Trial reporting is explicit.
Batterman et al.,	Particulate matter concentrations in residences: an intervention study evaluating stand-alone filters and air conditioners	2012	126 households randomized into filter and CHW and room AC (enhanced intervention), filter and CHW visits (standard) and control group. Primary outcome is HEPA air filter in reducing PM concentration	No	Not blinded	Number of homes in each group and season were not balanced.	not reported	Multiple imputation	Yes. Adjustment made for household that passed home inspection and were eligible for an AC	Limitation: study sample size did not allow analyses to conduct interaction between season, filter use and AC and smoking-prognostic variables.

Bellinger et al.,	Neuropsychological and Renal Effects of Dental Amalgam in Children A Randomized Clinical Trial	2006	534 children of 6-10y. Amalgam or resin composite materials for caries treatment. Primary outcome is 5 year change to full scale IQ.	Yes	Single blinded. Outcome assessors are blinded.	2 Groups are similar in prognostic baseline covariates after randomization.	ITT	In primary analysis - method of last observation carried forward for complete dataset. Sensitivity analyses of multiple imputation conducted	Yes. Primary analysis- adjusted for baseline IQ score and randomization stratum.	Strength: Well-balanced baseline covariates, Limitations: short follow up period (5 y). Generalization of children younger than 5 may not apply. Underpowered to detect smaller reduction in IQ.
Boisson et al.,	Effect of Household-based Drinking Water Chlorination on Diarrhea among Children under Five Orissa, Idea: A Double-Blinded Randomized Placebo-Controlled Trial	2013	2163 children under 5 was randomized into intervention (sodium dichloisocyanurate tablets for water treatment) to place-control groups. Primary outcome is prevalence of Diarrhea based on child-days of observation.	Yes	Double blinded	2 Groups are similar in prognostic baseline covariates after randomization.	ITT	Missing outcomes were excluded from the analysis	Yes, Adjustment made for clustering within household	Big sample size study. Low adherence to the intervention.
Boisson et al.,	Field assessment of a Novel Household-Based Water Filteration Device: A Randomised, Placebo-Controlled Trial in the Democratic Republic of Congo	2010	240 household (1144 person) into 120 household in intervention and 120 in household in control group. Main outcome is the prevalence ratio of diarrhea.	Yes	Double blinded	2 Groups are similar in most prognostic baseline covariates after randomization.	ITT	Missing outcomes were excluded from the analysis	Yes, Adjustment made for clustering within household	Strength: Blinding assessment was conducted to validate on blinding procedure

Bradman et al.,	Community-Based Intervention to Reduce Pesticide Exposure to Farmworkers and Potential Take-Home Exposure to their Families	2008	44 strawberry workers randomized into 29 intervention (lightweight removal overalls and gloves) and 15 control group. Primary outcome is residues and malathion metabolites in workers urines.	No	Single blinded. Lab assessors are blinded	2 Groups are similar in prognostic baseline covariates after randomization. However, number of intervention and control participants are different	Not reported	Missing outcomes were excluded from the analysis	Yes. Adjustment made on metabolite levels for creatinine in the urine analysis	Stratified data based on the potential exposure risk factors (age, number boxes picked, smoking status, glove use)
Braun et al.,	Effect of Residential Lead-Hazard Interventions on Childhood Blood Lead Concentrations and Neurobehavioral Outcomes A Randomized Clinical Trial	2018	355 women randomized intervention and control groups. Intervention is reduction of dust lead loading at home. Outcome neurobehavioral changes at different age points	Yes	Single blinded. Assessors are blinded.	2 Groups are similar in most prognostic baseline covariates after randomization.	ITT and pre-protocol analysis	Missing outcomes were excluded from the analysis	Yes. Adjusted made on concentration models for child age at testing and baseline dust loadings levels.	Strength: longitudinal follow-up limitations: high lost to follow-up cases and no information on handling on missing information.
Butz et al.,	A Randomized Trial of Air Cleaners and a Health Coach to Improve Indoor Air Quality for Inner-City Children With Asthma and Secondhand Smoke Exposure	2011	126 children randomized into 3 groups of air cleaner and health education (intervention), air cleaner group or control group. Primary outcome is changes in PM, air nicotine and urine cotinine concentration	Yes	Double blinded. Participants and assessors are blinded	2 Groups are similar in most prognostic baseline covariates after randomization.	Not reported	Missing outcomes were excluded from the analysis	Not reported	Strength: 3 groups

Carter et al.,	Home intervention in the treatment of asthma among inner-city children	2001	104 children randomized into 3 groups of intervention, control and true control groups. Primary outcome is unscheduled clinic visits for asthma and changes in mite and cockroach allergen levels.	No	Single blinded. Participants are blinded	2 Groups are similar in most prognostic baseline covariates after randomization.	Not reported	Missing outcomes were excluded from the analysis	Not reported	3 arm trial with control and true control groups limitations small sample size 85/104 participants completed the study
Chan-Yeung et al.,	The Canadian Childhood Asthma Primary Prevention Study: Outcomes at 7 years of age	2005	545 pregnant mothers were randomized. Multifaceted Intervention of avoidance of house dust, pets and environmental tobacco smoke and encouragement of breast-feeding.	No	Not reported	2 Groups are similar in prognostic baseline covariates after randomization.	Not reported	Missing outcomes were excluded from the analysis	Yes. Adjusted for SES, sex, race, maternal and paternal history of asthma	Limitations: complete case analysis. Does not indicate ITT or per-protocol
Chard et al.,	Impact of a school-based water, sanitation, and hygiene intervention on school absence, diarrhea, respiratory infection, and soil-transmitted helminths: results from the WASH HELPS cluster-randomized trial	2019	100 primary schools were randomized into 50 intervention (water supply, sanitation facilities, handwashing, drinking water filter and behavior) and 50 control group. Primary outcomes are student absence from diarrhea, respiratory infections.	No	Not blinded	Mentions of groups being similar in prognostic baseline covariates after randomization.	ITT and pre-protocol analysis	Missing outcomes were excluded from the analysis	Yes. Adjustment made for district and visit number, student sex, grade, school enrollment size and season.	Limitation: The paper does not include comparison of baseline characteristics in the groups.
Custovic et al.,	Effect of environmental manipulation in pregnancy and early life on respiratory symptoms and atopy during first year of life: a randomized trial	2001	291 high risk couples were randomized into active (allergen impermeable bedding and high filtration vacuum cleaning) 145 and control 146 groups. Outcome is signs and symptoms of atopic disease at age 1.	No	Single blinded. Assessors are blinded	2 Groups are similar in most prognostic baseline covariates after randomization.	Not reported	Missing outcomes were excluded from the analysis	Not reported	Limitations: many of the RCT procedures and statistical approaches are not reported

Eggleston et al.,	Home environmental intervention in inner-city asthma: a randomized controlled clinical trial	2005	100 children were randomized into intervention (HEPA air cleaner, allergen proof mattress and pillow encasings, pest management, and training on indoor allergen sources and tobacco smoke control)	No	Not blinded.	2 Groups are similar on baseline covariates after randomization.	Not reported	Missing outcomes were excluded from the analysis	Yes. Adjustment made on baseline symptoms of allergy	Limitations: analysis is not described. No indication of ITT or per-protocol. Allocation procedure not indicated.
Hellard et al.,	A randomized, blinded, controlled trial investigating the gastrointestinal health effects of drinking water quality	2001	600 families in Melbourne randomized into real and sham water treatment. Primary outcome is incidence of gastroenteritis (HCG)	No	Double blinded	2 Groups are similar in most prognostic baseline covariates after randomization.	Not reported	Not reported	Yes. Adjustment made for age sex, region of residence	The study does not have trial profile included
Kvestad et al.,	Fatty fish, hair mercury and cognitive function in Norwegian preschool children; Results from the randomized controlled trial FINS-KIDS	2018	232 children were randomized. 114 into intervention (fatty fish) group while118 into control (mean) group.	Yes	Single blinded. Clinical Assessors are blinded	2 Groups are similar in most prognostic baseline covariates after randomization.	Not reported	Missing outcomes were excluded from the analysis	Yes. Adjustment made for pre-total mercury level in hair and sex and SES.	Strength: well reported exposure and lab assessment. Limitations: Statistical approaches are lacking. No sensitivity analysis which lead to lack of validation on the primary outcome.

Lanphear et al.,	Long-Term Effect of Dust Control on Blood Lead Concentration	2000	275 urban children are randomized into intervention (cleaning equipment and visits for lead control) and control group. The primary outcome is the GM Blood lead level concentration	No	Not reported	2 Groups are similar in most prognostic baseline covariates after randomization.	Not reported	Missing outcomes were excluded from the analysis	Yes. Adjustment made on housing condition and black race	Limitations: many of the RCT procedures and statistical approaches are not reported
Lanphear et al.,	Effects of HEPA Air Cleaners on Unscheduled Asthma Visits and Asthma Symptoms for Children Exposed to Secondhand Tobacco Smoke	2010	effects of HEPA air cleaners, in the homes of 225 SHS exposed children with physician diagnosed asthma, on unscheduled asthma visits and symptoms.	Yes	Double blinded. Participants and field assessors are blinded	imbalance in unscheduled visits and PM in study population after randomization	ITT	Missing outcomes were excluded from the analysis	Yes. Adjusted for baseline exposure and asthma visit covariates.	limitations: imbalance in baseline covariates
Luczynska et al.,	A Randomized controlled trial of mite-allergen-impermeable bed covers in adult mite-sensitized asthmatics	2003	Total of 58 patients randomized but 55 continued and 3 disqualified after randomization. 30 in active and 25 in the placebo control group were randomized. Primary outcome is the peak flow.	No	Double blinded. Participants and assessors are blinded	2 Groups are similar in most prognostic baseline covariates after randomization.	Not reported	Missing outcomes were excluded from the analysis	Yes. Adjusted for age and sex.	Very strict eligibility criteria. Out of 55/3547 participants met the eligibility for the study. Small sample size with big dropout among participants
Mausezahl et al.,	Solar Drinking Water Disinfection (SODIS) to reduce Childhood Diarrhoea in Rural Bolivia: A cluster-Randomized, Controlled Trial	2009	225 household were randomized into intervention group (solar disinfection of water) 200 households into control group. Primary outcome is the incidence of gastrointestinal illness in children	Yes	Not blinded.	2 Groups are similar in most prognostic baseline covariates after randomization.	ITT	Missing outcomes were excluded from the analysis	Yes. Adjusted on child's age, sex, hand-washing, behavior and water treatment at baseline selected with a priori. Also, adjustment made on clustering	Dropout rate among 2 group almost equal even the study was not blinded

Morgan et al.,	Results of a Home-Based Environmental Intervention among Urban Children with Asthma	2004	937 children randomized into environmental intervention (remediation for exposure to allergens and tobacco smoke) and control group.	No	Not blinded. Participants or field evaluators are not blinded only interviewers were blinded to the group	2 Groups are similar in most prognostic baseline covariates after randomization.	ITT	Missing outcomes were excluded from the analysis	Yes. Adjustment made on baseline symptoms and study sites.	Not blinded to the participants and field assessors.
Rosa et al.,	Assessing the Impact of Water Filters and Improved Cook Stoves on Drinking Water Quality and Household Air Pollution: A Randomised Controlled Trial in Rwanda	2014	566 homes were randomized into 285 intervention (water filter and chimney stove) and 281 homes control group. Primary outcomes are fecal contamination in stored water in the homes and 24h concentration of $PM_{2.5}$	Yes. Lottery based	Not blinded	2 Groups are similar in most prognostic baseline covariates after randomization. Exception of availability of soap among households in the two group.	ITT	Missing outcomes were excluded from the analysis	Adjustment made on baseline PM measurement.	Limitations: low compliance of intervention. 26.9% of the intervention group were using intervention stove during visits.
Smith et al.,	Effect of reduction in household air pollution on childhood pneumonia in Guatemala (RESPIRE): a randomized controlled trial	2011	534 households with pregnant woman or young infant randomized into stove with chimney and open fire stove. Primary outcome is physician-diagnosed pneumonia.	Yes	Single blinded. Physicians are blinded.	2 Groups are similar in prognostic baseline covariates after randomization.	ITT	Multiple imputation	No.	Strength: Trial reporting is explicit. Big sample size limitation: single blinded which effected the differential rate on RSV.
Terreehorst et al.,	Evaluation of Impermeable Covers for bedding in Patients with Allergic Rhinitis	2003	276 patients with rhinitis randomized into intervention and control group for impermeable covers. Primary outcome is rhinitis severity.	No	Double blinded	2 Groups are similar in prognostic baseline covariates after randomization.	ITT	Missing outcomes were excluded from the analysis	Yes. Adjustment made on baseline differences in the two groups	Too many subgroup analysis (multiple allergens, characteristic of patient's home, level of exposure)

Woodcock	Control of Exposure to Mite Allergen and Allergen-Impermeable Bed Covers for Adults with Asthma	2003	1122 adults with asthma randomized into intervention (allergen – impermeable bed covers) and placebo control (non-impermeable bedding). Primary outcome is mean morning peak expiratory flow rate for 4 weeks.	No	Double blinded	2 Groups are similar in prognostic baseline covariates after randomization.	Not reported	Missing outcomes were excluded from the analysis	Yes. Adjustment made on baseline differences in the expiratory flow.	Limitations: statistical approach and handling of missing data is not described