An Air Cleaner Intervention Study of Air Pollution and Children's Cognitive Development: The Ulaanbaatar Gestation and Air Pollution Research (UGAAR) study

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Abstract

Background: Prenatal exposure to fine particulate matter ($PM_{2.5}$) may impair children's neurodevelopment. Effects of indoor $PM_{2.5}$ on neurodevelopment, and the neurodevelopmental benefits of using portable high efficiency particulate air (HEPA) filter air cleaners to reduce $PM_{2.5}$, have not been evaluated.

Objectives: My research aimed to (1) evaluate the impact of HEPA filter air cleaner use during pregnancy on neurodevelopment, (2) identify characteristics of children who benefitted the most after their mothers used HEPA filter air cleaner during pregnancy, and (3) examine the association between indoor $PM_{2.5}$ concentrations during pregnancy and neurodevelopment in childhood.

Methods: Study staff assigned 540 nonsmoking pregnant women at ≤ 18 weeks gestation to receive 1-2 portable HEPA filter air cleaners or no air cleaners during pregnancy. Health, demographic, and lifestyle data were collected through home and clinical visits and from clinic records. Maternal hair samples were analyzed for cortisol and dehydroepiandrosterone (DHEA). The primary outcome was full-scale intelligence quotient (FSIQ) measured by using the Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (WPPSI-IV), when children were a median of 48 months old. I estimated the effect of the intervention on mean FSIQ using multiple imputation with chained equations (MICE) in an intention to treat analysis. I also evaluated potential modifiers of the intervention-FSIQ relationship. Finally, I used estimates from a previously developed model of indoor $PM_{2.5}$ concentrations to examine the relationship between indoor $PM_{2.5}$ averaged over the full pregnancy and each trimester and FSIQ.

Results: The mean FSIQ among children in intervention group was 2.5 points (CI: −0:4, 5.4 points) higher than that of children in the control group. The largest between-group difference in the intervention's effect was a 7.5-point (95% CI: -0.7, 15.7) larger increase in mean FSIQ among children whose mothers did not take vitamins than among children whose mothers did take vitamins. A 9.4 $\mu g/m^3$ increase in indoor $PM_{2.5}$ concentration over the full pregnancy was associated with

a reduction of 1.1 points (95% CI: -3.7, 1.5) in mean FSIQ. A 20.7 $\mu g/m^3$ increase $PM_{2.5}$ concentrations during first trimester was associated with a reduction of 3.5 points (95% CI: 0.7, 6.6) in mean FSIQ.

Conclusions: Indoor $PM_{2.5}$, particularly during early pregnancy, may impair children's brain development but reducing exposure improved mean FSIQ scores. This benefit was more pronounced for children of mothers who did not take vitamins during pregnancy.

Keywords: $PM_{2.5}$, RCT, portable HEPA filter, neurodevelopment, IQ, stress

Dedication

This study is wholeheartedly dedicated to my beloved children, Temulen, Tsetsen and Enerel whose endless laughter and boundless curiosity have brought me immeasurable happiness and filled my life with meaning and purpose. They inspired me to be a voice for all children in Mongolia, advocating for their health and well-being. To my dear husband who selflessly put his career on hold to support me and my passion and faced every challenge that came our way with unwavering composure and endless love, I am eternally grateful.

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I would also like to express my sincere gratitude to my parents, who selflessly dedicated their lives to support my pursuit of passion. You worked tirelessly without complaints to ensure that I had every opportunity to pursue my dreams. Your unwavering belief, support and sacrifices have played a key role in shaping the person I am today, and I am forever grateful. To my sisters and brothers, I extend my gratitude for their guidance and encouragement.

Completing this dissertation has been a long and challenging journey, I am grateful to all those who have supported me along the way. Your contributions and belief in my abilities have been instrumental in my success.

Table of Contents

List of Tables

List of Figures

List of Acronyms

ASD   Autism spectrum disorder

CNS   Central nervous system

DHEA   Dehydroepiandrosterone

FSIQ   Full Scale-IQ

HEPA   High Efficiency particulate air

HOME   Home observation measurement of environment

HPA   Hypothalamic-pituitary-adrenal

ITT   Intention-to-treat

MICE   Multiple imputation with chained equations

PAH   Polycyclic aromatic hydrocarbons

PM   Particulate matter

$PM_{2.5}$ Fine particulate matter

PSS   Perceived Stress Scale

RCT   Randomized controlled trial

PTB   Preterm birth

UGAAR   Ulaanbaatar Gestation and Air Pollution Research

WASI   Wechsler Abbreviated Scale of Intelligence

WPPSI-IV   Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition

Preface

This thesis is organized into five chapters. Chapter one is an introductory chapter that provides a background, rationale, and the research questions addressed in this work. Chapter five serves as a summary of my work, synthesizing the key findings and providing an analysis of their significance. Chapters two, three, and four are research chapters that were written as manuscript for publication. At the time of this thesis submission, chapter two had been published in *Environmental Health Perspective* and chapter three had been accepted for publication in *Environmental Research*:

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Allen. Prenatal exposure to indoor PM2.5 and children's cognitive performance at 4 years of age: an observational analysis from the UGAAR randomized controlled trial.

Chapter 1.

Introduction

This literature review contains five sections. The first section provides a summary of the UGAAR study and its previous findings (1.1). In the second section, I briefly describe particulate matter, the major pollutant of interest in my research (1.2). The third section provides a background on measures of neurodevelopment in prenatal and postnatal periods (1.3). The fourth section provides a summary of the relationships between ambient air pollution and neurodevelopment (1.4). Finally, in the fifth section I discuss possible effect modifiers in the relationship between air pollution and neurodevelopment (1.5).

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

The UGAAR study is a randomized controlled trial designed to investigate the impact of air pollution exposure during gestation on children's health and development outcomes. Eligible pregnant women were randomly assigned to either an intervention group, which received 1-2 high efficiency particulate air (HEPA) filter air cleaners to the end of pregnancy, or a control group, which did not receive air cleaners. Because the air cleaner intervention was removed soon after the end of pregnancy, the UGAAR study is uniquely positioned to isolate the influence of prenatal exposure on development.

Previous analyses from UGAAR have focused on fetal growth, adiposity, and child behavioural development (Barn et al., 2019; Barn et al., 2018a; P. Barn et al., 2018b; Enkhbat et al., 2021, 2022; Tamana et al., 2021). Barn et al., (2018a) reported that using HEPA air cleaners reduced the mean indoor fine particulate matter concentration by 29% (95% CI: 21, 37%) (Barn et al., 2018a). The intervention was associated with an 85 g increase (95% CI: 3, 167 g) in mean term birth weight (Barn et al., 2018b). However, Enkhbat et al., (2021, 2022) did not find

benefits from use of air cleaners on parent-reported autistic traits or behaviour in children at age 4 (Enkhbat et al., 2021, 2022). Enkhbat and colleagues did report, however, that indoor $PM_{2.5}$ concentrations, particularly those during the first trimester of pregnancy, were associated with autism-related behaviours and other behaviour problems at age four (Enkhbat et al., 2022).

1.2. Air pollution

Air pollution is a leading environmental threat to human health (Health Effects Institute, 2020). Air pollution is a mixture of gases and particulate matter (PM) with different sizes, compositions, and shapes. The pollutants can be generated from natural sources such as forest fires and by human activities such as motor vehicles, industrial activity, power plants, and household combustion for heating and cooking (Block et al., 2012).

1.2.1. Particulate Matter

Particulate matter (PM) is a crucial component of air pollution and is often defined by its aerodynamic diameter. Particle size is important because it influences the amount and location of deposition within the respiratory tract. Specifically, PM has often been classified into three categories based on the particle size range: coarse particles larger than 2.5 μm in aerodynamic diameter, fine particles smaller than 2.5 μm in aerodynamic diameter ($PM_{2.5}$), and ultrafine particle smaller than 0.1 μm (World Health Organization, 2006).

PM can be also classified as primary particles, which are emitted directly into the atmosphere, and secondary particles that are formed from precursors through physical and chemical transformation in the atmosphere (Suzuki et al., 2003). The major sources of PM are natural sources including forest fires, pollen, and volcanic ash and anthropogenic activities such as fossil fuel combustion, industrial processes, construction, and agriculture.

1.2.2. Fine Particulate Matter

$PM_{2.5}$ is produced by mobile sources such as motor vehicles, stationary sources such as industrial facilities and power plants, natural sources like wildfires, and secondary formation in the atmosphere (Brockmeyer & D'Angiulli, 2016). The composition of $PM_{2.5}$ varies, but it commonly contains carbon, sulfate and nitrate (World Health Organization, 2016). Compared to larger particles, $PM_{2.5}$ can remain suspended in the air for a longer duration, be transported over longer distances, penetrate more readily into buildings, and be inhaled more deeply into the lungs (Kampa & Castanas, 2008; Pope & Dockery, 2006). Over 90% of the global population breathes air that exceeds the World Health Organization (WHO) $PM_{2.5}$ annual average guideline concentration of 5 ug/m^3 (Health Effects Institute, 2020).

1.3.   Neurodevelopment

Human brain development is a complex process. Over the course of gestation, considerable morphological changes take place in the fetal brain (Huang & Vasung, 2014). Although this major transformation takes place in the prenatal period, neurodevelopment continues through early life into late adolescence (Stiles & Jernigan, 2010). To understand how and why the human central nervous system (CNS) is vulnerable to environmental exposures such as air pollution, it is appropriate to first characterize the development of the CNS and explore periods of heightened vulnerability.

1.3.1. Neurodevelopment in the Prenatal Period

The human brain is susceptible to neurotoxins in utero due to the highly sequenced and complex processes involved in brain development. Neurons proliferate mostly during prenatal development and once damaged, neurons cannot be replaced or replicated, leading to permanent impairment (Rice & Barone, 2000; Rodier, 1995). These unique developmental processes make the CNS more susceptible than other organs to exogenous agents (Stiles & Jernigan, 2010), such that many of these

agents can cause damage in the CNS but comparatively little damage to other organs (Rodier, 1995).

The first stage of CNS development occurs during the embryonic period through the neurulation process in which neural tubes form. The neural plate, which is overlaying ectodermal tissue, is elevated to create neural folds and these folds merge and fuse to construct neural tubes in the cranial region (Greene & Copp, 2009). This neural tube process takes place from gestational day (GD) 18 to GD 28 (Rice & Barone, 2000). Globally at least 200,000 infants are born with neural tube defects each year; 75% of those affected die within the first five years of life (Blencowe et al., 2018).

Recent evidence indicates the importance of prenatal folate on normal brain development. Animal studies suggest that morphological and physiological alterations in the brain can occur when folate levels are either excessive or deficient during the prenatal period (Naninck et al., 2019). Specifically, studies have reported that folate is required for both DNA synthesis and DNA repairing processes in mice brains. Human studies indicate that pre-conceptional folic acid supplementation is associated with larger embryonic cerebellar size. Insufficient intake of folate during pregnancy has been associated with lower cognitive performance scores in childhood, although results are not consistent across studies (Naninck et al., 2019).

At the initial stage of CNS development, cells start to proliferate. The nerve cells that control human muscle movements are created prior to neurons that transport, relay and receive information. Nerves cells are more diverse than any other cell type in the human body. Other organs are constructed with comparatively fewer types of cells that formed early, and their numbers subsequently increase. However, the human brain has diverse types of neuron cells that are generated throughout the prenatal phase. Once the proper number of cells have been developed, cells migrate to their final destinations (Rodier, 1995). Cell migration in the CNS takes place at the early phase (7 to 18 gestational weeks) of

corticogenesis, the formation of the cerebral cortex, ensuring that the distance they must travel is short. Neurons can travel through this shorter distance from ventricular zones to the outer surface of the developing brain; however, when the brain increases in size during later developmental stages, neurons traverse through the basal process attaching to radial glial cells (Stiles & Jernigan, 2010).

Any environmental insult that occurs during this transfer period could cause abnormal locations of the neurons. For example, if glial guides are impaired, the neurons migrating through glial cells could be trapped and would no longer be able to reach their final destinations (Barkovich et al., 1987). Neurons that do not reach their proper position will not establish necessary communication with other neurons to deliver and receive information. The neural network is essential for developing brain and its proper functions (Barkovich & Kuzniecky, 2000). Although neurons can still make connections with other cells throughout our lives, the primary CNS structures are formed only during the prenatal period (Rodier, 1995).

After migrating, neurons start to grow longer and put forth receiving ends, dendrites, and transmitting ends, the axons. The surrounding environment is sampled for guidance cues; some are attractive, and others are repulsive. Through this signaling, the axons reach their designated cells and establish connections. These links are called synapses, which enable electrochemical information transfer through the neurons (Stiles & Jernigan, 2010).

When the appropriate cell connections are formed, apoptosis or natural cell death takes place to remove unnecessary nerve cells. This natural nerve cell death differs from necrosis, as during apoptosis cells are eliminated in a structured manner without causing inflammation, leaving the CNS with an appropriate quantity of functional neurons (Rice & Barone, 2000). The purpose of apoptosis is still unclear. Limited resources and nourishment from the target cells and space limitations on the membrane are thought to result in competition among mass-produced neurons. Further, some neurons may have migrated to an inappropriate location and elimination of these cells helps prevent brain development disorders

(Voci, 1992). Because apoptosis mainly occurs during the prenatal period, it is a crucial period in which exogenous agents could cause cell deaths leaving improper numbers of cells within the CNS (Rice & Barone, 2000).

Like apoptosis, which eliminates the excessively produced neurons during the developmental period, pruning helps achieve the optimal number of connections and efficient neural networking in the brain (Prechelt, 1997). The pruning process starts during fetal development and continues after birth (Stiles & Jernigan, 2010).

1.3.2. Neurodevelopment in the Postnatal Period

Although much of CNS development takes place during the prenatal period, some developmental processes continue after birth (Rice & Barone, 2000; Rodier, 1995). Postnatal developmental occurs gradually, which makes postnatal brain development vulnerable to environmental exposures (Dyck & Morrow, 2017). Because of the brain's plasticity, environmental factors and stimuli encountered during this development stage can modify brain development (Kolb & Gibb, 2011). This adaptation is thought to be regulated by myelination. The myelin is a membrane structure that wraps around the axons and increases the velocity of nerve signals (Shonkoff et al., 2000). Social and physical stimulants can influence the myelination process, in turn impacting CNS networking (Snaidero & Simons, 2014).

After birth, small numbers of neurons continue to form for the olfactory bulb and certain areas of the hippocampus. Glial cells, which support neurons, continue to form long after birth (Stiles & Jernigan, 2010). Other cell types are also generated from the late prenatal to postnatal periods. These include microglia, which are immune cells that act as macrophages to digest and destroy pathogens and dead cells; oligodendroglia, which wrap around axons to form myelin in the CNS; and Schwann cells that form myelin in the peripheral nervous system (Rice & Barone, 2000). Just as neurons and glial cells are produced in excess then pruned during the prenatal period, the pruning of the synapses occurs mostly during the postnatal period (Stiles & Jernigan, 2010).

1.4. Epidemiologic Evidence of Air Pollution and Neurodevelopmental Dysfunction and Delay

Several epidemiologic studies have examined relationships between air pollution exposure and neurodevelopment in children. A 2015 meta-analysis incorporated 31 studies focused on ambient air pollution and children's neuropsychological development (Suades-González et al., 2015). PM, NO_x and polycyclic aromatic hydrocarbons (PAHs) were the most commonly studied pollutants, but some studies included ozone, black carbon, and carbon monoxide (CO). Intelligence quotient (IQ) was the most studied outcome, and the studies utilized several neuropsychological tests including the Wechsler Intelligence Scale of Children (WISC) and Gesell Developmental Scale (GDS). Participants' ages ranged from 6 month to 17 years. The authors concluded that there is an association between pre or postnatal PAH exposure and reduced global IQ in children. The authors also noted that there is an association of both pre and postnatal exposure to $PM_{2.5}$ and NO_x with autism spectrum disorder (ASD). Due to the limited number of studies and their low quality, the other exposure-outcome relationships were characterized as having inadequate or insufficient evidence (Suades-González et al., 2015). Another systematic review paper in 2016 included 31 studies exploring the association between air pollution exposure and cognitive functions across the lifespan (Clifford et al., 2016). That review included 18 studies that investigated children between one and 14 years of age. PM, PAH, black carbon, and NO_2 were the most frequently studied pollutants. Cognitive outcomes in childhood were most commonly assessed by the Raven Coloured Progressive Matrices and the Bayley Scales of Infant Development. The review divided studies of children into those focused primarily on prenatal or postnatal exposure. The authors concluded that the evidence is suggestive of a relationship between prenatal and postnatal air pollution – particularly traffic-related air pollution (TRAP) – and several cognitive measures in childhood including neurodevelopment, intelligence, and memory. The review also highlighted some evidence of effect modification by sex, with boys being more susceptible. Finally, the review noted associations between prenatal exposure to air pollution and intelligence at 3-5 years of age (Clifford et al., 2016).

Several more studies have been published since Clifford and colleagues reviewed the literature in 2016. Pujol et al. (2016) assessed the impact of TRAP on 263 children between 8 to 12 years of age as a part of the BREATHE project in Barcelona, Spain. The pollutants evaluated in the study were elemental carbon and NO_2, measured both in a classroom and outdoor playground. Computerized tests were used to measure working memory, motor response speed and attention. Children whose schools were in high-traffic areas had a significantly slower reaction time. The authors concluded that higher exposure contributed to slower brain maturation in children (Pujol et al., 2016).

Chiu et al. (2016) explored the association between prenatal exposure to $PM_{2.5}$ and children's neurodevelopment at age 6. The investigators used the Wechsler Intelligence Scale for Children (WISC) to measure IQ, Conners' Continuous Performance Test-II (CPT-II) to evaluate attention and response, and the Wide Range Assessment of Memory & Learning, 2nd Edition (WRAML-2) to measure immediate and delayed memory. The sex-stratified analyses revealed a significant association between $PM_{2.5}$ exposure in late pregnancy and lower IQ score in boys only. Furthermore, higher exposure to $PM_{2.5}$ during mid-pregnancy was associated with a lower sustained attention resulting in omission errors (not doing what they are requested to do) among boys. However, in girls, poorer general memory, lower attention-concentration, and visual memory were associated with higher exposure to $PM_{2.5}$ regardless of the specific period of pregnancy. The authors concluded that $PM_{2.5}$ may have "sex-specific and time-dependent" adverse effects on cognitive and behavioural development (Chiu et al., 2016).

A recent meta-analysis examined 10 studies assessing prenatal exposure to NO_2 on children's neurodevelopment outcomes such as cognition, language, psychomotor, emotion, and IQ, among children 6 months to 8 years old (Shang et al., 2020). Most of the studies were prospective birth cohorts in Europe or Asia. Although the studies did not support an association with general cognitive and language scores, the authors estimated that a 10 ug/m^3 increase in prenatal exposure to NO_2 was associated with a 0.76-point decrease in mean global

psychomotor scores (95% CI, -1.34, -0.18) and a 0.63-point decrease in mean fine psychomotor scores (95% CI, -1.09, 0.16) in children (Shang et al., 2020).

Most recently, Ni and colleagues studied the relationship between prenatal and postnatal exposure to NO_2 and $PM_{2.5}$ and child behaviour and cognition among 1,967 mother-child dyads from three U.S. birth cohorts (Ni et al., 2022). During a clinical visit at 4 – 6 years of age, the children completed the Child Behavior Checklist, and cognitive assessments using the Stanford-Binet Intelligence Scale, Wechsler Intelligence Scale for Children, and Wechsler Preschool and Primary Scale of Intelligence. The authors found no association between prenatal exposure to NO_2 and cognition. However, they found that a 2 ppb contrast in NO_2 during the first trimester, second trimester, and whole pregnancy were associated with 0.70-unit (95% CI: 0.13, 1.27), 0.92-unit (95% CI: 0.31, 1.53), and 1.24-unit (95% CI: 0.39, 2.08) changes in total behavioural problem scores, respectively. For $PM_{2.5}$, the authors found that each 2 µg/m^3 increase in postnatal exposure was associated with a 3.59-unit (95%, CI: 0.35, 6.84) increase in mean total behavioural problem scores and a 2.63-unit lower (95%, CI: -5.08, -0.17) mean IQ at age 2-4 years (Ni et al., 2022).

1.4.1. Possible Biological Mechanisms Linking Air Pollution Exposure with Children's Neurodevelopment

Prenatal exposure:

The biological mechanisms linking air pollution exposure during pregnancy and children's neurodevelopment are still not well understood. However, some possible mechanisms have been suggested.

A recent study has shown that black carbon particles, a component of combustion-derived particulate matter, can be found on the fetal side of the human placenta, indicating that nano-sized particles may be able to pass through the placental barrier (Bové et al., 2019). This is consistent with previous studies demonstrating the translocation of nanosized particles and silver nanoparticles across the

placental barrier (Vidmar et al., 2018; Wick et al., 2010). It is also hypothesized that exposure to particulate matter may impair the blood-placental-barrier, allowing particles to enter the fetal brain directly (Onoda et al., 2014). Once inside the fetus, the translocated particles can trigger inflammatory responses in the fetal brain (Yi et al., 2022). Additionally, exposure to particulate matter can induce systemic inflammatory responses in both the mother and fetus, leading to release of pro-inflammatory cytokines that can cross the placental barrier and cause neuroinflammation in the developing brain (Morris et al., 2021). Inflammation and oxidative stress have been suggested as key mechanisms through which prenatal exposure to air pollution can impact fetal brain-development. Moreover, exposure to particulate matter can increase the production of reactive oxygen species, which can travel through the mother's circulations and reach to fetus' organs, potentially impairing development (Daellenbach et al., 2020). Furthermore, it has been observed that exposure $PM_{2.5}$ can lead to fetal growth restriction, which in turn may impair childhood neurodevelopment (Michikawa et al., 2017). While the understanding of these mechanisms is still evolving, these studies provide important insights into how air pollution exposure during pregnancy may affect the developing brain.

Postnatal exposure:

Observations from animal experiments, postmortem human studies, and epidemiological studies have provided valuable information on potential mechanisms linking air pollution with the human CNS.

The mechanisms through which air pollution affects the human brain vary depending on the composition of the air pollution and the timing of the exposure (Allen et al., 2017). Based on current evidence, air pollutants may act on the brain through multiple, overlapping mechanisms. The blood brain barrier (BBB) is critical for maintaining homeostasis and selectively allowing substances to pass from the systemic circulation to the brain (Saunders et al., 2012). Pollutants may cause oxidative stress in the brain, thereby inducing systemic inflammation and

generating signaling cytokines that can pass through the BBB. In addition, pollutants may contact the brain directly, either by passing into the bloodstream and through the BBB or by direct transport through the olfactory bulb (Genc et al., 2012).

Oxidative stress and inflammation

Oxidative stress results from a lack of antioxidants and/or a surplus of reactive oxygen species (ROS), which contain unpaired electrons (Rahal et al., 2014). When the human body identifies exogenous agents, immune cells naturally produce these ROS (Hossain et al., 2011). Although these unstable and reactive free radicals are a natural part of the immune response, a surplus of ROS can lead to oxidative stress when the available antioxidants in tissues and cells are overwhelmed (Knight, 2000).

When ROS overcome the natural defences of antioxidants, cytokines and chemokines initiate a proinflammatory response (Yang et al., 2007). In addition, once air pollutants deposit in the airway, epithelial cells give rise to macrophages, which in turn leads to increased concentrations of inflammatory cytokines such as interleukin-1β (IL-1β) and interleukin-6 (IL-6). When in the systemic circulation, these cytokines can move into the central nervous system by crossing the BBB. There the cytokines signal the neurons to initiate inflammation in the brain (Block & Calderón-Garcidueñas, 2009; Brockmeyer & D'Angiulli, 2016).

In-Vivo Studies:

Animal experimental studies have enhanced our understanding of the biological mechanisms through which air pollution affects the CNS. Many animal studies have focused specifically on diesel exhaust particles. In one study, after exposing rats to diesel exhaust for a month the investigators found increased levels of protein nitration, a marker of oxidative stress, in the brain and generalized neuroinflammation (Levesque et al., 2011). More recently, adult mice exposed to diesel particles for 6 hours showed increased lipid peroxidation and neuroinflammation in the hippocampus and the olfactory bulb. Lipid peroxidation

is another indicator of oxidative stress. Lipid peroxidation occurs when oxidation products such as ROS attack the fatty acids and damage the cell membranes and eventually the cells themselves (Costa et al., 2017). Gerlofs-Nijland and colleagues randomly allocated male rats into a group exposed to diesel exhaust or a control group. After exposing the rats for four weeks, the authors reported the presence of proinflammatory cytokines, TNF-α and IL-1α, in the olfactory bulb, hippocampus, and cerebellum. These cytokines were significantly increased in the striatum of the diesel exposed rats when compared to the unexposed rats (Gerlofs-Nijland et al., 2010). Another experimental study found that the diesel engine exhaust caused increased concentrations of TNF-α in serum and in the whole brains of rats. The highest level of proinflammatory response was in the midbrain (Levesque et al., 2011).

Scientists have also exposed experimental animals to different sizes of PM to determine their impacts on CNS oxidative stress and inflammation. In one study, the olfactory bulb, cerebral cortex and hippocampus of rats were exposed to three different concentrations of $PM_{2.5}$. $PM_{2.5}$-induced lipid peroxidation was observed in the hippocampus and led to oxidative imbalance in neuron cells (Fagundes et al., 2015). Another experimental study exposed adult mice to nano-sized PM for 5, 20 and 45 cumulative hours and found elevated 3-Nitrotyrosine (3-NT), a biochemical marker of lipid oxidation, in the olfactory neuroepithelium. After 45 hours of exposure, 3-NT was elevated in both the olfactory neuroepithelium and the olfactory bulb (Cheng et al., 2016). A study in which rats were exposed to $PM_{2.5}$ pre- and postnatally produced increased oxidative stress in the cortex of the brain and short-term memory impairments (Zanchi et al., 2010). Mexico City is among the most highly polluted cities and in a 2008 study, researchers in Mexico City used magnetic resonance imagining (MRI) to determine the impact of ambient air pollution on healthy young dogs. There was significant upregulation of cyclooxygenase 2 (COX2), which is expressed in response to cytokines and inflammatory conditions in the brain (Minghetti, 2004). In addition, increased levels of interleukin 1 β (IL-1β), a proinflammatory cytokine that responds to injury in the white matter, was observed (Calderón-Garcidueñas et al., 2008). Correspondingly,

ApoE-/- mice were shown to have more proinflammatory cytokines in the brain after exposure to PM (Campbell et al., 2005).

Human Studies:

A 2006 literature review summarized three ways that PM can induce oxidative stress in the human brain (Knaapen et al., 2004). First, the surfaces of particles are often covered with organic compounds and transition metals that can lead to highly reactive free radicals in cells, which can cause damage in lipids and proteins (Peters et al., 2006). Second, PM may cause mitochondrial dysfunction, especially in the neuronal mitochondria, which in turn can generate free radicals. Third, PM exposure can lead to the production of ROS and oxidative stress through the activation of phagocytic oxidative burst in inflammatory cells (Knaapen et al., 2004; Risom et al., 2005). The first mechanism involves the acellular generation of ROS, whereas the latter two involve the intracellular formation of ROS (Knaapen et al., 2004). In addition, oxidative stress may alter gene expression and indirectly oxidize proteins and lipids (Luo et al., 2006). A 2017 study exposed human neuroblastoma cells to diesel exhaust particles at varying concentrations for 3 or 24 hours. The researchers reported a significant decrease in cell viability in correlation with increasing concentrations of diesel exhaust. Gluconeogenic enzymes such as phosphoenolpyruvate carboxykinase (PEPCK) were upregulated in the exposed neurons in association with oxidative stress (Ji et al., 2019). A study conducted by Campbell and colleagues was the first to use a human brain cell to explore the toxicity of ultrafine particles (UFP). The authors exposed human neurons, astrocytes, and microglia to UFP for 24 hours. Contrary to the results from Ji and colleagues, Campbell et al. reported decreased ROS in the exposed neurons and no alteration in cell morphology or viability. The authors suggest that this surprising finding may be related to changes in human neuronal bioenergetics and mitochondrial dynamics (Campbell et al., 2014).

Clinical post-mortem human studies have also been used to investigate the association between air pollution and brain damage. Calderon-Garcidueñas et al., (2008) conducted a study on deceased human subjects from Mexico City, a highly

polluted city, and a control city where pollution concentrations are below the US standards. The authors investigated the presence of BBB disruption and trafficking inflammatory cell expression in the residents younger than 25 years. In the control group, there was no evidence of BBB disruption and trafficking inflammatory cells CD163 and CD68 expression. However, in the exposed group, most of the participants had abnormal ZO-1 tight junction and expression of the inflammatory cells. The authors noted that exposure to UFP could prompt a chain of reaction involving disruption of the BBB and generation of inflammatory cells, which can pass through the BBB. The authors hypothesized that oxidative stress in early childhood could lead to neurodegenerative diseases such as Alzheimer's and Parkinson's later in life (Calderón-Garcidueñas et al., 2008). Later, the same authors conducted a similar study in which autopsy results from individuals from highly polluted cities were compared to those from less polluted locations. The study revealed an elevated level of COX2 in the hippocampus of subjects from the highly polluted cities. The investigators also found typical proinflammatory cytokines, interleukins, and an indication of systemic inflammation in the children from the highly polluted locations (Calderón-Garcidueñas, Mora-Tiscareño, et al., 2012).

Despite ethical and other concerns over exposing humans to pollutants, a clinal trial involving healthy volunteers investigated the relationship between air pollution and systemic inflammation in the brain (Cliff et al., 2016). Thirty-six healthy individuals were exposed to diesel exhaust or filtered air for two hours in a blinded crossover study to examine the acute effect of TRAP on biomarkers of systemic inflammation in the CNS. The order of the exposure was randomized, and participants had a four-week washout period between sessions. Blood was collected 24 hours post exposure and analyzed for IL-6 and TNF- α. Contrary to previous findings, the investigators did not find any associations between exposure and IL-6 or TNF-α (Cliff et al., 2016).

Direct translocation:

Several studies have provided evidence that PM can reach the brain through the olfactory bulb or the systemic circulation.

Olfactory Transport

Pharmaceutical researchers have done considerable work to understand pathways that transport drugs to the human brain. Cerebrospinal fluid, which is continuously discharged and reabsorbed while circulating between the brain tissue and olfactory mucosa, plays a key role in transporting drugs from the olfactory bulb to the central nervous system (Illum, 2004). Similarly, PM could also be taken up by the olfactory bulb and transported into the brain.

Researchers have used animal studies to understand the biological mechanisms through which air pollutants are transported through the olfactory bulb into the CNS. Oberdörster and colleagues (2004) exposed rats to ultrafine Carbon-13 particles for 6 hr. The animals were sacrificed at different periods (1, 3, 5 and 7 days) after the exposure. The authors reported that the concentrations of Carbon-13 particles in the olfactory bulb increased significantly as days of exposure increased. Based on their own findings and a review of the literature, the authors suggested that UFP deposited in the nose traveled along olfactory neurons to the CNS (Oberdörster et al., 2004). The authors also found particles in the cerebrum and cerebellum and speculated that UFP may have crossed the less tight or less developed epithelial section of the BBB (Oberdörster et al., 2004). In an earlier study of dogs, Oberdorster et al. (2002) reported that Carbon-13 particles accumulated in the liver before moving into the blood circulation (Oberdorster & Utell, 2002). Similarly, another study comparing dogs from locations with different levels of air pollution demonstrated olfactory bulb dysfunction and BBB deterioration in younger canines from a highly polluted city, along with glial cell death in older dogs due to long term exposure to air pollution (Oberdorster & Utell, 2002). These findings are supported by more recent animal and human studies,

which have reported similar transfer of chemicals through olfactory routes (Chalansonnet et al., 2018).

In contrast, Rao et al. (2003) suggested that olfactory pathways are not involved in transporting air pollutants to the brain. The researchers exposed 64 male rats to iron via inhalation for 90 minutes. Some rats were euthanized immediately after the exposure, while others were euthanized 1, 2, 4, 8 or 21 days after the exposure. The authors found a negligible quantity of iron in olfactory mucosa and no traces of iron in the brain. They concluded that iron particles are retained by the nasal tissues and that olfactory pathways were not utilized in translocation of iron into the brain (Rao et al., 2003).

Translocation through the systemic circulation

Although there is mixed evidence regarding the development of the BBB during the fetal and early infancy periods, there is a common belief that the BBB is not fully developed until approximately six months of age (Saunders et al., 2012). Therefore, the human brain may be particularly susceptible to air pollution during the fetal and early postnatal periods (Brockmeyer & D'Angiulli, 2016).

One study suggested that ambient pollutants, particularly $PM_{2.5}$ or UFP, could pass through the BBB and translocate into human brain tissues (Lockman et al., 2004). Due to its structured endothelial cell lining, the BBB prevents the passage of high molecular weight agents. However, free radicals that cover the PM surfaces can potentially compromise the integrity of this cell lining, thus allowing PM to translocate into the brain (Peters et al., 2006).

The BBB degradation has been shown to affect the onset and progression of many neurodegenerative diseases (Calderón-Garcidueñas et al., 2014). Exposures such as tobacco smoke, which contains large numbers of ROS, are known to negatively affect the cerebrovascular endothelium. Vascular inflammation is a one of the suggested mechanisms for which air pollution can damage the BBB (Hossain et al., 2009). A review paper of tobacco smoke and its impact on the cerebrovascular system concluded that exposure to cigarette smoke can damage the tight

endothelial junction in the BBB. This breakdown in the BBB system could allow unwanted agents to pass through, leading to neuronal death (Mazzone et al., 2010). These studies provide evidence that air pollution may damage and deteriorate the BBB, enabling translocation of foreign agents into the brain.

1.5. Possible effect modifiers

The literature suggests several possible modifiers of the association between air pollution and human brain development. Exploring these effect modifiers may provide additional insight into the underlying biological mechanisms.

1.5.1. Antioxidant Intake

The human antioxidant defense mechanisms include scavenging ROS, preventing the formation of ROS, and enhancing generation of endogenous antioxidants (Gilgun-Sherki et al., 2001). It has been suggested that endogenous and exogenous compounds both play important roles in the preventive antioxidants system (Ighodaro & Akinloye, 2018).

Endogenous antioxidant enzymes, such as superoxide dismutase, glutathione peroxidase, and catalase act as the first line of defense against ROS. These enzymes' primary role is to eradicate ROS and convert them into less harmful substances like oxygen and water (Ighodaro & Akinloye, 2018). In a randomized study, one group of mice was treated with superoxide dismutase and catalase, while mice in the control group received no treatment (Liu et al., 2003). After three months of treatment, the study achieved a total reversal of protein oxidation and partial reduction in lipid peroxidation. Furthermore, the treatment resulted in a significant reduction of oxidized nuclei acid in the hippocampus and amygdala of the mice brains (Liu et al., 2003). This result suggests that antioxidant defence agents such as superoxide dismutase and catalase could attenuate cell damage from air pollution-generated ROS.

The second key component of the antioxidant system is the nutrient-derived exogenous antioxidants, which neutralize ROS by donating an electron (Ighodaro & Akinloye, 2018). Vitamins C and E are two important nutrient-derived antioxidants. Vitamin E mainly comes from fruits and vegetables and is essential to antioxidant defence as it protects lipids from oxidation (Duthie, 2003) by preventing promotion of ROS in lipid contents (Gilgun-Sherki et al., 2001). Vitamin C, or ascorbic acid, is another important antioxidant humans cannot synthesize endogenously. Aside from playing a key role in antioxidant defense by scavenging ROS, vitamin C also plays a role in the regeneration of Vitamin E (Gilgun-Sherki et al., 2001).

There is evidence that the intake of these antioxidants can attenuate air pollution-induced oxidative stress (Hossain et al., 2011). An in vitro study examined the effectiveness of antioxidants' prevention mechanisms on the human BBB after exposure to tobacco smoke. The investigators concluded that exposure to tobacco smoke used up the available first line of antioxidant defense within 15 minutes. Therefore, the protective lining of the BBB could be enhanced with a continuous supply of these antioxidants (Hossain et al., 2011). In an earlier observational birth cohort study, researchers investigated the role of prenatal and postnatal antioxidants in modifying associations between air pollution and neurodevelopment among 14-month-old children. The investigators assessed maternal intake of fruits and vegetables during pregnancy using food frequency questionnaires. NO_2 and benzene were both inversely but non-significantly associated with children's scores on the Bayley Scales of Infant and Toddler Development. The associations were modified by self-reported fruit and vegetable intake. The authors concluded that maternal consumption of antioxidant-rich diets during pregnancy may attenuate the negative impacts of air pollution on children's brain development (Guxens et al., 2012). These findings were supported by an in vitro study using human BBB endothelial cells, which indicated that antioxidants protect against BBB damage from tobacco smoke (Kaisar et al., 2015). The authors noted that all five antioxidants studied reduced the negative impacts of tobacco smoke on the BBB, but the greatest impact resulted from resveratrol, lipoic acid, and melatonin. Resveratrol has been gaining attention due to its protective

effect on the BBB during ischemia, and there is evidence that it has anticancer, anti-inflammatory, anti-aging, and anti-diabetic effects. Lipoic acid plays a role in regeneration of vitamin C and E and boosting antioxidant defense. Melatonin is also a powerful antioxidant (Kaisar et al., 2015).

1.5.2. Folate

Folate, also known as vitamin B9, is an essential dietary micronutrient for fetal development. During pregnancy, folate concentrations in maternal blood are substantially reduced due to accelerated cell proliferation and growth. As a result, dietary intake of folate is particularly important during pregnancy (McGarel et al., 2015). Folate is thought to influence neural development by altering DNA methylation and gene expression, and folic acid deficiency during early pregnancy is a well-established risk factor for neural tube defects (Chmielewska et al., 2016).

Several epidemiologic studies have reported associations between folate and neurocognitive outcomes. Julvez and colleagues (2009) evaluated the relationship between maternal intake of folic acid during pregnancy and children's neurodevelopment at four years of age. After adjusting for potential confounders, the authors found that intake of folic acid was associated with higher scores on tests of verbal, motor, and verbal-executive function (Julvez et al., 2009). Another birth cohort study enrolled 542 children between 9 and 10 years of age and assessed their performance in cognitive domains such as long and short-term memory, reasoning ability, visuo-spatial ability, word order, pattern reasoning, and concentration. After adjusting for sex and age, the authors reported an association between maternal folate concentrations in blood and two areas of cognitive performance: word order and pattern reasoning (Veena et al., 2010). A large prospective study of 40,000 children assessed associations between maternal intake of folic acid, from pre-conception to eight weeks of gestation, with parent-reported language delay at age 3. After adjusting for relevant confounders, intake of folic acid was associated with reduced risk of severe language delay (Roth et al., 2012). Similarly, a longitudinal study assessed the cognitive abilities of 1,210

children and found that supplemental intake of folic acid during early pregnancy was associated with lower Peabody Picture Vocabulary Test III scores, indicating receptive language and intelligence delays (Villamor et al., 2012).

Few studies evaluated the interaction between air pollution and folic acid intake on brain development. In a placebo-controlled crossover trial, Zhong and colleagues exposed ten human subjects to concentrated $PM_{2.5}$ at 250 ug/m^3 for 2 hr after providing a placebo or vitamin B supplement for four weeks. Exposure to $PM_{2.5}$ altered DNA methylation in CD4 T-helper cells, which generate cytokines responsible for proinflammatory responses. Supplementary intake of vitamin B attenuated this negative impact by up to 76%. Furthermore, Vitamin B intake prevented $PM_{2.5}$-induced alterations of mitochondrial DNA 24 hours after exposure (Zhong et al., 2017). Similar results were reported from a case-control study of over 300 autistic children and 260 normally developing control children in California. Folic acid intake during pregnancy was self-reported, and air pollution exposures were calculated using residential histories and measurements from government monitoring stations. Among those with high periconceptional folic acid intake, NO_2 was not associated with ASD (OR = 0.74 per 14.18 ppb contrast in NO_2, 95% CI: 0.46-1.19). However, among those with low periconceptional folic acid intake, NO_2 was marginally associated with ASD (OR=1.53 per 14.18 ppb contrast in NO_2, 95% CI: 0.91-2.56). The authors concluded that for mothers living in highly polluted areas during pregnancy, dietary intake of folic acid during early pregnancy lowered the risk of ASD (Goodrich et al., 2018). A recent prospective cohort study in USA examined the association between ambient air pollution during pregnancy and child IQ measure at age 4 to 6. The authors found that a 5 ug/m^3 increase in PM_{10} concentration was associated with 6.8-point (95% CI: 1.4, 12.3) decrease in children's FSIQ among mothers who had lower prenatal plasma folate in the second trimester. There was no association between PM_{10} and FSIQ among participants with higher plasma folate. The authors suggested that prenatal folate may reduce the neurotoxic effect of air pollution on brain development (Loftus et al., 2019).

1.5.3. Sex

Due to hormonal and genetic influences, human brain development differs between females and males from early gestation. Developmental, anatomical, and functional differences may lead to sex-dependant effects on neurological dysfunctions (Ruszkiewicz et al., 2019).

Several animal experimental studies have found that male rodents have higher susceptibility to environmental toxicants. Torres-Rojas and colleagues (2018) reviewed human and animal studies of sex differences in susceptibility to several environmental toxicants. Their review found that the male mice tend to be vulnerable to neurotoxicity from air pollution. Specifically, the reviewed studies consistently showed that neurons of male mice were more susceptible to air pollutant induced oxidative stress than neurons of female mice (Torres-Rojas & Jones, 2018). Exposure to diesel exhaust caused greater increases in malondialdehyde, an indicator of oxidative stress, in male mice brains than in the brains of female mice (Cole et al., 2016; Giordano et al., 2013).

Several epidemiological studies have also reported greater vulnerability among boys. Chiu et al. (2013) reported that school-aged boys were more susceptible than girls to the effects of TRAP on some domains of cognitive function (Chiu et al., 2013), possibly due to sex-specific hormones (Chiu et al., 2016). Although human brain mass and size differ from person to person, the characteristics of specific brain regions differ between females and males. For example, the average male brain contains more white matter, while the average female brain contains more grey matter (Baron-Cohen, 2005). A recent systematic review noted that developmental and learning delays are twice as high in male children than in females. For neurodevelopmental disorders such as ASD and ADHD, this ratio is about 4 to 1, suggesting that male children are more vulnerable to neurodevelopmental conditions (Kern et al., 2017).

Synaptic connectivity is dependent on the axons and their elongations, and gonadal steroids could influence this connectivity through microtubule formation

(Melcangi et al., 2008). By promoting microtubule-associated proteins, estrogen and progesterone influence a stabilizing and lengthening effect on axons and dendrites, leading to better synaptic connectivity (Ferreira & Caceres, 1991). In an in vivo study of rats, estrogen was found to down-regulate the concentrations of cytokines produced by a proinflammatory process and to increase the level of anti-inflammatory cytokines (Shivers & Farago, 2016). A review paper noted that progesterone produced by glial cells in females could also enhance myelination and cellular branching (Garcia-Segura & Melcangi, 2006).

The mitochondrial enzyme paraoxonase – 2 (PON2) has anti-inflammatory properties and acts as an antioxidant that scavenges free radicals produced by air pollution, thereby protecting cells from oxidative stress-induced neurotoxicity (Costa et al., 2017). In all brain regions and cell types studied, and in several species including humans, PON2 levels were found to be higher in females than in males (Giordano et al., 2013). Hypothesizing that male mice would be more susceptible to TRAP due to lower levels of PON2, a group of scientists examined mice brains after exposing the animals to diesel exhaust particulate matter. The authors found that relative to control mice, diesel exposure resulted in a 2.1-fold increase in neuron death among males and a 1.6-fold increase among females (Roqué et al., 2016).

1.5.4. Stress

Prenatal maternal stress has been shown to affect several brain regions including the hippocampus, cerebellum, and hypothalamus and has been consistently linked with neurobehavioral and cognitive effects in infants and children (Monk et al., 2012; Talge et al., 2007).

There is now limited evidence that maternal psychosocial stress may also modify associations between prenatal air pollution exposure and cognitive development in childhood. Bolton and colleagues (2013) conducted an experimental study to explore the overlap between the cognitive effects of psychosocial stress and air pollution in mice. After exposing pregnant mice to diesel exhaust particles (DEP)

throughout gestation, the authors placed the mice in a nest material restriction (NR) cage to induce maternal stress during the third trimester. The study resulted in significant increased anxiety in the offspring within the DEP and NR group compared to the controls. Further, post hoc analyses showed significantly more anxiety in male mice in the DEP/NR group than the male mice in the DEP group not exposed to NR. The investigators also assessed the offspring's hippocampal-dependent memory by training them to associate a foot shock with freezing behaviour, which is a rodent fear response. DEP/NR mice, especially males, showed significantly less freeze when compared to the other groups. The authors concluded that maternal DEP and NP exposure both caused significant memory deficits and anxiety among male offspring (Bolton et al., 2013).

Few epidemiologic studies have evaluated the interaction between air pollution and maternal stress on children's neurocognitive development. In one study, researchers enrolled a low-income population of 200 mother-child dyads with Dominican and African American backgrounds (Rauh et al., 2004). The investigators evaluated the effects of prenatal environmental tobacco smoke (ETS) exposure and material hardship on mental development index (MDI) scores. The main effect of ETS was alone associated with 4.8-point (p=0.003) reduction in MDI; however, in the interaction model ETS and maternal hardship were associated with 7.1-point reduction (p=0.03) (Rauh et al., 2004). A more recent study assessed the interaction between maternal distress and exposure to PAHs on children's neurobehavioral outcomes in a longitudinal birth cohort in Poland. The investigators assessed distress among 240 mothers during the second trimester using a standardized measure of psychological stress, the Psychiatric Epidemiology Research Instrument-Demoralization (PERI-D). Children's behaviour was assessed at 6 to 9 years using the mother-reported Child Behaviour Checklist (CBCL). The researchers reported a significant interaction between prenatal PAH exposure and maternal stress on CBCL scores, including anxious and depressed symptoms and aggressive behaviour (Perera et al., 2013).

Chapter 2.   Portable HEPA Filter Air Cleaner Use during Pregnancy and Children's Cognitive Performance at Four Years of Age: The UGAAR Randomized Controlled Trial

2.1. Abstract

Background: Developmental exposure to air pollution is associated with diminished cognitive abilities in observational studies, but no randomized controlled trial has examined the effect of reducing air pollution on cognition in children.

Objectives: We sought to quantify the impact of reducing exposure to particulate matter (PM) during pregnancy on children's cognitive performance at four years of age.

Methods: In this single-blind, parallel-group, randomized controlled trial in Ulaanbaatar, Mongolia we randomly assigned 540 non-smoking pregnant women (268 intervention and 272 control) to receive 1-2 portable high efficiency particulate air (HEPA) filter air cleaners or no air cleaners. The air cleaners were used from a median of 11 weeks' gestation until the end of pregnancy. The primary outcome was full-scale intelligence quotient (FSIQ) assessed using the Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (WPPSI-IV) when children were a median of 48 months old. We imputed missing outcome data using multiple imputation with chained equations and our primary analysis was by intention to treat.

Results: After excluding known miscarriages, still births, neonatal deaths, and medical conditions that impeded cognitive testing and imputation, 475 (233 control and 242 intervention) children were included in our analyses. In an unadjusted analysis, the mean FSIQ of children who were randomly assigned to the intervention group was 2.5 points (95% CI: -0.4, 5.4 points) higher than children in

the control group. After adjustment to account for an imbalance in preterm birth between groups, the effect estimate increased to 2.8 points (95% CI: -0.1, 5.7).

Conclusions: Reducing PM air pollution during pregnancy may improve cognitive performance in childhood

Declaration of Interests

Woongjin-Coway provided discounted air cleaners modified for this study. The company had no role in study design, analysis, interpretation, manuscript preparation, or the decision to publish. The authors have no other conflicts of interest to disclose.

2.2. Introduction

Exposure to fine particulate matter ($PM_{2.5}$) air pollution during pregnancy is associated with fetal growth restriction and shorter gestation (Yuan et al., 2019). In turn, an unfavorable intrauterine environment may alter developmental programming and increase risk of disease and disability later in life (Padmanabhan et al., 2016). This paradigm is consistent with observational evidence of associations between prenatal exposure to air pollution and impaired neurodevelopment (Clifford et al., 2016).

Specific mechanisms underlying air pollution's impact on brain development have not been definitively established, but plausible mechanisms have been identified (Allen et al., 2017). The prenatal period and the first year of life are key phases in the development of neural networks. The speed and complexity of brain development, combined with the immature detoxification mechanisms in early life, makes the developing brain particularly vulnerable to toxicants. If a toxicant impairs a critical, time-dependent process in the developing brain there is little chance for repair (Grandjean & Landrigan, 2006).

To our knowledge, no study has evaluated whether reducing particle exposure during pregnancy improves children's neurodevelopment. High efficiency

particulate air (HEPA) filter air cleaners ("HEPA cleaners") have been shown to reduce $PM_{2.5}$ concentrations by 29-82% inside residences, where individuals spend most of their time (Allen & Barn, 2020). In addition, outdoor particles penetrate into buildings and in many homes most indoor $PM_{2.5}$ is from outdoor sources (Allen et al., 2012). Thus, reducing particulate matter (PM) indoors may mitigate the health impacts of outdoor emissions (Xiang et al., 2019).

Our objective was to evaluate the impact of reducing indoor PM using portable HEPA cleaners during pregnancy on children's cognitive performance at four years of age. Specifically, we tested the hypothesis that children born to women randomly assigned to use portable HEPA cleaners during pregnancy would have higher mean cognitive scores at age 4 years than children whose mothers were not assigned to use HEPA cleaners.

2.3. Methods

2.3.1. Trial Design

The Ulaanbaatar Gestation and Air Pollution Research (UGAAR) study is a single-blind parallel-group randomized controlled trial (RCT) designed to estimate the effect of portable HEPA cleaner use during pregnancy on fetal growth and early childhood development (ClinicalTrials.gov: NCT01741051). The study was approved by the Simon Fraser University Office of Research Ethics and the Medical Ethics Approval Committee of the Mongolian Ministry of Health.

Ulaanbaatar, the capital city of Mongolia, has some of the world's worst air quality. The city's population-weighted annual average $PM_{2.5}$ concentration is more than ten times the World Health Organization (WHO) guideline concentration of 5 µg/m^3 (Hill et al., 2017). Approximately half of the Mongolian population lives in Ulaanbaatar and over 60% of the city's residents live in neighborhoods consisting of traditional Mongolian felt-lined yurts (gers) and poorly constructed wood or brick homes (Asian Development Bank, 2017). Coal emissions from home heating stoves in these neighborhoods account for 45–70% of the total outdoor PM2.5

concentrations in the city (Allen et al., 2013). The city's remaining residents live in apartments that receive heat supplied by coal-fired heat and power stations or heat-only boilers (Hill et al., 2017).

2.3.2. Participants

We recruited participants at two perinatal health clinics in Ulaanbaatar between January 2014 and May 2015. Two study coordinators enrolled 540 pregnant women who met the following criteria: ≥ 18 years old, ≤ 18 weeks into a single gestation pregnancy, non-smoker, living in an apartment, not using air cleaner(s) at enrollment, and planning to give birth in a medical facility in Ulaanbaatar. Our original criterion for gestational age at enrollment was 13 weeks (first trimester), but shortly after enrollment began, we changed the criterion to 18 weeks to increase enrollment. Most participants (81%) enrolled at ≤ 13 weeks. We excluded women living in ger neighborhoods because they have unreliable electricity and gers often have high air exchange, which can make HEPA cleaners less effective. In addition, heating stoves in gers can emit pollution indoors, which could limit generalizability of results.

Study staff obtained written informed consent from each participant before the start of data collection. Participants were compensated up to 325,000 Mongolian tugriks (approximately $130 USD). We pro-rated compensation depending on the activities that participants completed.

2.3.3. Randomization and blinding

Study staff confirmed eligibility before participants provided written consent. A study coordinator assigned participants to the control or intervention group at a 1:1 ratio using sealed opaque envelopes containing cards (generated by the principal investigator, RWA) indicating "filter" or "control". After a woman consented to participate, a study coordinator opened the next envelope in the sequence and informed the participant of her assignment. The envelope was then discarded, and the next envelope was opened when the next participant enrolled. Participants

were not blinded to their intervention status, but personnel who conducted cognitive testing were blinded.

2.3.4. Intervention

We deployed one or two HEPA cleaners (Coway AP-1009CH) in the homes of participants in the intervention group. These HEPA cleaners have a clean air delivery rate (CADR) for tobacco smoke (0.09–1.0 μm particles) of 149 ft^3/m, which is sufficient for rooms of approximately 22 m^2. The control group received no HEPA cleaners. At our request, the manufacturer modified the HEPA cleaners to run at the second-highest fan setting (because of concerns noise at the highest setting), and disabled a colored light that indicates the particle concentration range. We installed the HEPA cleaners in intervention homes shortly after participants enrolled. We placed an air cleaner in the main living area of all apartments, and in larger apartments (≥40 m^2), we placed a second unit in the participant's bedroom. We encouraged participants to use the HEPA cleaners continuously. We did not replace the HEPA filters during the study, and we retrieved the HEPA cleaners shortly after pregnancy ended.

2.3.5. Prenatal procedures

During the intervention, we measured $PM_{2.5}$ in participants' homes over two seven-day sampling campaigns using Dylos laser particles counters (DC1700; Dylos Corporation, Riverside, California). The early- and late-pregnancy measurements were made at a median of 11 weeks and 30 weeks gestation, respectively. Full details on the prenatal $PM_{2.5}$ measurement campaigns are provided elsewhere (Barn, Gombojav, Ochir, Laagan, et al., 2018). Participants came to our study office between 5–19 weeks of pregnancy and again between 24 and 37 weeks. At both times we administered a questionnaire to obtain information on family demographics (e.g., parents' ages and education, monthly family income), behavior (e.g. smoking, alcohol consumption), health (e.g. pre-pregnancy body mass index), and previous pregnancies. We also collected a venous whole blood

sample during the second visit and analyzed it for lead, mercury, and cadmium concentrations.

We obtained clinic records and recorded birth weight, length, head circumference, gestational age, sex, and mode of delivery. We also used clinic records to identify stillbirths, pregnancy complications and co-morbidities (Barn et al. 2018). The occurrence and timing of spontaneous abortions was self-reported by participants.

2.3.6. Postnatal procedures

When the children were a median of 15.4 months old (range: 7.7 to 28.9 months), we invited all living mother-child dyads to re-enroll in a follow-up study of postnatal development. At re-enrollment we administered a questionnaire on housing and the child's diet, health, and activities since birth. We administered additional questionnaires at six-month intervals thereafter.

We visited participants' homes annually around the time of the child's birthday. At the same time, we measured $PM_{2.5}$ over seven days in a convenience sample of participants' homes based on the availability of monitors. During the first postnatal home visit we also assessed the quality and quantity of nurturing and stimulation using the Home Observation Measurement of the Environment (HOME) assessment (Elardo & Bradley, 1981).

The mothers and children visited our study office when the children were approximately two and four years of age. At the two-year visit we collected a venous whole blood sample from the children for analysis of lead, mercury, and cadmium and administered the matrix reasoning and vocabulary subtests of the Wechsler Abbreviated Scale of Intelligence (WASI) to the mothers (Irby & Floyd, 2013).

2.3.7. Outcomes

During the four-year visit we measured children's cognitive performance using the Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (WPPSI–IV) (Wechsler, 2012). The WPPSI-IV is a widely accepted measure of cognitive functioning in children aged 2 years and 6 months to 7 years and 7 months. The WPPSI-IV has been used in studies of environmental hazards (Kippler et al., 2012; Perera et al., 2012; Perera et al., 2009) and has been used in Bangladesh (Wasserman et al., 2007), Brazil (Santo et al., 2009), China (Perera et al., 2009), and Iran (Razavieh & Shahim, 1992). Native Mongolian speakers translated all English WPPSI-IV materials. We refined the WPPSI-IV by piloting it on Mongolian children, updating the translations, and piloting on additional children before assessing the UGAAR cohort. Two Mongolian assessors were trained to administer and score the WPPSI-IV by a co-investigator (DCB) with extensive experience in cognitive testing. Specifically, prior to data collection we conducted a two-week in-person WPPSI-IV training session in Ulaanbaatar followed by approximately three months of practice testing, which was videotaped and reviewed by the trainer.

We administered ten WPPSI-IV subtests (information, similarities, block design, object assembly, matrix reasoning, picture concepts, picture memory, zoo locations, bug search and cancellation) to children at a median age of 48 months (range: 48 to 51 months). We videotaped the assessments and reviewed them periodically for quality control.

Our primary outcome was full-scale intelligence quotient (FSIQ), which is derived by combining scores from six WPPSI-IV subtests. Our secondary outcomes were verbal comprehension, visual spatial, fluid reasoning, working memory, processing speed, non-verbal, general ability, and cognitive proficiency. FSIQ indicates a child's general intellectual functioning. The other indices provide process-specific measurements.

2.3.8. Sample Size

The UGAAR study was initially focused on fetal growth, so our sample size calculations were based on term birth weight (Barn et al. 2018). We estimated that 540 participants were needed assuming 18% attrition, a type I error rate of 0.05 (2-sided), and a type II error rate of 0.20.

2.3.9. Statistical analysis

We generated descriptive statistics for maternal baseline characteristics. Calculating composite WPPSI-IV scores requires scaling raw scores using the distribution from a reference population. With no Mongolian reference population, we scaled the distribution of raw scores from the UGAAR cohort to match the mean and standard deviation of the Canadian reference population, which included children 48 to 91 months old who were assessed from July to August 2012 (Table A.1) (Wechsler, 2012). This allowed us to convert raw scores to scaled scores and combine scaled scores into indices according to the WPPSI-IV protocol.

To assess the validity of the WPPSI-IV in this setting we evaluated unadjusted relationships between WPPSI-IV FSIQ scores and established predictors of cognitive performance in young children: preterm birth (PTB, <37 weeks) (Kerr-Wilson et al., 2012), sex (Kern et al., 2017), maternal intelligence (mothers' WASI matrix reasoning and vocabulary raw scores) (Eriksen et al., 2013), and HOME scores (Tong et al., 2007). For binary predictors (PTB and sex), FSIQ effect estimates are expressed as a difference in mean FSIQ scores between children born preterm and full term and between boys and girls. For continuous predictors (WASI and HOME scores), FSIQ effect estimates are reported per interquartile range contrast.

Our primary analysis was by intention-to-treat (ITT) and included 475 children (233 control and 242 intervention); a secondary analysis included 383 complete cases. The participants in the ITT analysis comprise the full cohort except those who withdrew prior to baseline data collection (N = 8), pregnancy losses (N = 46),

neonatal deaths (N = 5), and children with a medical condition that may affect WPPSI-IV testing or our ability to impute scores (N = 6; one with Down's syndrome, one with a hearing and speech impairment, one with cerebral palsy and three with autism spectrum disorder, ASD). We imputed scores for 92 children who failed to complete one or more WPPSI-IV subtests assuming data were missing at random. We generated 20 imputed data sets using multiple imputation with chained equations (MICE) (SAS Proc MI and Proc MIANALYZE) after stratifying by treatment group. We included in the imputation model variables associated with missingness and/or FSIQ: child's sex, enrollment season, previous pregnancy, self-reported air cleaner usage and vitamin intake at baseline, father's body mass index, mother's alcohol intake during pregnancy, birth term, head circumference at birth, and the completed WPPSI-IV subtest raw scores.

In both our ITT and complete case analyses, we used linear regression to estimate the effect of the intervention on mean WPPSI-IV scores. Five control group participants incorrectly received the intervention, while three intervention participants did not receive HEPA cleaners; we analyzed the data according to original group assignments. We report unadjusted effect estimates and estimates adjusted for preterm birth (PTB) because we previously found that the intervention was associated with lower risk of spontaneous abortion and higher risk of PTB (Barn et al. 2018). We speculated that the intervention allowed those who otherwise might have died in utero to survive, but be born preterm (Barn et al. 2018). Although PTB may be on the causal pathway, we adjusted for PTB to balance the frequency of PTB between the control and intervention groups. In a pre-planned analysis, we also quantified the intervention's effect on FSIQ after stratifying by household smoking behavior.

We also conducted several post hoc analyses. In the ITT analysis we estimated the effect of the intervention on FSIQ after adjusting for child's sex and after excluding eight participants who mistakenly received or did not receive HEPA cleaners. In addition to the intervention's effect on mean WPPSI-IV scores, we were also interested in effects at different parts of the FSIQ distribution. Thus, we

used quantile regression to estimate the intervention's effect at each decile of the FSIQ distribution among complete cases.

2.4. Results

We recruited 540 pregnant women from January 9, 2014 to May 1, 2015 and randomly assigned 272 to the control group and 268 to the intervention group (Figure 1). Participants were enrolled at a median (25th, 75th percentile) of 11 weeks (9, 13 weeks) gestation in the control group and 11 weeks (8, 13 weeks) gestation in intervention group. We observed 514 women (253 control and 261 intervention) to the end of pregnancy. There were 46 known pregnancy losses (28 control and 18 intervention), 468 live births (225 control and 243 intervention), and five neonatal deaths (1 control and 4 intervention). We enrolled 416 participants (194 control and 222 intervention) into the postnatal study, and 383 children (182 control and 201 intervention) completed the WPPSI-IV between September 28, 2018 and January 8, 2020.
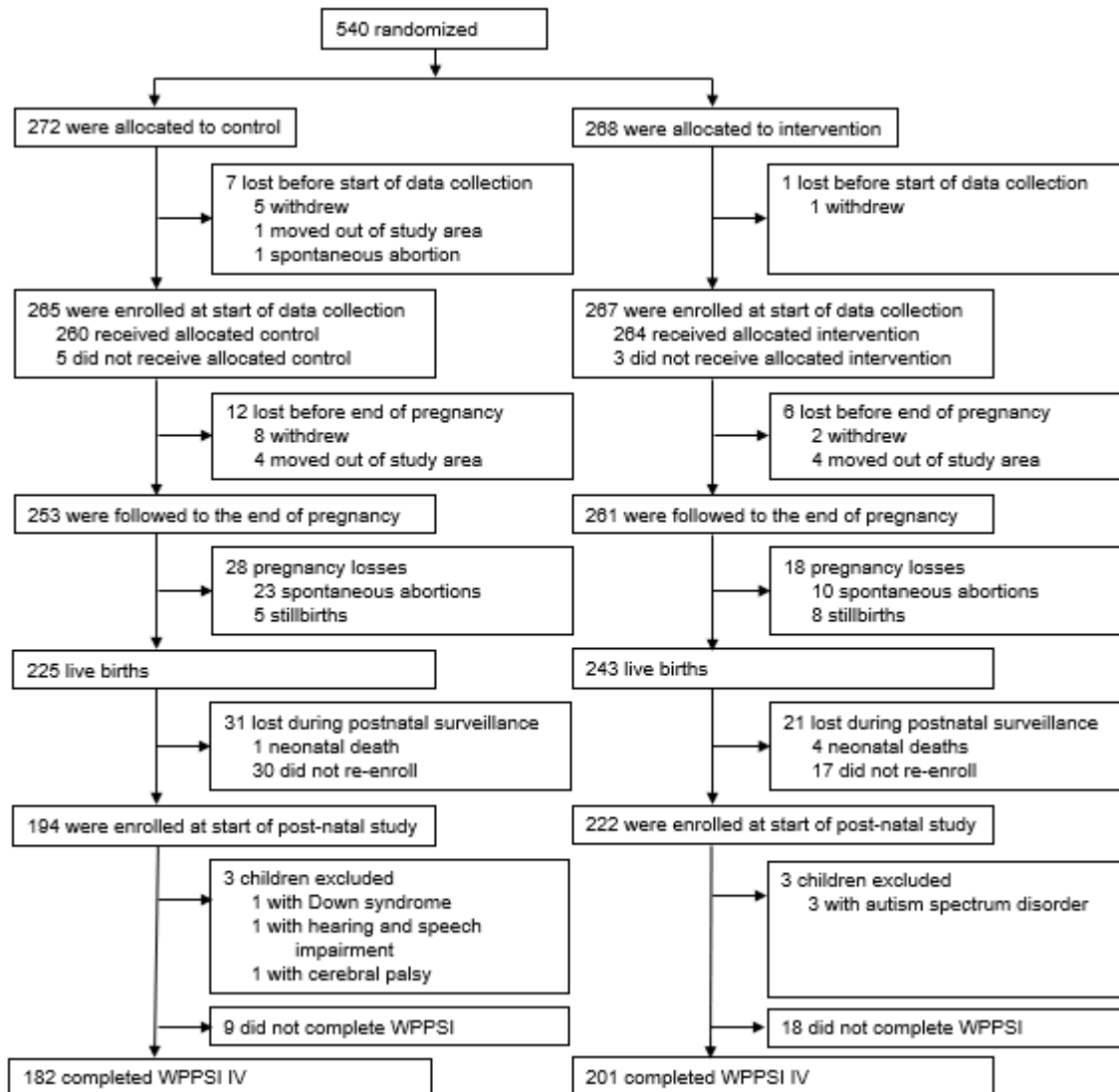
Figure 2.1.   Profile for the Ulaanbaatar Gestation and Air Pollution Research (UGAAR) high efficiency particulate air (HEPA) filter air cleaner trial in Ulaanbaatar, Mongolia.

Note: WPPSI-IV = Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition

2.4.1. Baseline characteristics

Baseline characteristics were comparable between intervention and control groups (Table 2.1, Table A.2). The median (25th, 75th percentile) maternal ages at enrollment in the control and intervention groups were 28 years (25, 32 years) and

34

29 years (25, 33 years), respectively. Approximately half of the women lived with a smoker at enrollment and about 80% had a university degree.

Table 2.1. **Select baseline variables for participants (N = 475) included in the intention-to-treat analysis of the UGAAR trial in Ulaanbaatar, Mongolia, 2014-2015 (n=475)**

	Control (n=233) Median (25th, 75th percentile) or N (%)	Intervention (n=242) Median (25th, 75th percentile) or N (%)
Maternal age at enrollment	28 (25, 32)	29 (25, 33)
Not reported, N (%)	6 (2.6)	6 (2.5)
Weeks pregnant at enrollment	11 (9, 13)	11 (8, 13)
Not reported, N (%)	8 (3.4)	12 (4.9)
Enrollment season		
Winter	76 (32.6)	72 (29.8)
Spring	73 (31.3)	65 (26.7)
Summer	24 (10.3)	31 (12.8)
Fall	60 (25.8)	74 (30.6)
Marital status		
Married or common-law	183 (78.5)	209 (86.4)
Not married or common-law	49 (21.0)	33 (13.6)
Not reported, N (%)	1 (0.4)	0 (0.0)
Lived with a smoker at enrollment		
Yes	117 (50.2)	119 (49.2)
No	111 (47.6)	119 (49.2)
Not reported, N (%)	5 (2.2)	4 (1.7)
Maternal education		
Completed university	187 (80.3)	193 (79.8)
Did not complete university	31 (13.3)	29 (12.0)
Not reported, N (%)	15 (6.4)	20 (8.3)
Monthly household income[a]		
≥ 800,000 Tugrik	182 (78.1)	191 (78.9)
< 800,000 Tugrik	46 (19.7)	47 (19.4)
Not reported, N (%)	5 (2.2)	4 (1.7)
Parity		
0	73 (31.3)	79 (32.6)
1	92 (39.5)	88 (36.4)
≥2	51 (22.0)	62 (25.6)
Not reported, N (%)	17 (7.3)	13 (5.4)

Percentages may not total 100 due to rounding.
[a]At the time of data collection 800,000 tugriks was equivalent to approximately $360 USD.

2.4.2. Pregnancy and childhood characteristics

Intervention group participants reported using the HEPA cleaners for a median (25th, 75th percentile) of 70% (60%, 80%) of time during pregnancy (Barn et al., 2018b). Just under half of the study population reported living with a smoker during pregnancy. Maternal intelligence measured by WASI did not differ between the

control and intervention groups (Table 2.2). Breastfeeding frequency and duration were also similar between groups (Table 2.2). Maternal blood lead and mercury concentrations measured late in pregnancy were similar between groups, but blood cadmium concentrations were 14% lower (95% CI: 4, 23%) among intervention participants (Barn et al. 2018a). We obtained information on gestational age at birth for 455 (220 control and 235 intervention) of the children included in the ITT analysis. Among those children, preterm birth occurred more frequently in the intervention group (24 or 9.9%) than in the control group (13 or 5.9%) (Table 2.2). Children's blood metals concentrations at two years of age were similar between groups as were HOME inventory total scores. The portion of intervention and control group participants who reported using their own air cleaner after birth was 14% and 17%, respectively. Postnatal air cleaner use was reported by 17% of mothers who completed university and 15% of mothers who did not. Seven percent of families earning less than 800,000 tugriks per month at baseline reported using an air cleaner after their child's birth. Among those who earned more than 800,000 tugriks per month, 17% reported postnatal use of an air cleaner. Mothers of children who did not participate in WPPSI-IV testing were younger, more likely to be in the control group, and more likely to have enrolled in winter compared to mothers of those who participated in testing (Table A.3).

Table 2.2.   **Select variables measured during pregnancy and after birth for dyads included in the intention-to-treat analysis of the UGAAR trial in Ulaanbaatar, Mongolia, 2014-2019 (n=475)**

	Control (n=233) Median (25th, 75th percentile) or N (%)	Intervention (n=242) Median (25th, 75th percentile) or N (%)
Maternal Characteristics		
Delivery type		
Cesarian	86 (37.0)	85 (35.1)
Vaginal	134 (57.5)	151 (62.4)
Unknown, N (%)	13 (5.6)	6 (2.5)
Blood lead concentration (ug/dL)	1.46 (1.17, 1.80)	1.43 (1.17, 1.86)
Not measured, N (%)	61 (26.2)	43 (17.8)
Blood cadmium concentration(ug/L)	0.22 (0.16, 0.31)	0.19 (0.14, 0.28)
Not measured, N (%)	61 (26.2)	43 (17.8)

Blood mercury concentration (ug/L)	0.31 (0.22, 0.54)	0.30 (0.20, 0.44)
Not measured, N (%)	61 (26.2)	43 (17.8)
WASI Matrix Reasoning Raw Score	16.0 (12, 19)	17.0 (13, 19)
Not measured, N (%)	58 (24.9)	33 (13.6)
WASI Vocabulary Raw Score	36 (32, 39)	35 (31, 39)
Not measured, N (%)	58 (24.9)	33 (13.6)
Child Characteristics		
Sex		
Female	110 (47.2)	109 (45.0)
Male	112 (48.6)	126 (52.1)
Unknown, N (%)	11 (4.7)	7 (2.9)
Birth Term		
Pre-Term (<37 weeks)	13 (5.6)	24 (9.9)
Term (≥37 weeks)	207 (88.8)	211 (87.2)
Unknown, N (%)	13 (5.6)	7 (2.9)
Season of birth		
Winter	26 (11.2)	35 (14.5)
Spring	51 (21.9)	56 (23.1)
Summer	69 (29.6)	78 (32.2)
Fall	74 (31.7)	66 (27.3)
Unknown, N (%)	13 (5.6)	7 (2.9)
Breastfed infant		
Never	6 (2.6)	5 (2.1)
<12 months	43 (18.5)	53 (21.9)
≥12 months	139 (59.7)	156 (64.5)
Not reported, N (%)	45 (19.3)	28 (11.8)
HOME inventory total score	30.0 (28.0, 32.5)	30.0 (27.0, 34.0)
Not measured, N (%)	76 (32.6)	77 (31.8)
Blood lead concentration at 2 years of age (ug/dL)	2.60 (1.86, 3.63)	2.47 (1.68, 3.47)
Not measured, N (%)	80 (34.3)	68 (28.1)
Blood cadmium concentration at 2 years of age (ug/dL)	0.05 (0.04, 0.08)	0.05 (0.04, 0.08)
Not measured, N (%)	80 (34.3)	68 (28.1)
Blood mercury concentration at 2 years of age (ug/dL)	0.18 (0.13, 0.25)	0.18 (0.13, 0.27)
Not measured, N (%)	80 (34.3)	68 (28.1)
Child's age at WPPSI-IV assessment (months)	48.0 (48, 48)	48.0 (48, 48)
No WPPSI-IV, N (%)	51 (21.9)	40 (16.5)
HEPA filter air cleaner usage after birth		
Yes	39 (16.8)	33 (13.6)
No	133 (57.0)	162 (66.9)
Not reported, N (%)	61 (26.2)	47 (19.4)

Percentages may not total 100 due to rounding.

HOME = Home Observation Measurement of the Environment.

WASI = Wechsler Abbreviated Scale of Intelligence

WPPSI-IV = Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition

HEPA = High Efficiency Particulate Air

2.4.3. Pollution concentrations

We previously reported a difference of 29% (95% CI: 21, 37%) in $PM_{2.5}$ concentrations between groups, with geometric means of 24.5 μg/m^3 in the control group and 17.3 μg/m^3 in the intervention group (Table A.4) (Barn et al. 2018a). The HEPA air cleaners were removed shortly after pregnancy ended and indoor $PM_{2.5}$ concentrations during childhood were comparable between control and intervention homes (3% lower in intervention homes, 95% CI: -17, 9%).

2.4.4. Correlates of WPPSI-IV Scores

Among complete cases, male sex and PTB were associated with 6.3-point (95% CI: 3.5,9.1; N = 383) and 6.8-point (95% CI: 1.6, 12.0; N = 382) lower mean FSIQ scores, respectively. Interquartile range increases in maternal WASI vocabulary and matrix reasoning raw scores were associated with 1.6-point (95% CI: 0.0, 3.3, N = 363) and 3.5-point (95% CI: 1.7, 5.3; N = 363) higher mean FSIQ scores, respectively. An interquartile range increase in HOME score was associated with a 3.2-point (95% CI: 1.3, 5.0; N = 301) higher mean FSIQ score.

2.4.5. Intervention effects

In the imputed ITT analysis, children in the intervention group had a 2.5-point (95% CI: -0.4, 5.4) higher mean FSIQ than children in the control group (Table 2.3). Adjusting for PTB increased the estimate to 2.8 points (95% CI: -0.1, 5.7), and after adjustment for both PTB and child's sex the effect estimate was 3.0 points (95% CI: 0.2, 5.9). Excluding eight participants who incorrectly received or did not receive the HEPA cleaners had little effect on the estimate (2.5 points; 95% CI: -0.5, 5.4).

In the complete case analysis, children in the intervention group had a 2.8-point (95% CI: 0.0, 5.7) higher mean FSIQ score in an unadjusted analysis and a 3.2-point (95% CI: 0.3, 6.0) higher mean FSIQ after adjustment for PTB (Table 2.3).

In the ITT analysis, mean scores for secondary outcomes were consistently higher in the intervention group (Table 2.3). However, only the effect estimates for verbal comprehension had confidence intervals that did not span the null (3.5 points, 95% CI: 0.2, 6.8).

Table 2.3. Mean WPPSI-IV composite scores and estimated intervention effects in primary intention-to-treat (N = 475) and secondary complete case (N = 383) analyses from the UGAAR trial in Ulaanbaatar, Mongolia.

	Intention-To-Treat Analysis				Complete Case Analysis			
	Mean Score (standard deviation)		Unadjusted intervention effect estimate	Adjusted intervention effect estimate[a]	Mean Score (standard deviation)		Unadjusted intervention effect estimate	Adjusted intervention effect estimate[a]
	Control	Intervention			Control	Intervention		
	N = 233	N = 242	(95% CI)	(95% CI)	N = 182	N = 201	(95% CI)	(95% CI)
Full Scale IQ	97.3 (15.2)	99.8 (13.9)	2.5 (-0.4, 5.4)	2.8 (-0.1, 5.7)	97.3 (14.9)	100.1 (13.5)	2.8 (0.0, 5.7)	3.2 (0.3, 6.0)
Verbal Comprehension	97.3 (16.5)	100.8 (16.1)	3.5 (0.2, 6.8)	3.8 (0.4, 7.1)	97.4 (15.8)	101.2 (15.5)	3.8 (0.6, 6.9)	4.2 (1.1, 7.4)
Visual Spatial	94.5 (16.3)	95.6 (15.1)	1.0 (-2.4, 3.9)	1.2 (-1.9, 4.3)	94.5 (15.7)	95.7 (14.5)	1.2 (-1.8, 4.2)	1.3 (-1.8, 4.4)
Fluid Reasoning	97.7 (16.9)	98.5 (17.0)	0.8 (-2.5, 4.1)	1.0 (-2.3, 4.3)	97.8 (16.4)	98.8 (16.6)	0.9 (-2.4, 4.3)	1.0 (-2.3, 4.3)
Working Memory	103.0 (15.1)	104.3 (14.3)	1.3 (-1.5, 4.2)	1.4 (-1.5, 4.3)	103.1 (14.5)	104.5 (13.3)	1.4 (-1.4, 4.2)	1.5 (-1.3, 4.4)
Processing speed	99.0 (14.1)	99.6 (13.7)	0.6 (-2.2, 3.4)	0.7 (-2.0, 3.5)	99.0 (13.6)	99.9 (13.1)	0.9 (-1.7, 3.6)	1.1 (-1.6, 3.8)
Non-Verbal	97.8 (15.8)	99.1 (14.7)	1.4 (-1.6, 4.3)	1.6 (-1.4, 4.5)	97.8 (15.5)	99.5 (14.1)	1.7 (-1.3, 4.7)	1.9 (-1.1, 4.8)
General Ability	96.9 (15.9)	99.6 (14.7)	2.6 (-0.4, 5.8)	3.0 (-0.2, 6.1)	97.0 (15.4)	99.9 (14.2)	2.9 (-0.1, 5.8)	3.2 (0.2, 6.2)
Cognitive Proficiency	101.5 (15.0)	102.6 (13.8)	1.1 (-1.7, 3.9)	1.3 (-1.5, 4.1)	101.5 (14.5)	102.9 (13.0)	1.4 (-1.4, 4.1)	1.4 (-1.2, 4.3)

[a] adjusted for pre-term birth
WPPSI-IV = Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition.

In a stratified ITT analysis, the effect of the intervention on mean FSIQ was 1.9 points (95% CI: -2.1, 5.9) among children whose mothers lived with a smoker at baseline and 3.2 points (95% CI: -0.9, 7.4 points) among those whose mothers did not live with a smoker. Stratified results among complete cases were similar to those from the ITT analysis for children whose mothers did (2.0 points; 95% CI: -2.0, 6.4) and did not (3.6 points; 95% CI: -0.5, 7.7) live with a smoker. In a post hoc quantile regression analysis of complete cases the effect of the intervention on FSIQ was more pronounced among children at the lower end of the FSIQ distribution (Figure 2.3, Table A.5).
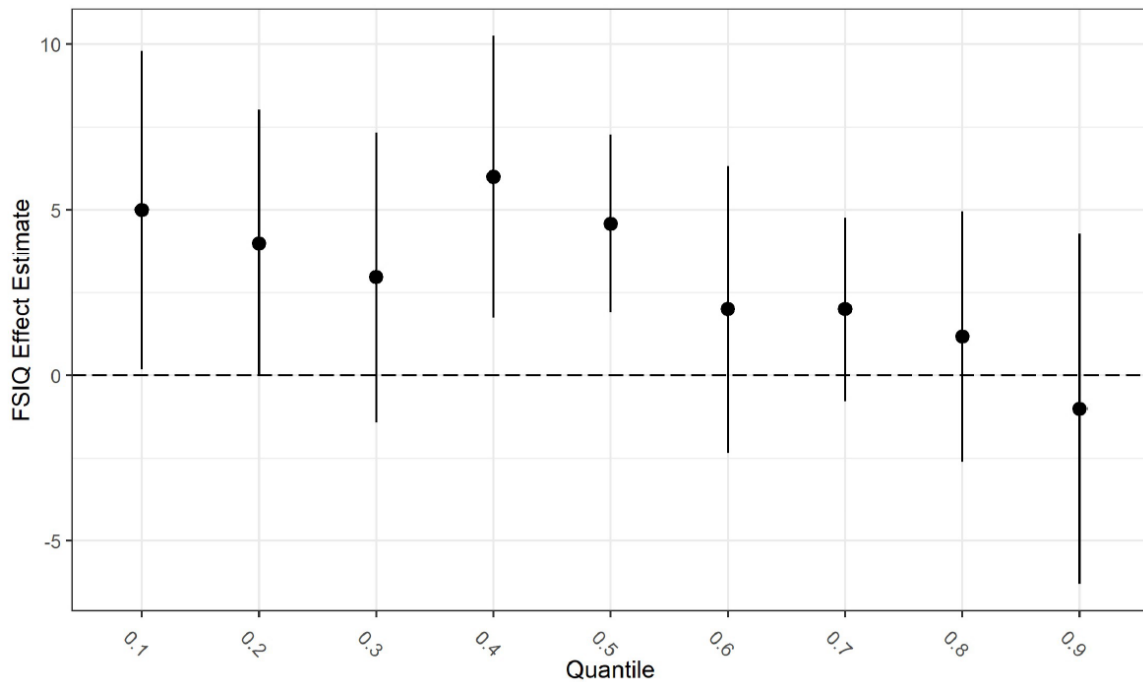
Figure 2.2. **Estimated effects of the intervention on full-scale IQ (FSIQ) from an unadjusted complete case (*n* = 383) quantile regression analysis.**

Note: Dots represent the point estimate of the intervention's effect on a give quantile of the FSIQ distribution, and lines represent 95% confidence intervals around that estimate. Full reporting of corresponding values is provided in Table A.5.

2.5. Discussion

To our knowledge, this is the first RCT of reductions in air pollution during pregnancy and cognitive performance in childhood. In this cohort of women living in a polluted community, the use of air cleaners from late in the first trimester to the end of pregnancy increased mean FSIQ at four years of age by 2.5 points (95% CI: -0.4, 5.4 points). Estimated effects on mean FSIQ were slightly larger after adjusting for PTB (2.8 points; 95% CI: -0.1, 5.7 points) and among complete cases (2.8 points, 95% CI: 0.0, 5.7 points). These results indicate that reducing particulate matter air pollution exposure during pregnancy could be beneficial for cognitive development.

Observational studies suggest that prenatal exposure to ambient air pollution is associated with impaired neurodevelopment at 3-5 years of age (Clifford et al., 2016). Several studies also suggest that exposure to airborne polycyclic aromatic hydrocarbons (PAHs) plays a key role. A 2015 meta-analysis, which incorporated 31 studies of children aged 6 months to 17 years, concluded that there is sufficient evidence of a causal association between developmental PAH exposure and reduced global IQ in children (Suades-González et al., 2015). A magnetic resonance imaging study reported an association between third trimester exposure to PAHs and reductions in white matter surface among children 7-9 years of age.28 Particle-bound PAHs are found mostly in the $PM_{2.5}$ size range (Da Limu et al., 2013a). The $PM_{2.5}$ in Ulaanbaatar comes primarily from coal combustion, a major source of PAHs.

Consistent with two observational studies, we found significantly greater mean verbal comprehension index scores among children in the intervention group. In an Italian birth cohort study, investigators administered the Wechsler Intelligence Scale for Children (3rd Edition) when children were 7 years old and found that exposure during pregnancy to nitrogen dioxide, a marker of traffic emissions, was associated only with lower mean verbal IQ and verbal comprehension index scores (Porta et al., 2016). In a U.S. study of 4- to 6-year old children administered the

Stanford Binet Intelligence Scales (5th Edition), Loftus et al., (Loftus et al., 2019). reported that PM_{10} exposure during pregnancy was associated with both verbal IQ and nonverbal IQ, but that associations with verbal IQ were stronger and more precise. Collectively, these studies suggest that verbal skills may be particularly sensitive to air pollution exposure.

Because air pollution is ubiquitous, with more than 90% of the world's population breathing $PM_{2.5}$ concentrations above the WHO guideline of 5 $\mu g/m^3$, the population-level impacts of air pollution on brain development could be substantial even if the individual-level effects are modest (Bellinger, 2012). Modest changes in cognitive development can also have economic impacts; for example, studies in the US have estimated that a 1-point reduction in IQ reduces annual earnings by an average of up to 3% (Salkever, 2014).

The randomized deployment of HEPA cleaners in this study provides two important insights. First, because HEPA cleaners reduce particle concentrations more than gases, our results indicate that particle exposure independently affects cognitive development. Second, because exposure during pregnancy is often correlated with exposure after birth, it is difficult in observational studies to evaluate the specific impacts of prenatal exposure (Heinrich & Thiering, 2018). In our trial, however, participants used the air cleaners only until the end of pregnancy so $PM_{2.5}$ concentrations were 29% lower among intervention participants during pregnancy but similar during childhood (Barn et al. 2018a). Therefore, our results suggest that reducing PM exposure during pregnancy improves cognitive development in childhood.

Our estimated difference of 2.5 to 3.2 points in mean FSIQ is comparable to the impact of more widely recognized factors affecting neurodevelopment. For example, late PTB (34-37 weeks) is estimated to reduce mean FSIQ by 3.6 points (Allotey et al., 2018) and the long-term impact of mild traumatic brain injury in childhood on mean FSIQ is approximately 4.5 points (Babikian & Asarnow, 2009). In a pooled analysis of lead exposure and IQ, we reported that an increase in blood

lead concentration from 2.4 to 10 µg/dL was associated with a 3.8-point reduction in IQ among 5- to 10-year old children (Lanphear et al., 2005).

This study was motivated primarily by observational evidence linking outdoor air pollution with neurodevelopment, but nearly half of the women lived with a smoker at enrollment. In a stratified ITT analysis, we found that the effect of the intervention on FSIQ was more pronounced among children whose mothers did not live with a smoker at baseline. Thus, the benefits of the intervention were probably not primarily due to reductions in exposure to second-hand smoke.

A post hoc quantile regression analysis suggested that the intervention may be most beneficial among children at the lower end of the FSIQ score distribution. Quantile regression has not been widely used in studies of pollutants and neurodevelopment. In a study of children's blood lead levels before age 3 and Wisconsin Knowledge and Concepts Exam (WKCE) scores, effect estimates of lead exposure on reading and math performance scores were greater at the lower end of the math and reading score distributions (Magzamen et al., 2015). In contrast, a study of early-life cadmium exposure and WPPSI scores in Bangladesh found similar associations across the distribution of scores (Kippler et al., 2012).

Our study had some limitations. The sample size was based on term birth weight, the original outcome of the study, so we may have been underpowered to identify differences in mean FSIQ. Power was further limited by the relatively modest 29% reduction in geometric mean indoor $PM_{2.5}$ concentrations. We excluded ger household because ger neighborhoods have unreliable electricity and gers often have higher indoor pollution emissions, which could limit generalizability of results. This exclusion may have also limited our exposure gradient. We measured indoor $PM_{2.5}$ as a proxy for personal exposure, and although the intervention reduced residential concentrations, reductions in exposure were likely attenuated by exposure in other locations (Allen & Barn, 2020). FSIQ has been criticized, especially when used in culturally and racially heterogenous settings. Despite its limitations, FSIQ was an appropriate primary outcome in this study of a relatively

ethnically and culturally homogenous population. Moreover, we were interested in comparing mean scores between groups, not diagnosis or quantifying the abilities of individual children. Further, there is still much uncertainty on the specific brain regions and functions that are most impacted by air pollution (de Prado Bert et al., 2018). Therefore, despite its limitations, we determined that using a summary measure, like FSIQ, in this experimental study design was more useful than measures of specific neurodevelopmental domains (Raiford & Coalson, 2014). Conducting standardized cognitive testing in young children is inherently challenging. Performance on these tests can be influenced by the child's level of interest and engagement. While this may have contributed random error in our outcome variables, those errors would likely be non-differential and lead to an underestimation of the intervention's effect.

We are not aware of any previous studies that used the WPPSI-IV in Mongolia. We translated the WPPSI-IV and refined the translations based on pilot testing in Mongolian children before collecting data from UGAAR participants. There is no Mongolian reference population, so we scaled the raw scores to match those of the Canadian reference population then calculated scaled scores and composite indices. Any errors in WPPSI scores introduced by this procedure were likely non-differential. In addition, we found that preterm birth, sex, maternal intelligence, and HOME scores were all associated with WPPSI-IV scores which gives us more confidence in the validity of our outcome measurements.

We did not blind participants with sham air cleaners. This may have contributed to a higher frequency of withdrawal among control participants, which in turn may have led to selection bias. The estimated intervention effects were attenuated in the ITT analyses compared to the complete case analyses. Because mothers were aware of their intervention status during pregnancy, it is possible that those who received the air cleaners during pregnancy interacted differently with their children, which could have influenced development. This is unlikely, however, because HOME scores, which indicate the quality of a child's home environment, were similar in intervention and control homes. The assessors who administered the

WPPSI-IV were blinded to participants' treatment group assignments, so information bias is unlikely.

Our results might have been affected by the live birth bias, a form of selection bias that can occur in birth cohort studies of childhood outcomes, which are measured only among live-born children (Leung et al., 2021). We previously reported a lower risk of spontaneous abortion among participants in the intervention group (Barn et al. 2018b). Thus, we may have underestimated the benefits of this intervention if an unmeasured exposure both increased the risk of fetal death and reduced WPPSI-IV scores (Leung et al., 2021). Because the difference in spontaneous abortions contributed to differences in PTB (Barn et al. 2018b), we attempted to account for some of this bias by adjusting for PTB in regression models. This adjustment corrected the imbalance in PTB between treatment groups, but it also blocked any effect of the intervention on WPPSI-IV scores that is mediated by PTB.

We did not include in the ITT analysis six children with medical conditions that could affect WPPSI-IV performance and the reliability of imputed scores. Three children had conditions with no plausible link to air pollution, but three children from the intervention group had been diagnosed with ASD, which has been associated with air pollution (Pagalan et al., 2019). While withholding these children from the imputation may have introduced some bias, imputation of WPPSI-IV scores for these children would be unreliable because ASD is a heterogenous disorder and the relationship between ASD and FSIQ varies widely. For example, estimates of the prevalence of intellectual disability (FSIQ < 70) among school-age children with ASD range from 11 to 65% and a substantial fraction of children with ASD have average or above average intelligence (Lord et al., 2018). In addition, children with ASD often have very pronounced strengths and weaknesses on subtests (Charman et al., 2011) so standard tests like the WPPSI-IV and summary measures like FSIQ may have limited value for characterizing the cognitive abilities of these children (Courchesne et al., 2019).

2.6. Conclusions

Our results indicate that reducing air pollution exposure during pregnancy improved cognitive performance in 4-year-old children. In much of the world air pollution will threaten public health for the foreseeable future. Portable air cleaners may help to reduce the neurodevelopmental impacts of air pollution until emissions can be brought under control.

Chapter 3. Who benefits most from a prenatal HEPA filter air cleaner intervention on childhood cognitive development? The UGAAR randomized controlled trial

3.1. Abstract

Background: Air pollution exposure during pregnancy affects children's brain function. Maternal stress and nutrition, socioeconomic status, and the child's sex may modify this relationship.

Objective: To identify characteristics of children with the largest increases in full-scale IQ (FSIQ) after their mothers used HEPA filter air cleaners during pregnancy.

Methods: In this randomized controlled trial we randomly assigned women to receive 1-2 air cleaners or no air cleaners during pregnancy. We analyzed maternal hair samples for cortisol and dehydroepiandrosterone (DHEA). When the children were 48 months old, we measured FSIQ with the Wechsler Preschool and Primary Scale of Intelligence. We evaluated ten potential modifiers of the intervention-FSIQ relationship using interaction terms in separate regression models. To account for correlations between modifiers, we also used a single regression model containing main effects and intervention x modifier terms for all potential modifiers.

Results: Among 242 mother-child dyads with complete data, the intervention was associated with a 2.3-point increase (95% CI: -1.5, 6.0 points) in mean FSIQ. The intervention improved mean FSIQ among children of mothers in the bottom (5.4 points; 95% CI: -0.8, 11.5) and top cortisol tertiles (6.1 points; 95% CI: 0.5, 11.8), but not among those whose mothers were in the middle tertile. The largest between-group difference in the intervention's effect was a 7.5-point (95% CI: -0.7, 15.7) larger increase in mean FSIQ among children whose mothers did not take vitamins than among children whose mothers did take vitamins (interaction p-value = 0.07). We also observed larger benefits among children whose mothers did not

complete university, and those with lower hair DHEA concentrations, hair cortisol concentrations outside the middle tertile, or more perceived stress.

Conclusion: The benefits of reducing air pollution during pregnancy on brain development may be greatest for mothers who do not take vitamins, experience more stress, or have less education.

3.2. Introduction

Experimental and epidemiological evidence suggests that air pollution and other stressors negatively affect development of the central nervous system (Block et al., 2012; Brockmeyer & D'Angiulli, 2016). Observational studies have reported associations between air pollution exposure during pregnancy and brain functions including hyperactivity, autism spectrum disorder, and decreased cognitive function (Clifford et al., 2016). These alterations in brain function may have lifelong consequences such as poor school performance, diminished economic productivity, and increased risk of antisocial and criminal behaviour (Grandjean & Landrigan, 2006).

Several factors may modify the relationship between air pollution during early brain development and brain function. Maternal psychological stress is of particular interest because it is modifiable and may share a common physiological pathway with environmental pollutants (Erickson & Arbour, 2014; Kodavanti, 2019; Snow et al., 2018; Wright, 2009). Self-reported maternal stress or material hardship can modify the effects of air pollution on children's behaviors and intelligence (Perera et al., 2013; Vishnevetsky et al., 2015). To our knowledge, however, investigators have not examined whether the impact of air pollution is modified by parental stress measured using markers of biological stress.

Cortisol, a glucocorticoid hormone linked to the stress response in humans, is important in coping with stressors through activation of the hypothalamic-pituitary-adrenal (HPA) axis. With acute stressors, HPA hyperactivation typically results in increased cortisol levels that quickly return to basal levels. Chronic stressors, however, can lead to changes in HPA axis activity (Basson et al., 2019). For example, cortisol secretion might initially increase during chronic stress, but prolonged periods of hyperreactivity can result in blunted cortisol levels (Fries et al., 2005). Such changes in HPA axis activity, including blunted cortisol, have been associated with increased susceptibility to depression and anxiety (Basson et al., 2019; Daskalakis et al., 2013; Hertzman & Boyce, 2010).

In addition to cortisol, adrenal glands also secrete dehydroepiandrosterone (DHEA), a steroid with glucocorticoid antagonist properties (Stárka et al., 2015) that influences brain development and cognition (Quinn et al., 2018) and may offset the effects of cortisol in select brain regions (Kamin & Kertes, 2017). Thus, quantifying levels of both cortisol and DHEA, and the balance between the two, may enhance our understanding of HPA axis activity (Sollberger & Ehlert, 2016).

In addition to maternal stress, investigators have found other factors that may modify the effects of air pollution on brain development; these include socioeconomic status (SES), nutrition, and the child's sex (Chiu et al., 2016; Hossain et al., 2011; O'Neill et al., 2003). Lower SES may introduce other disadvantages including lack of access to care or inadequate care and residential proximity to polluting sources, thus increasing susceptibility to the neurotoxic effects of air pollution (Calderón-Garcidueñas et al., 2012). Nutrition is also a plausible modifier because the intake of vitamins and antioxidants, such as folate, may attenuate air pollution-induced oxidative stress and the negative effects of air pollution on neurodevelopment (Goodrich et al., 2018; Hossain et al., 2011; Loftus et al., 2019). The neurodevelopmental effects of air pollution may also differ by sex (Chiu et al., 2016; Rahman et al., 2022). For example, Peterson and colleagues reported that associations between fine particulate matter ($PM_{2.5}$) exposure during gestation and brain development were stronger in boys, while associations with polycyclic aromatic hydrocarbons (PAHs) were stronger in girls (Peterson et al., 2022a). Differences in estimated $PM_{2.5}$ effects between girls and boys have also been reported for studies of behavioral problems in childhood (Chiu et al., 2016; Wang et al., 2017).

We recently published an analysis from the Ulaanbaatar Gestation and Air Pollution Research (UGAAR) randomized controlled trial. There we reported that the use of high efficiency particulate air (HEPA) filter air cleaners ("HEPA cleaners") during pregnancy was associated with a 2.8-point (95% CI: 0.0, 5.7 point) increase in mean full-scale IQ (FSIQ) in four-year old children (Ulziikhuu et al., 2022). In a quantile regression analysis, we observed greater benefits of the

intervention for children at the low end of the FSIQ distribution (Ulziikhuu et al., 2022). In the present analysis we sought to identify groups of children that benefitted the most from this intervention.

3.3. Methods

The UGAAR study has been described in detail (Ulziikhuu et al., 2022). We conducted the trial in Ulaanbaatar, Mongolia's polluted capital city. We recruited 540 pregnant women from two prenatal health clinics in the city's centrally located Sukhbaatar district who met the following criteria: ≥ 18 years old, ≤ 18 weeks into a singleton pregnancy, non-smoker, living in an apartment, not using air cleaner(s) at enrollment, and planning to give birth in a medical facility in Ulaanbaatar. The study was approved by the Simon Fraser University Office of Research Ethics and the Medical Ethics Approval Committee of the Mongolian Ministry of Health.

3.3.1. Intervention

The intervention group received one or two HEPA cleaners (Coway AP-1009CH), depending on home size. The control group received no HEPA cleaners. We deployed the HEPA cleaners in intervention homes shortly after enrollment at a median (25th, 75th percentile) gestational age of 11 weeks (9, 13 weeks) (Barn, et al. 2018b). For smaller homes (<40 m^2), we placed an air cleaner in the main living area; for larger apartments (≥40 m^2) we placed a second air cleaner in the participant's bedroom. We did not replace the HEPA filters during the study period, and we collected the HEPA cleaners shortly after pregnancy ended. This was a single blind trial; the participants knew their intervention status, but staff responsible for cognitive assessment were blinded.

3.3.2. Prenatal Procedures

During early (5 to 18 weeks) and late gestation (24 to 37 weeks), we administered questionnaires to obtain information on health, medical history, and lifestyle factors such as income, smoking, education, and vitamin intake (Barn et al. 2018b). We

also asked participants to complete the four-question Perceived Stress Scale (PSS-4) as part of both prenatal questionnaires. The PSS-4 is a widely used tool in which participants rate their feelings using a five-point Likert scale to indicate their perceived stress over the previous month (Cohen et al., 1983; Lesage et al., 2012; Mitchell et al., 208; Warttig et al., 2013).

We collected hair samples from the women shortly after enrollment (4 to 16 weeks gestation) and again later in pregnancy (28 to 41 weeks gestation). We cut approximately 30-50 strands (~ 30 mg) of hair close to the scalp from the occipital area. Some of the hair samples, particularly those collected in late pregnancy, were analyzed for nicotine using a destructive assay (Barn et al. 2018a). We analyzed a four cm hair sample from the remaining participants for maternal cortisol and DHEA concentrations to obtain a measure of overall hormone levels over approximately four months prior to sample collection. To remove contaminants, we washed the hair samples twice in 10 ml isopropanol using a Bio-Tek ELx50 washer and air-dried for 48 hours following each wash. Next, we pulverized the samples into fine powder using a using a Retsch MM301 Grinder, at 2.5 Hz for 2.5 min, and extracted twice for 24 hours with methanol to ensure complete release of steroids into the solvent. The solvent was then dried down using a Savant Speed Vac Plus at medium dry. We reconstituted the dried samples with 250 μl buffer. Hormones were measured using the commercially available high sensitivity enzyme immunoassay kits (#1-3002 for cortisol and #1-1202 for DHEA; Salimetrics LLC, State College, PA) according to the standard protocols. We standardized the concentrations of hormones by the weight of the hair. For this analysis, we relied on the early pregnancy hair samples because they were available for more participants. We used the late pregnancy samples only to evaluate the stability of cortisol and DHEA concentrations over the course of pregnancy.

3.3.3. Postnatal procedures

We invited all living mother-child dyads to a follow-up study when the children were a median of 15.4 months of age (range: 7.7 to 28.9 months). At this follow-up enrollment and then at six-month intervals thereafter we administered questionnaires on housing characteristics and the child's diet, health, and activities.

We invited mothers and children to our study office when the children were approximately two and four years of age. At the two-year visit, trained assessors administered the matrix reasoning and vocabulary subtests of the Wechsler Abbreviated Scale of Intelligence (WASI) to assess the mothers' intelligence.

3.3.4. Outcome measurements

At the four-year visit we assessed the children's cognitive performance using the Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (WPPSI–IV) (Ulziikhuu et al., 2022). We administered ten WPPSI-IV subtests to the children at a median age of 48 months (range: 48 to 51 months). The outcome of interest in this analysis was the full-scale intelligence quotient (FSIQ), which is derived by combining scores from six WPPSI-IV subtests.

3.3.5. Potential sources of intervention effect heterogeneity

We identified the following potential effect modifiers by searching published studies of air pollution and neurodevelopment: maternal folate status (Loftus et al., 2019), maternal stress (Perera et al., 2013; Vishnevetsky et al., 2015), socioeconomic status (Loftus et al., 2020; Siddique et al., 2011) and child's sex (Chiu et al., 2016; Peterson et al., 2022a). Based on our literature review, we selected the following variables from the UGAAR cohort for inclusion in our analysis of intervention effect heterogeneity: vitamin intake in early pregnancy, hair concentrations of cortisol and DHEA (and the cortisol:DHEA ratio) in early pregnancy, PSS-4 score in early

pregnancy, maternal education at baseline, monthly family income at baseline, and the child's sex.

In addition, because the timing of exposure to toxic chemicals can influence brain development (Grandjean & Landrigan, 2006), we hypothesized that children of women who received the air cleaners earlier in their pregnancy might benefit more from the intervention (Grandjean & Landrigan, 2006). Therefore, we evaluated the influence of gestational age at enrollment on the intervention-FSIQ relationship. Because outdoor air pollution in Ulaanbaatar varies considerably between seasons, with higher pollution during colder months (Allen et al., 2013), we also explored the influence of season of enrollment on the effect estimates. Finally, because maternal intelligence is associated with children's FSIQ scores and we previously found in a quantile regression analysis that children with lower FSIQ scores benefitted most from the intervention (Ulziikhuu et al., 2022), we hypothesized that the intervention might be more beneficial to the children of women with lower WASI scores. Although the WASI was administered to mothers when the children were approximately two years of age, we assumed that maternal intelligence is stable over time and that WASI matrix reasoning scores represent maternal intelligence at baseline.

3.3.6. Statistical analysis

We dichotomized the potential effect modifiers to allow for comparisons of the magnitude of effect heterogeneity between modifiers that were measured as continuous (e.g., hormone concentrations and maternal intelligence) and categorical variables (e.g., education and income). Because the relationship between stress and cognitive performance may be nonlinear (De Veld et al., 2014; Hertzman & Boyce, 2010), we first evaluated the effect of the intervention on FSIQ across hair hormone concentration tertiles and quartiles before dichotomizing. We grouped maternal education into those who did and did not complete university and season of enrollment into colder (October-March) and warmer (April-September) months. We dichotomized the remaining continuous variables at the

median and the remaining categorical variables into groups with approximately equal numbers of participants. Because the potential effect modifiers might be correlated with one another, we estimated the correlations between all pairs of binary variables using the phi correlation coefficient.

We evaluated effect heterogeneity in two ways. First, we evaluated the influence of each potential modifier on the intervention-FSIQ relationship individually using separate multiple linear regression models with an intervention x modifier interaction. Second, we ran a multiple linear regression model containing main effects and intervention x modifier interactions for all potential effect modifiers (excluding the cortisol:DHEA ratio because cortisol and DHEA were already included in the model). This allowed us to quantify the magnitude of intervention effect heterogeneity from each modifier while simultaneously adjusting for the other variables to account for a lack of independence between modifiers (Vanderweele et al., 2019).

We also conducted two sensitivity analyses. Some hair treatments, such as coloring, bleaching, straightening or perms have been found to influence hair cortisol concentrations (Wosu et al., 2013). Therefore, we re-ran all models after excluding 62 participants who reported such hair treatments. We conducted a second sensitivity analysis to evaluate results from more parsimonious multivariate models. Specifically, for the modifiers responsible for the most intervention effect heterogeneity in our main analyses, we ran multiple linear regression models containing main effects and intervention x modifier interactions for the modifier of interest and variables correlated (phi coefficient) at p<0.20 with the modifier of interest.

3.4. Results

A total of 272 women were randomly assigned to the control group and 268 were randomly assigned to the intervention group between January 9, 2014 to May 1, 2015. Twenty-seven percent of intervention homes received one air cleaner and

73% received two air cleaners (Barn et al. 2018b). We followed 514 women (253 control and 261 intervention) to the end of their pregnancy. There were 468 live births (225 control and 243 intervention), 46 pregnancy losses (28 control and 18 intervention), and five neonatal deaths (1 control and 4 intervention). A total of 416 participants (194 control and 222 intervention) enrolled in the postnatal follow-up study; 383 (182 control and 201 intervention) children completed the WPPSI-IV testing between September 28, 2018 and January 8, 2020 (Ulziikhuu et al., 2022).

Among the 383 women whose children completed the WPPSI-IV, hair cortisol and DHEA concentrations were quantified for 77% (293 of 383). Women who had early pregnancy cortisol and DHEA concentrations tended to be older, were more likely to be in the control group, and had lower WASI scores and higher household incomes than women whose hair samples were not collected or analyzed (Table B.1). The availability of the remaining variables ranged from 93% (357 of 383) for maternal education to 100% for maternal age and child's sex. We had complete data on FSIQ and all potential effect modifiers for 242 participants (118 control and 124 intervention).

3.4.1. Baseline and pregnancy characteristics

At baseline, the distributions of most potential effect modifiers were similar between the control and intervention groups (Table 2.1). Participants were enrolled in the study at a median gestational age of 11 weeks (IQR: 8, 13) when mothers were a median age of 29 years old (IQR: 25, 34). Over 70% of the participants in both groups reported taking vitamins early in pregnancy. Median (25th-75th percentile) cortisol concentrations were higher in the intervention group (5.6 pg/mg; 4.5-7.2 pg/mg) than in the control group (5.2 pg/mg; 4.0-6.9 pg/mg; p=0.08), but DHEA concentrations and PSS-4 scores were similar between groups. We previously reported that the HEPA cleaners were used 70% of the time by intervention group participants (Barn et al. 2018b).

Table 3.1. **Select maternal and child variables for 383 participants who completed the Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (WPPSI–IV).**

	Control (N=182) median (25th, 75th percentile) or N(%)	Intervention (N=201) median (25th, 75th percentile) or N(%)	P value[a]
Gestational age at enrollment (weeks)	11 (9, 12)	11 (8, 13)	0.70
Not reported, N (%)	8 (4.4)	12 (6.0)	
Enrollment season			
Winter	56 (30.8)	57 (28.4)	
Spring	57 (31.3)	54 (26.9)	0.25
Summer	22 (12.1)	27 (13.4)	
Fall	47 (25.8)	63 (31.3)	
Monthly household income (Tugriks)			
<1,200,000	120 (57.0)	104 (52.3)	
≥1,200,000	77 (43.0)	95 (47.7)	0.36
Not reported, N (%)	3 (1.6)	2 (1.0)	
Maternal education			
Completed university	24 (14.0)	23 (12.4)	
Did not complete university	147 (86.0)	163 (87.6)	0.64
Not reported, N (%)	11 (6.0)	15 (3.0)	
Vitamin intake at early pregnancy			
Yes	129 (73.30)	153 (78.9)	
No	47 (26.7)	41 (21.1)	0.21
Not reported, N (%)	6 (3.3)	7 (3.5)	
Hair cortisol concentration (pg/mg) at early pregnancy	5.2 (4.0, 6.9)	5.6 (4.5, 7.2)	0.08
Not measured, N (%)	38 (20.1)	52 (25.9)	
Hair DHEA concentration (pg/mg) at early pregnancy	13.4 (9.2, 19.0)	13.8 (9.9, 18.5)	0.98
Not measured, N (%)	38 (20.1)	52 (25.9)	
PSS 4 score at early pregnancy	5.0 (4.0, 7.0)	6.0 (4.0, 7.0)	0.89
Not measured, N (%)	3 (1.6)	2 (1.0)	
Maternal Intelligence (WASI Matrix reasoning score)	16 (12, 19)	17 (13, 19)	0.36
Not measured, N (%)	14 (7.7)	6(3.0)	
Sex			
Female	88 (48.4)	96 (47.8)	0.91
Male	94 (51.7)	105 (52.2)	

3.4.2. Air Pollution Concentrations

We previously reported that the air cleaners reduced the geometric mean indoor $PM_{2.5}$ concentration by 29% from 24.5 µg/m^3 in control homes to 17.3 µg/m^3 in intervention homes (Barn et al., 2018a). The HEPA cleaners were removed shortly after birth, after which mean $PM_{2.5}$ concentrations were similar between the intervention and control groups (3% lower in intervention homes; 95% CI: −17% to 9%) (Ulziikhuu et al., 2022).

3.4.3. Correlations between stress markers

Among 71 participating mothers who had hair cortisol and DHEA concentrations measured in both early and late pregnancy, we found moderate correlations for cortisol (Spearman's r = 0.61), DHEA (r = 0.66), and the cortisol:DHEA ratio (r = 0.50). The correlation between early and late PSS-4 scores was lower (r = 0.23; N = 271) (Table B.2). Hair stress biomarkers were not correlated with PSS-4 scores (r = -0.07 to 0.12).

3.4.4. Intervention effect heterogeneity

Among 293 dyads with maternal hair cortisol and DHEA concentrations and a childhood FSIQ measurement, we observed a "U-shaped" pattern in which the intervention improved mean FSIQ among children whose mothers were in the lowest (5.4 points; 95% CI: -0.8, 11.5) and highest hair cortisol tertiles (6.1 points; 95% CI: 0.5, 11.8), but not among children of mothers in the middle tertile (-2.5 point; 95% CI: -7.9, 2.8, Figure 3.1). Based on this result, in subsequent analyses we dichotomized the study sample into those in the middle cortisol tertile and those in the bottom or top cortisol tertile. After stratifying into tertiles of DHEA and the cortisol:DHEA ratio, we observed the greatest benefits among children whose mothers were in the lowest DHEA tertile (6.3-point increase in mean FSIQ; 95% CI: 1.0, 11.6) or the highest corstisol:DHEA ratio tertile (4.8-point increase in mean FSIQ; 95% CI: -0.6, 10.3). The trends across tertiles were monotonic, with increasing point estimates of the intervention's effect as DHEA decreased and as the C/D ratio increased (Figure 3.1). Thus, in subsequent analyses we dichotomized DHEA and the C/D ratio at the median. To evaluate the sensitivity of our results to the use of tertiles we also stratified by quartiles of maternal hair stress markers. The use of quartiles indicated the same patterns, including the "U-shaped" effect of cortisol on the intervention-FSIQ relationship (Figure B.1).
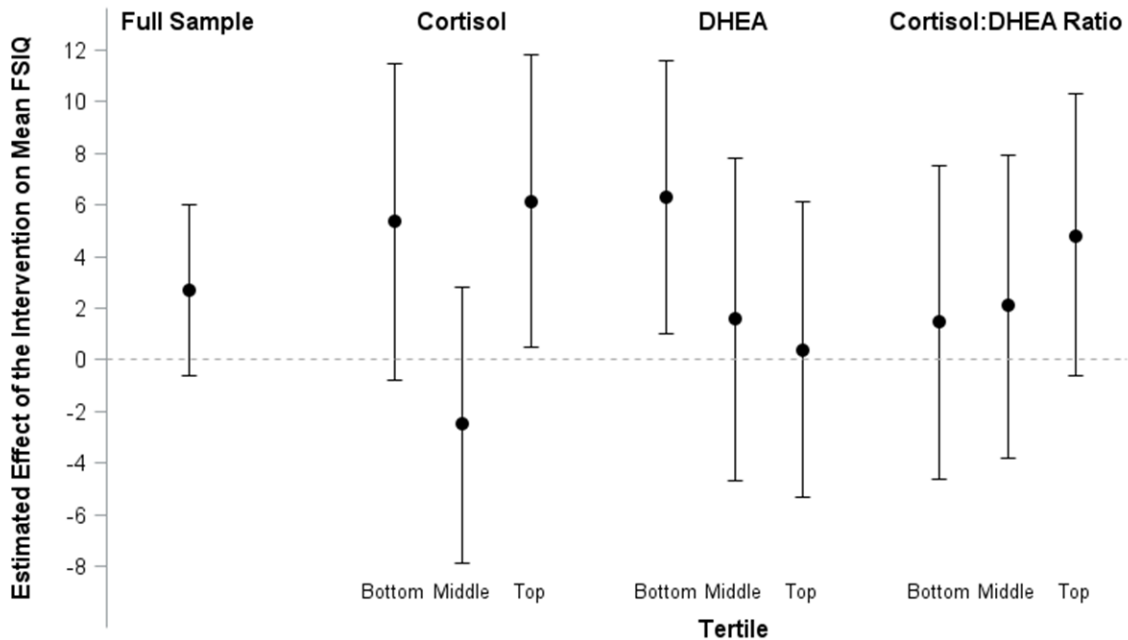
Figure 3.1. **Estimated effects of the air cleaner intervention on mean full-scale IQ (FSIQ) by tertiles of maternal hair stress markers (N = 293).**

We found that the potential effect modifiers were weakly correlated with one another (Table B.3). Across all pairs of binary variables, the strongest correlations were between maternal education and vitamin intake (phi correlation coefficient = 0.17, p<0.01), household income and maternal education (0.14, p=0.01), household income and enrollment in the cold season (-0.13, p<0.05), maternal education and enrollment in the cold season (0.12, p<0.05) and gestational age at enrollment and household income (0.11, p<0.05).

As previously reported, we found that children whose mothers were randomly assigned to the intervention group had a 2.8-point (95% CI 0.0, 5.7 points) higher mean FSIQ than children in the control group (Table 3.2) (Ulziikhuu et al., 2022). Among the subset of 242 mother-child dyads with complete data on potential effect modifiers, the intervention was associated with a 2.3-point increase (95% CI: -1.5, 6.0 points) in mean FSIQ.

Table 3.2.   Effects of the air cleaner intervention on mean FSIQ estimated from separate multiple regression models with an intervention x modifier interaction term.

Effect Modifier	Stratum	N	Mean (SD) FSIQ		Estimated Effect of the Intervention on Mean FSIQ				Interaction P-value
			Control	Intervention	Effect Estimate	Lower 95%	Upper 95%	p-value	
	All	383	97.2 (15.0)	100.1 (13.4)	2.8	0.0	5.7	0.05	-----
Gestational age at enrollment	< 11 weeks	175	96.2 (14.8)	100.4 (13.4)	4.2	-0.0	8.4	0.05	0.35
	≥ 11 weeks	188	98.0 (15.5)	99.4 (13.3)	1.4	-2.7	5.6	0.50	
Enrollment season	October-March	242	96.1 (14.7)	99.6 (13.4)	3.5	-0.1	7.0	0.06	0.59
	April-September	141	99.2 (15.4)	101.0 (13.4)	1.9	-2.9	6.7	0.45	
Vitamin intake at early pregnancy	No	88	94.0 (16.5)	100.2 (11.2)	6.2	0.1	12.3	0.05	0.15
	Yes	282	98.9 (14.3)	100.2 (13.9)	1.2	-2.1	4.6	0.46	
Household income	< 1,200,000 MNT	206	95.9 (14.4)	99.8 (12.6)	3.9	0.2	7.6	0.04	0.40
	≥ 1,200,000 MNT	172	99.2 (15.9)	100.5 (14.3)	1.4	-3.1	5.9	0.55	
Maternal education	Did not complete university	47	93.2 (11.8)	100.2 (13.2)	7.0	-0.3	14.4	0.06	0.28
	Completed university	310	98.2 (15.6)	100.3 (16.7)	2.2	-1.1	5.4	0.20	
Maternal intelligence[a]	≤Median	184	94.3 (13.9)	98.7 (13.8)	4.3	0.3	8.4	0.03	0.40
	>Median	179	99.9 (15.8)	101.8 (12.9)	1.9	-2.3	6.1	0.38	

Maternal hair cortisol concentration in early pregnancy	Middle tertile	98	99.8 (14.3)	97.2 (12.6)	-2.5	-7.9	2.8	0.35	
	Bottom or top tertile	195	96.4 (15.7)	101.8 (13.5)	5.3	1.2	9.5	0.01	0.02
Maternal hair DHEA concentration in early pregnancy	≤Median	147	97.7 (15.6)	102.5 (11.9)	4.7	0.2	9.2	0.04	0.24
	>Median	146	97.2 (15.2)	98.0 (14.3)	0.8	-4.1	5.6	0.75	
Cortisol / DHEA hair concentration ratio at early pregnancy	≤Median	146	98.4 (16.2)	99.7 (15.2)	1.2	-3.9	6.4	0.63	0.38
	>Median	147	96.4 (14.4)	100.6 (11.6)	4.2	-0.0	8.4	0.05	
Perceived stress score in early pregnancy[b]	≤Median	194	97.7 (15.1)	99.5 (13.9)	1.8	-2.3	6.0	0.38	0.51
	>Median	184	96.4 (14.9)	100.7 (12.9)	3.7	-0.3	7.8	0.07	
Child's sex	Female	184	99.9 (15.6)	104.1 (12.8)	4.2	0.1	8.3	0.05	0.40
	Male	199	94.7 (14.1)	96.6 (12.9)	1.8	-1.9	5.6	0.34	

When we evaluated potential effect modifiers one by one, only hair cortisol had an interaction p-value <0.05, with greater intervention benefits on FSIQ among those outside the middle cortisol tertile (5.3 points; 95% CI: 1.2, 9.5) than among those in the middle tertile (-2.5 points; 95% CI: -7.9, 2.8; Table 3.2). We also found an indication of differences in the benefits of this intervention between the children of 282 women who took vitamins during early pregnancy (1.2-point increase; 95% CI: -2.1, 4.6) and the 88 who did not (6.2-point increase, 95% CI: 0.1, 12.3; interaction p-value = 0.15).

In a regression model incorporating all main effects and interaction terms, the largest between-group difference in the intervention's beneficial effect was for vitamin intake during early pregnancy, with a mean FSIQ increase 7.5 points larger (95% CI: -0.7, 15.7) among children of mothers who did not take vitamins than among children whose mothers did take vitamins (interaction p-value = 0.07; Table 3.3). The next largest between-group differences were for maternal education (7.2-point greater mean FSIQ increase among children of mothers who did not complete university, interaction p-value = 0.22), DHEA concentrations (5.6-point greater mean FSIQ increase among children of mothers with hair DHEA concentration below the median, interaction p-value = 0.12), cortisol concentrations (5.5-point greater mean FSIQ increase among children of mothers with hair cortisol concentration outside the middle tertile, interaction p-value = 0.14), perceived stress scores (5.1-point greater mean FSIQ increase among children of mothers with PSS-4 total scores above the median, interaction p-value = 0.16), and maternal intelligence (4.4-point greater mean FSIQ increase among children of mothers with WASI matrix reasoning scores below the median, interaction p-value =0.20).

Table 3.3.   Sources of heterogeneity in the estimated effect of the air cleaner intervention on mean FSIQ estimated from a regression model incorporating all main effects and interaction terms (N = 242).

Effect modifier	Group that benefitted more	Estimated between-group difference in the intervention's effect on mean FSIQ	Lower 95%	Upper 95%	Interaction P-value
Maternal vitamin intake in early pregnancy	No vitamin intake	7.5	-0.7	15.7	0.07
Maternal education	Did not complete university	7.2	-4.2	18.6	0.22
Maternal hair DHEA concentration in early pregnancy	Hair DHEA below the median	5.6	-1.4	12.5	0.12
Maternal hair cortisol concentration in early pregnancy	Hair cortisol in bottom or top tertile	5.5	-1.8	12.8	0.14
Maternal perceived stress[a] in early pregnancy	Perceived stress score above the median	5.1	-2.0	12.1	0.16
Maternal intelligence[b]	Maternal intelligence score below the median	4.4	-2.5	11.3	0.20
Enrollment season	Enrolled October-March	2.5	-5.0	10.0	0.51
Gestational age at enrollment	Women who enrolled at 11 weeks gestation or later	2.1	-5.0	9.3	0.56
Child's sex	Female children	2.0	-5.1	8.9	0.59
Household income	Household income below the median	0.9	-6.2	8.0	0.81

The results for vitamin intake, cortisol, and DHEA were similar after excluding women who reported treating their hair (Tables B.4 and B.5). In this sensitivity analysis, the largest between-group difference in the intervention's effect was once again for vitamin intake in early pregnancy, with an 8.6-point (95% CI: -0.9, 18.1) greater benefit in mean FSIQ among children whose mothers did not take vitamins than among children whose mothers did take vitamins (interaction p-value= 0.08) (Table B.4). In contrast, the estimated effect heterogeneity due to maternal education and perceived stress were reduced substantially after removing participants who reported hair treatments.

Finally, in additional sensitivity analyses, we used more parsimonious models to further evaluate effect heterogeneity for the modifiers identified in our primary analyses as having the largest influence on the intervention's benefits (vitamin intake, maternal education, DHEA, and cortisol). Maternal vitamin intake was correlated at $p<0.20$ only with binary indicators of household income, gestational age at enrollment, and maternal education. In a model containing main effects and intervention x modifier interactions for these variables, the difference in FSIQ benefit between children whose mothers who did not take vitamins and those whose mothers did was attenuated to 4.2 points (95% CI: -3.3, 11.7, interaction p-value = 0.28; Table B.6). In a more parsimonious model for maternal education, the difference in FSIQ benefit between children whose mothers who did not complete university and those who did was attenuated to 4.8 points (95% CI: -6.5, 16.0, interaction p-value = 0.40; Table B.6). In a model containing main effects and intervention x modifier interactions for maternal hair DHEA concentration and its correlates, the difference in FSIQ benefit between children of mothers with hair DHEA below the median was to 5.0 points (95% CI: -2.0, 12.0, interaction p-value = 0.16; Table B.6) greater than children whose mothers had hair DHEA above the median. No variables were correlated at $p<0.20$ with hair cortisol.

3.5. Discussion

We previously reported that the use of air cleaners during pregnancy increased mean FSIQ at four years of age by 2.8 points (95% CI: 0.0, 5.7 points) and that the intervention was more beneficial for children with lower FSIQ scores (Ulziikhuu et al., 2022). In the present study, we found a significant interaction between the intervention and hair cortisol, with the greatest intervention benefits among children of mothers outside the middle cortisol tertile. In a multivariable analysis we found that the largest sources of intervention effect heterogeneity were vitamin intake during early pregnancy (greater benefit among children of mothers who did not take vitamins), maternal education (greater benefit among children of mothers who did not complete university), HPA axis activity as indicated by hair cortisol (greater benefit among children of mothers outside the middle hair cortisol tertile) and DHEA concentrations (greater benefit among children of mothers with DHEA concentrations below the median), and perceived stress (greater benefit among children of mothers with PSS-4 scores above the median). In sensitivity analyses, estimates of effect heterogeneity due to maternal vitamin intake, cortisol, and DHEA were reasonably consistent. In contrast, results for maternal education and perceived stress were more variable.

The difference in the intervention's effect by vitamin intake is broadly consistent with observations that the relationship between prenatal exposure to ambient air pollution and children's cognitive development is modified by nutritional status (Goodrich et al., 2018; Guxens et al., 2012; Loftus et al., 2019; Péter et al., 2015). Differences in intervention effects by self-reported vitamin intake in early pregnancy are also supported by observational studies suggesting that vitamins such as B, C, D, and E, and omega-3 fatty acids, may protect against the negative effects of air pollution (Péter et al., 2015).

Intake of antioxidant-rich foods has also been shown to attenuate the neurotoxic effect of air pollution (Guxens et al., 2012). This is biologically plausible, since oxidative stress and inflammation are key biological mechanisms through which

prenatal air pollution may affect neurodevelopment (Xu et al., 2016). Further, vitamin intake in our study may also be a proxy for prenatal folate status. Folate's important role in preventing neural tube defects may extend to improvement of cognitive function directly (Gao et al., 2016). In a birth cohort study in Tennessee, Loftus et al., (2019) found that the effect of prenatal air pollution on cognition in childhood was modified by prenatal folate. They reported that a 5 μg/m^3 increase in PM$_{10}$ was associated with a 6.8-point (95% CI: 1.4, 12.3) decrease FSIQ among children born to mothers in the lowest folate quartile during pregnancy; no association was observed between PM$_{10}$ and FSIQ among those in the highest folate quartile. Folic acid intake in early pregnancy was also reported to modify the association between air pollution and autism spectrum disorder (ASD) risk (Goodrich et al., 2018).

As part of a national health program in Mongolia, pregnant women are eligible to receive free multi-micronutrient supplements through prenatal care units. However, not all women receive the supplements (Ministry of Health, 2017). Moreover, the timing of folate intake may be important (Naninck et al., 2019), and some women may become aware of their pregnancy too late for folate to provide benefits on fetal neurodevelopment.

We found greater benefits of air cleaners for children of less educated mothers. More educated mothers may be at lower risk of maternal depression, have greater knowledge about child development, may possess a variety of child-rearing strategies, and be more likely to access and benefit from available services (Walker et al., 2011). Thus, the benefits of maternal education on neurodevelopment in childhood may offset some of the negative impacts of gestational air pollution exposure.

Our results also suggest that the benefits of air pollution reductions during pregnancy may be greater among children whose mothers have higher perceived and/or physiologic stress. High levels of glucocorticoids may inhibit neuron growth in the developing central nervous system and cause neuron cell death (Sandman

et al., 2012). Higher maternal cortisol has been linked with lower verbal IQ scores (Lewinn et al., 2009), and a recent prospective cluster-randomized controlled trial found improved child behavioral outcomes when hair cortisol concentrations and cortisol/DHEA ratios decreased (Mclean et al., 2022). DHEA is strongly involved in the stress response system, influences brain development and cognition (Quinn et al., 2018), and is protective against negative effects of glucocorticoids (Greaves et al., 2019). A review study reported a positive association between DHEA and global cognition, attention, verbal fluency and working memory (Junqueira De Menezes et al., 2016).

Children born to women with the lowest tertile of hair cortisol also appeared to benefit more from the intervention than children born to with women with the middle tertile. Blunted cortisol, which often occurs in depression and anxiety disorders, reflects the HPA axis response that typically results from chronic stress (Fries et al., 2005; Wells et al., 2014). A meta-analysis of over 20 studies supported an association between early life adversity and low or blunted cortisol (Bunea et al., 2017).

Stress hormones and perceived stress both appeared to modify the benefits of this intervention. However, stress hormones were not correlated with self-reported perceived stress. This result, which is consistent with previous studies (Dettenborn et al., 2010; O'brien et al., 2012; Van Uum et al., 2009), has several possible explanations. First, because chronic stress can lead to blunted cortisol, the relationship between hair cortisol and perceived stress may be non-linear, with a reduction in hair cortisol concentrations at the highest levels of perceived stress (Wells et al., 2014). Hair hormone concentrations and perceived stress may also represent different time periods (Wells et al., 2014). In our case, the hair samples captured cortisol and DHEA concentrations over the previous four months, while the PSS-4 prompts respondents to indicate their feelings over the previous month. Finally, the lack of a correlation between stress hormones and perceived stress may be due to measurement error. To minimize demand on participants' time we

used the 4-question perceived stress scale. Evaluations of this abbreviated instrument have produced mixed results (Ingram et al., 2016; Warttig et al., 2013).

This study had some limitations. The sample size of the UGAAR study was based on birth weight, the original outcome of this trial, and we had limited power to detect interactions. Some hair samples were previously analyzed for nicotine using a destructive assay, and our regression model incorporating all main effects and interaction terms included only complete cases, which further reduced our study power and may have introduced some selection bias. The women included in this analysis were older, more likely to be in the control group, and had lower maternal WASI scores and higher household incomes than women whose hair samples were not collected or analyzed for cortisol and DHEA. This may explain the higher median cortisol concentration in the intervention group. We used HPA axis biomarkers collected early in pregnancy, but a small number of samples collected later in pregnancy confirmed that early- and late-pregnancy hair concentrations were correlated. We relied on self-report for many of the potential effect modifiers that we evaluated. We grouped the bottom and top cortisol tertiles into a single group because stress can lead to both blunted and elevated cortisol and our preliminary analysis indicated that dyads in the bottom and top tertiles benefitted from this intervention. However, being in the lowest cortisol tertile does not necessarily indicate a blunted cortisol response. By dichotomizing the effect modifiers to allow for comparisons of effect estimates, we may have reduced the likelihood of detecting the biologically relevant zones of the effect modifiers. Although IQ has been criticized (Hampshire et al., 2012), we believe it is a useful measure of cognition in this relatively ethnically and culturally homogeneous study population. Furthermore, we were only interested in comparing mean FSIQ scores, not diagnosis or quantifying the abilities of individual children. Finally, we were unable to identify the specific nutrient(s) responsible for heterogeneity in the intervention's effect because we relied on the use of vitamin intake as a general indicator of nutritional status. Our questionnaires included questions about folate intake, but the response rates to these questions were poor.

This study also had several strengths. To our knowledge this is the first study to evaluate stress hormones as modifiers of the relationship between air pollution and cognitive development. Previous studies have evaluated associations between air pollution exposure and stress hormones (Hajat et al., 2019; Miller et al., 2020; Thomson et al., 2021; Toledo-Corral et al., 2021; Verheyen et al., 2021) or effect modification by self-reported indicators of hardship or perceived stress (Perera et al., 2013; Vishnevetsky et al., 2015). In addition, most previous studies of stress hormones quantified cortisol alone to evaluate HPA activity (O'Connor et al., 2021). Here we included DHEA as an additional measure of HPA activity due to its generally opposing biological and neurological functions to cortisol (Kamin & Kertes, 2017). This also prompted us to examine the cortisol:DHEA ratio as an additional index of HPA function (Kamin & Kertes, 2017). Cortisol varies considerably over time, so concentrations in serum, saliva and urine are commonly used measures of acute stress (Russell et al., 2012; Sarkar et al., 2013). In this study, we used cortisol and DHEA in hair as an integrated index of hormone concentrations to indicate exposure to stress and long-term HPA axis function (Dettenborn et al., 2010; Kirschbaum et al., 2009; Van Holland et al., 2012). Although many potential effect modifiers are likely be correlated, previous studies examining modification of the relationship between air pollution and cognitive performance have evaluated one effect modifier at a time (Chiu et al., 2016; Hossain et al., 2011; Loftus et al., 2019; Peterson et al., 2022a; Rahman et al., 2022; Wang et al., 2017). To our knowledge, no previous study examined multiple effect modifiers simultaneously to account for the relationships between them (Vanderweele et al., 2019).

3.6. Conclusions

Reducing emissions is the solution to protect children's developing brains from the effects of air pollution. However, in highly polluted communities air cleaners may be a useful harm reduction strategy until emissions can be controlled (Allen & Barn, 2020). Some have proposed prioritizing emissions reductions that improve health equity (Jonathan et al., 2007; Martenies et al., 2018; Nguyen & Marshall, 2018).

Understanding who benefits most from household-level exposure reductions may also inform strategies for improving health equity by prioritizing those most likely to benefit.

Chapter 4.   Prenatal exposure to indoor PM$_{2.5}$ and children's cognitive performance at 4 years of age: an observational analysis from the UGAAR randomized controlled trial

4.1. Abstract

Background: Outdoor fine particulate matter (PM$_{2.5}$) concentrations during pregnancy are linked to reduced cognitive performance in children. We previously reported that portable HEPA filter air cleaners use during pregnancy improved children's mean full-scale IQ (FSIQ), but associations with indoor PM$_{2.5}$ have not been explored. We aimed to quantify the association between indoor PM$_{2.5}$ during pregnancy and FSIQ in childhood.

Methods: We conducted an observational analysis using data from the Ulaanbaatar Gestation and Air Pollution Research (UGAAR) study. Using a previously developed model of weekly indoor PM$_{2.5}$ concentrations, we estimated the average concentrations in participants' homes over the full pregnancy and in each trimester. When the children were four years old, we measured FSIQ using the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-IV). We used multiple linear regression to assess the adjusted relationships between interquartile range (IQR) contrasts in indoor PM$_{2.5}$ during pregnancy and FSIQ among 475 mother-child dyads.

Results: A 9.4 μg/m^3 increase in indoor PM$_{2.5}$ concentration over the full pregnancy was associated with a reduction of 1.1 points (95% CI: -3.7, 1.5) in mean FSIQ. The strongest association between PM$_{2.5}$ concentrations and FSIQ was in the first trimester, when a 20.7 μg/m^3 contrast was associated with a 3.5-point reduction (95% CI: 0.7, 6.6) in mean FSIQ.

Conclusions: Indoor PM$_{2.5}$ during early pregnancy may impair brain development, leading to lower mean FSIQ scores in four-year old children. These results, combined with our previous analysis of HEPA filter air cleaners, indicate that

reducing PM$_{2.5}$ exposure during pregnancy has beneficial effects on neurodevelopment.

4.2.   Introduction

The developing brain is particularly vulnerable to environmental exposures during fetal development (Grandjean & Landrigan, 2006). Several studies have highlighted the potential impacts of exposure to particulate matter air pollution (PM) during pregnancy on early central nervous system development (Volk et al., 2021). Plausible biological mechanisms, such as oxidative stress and neuroinflammation, have been identified (Calderón-Garcidueñas et al., 2008).

Results from several observational studies indicate that outdoor PM concentrations during fetal development are associated with reduced cognitive performance in children (Clifford et al., 2016; Loftus et al., 2019; Volk et al., 2021; Wang et al., 2022), but questions persist about which stage of brain development is most important. Ha and colleagues reported that outdoor concentrations of fine PM (PM$_{2.5}$) during the first and third trimesters, but not the second trimester, were associated with an increased risk of impairments in communication, problem solving, and personal-social domains (Ha et al., 2019). A prospective birth cohort study conducted in Mexico City indicated that exposure to PM$_{2.5}$ only during the first trimester was associated with impaired behavioral development in 4- to 5-year-old children (McGuinn et al., 2020). Li et al (Li et al., 2021) reported that exposure to outdoor PM$_{2.5}$ during the first trimester of pregnancy was linked to lower cognitive and motor development scores in 24-month-old children. Morgan and colleagues found that PM$_{2.5}$ and PM$_{10}$ concentrations during pregnancy were both associated with lower composite cognitive scores in 2-year-old children, with strongest associations for PM concentrations in mid to late pregnancy (Morgan et al., 2023).

Other studies have examined the association between early life exposure to indoor air pollutants – such as PM$_{10}$ (Christensen et al., 2022), tobacco smoke

(Christensen et al., 2022), incense burning (Wei et al., 2018) and gas cooking (Vrijheid et al., 2012) – and neurodevelopment in early childhood. No previous study has specifically examined associations between indoor $PM_{2.5}$ concentrations and neurodevelopment. The indoor environment may be important because most people spend considerable time indoors (Nethery et al., 2008; Matz et al., 2014). $PM_{2.5}$ readily infiltrates into buildings, and a substantial portion of exposure to outdoor-generated $PM_{2.5}$ occurs indoors (Azimi & Stephens, 2018; Xiang et al., 2019).

In the Ulaanbaatar Gestation and Air Pollution Research (UGAAR) randomized controlled trial, we previously reported that using portable air cleaners during pregnancy reduced mean indoor $PM_{2.5}$ concentrations by 29% (21, 37%) and maternal blood cadmium concentrations by 14% (95% CI: 4, 23%) (Barn et al., 2018). Cadmium is a component of $PM_{2.5}$ generated from coal combustion (Barn et al., 2019; Nishikawa et al., 2011) and tobacco smoke (Garner & Levallois, 2016) that has been associated with negative impacts on cognitive development (Liu et al., 2019). In a more recent analysis, we observed that use of air cleaners during pregnancy was associated with a 2.8-point (95% CI: -0.1, 5.7 point) increase in children's mean full-scale IQ (FSIQ) at four years of age. However, because HEPA cleaners filter particles outside the $PM_{2.5}$ size range, we were unable to isolate the specific impact of reducing $PM_{2.5}$ on the observed FSIQ benefits (Gehring & Gascon, 2022).

In this analysis, we sought to quantify the association between indoor $PM_{2.5}$ and child cognitive performance in the UGAAR study population. Specifically, we evaluated associations between indoor $PM_{2.5}$ concentrations over the full pregnancy, and during each trimester, and mean FSIQ at age four. We also evaluated the potentially mediating role of maternal cadmium exposure in the $PM_{2.5}$-FSIQ associations (Liu et al., 2019; Gehring & Gascon, 2022).

4.3. Methods

4.3.1. Trial Design

The UGAAR trial was designed to examine the impact of using portable HEPA filter air cleaners ("HEPA cleaners") during pregnancy on fetal growth and early childhood development (ClinicalTrials.gov: NCT01741051). The UGAAR study has been described elsewhere (Barn et al., 2018; Barn et al., 2019; Ulziikhuu et al., 2022). In brief, 540 participants in Ulaanbaatar, Mongolia were randomly assigned to either the intervention group or control group at a 1:1 ratio. The intervention group received one or two HEPA cleaners (depending on home size), which were used from enrollment until childbirth. Participants were encouraged to use the air cleaners continuously throughout the study period. The control group did not receive any air cleaners. The study was approved by the Simon Fraser University Office of Research Ethics and the Medical Ethics Approval Committee of the Mongolian Ministry of Health.

4.3.2. Participants

We enrolled pregnant women who met the following criteria: ≥ 18 years old, ≤ 18 weeks into a single gestation pregnancy, non-smoker, living in an apartment, not using air cleaner(s) at enrollment, and planning to give birth in a medical facility in Ulaanbaatar. Most participants (475 or 87%) enrolled at ≤ 13 weeks. We excluded women living in ger (traditional Mongolian yurt) households because electricity is unreliable in ger neighborhoods and gers may have high air exchange rates, which would make HEPA cleaners less effective. In addition, ger households generally have a wood- or coal-burning stove that can be an important indoor source of pollution, and we were primarily interested in the effects of community air pollution. All participants provided written informed consent prior to data collection.

4.3.3. Data collection

Participants visited our office between 5-19 weeks gestation and again between 24-37 weeks gestation. At both visits, we administered a questionnaire to gather information about the participants' demographics, behavior, health, and previous pregnancies. During the second visit, we also collected a whole blood sample, which was analyzed for lead, mercury, and cadmium concentrations. We obtained gestational age at birth, birth weight, head circumference, and the child's sex from medical records.

At approximately the same time as the clinic visits, study staff visited participants' homes to deploy Dylos laser particles counters (DC1700; Dylos Corporation, Riverside, California), which were retrieved seven days later. We co-located a gravimetric $PM_{2.5}$ sampler with the Dylos in 23 homes and used these co-located measurements to develop an equation for converting Dylos particle counts to $PM_{2.5}$ mass concentrations (Barn et al., 2018). Full details on the prenatal $PM_{2.5}$ measurement campaigns are provided elsewhere (Barn et al., 2018).

During the first home visit, the staff also measured the area and volume of each room and determined the building location with a global positioning system (GPS) device. The home assessment was repeated during the second home visit if the participant moved between visits.

We invited all living mother-child dyads to re-enroll in a follow-up study of early childhood development when the children were a median of 15.4 months old (range: 7.7 to 28.9 months). At re-enrollment and then at six-month intervals, we administered questionnaires on housing and the child's diet, health, and activities. Study technicians assessed the quality of nurturing and stimulation using the Home Observation Measurement of the Environment (HOME) inventory during home visits roughly corresponding with the child's first birthday.

We invited mothers and children to our study office when the children were approximately two and four years of age. At age two we obtained a venous whole blood sample from children for analysis of lead, mercury, and cadmium. Trained assessors also administered the matrix reasoning and vocabulary subtests of the Wechsler Abbreviated Scale of Intelligence (WASI) to the mothers during the two-year visit.

4.3.4. Exposure Assessment

To estimate residential indoor $PM_{2.5}$ concentrations during pregnancy, we used the weekly Dylos $PM_{2.5}$ measurements to calibrate a blended multiple linear regression / random forest regression model adjusting for 87 potential predictor variables obtained from outdoor monitoring data, questionnaires, home assessments, and geographic data sets. In a 10-fold cross-validation comparing weekly measurements and model predictions, the model had an R^2 of 81.5% (Yuchi et al., 2019). We used this model to predict the $PM_{2.5}$ concentrations in participants' homes during each week of pregnancy (Yuchi et al., 2019). For this analysis, we averaged the weekly predictions across each trimester and across the full pregnancy for each participant.

4.3.5. Outcome Assessment

Details of the outcome assessment were published previously (Ulziikhuu et al., 2022). Briefly, we assessed children's cognitive performance using the Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (WPPSI–IV) (Wechsler, 2012). We translated English WPPSI-IV materials into Mongolian and refined the translations by pilot testing on Mongolian children. Study personnel were trained to administer and score the WPPSI-IV during a two-week in-person WPPSI-IV training session in Ulaanbaatar followed by approximately three months of practice testing, which was videotaped and reviewed by the trainer.

77

We administered ten WPPSI-IV subtests when the children were a median age of 48 months (range: 48 to 51 months) old. Calculating composite WPPSI-IV scores requires scaling raw scores using the distribution from a reference population. As there is no Mongolian reference population available, we used the raw scores from the UGAAR cohort and scaled them to match the mean and standard deviation of the Canadian reference population (Ulziikhuu et al., 2022). This enabled us to convert the raw scores to scaled scores and then combine the scaled scores into indices according to the WPPSI-IV guidelines.

Our primary outcome was full-scale intelligence quotient (FSIQ), which is derived by combining scores from six WPPSI-IV subtests and indicates the level of a child's general intellectual functioning. Our secondary outcomes included five process-specific indices: verbal comprehension index (VCI), visual spatial index (VSI), fluid reasoning index (FRI), working memory index (WMI) and processing speed index (PSI).

4.3.6. Data Analysis

We estimated the relationship between the indoor $PM_{2.5}$ concentrations, averaged over the full pregnancy or trimesters, and FSIQ. Our primary analysis included 475 mothers and children. The 475 children in the primary analysis represent the full UGAAR cohort except those whose mothers withdrew prior to baseline data collection (n=8), pregnancy losses (N=46), neonatal deaths (n=5), and children with a medical condition that may affect WPPSI-IV testing or our ability to impute scores (n=6, one with Down syndrome, one with a hearing and speech impairment, one with cerebral palsy, and three with autism spectrum disorder [ASD]) (Ulziikhuu et al., 2022).

We imputed scores for 92 children who failed to complete one or more WPPSI-IV subtests assuming data were missing at random. We generated 20 imputed data sets using multiple imputation with chained equations (MICE) (SAS Proc MI and Proc MIANALYZE) after stratifying by treatment group. As in our previous

intention-to-treat analysis of the air cleaner intervention, we included variables in the imputation model that were associated with missingness and/or FSIQ: enrollment season, previous pregnancy, self-reported air cleaner usage and vitamin intake at baseline, father's body mass index at baseline, mother's alcohol intake during pregnancy, child's sex, preterm birth, and head circumference at birth. We also included in the imputation model the completed WPPSI-IV subtest raw scores, WPPSI-IV composite scores, indoor $PM_{2.5}$ over the full pregnancy and in each of the three trimesters, and the adjustment variables included in primary and/or secondary analyses, which are described below.

After generating 20 imputed data sets, we fitted a linear regression model of FSIQ on indoor $PM_{2.5}$, while adjusting for potential confounders. We used a directed acyclic graph to visualize the relationships between variables (Figure C.1). In our primary model we adjusted for the following potential confounders: intervention group, monthly family income at enrollment (<800,000, 800,000 to 1,199,999, and ≥ 1,200,000 tugriks), mother's education (< or ≥ university degree), enrollment season, and household smoking status at enrollment (yes/no). Although child's sex is unlikely to confound the $PM_{2.5}$-FSIQ relationship, in our primary model we also adjusted for child's sex because it is a major source of variability in FSIQ (Table 4.1) (Ulziikhuu et al., 2022). Trimester-specific models were also adjusted for $PM_{2.5}$ concentrations in other trimesters. We pooled the 20 $PM_{2.5}$ effect estimates and present the effect estimates per interquartile range (IQR) contrast in indoor $PM_{2.5}$.

We conducted several sensitivity analyses of the associations between $PM_{2.5}$ and WPPSI-IV scores. To evaluate the sensitivity of our results to the imputation of missing WPPSI-IV scores, we estimated the $PM_{2.5}$ and WPPSI-IV scores associations after limiting the 20 imputed data sets to the 382 dyads for which we had a valid WPPSI-IV assessment and an estimate of indoor $PM_{2.5}$ concentration during pregnancy (one dyad did not have a modeled indoor $PM_{2.5}$ concentration due to missing data for predictors in the $PM_{2.5}$ model). Using the imputed data sets

in this sensitivity analysis allowed us to include dyads with missing observations in the adjustment variables.

As with our previous intention-to-treat analysis of the intervention (Ulziikhuu et al., 2022), we conducted a sensitivity analysis to estimate the $PM_{2.5}$-FSIQ association after stratifying the 475 mother-child dyads by household smoking behavior at early pregnancy. This sensitivity analysis was intended to evaluate the influence of indoor-generated PM on our results.

In analyses of the full sample of 475 participants, we also evaluated the sensitivity of our FSIQ results to the adjustment variables included in our models. First, in addition to the variables in our primary model, we also adjusted for: mother's pre-pregnancy BMI, mother's intelligence (WASI matrix reasoning and vocabulary raw scores), parity (0, 1, ≥2), mother's age at enrollment, mother's multivitamin intake at enrollment (yes/no), mother's alcohol consumption during pregnancy (yes/no), HOME score when child was one year old, breastfeeding status (never, <12 months, ≥12 months), and child's blood lead concentration at age two (log-2 transformed). Finally, we also estimated the $PM_{2.5}$-FSIQ associations after adding maternal blood cadmium (log-2 transformed) or lead concentrations (log-2 transformed) in pregnancy to our primary model. We did not adjust for maternal cadmium or lead in our primary model because both are associated with coal combustion and are therefore components of $PM_{2.5}$ in Ulaanbaatar (Nishikawa et al., 2011; Barn et al., 2019). Adjusting for these metals blocks any effect of $PM_{2.5}$ on WPPSI-IV scores that is mediated by lead or cadmium.

Role of the funding source

4.4. Results

We observed 514 women to the end of pregnancy. There were 46 known pregnancy losses, 468 live births, and five neonatal deaths. A total of 416 participants enrolled in the postnatal study, and 383 completed the WPPSI-IV between September 28, 2018 and January 8, 2020.

4.4.1. Participant Characteristics

The median (25th-75th percentile) maternal age at enrollment was 29 years (25 – 33 years) at a gestational age of 11 weeks (9 – 13 weeks) (Table 4.1). Most participants completed university (80.9%) and approximately half lived with a smoker at enrollment.

Some of the 382 dyads with modeled indoor $PM_{2.5}$ and a valid WPPSI-IV assessment had missing covariate data. The frequency of missing observations ranged from 0% (intervention status, enrollment season, child's sex) to 21.2% (HOME score).

Mothers of children who did not participate in the WPPSI-IV assessment were younger, more likely to be in the control group, and more likely to have enrolled in winter than those whose children completed the WPPSI-IV (Table C.1).

4.4.2. Pollutant Concentrations

The median (25th-75th percentile) indoor $PM_{2.5}$ over the full pregnancy was 28.3 μg/m^3 (24.5 – 33.9 μg/m^3) (Table 4.1). The median (25th-75th percentile) indoor $PM_{2.5}$ concentrations in the first, second, and third trimester were 30.1 μg/m^3 (20.4 – 41.1), 27.3 μg/m^3 (18.5 – 39.7 μg/m^3), and 21.5 μg/m^3 (16.4 – 29.7 μg/m^3), respectively.

Table 4.1. Select characteristics of the study participants by children's full-scale IQ (FSIQ) tertile among dyads with a valid WPPSI-IV assessment (N = 382).

	Full sample	FSIQ Bottom Tertile (64.0 – 92.0)	FSIQ Middle Tertile (93.0 – 105.0)	FSIQ Top Tertile (106.0 – 137.0)
	N = 382	N = 133	N = 124	N=125
	Median (25th, 75th percentile) or N (%)	Median (25th, 75th percentile) or N (%)	Median (25th, 75th percentile) or N (%)	Median (25th, 75th percentile) or N (%)
Intervention status				
Intervention	201 (52.6)	60 (45.1)	69 (54.8)	73 (58.4)
Control	181 (47.4)	73 (54.9)	56 (45.2)	52 (41.6)
Maternal age at enrollment	29.0 (25.0, 33.0)	28.0 (24.0, 33.0)	29.0 (25.0, 33.0)	29.0 (25.0, 33.0)
Not reported, N (%)	10 (2.6)	4 (3.0)	4 (3.2)	2 (1.6)
Maternal pre-pregnancy BMI	21.5 (19.6, 24.2)	21.5 (19.6, 24.0)	21.5 (19.1, 24.3)	21.6 (20.0, 23.8)
Not reported, N (%)	26 (6.8)	9 (6.8)	8 (6.5)	9 (7.3)
Enrollment season				
Winter	113 (29.6)	50 (37.6)	31 (25.0)	32 (25.6)
Spring	110 (28.8)	29 (21.8)	43 (34.7)	38 (30.4)
Summer	49 (12.8)	20 (15.0)	13 (10.5)	16 (12.8)
Fall	110 (28.8)	34 (25.6)	37 (29.8)	39 (31.2)
Lived with a smoker at enrollment				
Yes	173 (45.3)	63 (47.4)	55 (44.4)	55 (44.0)
No	200 (52.4)	67 (50.4)	63 (50.8)	70 (56.0)
Not reported, N (%)	9 (2.4)	3 (2.3)	6 (4.8)	0 (0.0)
Maternal education				
Completed university	309 (80.9)	106 (79.7)	96 (77.4)	107 (85.6)
Did not complete university	47 (12.3)	17 (12.8)	20 (16.1)	10 (8.0)
Not reported, N (%)	26 (6.8)	10 (7.5)	8 (6.5)	8 (6.4)
Monthly household income[a]				
<800,000 Tugrik	71 (18.6)	25 (18.8)	23 (18.6)	23 (18.4)
800,000 – 1,190,000 Tugrik	127 (33.3)	49 (36.8)	41 (33.1)	37 (29.6)
≥1,200,000 Tugrik	169 (44.2)	53 (39.9)	53 (42.7)	63 (50.4)
Not reported, N (%)	15 (3.9)	6 (4.5)	7 (5.7)	2 (1.6)
Maternal alcohol consumption				
Yes	175 (45.8)	49 (36.8)	64 (51.6)	62 (49.6)
No	193 (505)	78 (58.7)	54 (43.6)	61 (48.8)
Not reported, N (%)	14 (3.7)	6 (4.5)	6 (4.8)	2 (1.6)
Maternal vitamin intake at enrollment				
Yes	281 (73.6)	92 (69.2)	96 (76.6)	94 (75.2)
No	88 (23.0)	33 (24.8)	27 (21.8)	28 (22.4)
Not reported, N (%)	13 (3.4)	8 (6.0)	2 (1.6)	3 (2.4)
Maternal blood cadmium concentration	0.2 (0.1, 0.3)	0.20 (0.16, 0.30)	0.18 (0.13, 0.28)	0.20 (0.15, 0.28)
Not measured, N (%)	61 (16.0)	30 (22.6)	11 (8.9)	20 (16.0)
Maternal blood lead concentration	1.4 (1.2, 1.8)	1.5 (1.2, 1.8)	1.4 (1.1, 1.9)	1.4 (1.2, 1.8)
Not measured, N (%)	61 (16.0)	30 (22.6)	11 (8.9)	20 (16.0)
Parity				
0	131 (34.3)	45 (33.8)	42 (33.9)	44 (35.2)
1	148 (28.7)	55 (41.4)	42 (33.9)	51 (40.8)
≥2	101 (26.4)	32 (24.1)	39 (31.5)	30 (24.0)
Not reported, N (%)	2 (0.5)	1 (0.8)	1 (0.8)	0 (0.0)
Child's sex				
Boy	198 (51.8)	84 (63.2)	68 (54.8)	46 (36.8)
Girl	184 (48.2)	49 (36.8)	56 (45.2)	79 (63.2)
Maternal intelligence (WASI Matrix Reasoning Score)	16.0 (12.0, 19.0)	15.0 (9.0, 18.0)		

Not measured, N (%)	20 (5.2)	6 (4.5)	17.0 (12.0, 19.0) 6 (4.8)	17.0 (14.0, 20.0) 8 (6.4)
Maternal intelligence (WASI Vocabulary Score) Not measured, N (%)	35.0 (32.0, 39.0) 20 (5.2)	34.0 (31.0, 39.0) 6 (4.5)	36.0 (32.0, 39.0) 6 (4.8)	36.0 (32.0, 39.0) 8 (6.4)
Breasted Infants Never < 12 months ≥ 12 months Not reported, (N %)	9 (2.4) 91 (23.8) 277 (72.5) 5 (1.3)	2 (1.5) 35 (26.3) 94 (70.6) 2 (1.5)	6 (4.8) 26 (21.0) 91 (73.4) 1 (0.8)	1 (0.8) 30 (24.0) 92 (73.6) 2 (1.6)
HOME Score Not measured, N (%)	31.0 (28.0, 33.0) 81 (21.2)	30.0 (27.0, 32.0) 26 (20.0)	31.0 (28.0, 33.0) 26 (21.0)	31.0 (29.0, 35.0) 29 (23.2)
Child blood lead concentration Not measured, N (%)	2.6 (1.8, 3.5) 72 (18.8)	2.7 (1.8, 3.8) 27 (20.3)	2.7 (1.8, 3.7) 17 (13.7)	1.3 (1.7, 3.3) 28 (22.4)
PM$_{2.5}$ concentration during full pregnancy in µg/m^3	28.2 (24.2, 33.8)	28.7 (24.9, 34.1)	28.0 (23.8, 33.3)	27.7 (24.0, 33.0)
PM$_{2.5}$ concentration during first trimester in µg/m^3	29.5 (20.4, 40.0)	34.7 (21.8, 40.9)	28.2 (20.9, 39.6)	26.2 (17.8, 40.0)
PM$_{2.5}$ concentration during second trimester in µg/m^3	27.2 (17.9, 39.5)	27.8 (19.2, 40.3)	27.5 (16.9, 38.2)	26.6 (17.6, 39.7)
PM$_{2.5}$ concentration during third trimester in µg/m^3	21.6 (16.6, 29.7)	21.2 (15.7, 31.0)	21.1 (16.7, 29.6)	22.2 (17.2, 29.4)

Percentages may not total 100 due to rounding.
[a]At the time of data collection 800,000 tugriks was equivalent to approximately $360 USD.
HOME = Home Observation Measurement of the Environment.
WPPSI-IV = Wechsler Preschool and Primary Scale of Intelligence. Fourth Edition

4.4.3. Indoor PM2.5 and Full-scale IQ

In the primary model for the full population of 475 participants, an IQR (9.4 µg/m^3) increase in indoor PM$_{2.5}$ concentration during the entire pregnancy was associated with a change of -1.1 points (95% CI: -3.7, 1.5 points) in children's mean FSIQ (Figure 4.1).

An IQR (20.7 µg/m^3) increase in indoor PM$_{2.5}$ concentration during the first trimester was associated with a 3.5-point reduction (95% CI: 0.7, 6.6) in mean FSIQ (Figure 4.1). Indoor PM$_{2.5}$ concentrations during the second and third trimesters exposure had smaller effects on FSIQ and confidence intervals that spanned the null (Figure 4.1.). Results from a model with additional adjustment

variables also indicated that indoor $PM_{2.5}$ during the first trimester had the strongest association with FSIQ (Table C.2.).
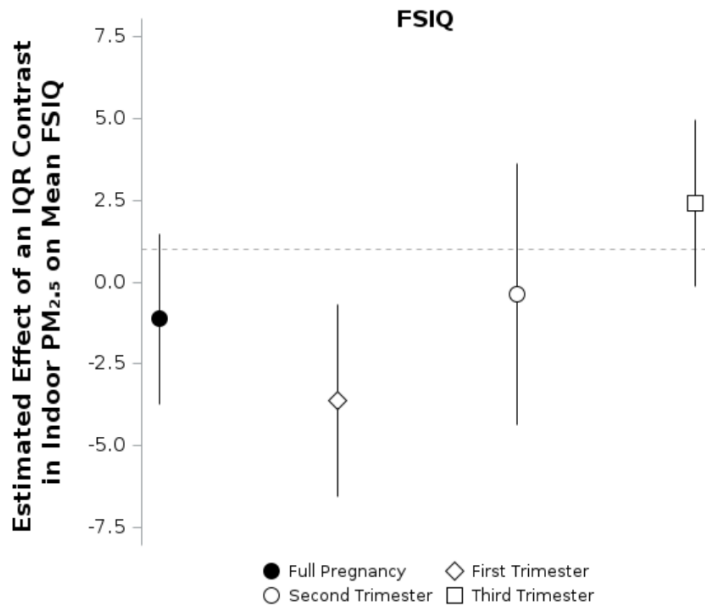
Figure 4.1. **Estimated changes in mean full-scale IQ (FSIQ) per interquartile range (IQR) contrast in indoor $PM_{2.5}$ concentration (N=475)**

The regression models were adjusted for intervention group, monthly family income at enrollment (<800,000, 800,000 to 1,199,999, and ≥ 1,200,000 tugriks), mother's education (< or ≥ university degree), enrollment season, household smoking status at enrollment (yes/no) and child's sex. Trimester-specific models were also adjusted for $PM_{2.5}$ concentrations in other trimesters.

NOTE: Full pregnancy indoor $PM_{2.5}$ exposure IQR contract = 9.4 $\mu g/m^3$, 1st trimester indoor $PM_{2.5}$ exposure IQR contract = 20.7 $\mu g/m^3$, 2nd trimester indoor $PM_{2.5}$ exposure IQR contract = 21.2 $\mu g/m^3$, 3rd trimester indoor $PM_{2.5}$ exposure IQR contract = 13.3 $\mu g/m^3$.

For secondary outcomes, full pregnancy indoor $PM_{2.5}$ was generally associated with small changes in WPPSI-IV scores, with confidence intervals that spanned no effect (Figure 4.2). Higher indoor $PM_{2.5}$ concentrations during the first trimester were generally associated with the largest reductions in WPPSI-IV mean scores, with the most pronounced effects on verbal comprehension index (-3.1 points, 95% CI: -6.6, 0.5 points) and visual spatial index (-2.6 points, 95% CI: -5.8, 0.6 points). For other trimesters, the only estimate that did not span the null was a 4.1-point

change (95% CI: 1.1, 7.1) in fluid reasoning index per IQR increase in third trimester PM$_{2.5}$.
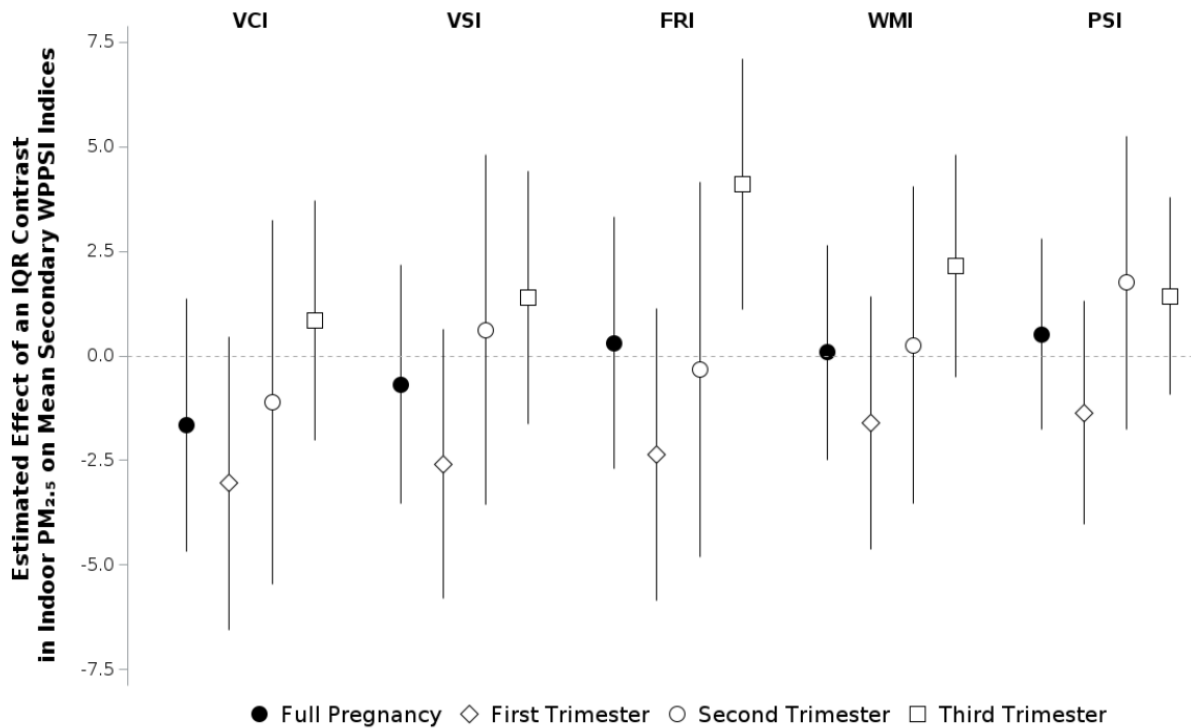
Figure 4.2.   Estimated changes in mean WPPSI-IV secondary indices per interquartile range (IQR) contrast in indoor PM$_{2.5}$ concentration (N=475)

The regression models were adjusted for intervention group, monthly family income at enrollment (<800,000, 800,000 to 1,199,999, and ≥ 1,200,000 tugriks), mother's education (< or ≥ university degree), enrollment season, household smoking status at enrollment (yes/no) and child's sex. Trimester-specific models were also adjusted for PM$_{2.5}$ concentrations in other trimesters.

NOTE: Full pregnancy indoor PM$_{2.5}$ exposure IQR contract = 9.4 µg/m^3, 1st trimester indoor PM$_{2.5}$ exposure IQR contract = 20.7 µg/m^3, 2nd trimester indoor PM$_{2.5}$ exposure IQR contract = 21.2 µg/m^3, 3rd trimester indoor PM$_{2.5}$ exposure IQR contract = 13.3 µg/m^3.

VCI = verbal comprehension index, VSI = visual spatial index, FRI = fluid reasoning index, WMI = working memory index, PSI = processing speed index.

Results were generally similar among 382 participants who completed the WPPSI-IV. The effect of an IQR contrast in full pregnancy indoor PM$_{2.5}$ on FSIQ was -1.0 points (95% CI: -3.3, 1.3 points) (Figure C.2). An IQR (20.7 µg/m^3) increase in indoor PM$_{2.5}$ concentration during the first trimester was associated with a change of -3.0 points (95% CI: -5.7, -0.2) in mean FSIQ (Figure C.2). Indoor PM$_{2.5}$

concentrations during the second and third trimesters had smaller effects on FSIQ, with confidence intervals that included the null (Figure C.2).

After stratifying the full sample of 475 dyads by household smoking status at baseline, we found stronger evidence of negative effects of indoor $PM_{2.5}$ on FSIQ in non-smoking households (Table C.3). For example, the effect estimates for full pregnancy $PM_{2.5}$ in non-smoking and smoking households were -1.7 points (95% CI: -5.2, 1.7 points) and 0.7 points (95% CI: -2.9, 4.3 points), respectively. The effect estimates for the first trimester $PM_{2.5}$ in non-smoking and smoking households were -5.6 points (95% CI: -10.1, -1.2 points) and -1.3 points (95% CI: -5.9, 3.2 points), respectively.

Inclusion of maternal blood cadmium or lead in the regression model had modest impacts on the FSIQ estimates (Table C.2). When cadmium was included in the model the full pregnancy and first trimester $PM_{2.5}$ effect estimates were -0.8 points (95% CI: -3.4, 1.8 points) and -4.0 points (95% CI: -7.5, -0.6 points), respectively. Inclusion of maternal blood lead had no effect on the full pregnancy $PM_{2.5}$ estimate, but the first trimester effect estimate changed to -3.6 points (95% CI: -6.6, -0.7).

4.5. Discussion

We found that indoor $PM_{2.5}$ during the first trimester of pregnancy was associated with a lower mean FSIQ in four-year old children. These results reinforce our previous findings from this study population that children whose mothers were randomized to use HEPA filter air cleaners during pregnancy had higher mean FSIQ and suggest that these benefits were due, at least in part, to reductions in $PM_{2.5}$ (Ulziikhuu et al., 2022). The association with verbal comprehension index is also consistent with our previously observed benefits of air cleaner use and with the hypothesis that verbal skills may be particularly sensitive to $PM_{2.5}$ exposure during pregnancy (Porta et al., 2016; Loftus et al., 2019).

Our results add to a growing literature implicating $PM_{2.5}$ as a threat to brain development. A 2015 meta-analysis included over 30 epidemiological studies of ambient air pollution and neurocognitive and neurobehavioral outcomes in children (Suades-Gonzalez et al., 2015). The results supported an association between outdoor $PM_{2.5}$ concentrations during pregnancy and reduced cognitive, language, and motor development in children. A 2016 review found that prenatal $PM_{2.5}$ exposure, assessed using outdoor concentrations as a proxy, was associated with lower scores on intelligence tests and poorer overall neurodevelopment in children (Clifford et al., 2016). More recent studies provide additional evidence that outdoor $PM_{2.5}$ concentrations during pregnancy are associated with reduced cognitive performance in childhood (Ha et al., 2019; Li et al., 2021; Loftus et al., 2019; Morgan et al., 2023).

Our results also suggest that $PM_{2.5}$ exposure in early pregnancy may be especially detrimental to cognitive development. This finding is biologically plausible since cell proliferation and migration in the central nervous system take place early in brain development and lead to the formation of the cerebral cortex (Stiles & Jernigan, 2010). Exposure to $PM_{2.5}$ during the first trimester has been associated with fetal growth restriction (Michikawa et al., 2017), which in turn may impair childhood neurodevelopment (Wiles et al., 2006; Levine et al., 2015). First trimester exposure to $PM_{2.5}$ was associated with lower scores in adaptive skills and increased reporting of attention and withdrawal symptoms in children in a Mexico City study, while no such association was observed for $PM_{2.5}$ over the entire pregnancy or in the second or third trimesters (McGuinn et al., 2020). A recent study in China indicated that first trimester exposure to $PM_{2.5}$ was associated with reductions in mental development index and psychomotor development index at approximately two years of age (Li et al., 2021). In contrast, other observational studies suggested that $PM_{2.5}$ exposures in mid to late pregnancy may be most important (Ha et al., 2019; Morgan et al., 2023).

The observation that first trimester $PM_{2.5}$ concentrations had the strongest associations with cognition are consistent with our previous work on behavior problem scores in the UGAAR cohort (Enkhbat et al., 2021, 2022). If exposure early in pregnancy is most important for brain development, our previous intention-to-treat analysis may have underestimated the potential benefits of using air cleaners (Ulziikhuu et al., 2022). Participants enrolled in this study at a median of 11 weeks, so for most women the air cleaners were deployed late in the first trimester. Use of air cleaners over the entire pregnancy may be more beneficial.

We (Ulziikhuu et al., 2022) and others (Gehring & Gascon, 2022) speculated that the benefits of using air cleaners on FSIQ were partly mediated by reductions in cadmium exposure because: 1) use of air cleaners reduced maternal blood cadmium concentrations (Barn et al., 2018), 2) cadmium was associated with lower mean birth weight (Barn et al., 2019), and 3) intrauterine growth restriction is associated with impaired neurodevelopment (Levine et al., 2015). A 2019 meta-analysis of nine studies indicated an association between prenatal exposure to cadmium and lower cognitive function among children aged one to five years (Liu et al., 2019). More recently, Liu et al. reported that maternal serum cadmium concentrations were inversely associated with language and development quotient among children aged 2 to 3 years (Liu et al., 2022). In sensitivity analyses, we adjusted for blood cadmium and lead concentrations to block the effect of $PM_{2.5}$ on FSIQ that is mediated by exposure to these metals. Accounting for these exposures during pregnancy did not alter the conclusion that first trimester $PM_{2.5}$ exposure negatively affects children's cognitive development.

While the $PM_{2.5}$ effects in this study do not appear to be driven by cadmium, we were unable to identify the $PM_{2.5}$ constituent(s) responsible for the association with cognition. Polycyclic aromatic hydrocarbons (PAHs) are one potentially important component of the $PM_{2.5}$ mixture. PAHs have been linked to neurodevelopmental effects in previous studies (Jedrychowski et al., 2015; Desrochers-Couture et al., 2018). PAHs are found almost entirely on particles in the $PM_{2.5}$ size range (Guo et

al., 2003; Limu et al., 2013) and the $PM_{2.5}$ emissions in Ulaanbaatar are driven by coal combustion (Davy et al., 2011), a major source of PAHs (Ma et al., 2010).

Because outdoor particles infiltrate into buildings, indoor $PM_{2.5}$ contains a combination of indoor- and outdoor-generated PM (Allen et al., 2012) and studies suggest that indoor exposures are responsible for most health effects from outdoor-generated $PM_{2.5}$ (Azimi & Stephens, 2018; Xiang et al., 2019). Although we excluded ger households to eliminate the influence of indoor coal and wood combustion in this study, tobacco smoking is an important source of $PM_{2.5}$ in Ulaanbaatar (Hill et al., 2017), and nearly half of our participants reported living with a smoker at enrollment. In a sensitivity analysis, we stratified by household smoking status at enrollment and found stronger evidence of a $PM_{2.5}$-FSIQ association in non-smoking homes. For example, the estimated effects of first trimester indoor $PM_{2.5}$ concentrations on mean FSIQ in smoking and non-smoking homes were -1.3 (95% CI: -5.9, 3.2) and -5.6 (95% CI: -10.1, -1.2), respectively. This finding suggests that the association between indoor $PM_{2.5}$ and FSIQ is not primarily due to tobacco smoke particles and provides indirect evidence that the associations observed here are largely due to outdoor-generated $PM_{2.5}$.

The changes in mean FSIQ observed here may have important public health implications. Air pollution is a ubiquitous hazard, with over 90% of the world's population living in areas that exceed the World Health Organization annual average $PM_{2.5}$ guideline concentration of 5 $\mu g/m^3$ (Health Effects Institute, 2020). Previous studies have shown that widespread environmental hazards, including air pollution, can have large effects at the population level even if effects on individuals are modest (Nawrot et al., 2011; Bellinger, 2012).

This study had some limitations. Because of the logistical challenges and cost of measuring indoor $PM_{2.5}$ over pregnancy in a population of this size, we used 7-day measurements to calibrate a model for estimating full pregnancy and trimester-specific concentrations. Although our model performed well in cross-validation

(Yuchi et al., 2019), this approach may have introduced non-differential exposure misclassification leading to underestimation of PM$_{2.5}$ effect estimates. Due to missing outcome and covariate data, we used multiple imputation to facilitate analysis of the full UGAAR cohort, which may have reduced the precision of our effect estimates. The use of FSIQ in studies involving diverse cultural and racial populations has been criticized. However, in this study, which focused on a relatively homogenous population, we believe that FSIQ is an appropriate primary outcome. Moreover, our goal was to examine changes in mean cognitive function, not to evaluate the abilities of individual children or to diagnose impairments (Raiford & Coalson, 2014).

Six children with medical conditions that could potentially affect the results of the WPPSI-IV and the reliability of imputed scores were not included in our analysis. Three of these children had conditions with no connection to air pollution, but three children were diagnosed with autism spectrum disorder (ASD), which has been linked to air pollution (Pagalan et al., 2019). These children were not included in the imputation because ASD is a heterogenous disorder, and the relationship between ASD and FSIQ varies widely, making the imputation of scores unreliable (Lord et al., 2018). Furthermore, estimates of the prevalence of intellectual disability in school-age children with ASD varies widely and some children with ASD have average or above average intelligence (Charman et al., 2011).

This study also had several strengths. To our knowledge, no previous studies have reported on the relationship between indoor PM$_{2.5}$ concentrations during pregnancy and neurodevelopment in children. We collected data on a wide range of relevant exposures and characteristics, which allowed us to account for a variety of potentially important confounders in the PM$_{2.5}$-FSIQ relationship. The high pollution concentrations in Ulaanbaatar increased our exposure gradients, providing statistical power and improving our ability to detect associations.

Our results indicate that PM$_{2.5}$ air pollution exposure during early in utero development negatively affected cognitive performance in 4-year-old children. In stratified analyses we found that associations between PM$_{2.5}$ and FSIQ were more pronounced in non-smoking homes, suggesting that the associations were not primarily due to secondhand smoke exposure. These results, combined with those from our previous intention-to-treat analysis of HEPA filter air cleaners, provide evidence that reducing PM$_{2.5}$ exposure during pregnancy has beneficial effects on brain development in early life.

Acknowledgments

Chapter 5.   Discussion

5.1. Summary

Using data from a single blind randomized controlled trial in Ulaanbaatar, Mongolia, I investigated the impact of portable HEPA filter air cleaner use during pregnancy on children's cognitive performance at 4 years of age, identified groups of children that benefitted most from the intervention, and quantified the relationship between indoor $PM_{2.5}$ concentrations and children's cognitive performance.

5.1.1. Portable HEPA filter air cleaner use during pregnancy and children's cognitive performance at 4 years of age: the UGAAR randomized controlled trial (Chapter 2)

I found that the use of portable HEPA air cleaners during pregnancy was associated with a 2.5-point increase (95% CI: -0.4, 5.4) in mean FSIQ among children in the intervention compared to those in the control group. After adjusting for PTB, the estimates increased to 2.8 points (95% CI: -0.1, 5.7) and further adjustment for both PTB and child's sex increased the estimate to 3.0 points (95% CI: 0.2, 5.9). Additionally, I found that the intervention was associated with 3.5-point increase (95% CI: 0.2, 6.8) in mean verbal comprehension index. After stratifying by household smoking status during pregnancy, the effect of the intervention on mean FSIQ score was 1.9 points (95% CI: -2.1, 5.9) among children whose mothers lived with smoker and 3.2 points (95% CI: -0.9, 7.4) among children whose mothers did not live with smoker. These results suggest that the benefits of the intervention were not primarily due to reduced exposure to second-hand smoke at home. I also found that children at the lower end of the FSIQ distribution benefitted more from the intervention compared to those with higher FSIQ scores. Overall, I concluded that reducing particulate matter air pollution exposure during pregnancy improved cognitive performance in 4-year-old children.

5.1.2. Who benefits most from a prenatal HEPA filter air cleaner intervention on childhood cognitive development? The UGAAR randomized controlled trial (Chapter 3)

I found that the use of portable HEPA air cleaners during pregnancy improved mean FSIQ among children whose mothers were in the lowest (5.4 points; 95% CI: -0.8, 11.5) and highest hair cortisol tertiles (6.1 points; 95% CI: 0.5, 11.8), but not among children of mothers in the middle cortisol tertile (-2.5 point; 95% CI: -7.9, 2.8). After incorporating all the potential effect modifiers, I found that the largest between-group difference in the intervention's beneficial effect was for vitamin intake during early pregnancy, with a FSIQ increase 7.5 points larger (95% CI: -0.7, 15.7) among children of mothers who did not take vitamins than among children whose mothers did take vitamins. The next largest between-group differences were for maternal education, DHEA concentrations, cortisol concentrations, perceived stress, and maternal intelligence. I concluded that prioritizing women who are less educated, lack vitamin intake during pregnancy, and/or have more stress could potentially increase the benefits of reducing air pollution exposure during pregnancy.

5.1.3. Prenatal exposure to indoor PM$_{2.5}$ and children's cognitive performance at 4 years of age: an observational analysis from the UGAAR randomized controlled trial (Chapter 4)

I found that a 9.4 µg/m^3 increase in indoor PM$_{2.5}$ concentration during pregnancy was associated with a change of -1.1 points (95% CI: -3.7, 1.5) in mean FSIQ. I observed the strongest association with PM$_{2.5}$ concentrations in the first trimester; a 20.7 µg/m^3 increase in PM$_{2.5}$ was associated with a change of -3.5 points (95% CI: -6.6, -0.7) in mean FSIQ. Accounting for maternal blood lead and cadmium exposures during pregnancy did not alter the results. The estimated effects of first trimester indoor PM$_{2.5}$ concentrations on mean FSIQ in smoking and non-smoking homes were -1.3 (95% CI: -5.9, 3.2) and -5.6 (95% CI: -10.1, -1.2), respectively, suggesting that the association between indoor PM$_{2.5}$ and FSIQ is not primarily due to tobacco smoke particles. Combined with the results of my intention-to-treat

analysis of the air cleaner intervention (Chapter 2), these findings indicate that reducing $PM_{2.5}$ exposure during the prenatal period has beneficial effects on neurodevelopment.

5.2. Synthesis

My research indicates that exposure to indoor $PM_{2.5}$ during pregnancy can have a detrimental impact on cognitive performance in children. However, I have also demonstrated that a simple household-level intervention that reduces indoor PM concentrations can improve IQ scores in young children. The benefits were most pronounced among children whose mothers experienced more stress, had less education, and did not take vitamins during pregnancy.

Policies to reduce air pollution emissions often take decades to improve air quality (Fenger, 1999) and it is not always feasible for individuals to relocate to a less polluted location (Joanne Slater, 2018). This is particularly relevant for Ulaanbaatar's low-income inhabitants, who have migrated from rural areas in search of better opportunities and to escape harsh climate conditions. Therefore, it is important to identify 1) interventions that can reduce exposure and health risks in the near term, and/or 2) other modifiable risk factors that can be targeted to mitigate the effects of air pollution. One readily accessible intervention is the use of in-house portable air cleaners, which have been found to reduce PM concentrations in during wildfires (Barn et al., 2016; Henderson et al., 2005) and in highly polluted settings (Barn et al., 2018; Chen et al., 2015).

Numerous studies have investigated the health benefits of reducing air pollution using air cleaners. Two recent meta-analyses have summarized the benefits of indoor air cleaners on select cardiovascular and cardiorespiratory health outcomes (Liu et al., 2022; Xia et al., 2021). Blood pressure is one of the most studied outcomes and the meta-analyses identified a significant association between air purification and reductions in systolic blood pressure. However, no significant benefits on respiratory function parameters, such as forced expiratory volume,

were identified (Liu et al., 2022; Xia et al., 2021). Both meta-analyses identified limitations in the available evidence due to the short durations over which air purifiers have been studied (median duration of 7 days) and small samples sizes. Furthermore, the study populations limit the applicability of the current evidence to more diverse populations with different air pollution exposure levels (Liu et al., 2022; Xia et al., 2021).

Several modeling studies have assessed the potential benefits and costs of air cleaners as a public health intervention. Fisk and Chan projected that air cleaners could decrease hospital admissions and deaths attributed to $PM_{2.5}$ exposure during wildfires and the economic value of these prevented deaths far surpassed the cost of the intervention (Fisk & Chan, 2017). Martenies and Batterman estimated the asthma-related health costs and benefits of high efficiency filters in homes and schools in Detroit, Michigan. The cost of this intervention in schools, but not homes, would be well below the benefits from reduced asthma burden (Martenies & Batterman, 2018). In a more recent study, Cooper and colleagues (2022) conducted a modeling analysis to assess the potential benefits of reducing indoor $PM_{2.5}$ concentrations through the use of portable air purifiers. Their model projected an increase of over 100 days in life expectancy under a scenario in which portable air cleaners were used more than 15 hr per day, starting from birth and continuing until the age of 97 (Cooper et al., 2022). These results highlight the cost-effectiveness and potential long-term benefits of air cleaner use.

Despite their promise, it is important to carefully consider the introduction of HEPA air cleaners as an intervention to combat air pollution. Although previous studies have reported reductions in $PM_{2.5}$ concentrations ranging from 20% to 70%, the air cleaners were evaluated over relatively short durations, typically days to weeks (Laumbach & Cromar, 2022). Further, the efficiency of these devices is highly dependent on proper usage and regular maintenance. While portable HEPA filter air cleaners have been recommended by North American public health authorities during wildfire smoke events, there is a need for more specific guidelines on proper usage to ensure their effectiveness (Barn et al., 2016). Neglecting the regular

maintenance of the filter, for example, can cause it to become overloaded, resulting in particles bypassing the filter altogether (Rajagopalan et al., 2020). The initial investment, ongoing operational costs, and noise can also prevent consistent use of the air cleaner, which can further reduce its effectiveness.

Aside from the fact that effectiveness of these interventions is heavily reliant on users' knowledge and behaviour, it is also important to acknowledge that not everyone can afford or access air cleaners. This lack of equal access can create an unfair burden of exposure to and health impacts from air pollution. There may be disproportionate effects among marginalized populations, such as low-income communities, who often have limited resources to invest in expensive mitigation measures (Murage et al., 2020).

While household- or personal-level mitigation strategies such as portable HEPA filter air cleaners may be a useful supplement to air pollution control at the source, these interventions should not be viewed as a replacement for societal level actions. The responsibility to improve air pollution should be placed on governments, rather than burdening affected individuals with responsibility for their well-being (Laumbach et al., 2021).

In my study exploring the effects of HEPA air cleaners on children's brain development during pregnancy (Chapter 3), I found greater benefits among children whose mothers did not take vitamins, had more stress, and were less educated. These results suggest that targeting modifiable risk factors might also reduce the negative impacts of air pollution during pregnancy on children's development. While our goal is to reduce air pollution for everyone, a targeted approach that focuses on modifiable factors may be a more effective and efficient way to attenuate neurotoxic effects of air pollution and improve cognitive development. By better understanding and focusing on the contribution of the modifiable factors to the relationship between prenatal air pollution and children's cognitive development, we may help our children to reach their full potential.

One such risk factor is poor nutrition. Guxen and colleagues investigated the influence of fruit and vegetable intake during pregnancy on the relationship between air pollution and neurodevelopment in children. The authors found that consuming antioxidant-rich diets during pregnancy may mitigate the negative effect of air pollution on children's brain development (Guxens et al., 2012). A recent study has also found that maternal folate may attenuate the effects of air pollution on neurodevelopment (Loftus et al., 2019). However, it is worth noting that there are limited studies exploring the potential mitigating effect of nutrition and vitamin intake. Additionally, it remains unclear whether the vitamins themselves directly modify the effects or if they act as a proxy to other risk factors. Nonetheless, vitamin supplementation is a personally modifiable factor that can be easily supported by government policies and education campaigns. This presents a potential opportunity to reduce the negative impacts of air pollution on children's neurodevelopment. While Mongolia has a national health program that provides eligible pregnant women with free multi-micronutrients supplements, review of the program is needed to ensure that it benefits the public as much as possible (Ministry of Health, 2017).

The high pollution levels in developing countries like Mongolia pose a threat to public health but also provide research advantages. For example, the large exposure gradient in highly polluted settings provides statistical power to detect health effects. Despite potential limitations in generalizing study results, research conducted in highly polluted settings has quite consistently demonstrated negative effects of air pollution (Mannucci & Franchini, 2017). Nevertheless, most air pollution research has been conducted in high-income settings with relatively low pollution concentrations (Suades-González et al., 2015; Volk et al., 2021). An increasing number of epidemiologic studies indicate that $PM_{2.5}$ affects health at low concentrations and there does not appear to be a threshold concentration (Brauer et al., 2022; Dominici et al., 2019; Strak et al., 2021). In response to this evidence, the World Health Organization recently revised its guideline for the annual average outdoor concentrations of $PM_{2.5}$ from 10 ug/m^3 to 5 ug/m^3 (World Health Organization, 2021).

The revised WHO $PM_{2.5}$ guideline has particular importance to the residents of low-and middle-income countries, who were already living in $PM_{2.5}$ concentrations that far exceeded the previous annual guideline concentration (Pai et al., 2022). While air pollution has decreased dramatically in high-income countries over the past several decades (Gauderman et al., 2015), pollution in low- and middle-income countries has generally remained constant or increased (Health Effects Institute, 2020).

The evidence of effects at low pollution concentrations also suggests that considerable improvements in public health are possible, even in places with relatively low levels of pollution. For example, a recent study showed that achieving the WHO's revised $PM_{2.5}$ guideline limit in European cities could prevent an additional 50,000 premature deaths (Khomenko et al., 2021). In a recent large-scale study in Canada, where air pollution levels are relatively low compared to other parts of the world, researchers analyzed over 128 million person-years of data. The results provided strong evidence for a significant supralinear concentration-response relationship between $PM_{2.5}$ and non-accidental mortality (Pappin et al., 2019). This relationship was also consistently observed in other large cohort studies conducted in relatively unpolluted cities in the United States and Europe (Dominici et al., 2019). Considering that the relationship between $PM_{2.5}$ and mortality is particularly pronounced at low exposures, reduction of $PM_{2.5}$ concentration even in areas with low pollution is expected to yield public health benefits (Xia et al., 2021).

For decades, Mongolia has been grappling with severe air pollution that has obscured the once-eternal blue sky. The harsh weather conditions have forced many Mongolians to abandon their traditional way of life and migrate to the capital city, resulting in unplanned urbanization and rapid expansion of ger districts, where the majority of the city's residents now live (Asian Development Bank, 2018). As the ger district is not connected to the public heating system, residents in the ger district have had to rely on raw coal or other sources of unprocessed fuel for heat.

This burning of coal contributes approximately 80% of the ambient air pollution in the city (Sumiya et al., 2023).

Government-run air pollution monitoring stations were established in Ulaanbaatar in 2004, but these stations were limited in number and scope, monitoring only a few parameters such as NO_2, SO_2, temperature, and wind direction (The World Bank, 2011). It was not until 2007 that Mongolia established a National Air Quality Standard, which aimed to improve air quality and protect public health. Since then, efforts have been made to better understand the nature and extent of air pollution in Ulaanbaatar. The World Bank's UB Clean Air Program has played a key role in this effort, providing support for initiatives to monitor particulate matter concentrations and develop an emission inventory (Cardascia et al., 2022). In 2008 and 2009, an Air Monitoring and Health Impact Baseline study was conducted to establish air quality baselines, while additional air monitoring stations were installed throughout the city, including in the ger district for the first time (The World Bank, 2011). By 2016, Ulaanbaatar had become one of the most polluted cities in the world, with pollution levels surpassing those of other major cities such as New Delhi and Beijing. The city's average annual $PM_{2.5}$ concentration was over 25 times the then WHO guideline, posing significant health risks to its residents (UNICEF, 2018).

Due to unique living conditions and geographical topography, tackling Ulaanbaatar's air pollution requires tailored solutions. Since the early 2000s, the Mongolian government has been receiving financial aid from external sources to fight against air pollution in the country. As part of the early efforts to address the issue, an initiative funded by the Millennium Challenge Corporation (MCC) involved the distribution of improved stoves to the ger district. These improved stoves were intended to decrease daily coal usage and mitigate air pollution. While a study found that the stoves led to a significant reduction in $PM_{2.5}$ compared to traditional stoves, the initiative did not result in a significant decrease in daily coal consumption, and was eventually discontinued (UNDP, 2019).

Since 2010, the government implemented discounts on the electricity tariff during off-peak hours to support use of electric heaters (Government of Mongolia, 2012). Despite the availability of subsidized tariffs, electrical heating remains an unpopular option during harsh winters due to frequent power outages and voltage drops (Carlisle and Pevzner, 2019).

One of the most significant attempts to combat air pollution in Ulaanbaatar was the 2019 introduction of refined coal briquettes and a ban on individual and business use of raw coal in six districts. Ulaanbaatar's air quality improved shortly after the replacement of raw coal with briquettes, with a decrease of up to 50% in PM concentrations during the winter of 2019 - 2020 compared to the previous year (Ganbat et al., 2020). However, given that this improvement in air quality coincided with the Covid pandemic, it is difficult to isolate the impact of the coal briquette policy on air quality. Unfortunately, the downward trend in pollution did not continue and Ulaanbaatar is once again among the most polluted cities in the world (IQAir, 2021). In addition, the use of briquettes in the ger districts has not been well received by the residents and there are anecdotal reports of a strong sulfur odor when the briquettes are burned (Soomin Jun, 2021). Additionally, a recent study reported deaths and hospitalizations from carbon monoxide poisoning due to inadequate training and information on the proper use of the briquettes (Otgonbyamba et al., 2023). These incidents have contributed to the dissatisfaction of Ulaanbaatar's residents with this new heating solution.

Air pollution in Mongolia is an obvious problem, with visibility often limited to just a few meters during the winter months. This has led to increased awareness and activism among citizens, putting pressure on the government to act. Despite receiving significant international support and funding for more than a decade, the actions taken to combat air pollution in Mongolia have yet to yield satisfactory results. One generation of people has already endured and suffered from this crisis, and unfortunately, there is still no tangible hope for the future. Every morning, children in Ulaanbaatar wake up with a burning sensation in their throats, yet they remain joyful and hopeful for a brighter future. Little do they realize that

the haze outside is robbing them of their health and well-being, both now and in the years to come.

5.3. Strengths and limitations

This work had several limitations. The sample size in UGAAR was based on term birth weight as the primary outcome of the first phase of the study. This may have resulted in reduced statistical power to detect differences in the mean FSIQ and to identify potential effect modifiers. The research team excluded ger households from the study due to higher indoor pollution emissions that could limit generalizability of the results. This exclusion reduced the exposure gradient and potentially further decreased statistical power. To estimate full pregnancy and trimester-specific exposure concentrations, UGAAR investigators calibrated a model using indoor $PM_{2.5}$ measured over 7-day periods. This approach may have led to underestimation of the true $PM_{2.5}$ effect estimates due to non-differential exposure misclassification. Further, use of indoor $PM_{2.5}$ estimates as a proxy for personal exposure may have introduced additional exposure misclassification due to exposure in other locations. I imputed missing outcome and covariate data, which increased sample size but likely reduced the precision of effect estimates. Most of the data on potential effect modifiers were collected through self-reported questionnaires. My main outcome was FSIQ, which has been criticized for its cultural and racial biases.

Despite listed limitations, it is important to note that this research also had several key strengths. This RCT was first of its kind to evaluate impact of reducing air pollution on cognitive performance. While previous studies in this field mainly consist of observational studies, which can be limited by residual confounding, the experimental in nature of this RCT study minimized confounding. Further, most previous studies estimated outdoor concentrations of air pollution. This study was unique in that it specifically examined the relationship between indoor $PM_{2.5}$ concentrations and neurodevelopment. This is an important consideration as most people spend a considerable amount of time indoors. To my knowledge, no

previous studies have examined multiple effect modifiers simultaneously. By considering these factors, I aimed to determine whether the effects of the intervention differed across subgroups of participants, which helps inform priorities for exposure reduction efforts. I also evaluated the influence of hair stress hormones, specifically cortisol and DHEA, on the relationship between this intervention and neurodevelopment, as these biomarkers have not been considered as possible modifiers in previous studies.

5.4. Suggestions for future research

Despite the growing evidence of negative impacts of air pollution exposure during pregnancy, important knowledge gaps remain. These include uncertainties about biological mechanisms, the presence of an exposure threshold for non-mortality endpoints, the lifelong impacts of altered developmental trajectories, and characteristics that may modify the impacts of air pollution.

Understanding the biological mechanisms through which air pollution exposure during pregnancy affects neurocognitive outcomes in children should be a focus of future research in this field. Understanding these biological mechanisms can improve our interpretation of epidemiologic associations and aid our understanding of variations in susceptibility within a population. The complexity of the air pollution components and timing of exposure pose challenges in identifying a single biological mechanism. However, some mechanisms have been proposed to explain the effects of prenatal air pollution on brain development. One of the mechanisms that is gaining acceptance is oxidative stress inducing systemic inflammation (Brockmeyer & D'Angiulli, 2016). This is significant because maternal inflammation-induced cytokines during pregnancy could reach the fetal brain through placental transfer (Jonakait, 2007). Another plausible pathway suggests that air pollution particles could translocate from the mother's respiratory system, passing through placenta, and be transported to the fetus (Bové et al., 2019)

Recent studies suggest that the relationship between exposure to air pollution and its potential impacts on cardiovascular and respiratory health may be more

complex than previously thought, with indications that there may be no safe threshold and that even low levels of exposure could have negative effects on health (de Bont et al., 2022; Health Canada, 2021). While the presence or absence of a threshold may differ depending on the specific health endpoint, studies of neurodevelopment suggest adverse effects at low levels of exposure (Pagalan et al., 2019; Raz et al., 2015). One challenge in studying effects of low concentrations is the small exposure gradients, which limit statistical power. Researchers have overcome this limitation with large sample sizes (Pappin et al., 2019).

There have been relatively few studies of brain development outcomes with follow up beyond early childhood (Kusters et al., 2022; Margolis et al., 2021; Theron et al., 2021). Although much of brain development occurs during the prenatal and early postnatal periods, there is increasing evidence that brain development continues through adolescence (Fuhrmann et al., 2015). Further, behavioral and mental health issues such as internalizing problems tend to manifest more prominently during adolescence (Merikangas et al., 2010). This suggests that the impacts of early life exposure to air pollution on cognitive and behavioural abilities may endure throughout a child's development, potentially persisting as children age. Alternatively, effects may not become apparent until later in childhood, indicating a delayed manifestation of impact (Kusters et al., 2022). Supporting this notion, Margolis et. al., (2021), reported that prenatal exposure to PAH was associated with decreased reading skills, reading comprehension, and math skills among children with a mean age of 13.7 years (Margolis et al., 2021). Further, a prospective study revealed that exposure to $PM_{2.5}$ and PAH during pregnancy disrupts brain structure (either cortical thinning or thickening and enlargement of the white matter) of children aged between 6 and 14 years (Peterson et al., 2022b). UGAAR investigators should extend follow-up for as long as possible, and future birth cohort studies should seek to follow children over longer durations, to better understand the long-term impacts of prenatal air pollution exposure on neurodevelopment.

Recent research has highlighted the complex relationship between prenatal air pollution exposure and neurodevelopmental outcomes (Ni et al., 2022; Volk et al., 2021). My work has shown that other risk factors, such as maternal stress, malnutrition, and exposure to other toxins, may modify the adverse effects of air pollution on the developing brain. Conversely, interventions such as vitamin supplementation, increased access to education, and stress reduction may attenuate these effects. It will be essential for researchers to explore these modifiable risk factors and not only identify the most effective interventions for reducing exposure to air pollution, but also to identify characteristics that enhance the health benefits of those interventions. Decision makers can then use this knowledge to target relevant modifiers and work towards implementing solutions that benefit the broader public.

5.5. Conclusions

My research aimed to investigate the effects of reducing prenatal air pollution on neurodevelopment, identity effect modifiers, and evaluate impact of indoor $PM_{2.5}$ on cognitive performance. My findings provide strong evidence of the neurotoxic effects of air pollution exposure during gestation and highlight the urgent need to reduce air pollution to protect children's brains. Exploration of potential effect modifiers helped me identify subgroups of women who may benefit more from reducing air pollution during a critical period of development. Although we do not fully understand the complex relationship between air pollution and neurodevelopment, I urge immediate precautionary actions to reduce air pollution and protect children from its potentially lifelong impacts.

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Appendix A. Supplemental material for chapter two

Table A.1. Comparison of WPPSI-IV raw scores between UGAAR participants and the Canadian reference population.

WPPSI-IV Subtest	UGAAR Study Population Raw Scores Mean (Standard Deviation)[a]		Canadian Reference Population Raw Scores Mean (Standard Deviation)[b]	
Block Design	16.5	(3.5)	16.5	(3.5)
Information	13.3	(4.3)	16.5	(4.0)
Matrix Reasoning	5.8	(3.9)	9.0	(4.3)
Bug Search	11.0	(7.5)	16.5	(7.5)
Picture Memory	9.6	(3.8)	11.0	(3.8)
Similarities	7.4	(5.1)	12.5	(9.0)
Cancellation	25.7	(9.8)	24.0	(10.8)
Zoo Locations	9.1	(2.1)	9.0	(2.5)
Object Assembly	12.5	(7.2)	14.5	(7.8)
Picture Concepts	6.4	(3.7)	8.5	(4.8)

WPPSI-IV = Wechsler Preschool and Primary Scale of Intelligence. Fourth Edition
[a]The UGAAR study population was assessed at ages ranging from 48 to 51 months.
[a]The Canadian reference population was assessed at ages ranging from 48 to 91 months.

Table A.2. Select variables measured during pregnancy and after birth for dyads included in the intention-to-treat analysis (N = 475).

	Control (n=233) Median (25th, 75th percentile) or N (%)	Intervention (n=242) Median (25th, 75th percentile) or N (%)
MATERNAL CHARACTERISTICS		
Delivery type		
Cesarian	86 (37.0)	85 (35.1)
Vaginal	134 (57.5)	151 (62.4)
Unknown, N (%)	13 (5.6)	6 (2.5)
Blood lead concentration (ug/dL)	1.46 (1.17, 1.80)	1.43 (1.17, 1.86)
Not measured, N (%)	61 (26.2)	43 (17.8)
Blood cadmium concentration(ug/L)	0.22 (0.16, 0.31)	0.19 (0.14, 0.28)
Not measured, N (%)	61 (26.2)	43 (17.8)
Blood mercury concentration (ug/L)	0.31 (0.22, 0.54)	0.30 (0.20, 0.44)
Not measured, N (%)	61 (26.2)	43 (17.8)
WASI Matrix Reasoning Raw Score	16.0 (12, 19)	17.0 (13, 19)
Not measured, N (%)	58 (24.9)	33 (13.6)
WASI Vocabulary Raw Score	36 (32, 39)	35 (31, 39)
Not measured, N (%)	58 (24.9)	33 (13.6)
CHILD CHARACTERISTICS		
Sex		
Female	110 (47.2)	109 (45.0)
Male	111 (47.6)	126 (52.1)
Unknown, N (%)	12 (5.2)	7 (2.9)
Birth Term		
Pre-Term (<37 weeks)	13 (5.6)	24 (9.9)
Term (≥37 weeks)	207 (88.8)	211 (87.2)
Unknown, N (%)	13 (5.6)	7 (2.9)
Season of birth		
Winter	26 (11.2)	35 (14.5)
Spring	51 (21.9)	56 (23.1)
Summer	69 (29.6)	78 (32.2)
Fall	74 (31.7)	66 (27.3)
Unknown, N (%)	13 (5.6)	7 (2.9)
Breastfed Infant		
Never	6 (2.6)	5 (2.1)
<12 months	43 (15.5)	53 (21.9)
≥12 months	139 (59.7)	156 (64.5)
Not reported, N (%)	45 (19.3)	28 (11.8)
HOME inventory total score	30.0 (28.0, 32.5)	30.0 (27.0, 34.0)
Not measured, N (%)	76 (32.8)	77 (31.7)
Blood lead concentration at 2 years of age (ug/dL)	2.60 (1.86, 3.63)	2.47 (1.68, 3.47)
Not measured, N (%)	80 (34.3)	68 (28.1)
Blood cadmium concentration at 2 years of age (ug/dL)	0.05 (0.04, 0.08)	0.05 (0.04, 0.08)
Not measured, N (%)	80 (34.3)	68 (28.1)
Blood mercury concentration at 2 years of age (ug/dL)	0.18 (0.13, 0.25)	0.18 (0.13, 0.27)
Not measured, N (%)	80 (34.3)	68 (28.1)
Child's age at WPPSI-IV assessment (months)	48.0 (48, 48)	48.0 (48, 48)
No WPPSI-IV, N (%)	51 (21.9)	40 (16.5)
HEPA filter air cleaner usage after birth		
Yes	39 (16.8)	33 (13.6)
No	133 (57.01)	162 (66.9)
Not reported, N (%)	61 (26.2)	47 (19.4)

HOME= Home Observation Measurement of the Environment.
WASI= Wechsler Abbreviated Scale of Intelligence
WPPSI-IV = Wechsler Preschool and Primary Scale of Intelligence. Fourth Edition

Table A.3. Comparison of characteristics for participants who did (N = 383) and did not (N = 92) participate in WPPSI-IV testing.

	Participated in WPPSI-IV testing (N=383) Median (25th, 75th percentile) or N (%)	Did not participate in WPPSI-IV testing (N=92) Median (25th, 75th percentile) or N (%)
MATERNAL CHARACTERISTICS		
Treatment group		
Control	182 (47.5)	51 (55.4)
Intervention	201 (52.5)	41 (44.6)
Age at enrollment	29 (25, 33)	27 (24, 32)
Weeks pregnant at enrollment	11 (9, 13)	11 (9, 13)
Not reported, N (%)	20 (5.2)	0 (0.0)
Enrollment season		
Winter	113 (29.5)	35 (38.0)
Spring	111 (29.0)	27 (29.4)
Summer	49 (12.8)	6 (6.5)
Fall	110 (28.7)	24 (26.1)
Lived with a smoker at enrollment		
Yes	189 (49.3)	47 (51.1)
No	188 (49.1)	42 (45.6)
Not reported, N (%)	6 (1.6)	3 (3.3)
Marital Status		
Married/Common-law	319 (83.3)	73 (79.4)
Not married/Common-law	64 (16.7)	18 (19.6)
Not reported, N (%)	0 (0.0)	1 (1.1)
Education		
Completed university	310 (80.9)	70 (76.1)
Not completed university	47 (12.3)	13 (14.1)
Not reported, N (%)	26 (6.8)	9 (9.8)
Monthly household income		
< 800,000 Tugrik	74 (19.3)	19 (20.7)
≥ 800,000 Tugrik	304 (79.4)	69 (75.0)
Not reported, N (%)	5 (1.3)	4 (4.4)
Parity		
0	131 (34.2)	21 (22.8)
1	148 (38.6)	32 (34.8)
≥2	102 (26.6)	11 (12.0)
Not reported, N (%)	2 (0.5)	28 (30.4)
Delivery type		
Cesarian	145 (37.9)	26 (28.3)
Vaginal	237 (61.8)	48 (52.2)
Not reported, N (%)	1 (0.3)	18 (19.6)
Blood lead concentration (ug/dL)	1.4 (1.2, 1.8)	1.5 (1.2, 1.9)
Not measured N, (%)	62 (16.0)	42 (45.6)
Blood cadmium concentration (ug/L)	0.19 (0.15, 0.28)	0.26 (0.17, 0.38)
Not measured N, (%)	62 (16.0)	42 (45.6)
Blood mercury concentration (ug/L)	0.30 (0.21, 0.48)	0.33 (0.23, 0.53)
Not measured N, (%)	62 (16.0)	42 (45.6)
WASI Matrix Reasoning Raw Score	16 (12, 19)	17 (15, 19)
Not measured, N (%)	72 (18.0)	71 (77.2)
WASI Vocabulary Raw Score	35 (32, 39)	39 (31, 41)
Not measured, N (%)	20 (5.0)	71 (77.2)
CHILD CHARACTERISTICS		
Sex		
Female	184 (48.0)	35 (38.0)
Male	199 (51.9)	38 (41.3)
Unknown, N (%)	0 (0.0)	19 (20.6)
Birth Term		
Pre-Term (<37 weeks)	31 (8.1)	6 (6.5)
Term (>37 weeks)	351 (91.6)	67 (72.8)
Unknown, N (%)	1 (0.3)	19 (20.6)
Birth Season		
Winter	56 (14.6)	5 (5.4)
Spring	86 (22.5)	21 (22.8)
Summer	121 (91.6)	26 (28.3)

Fall	119 (31.1)	21 (22.8)
Unknown, N (%)	1 (0.3)	19 (20.6)
HOME inventory total score	30.0 (28.0, 33.0)	30.0 (28.0, 32.0)
Not measured, N (%)	82 (21.4)	71 (77.2)
Blood lead concentration at 2 years of age (µg/dL)	2.6 (1.8, 3.5)	2.1 (1.4, 4.1)
Not measured, N (%)	72 (18.8)	76 (82.6)
Blood cadmium concentration at 2 years of age (µg/L)	0.05 (0.04, 0.08)	0.06 (0.05, 0.09)
Not measured, N (%)	72 (18.8)	76 (82.6)
Blood mercury concentration at 2 years of age (µg/L)	0.18 (0.13, 0.26)	0.23 (0.14, 0.32)
Not measured, N (%)	72 (18.8)	76 (82.6)

HOME= Home Observation Measurement of the Environment.
WPPSI-IV = Wechsler Preschool and Primary Scale of Intelligence. Fourth Edition

Appendix B. Supplemental material for chapter three

Table B.1. Characteristics of participants who did (N = 293) and did not (N = 90) provide hair samples in early pregnancy for analysis of cortisol and DHEA.

	Glucocorticoids measured (n=293) median (25th, 75th) or N (%)	Glucocorticoids not measured (n=90) median (25th, 75th) or N (%)
Intervention group		
Intervention	149 (50.9)	52 (57.8)
Control	144 (49.1)	38 (42.2)
Maternal age at enrollment, years	30.0 (25.0, 33)	29.0 (26.0, 34.0)
Not reported, N (%)	19 (6.5)	1 (1.1)
Gestational age at enrollment, weeks	10.0 (8, 12)	11.5 (9.5, 13)
Not reported, N (%)	18 (6.1)	2 (2.2)
Monthly household income at baseline, Tugriks	150 (51.2)	56 (62.2)
<1,200,000	139 (47.4)	33 (36.7)
≥1,200,000	4 (1.4)	1 (1.1)
Not reported, N (%)		
Maternal education at baseline		
Completed university	237 (80.9)	73 (81.1)
Did not complete university	34 (11.6)	13 (14.4)
Not reported, N (%)	22 (7.5)	4 (4.4)
Vitamin intake in early pregnancy		
Yes	216 (73.7)	66 (73.3)
No	71 (24.2)	17 (18.9)
Not reported, N (%)	6 (2.0)	7 (7.8)
PSS 4 score in early pregnancy	5.0 (4.0, 7.0)	5.0 (4.0, 7.0)
Not measured, N (%)	2 (0.7)	3 (3.3)
Maternal WASI matrix reasoning raw score	16.0 (12.0, 19.0)	17.0 (14.0, 19.0)
Not measured, N (%)	11 (3.8)	9 (10.0)
Sex of the child		
Female	148 (50.5)	51 (56.7)
Male	145 (49.5)	39 (43.3)

Table B.2. Spearman correlations between stress biomarkers and perceived stress measured at two times in pregnancy.

	Early Cortisol	Late Cortisol	Early DHEA	Late DHEA	Early C/D ratio	Late C/D ratio	Early PSS-4	Late PSS-4
Early Cortisol								
Late Cortisol	0.61** (N=71)							
Early DHEA	0.27** (N=293)	0.20 (N=71)						
Late DHEA	0.49** (N=71)	0.45** (N=71)	0.66** (N=71)					
Early C/D ratio	0.40** (N=293)	0.19 (N=71)	-0.74 (N=293)	-0.31** (N=71)				
Late C/D ratio	-0.15 (N=71)	0.09 (N=71)	-0.59** N=71	-0.80** N=71)	0.50** (N=71)			
Early PSS-4	-0.07 (N=291)	0.05 (N=70)	0.02 (N=291)	0.10 (N=70)	-0.06 (N=291)	-0.12 N=70		
Late PSS-4	0.06 (N=273)	0.10 (N=66)	-0.07 (N=273)	-0.07 (N=66)	0.10 (N=273)	0.12 (N=66)	0.23** (N=271)	

*P<0.05
**P<0.01
DHEA = dehydroepiandrosterone
C/D ratio = cortisol / DHEA ratio
PSS-4 = Four-question perceived stress scale

Figure B.1. Estimated effects of the air cleaner intervention on mean full-scale IQ (FSIQ) by quartiles of maternal hair stress markers (N = 293).
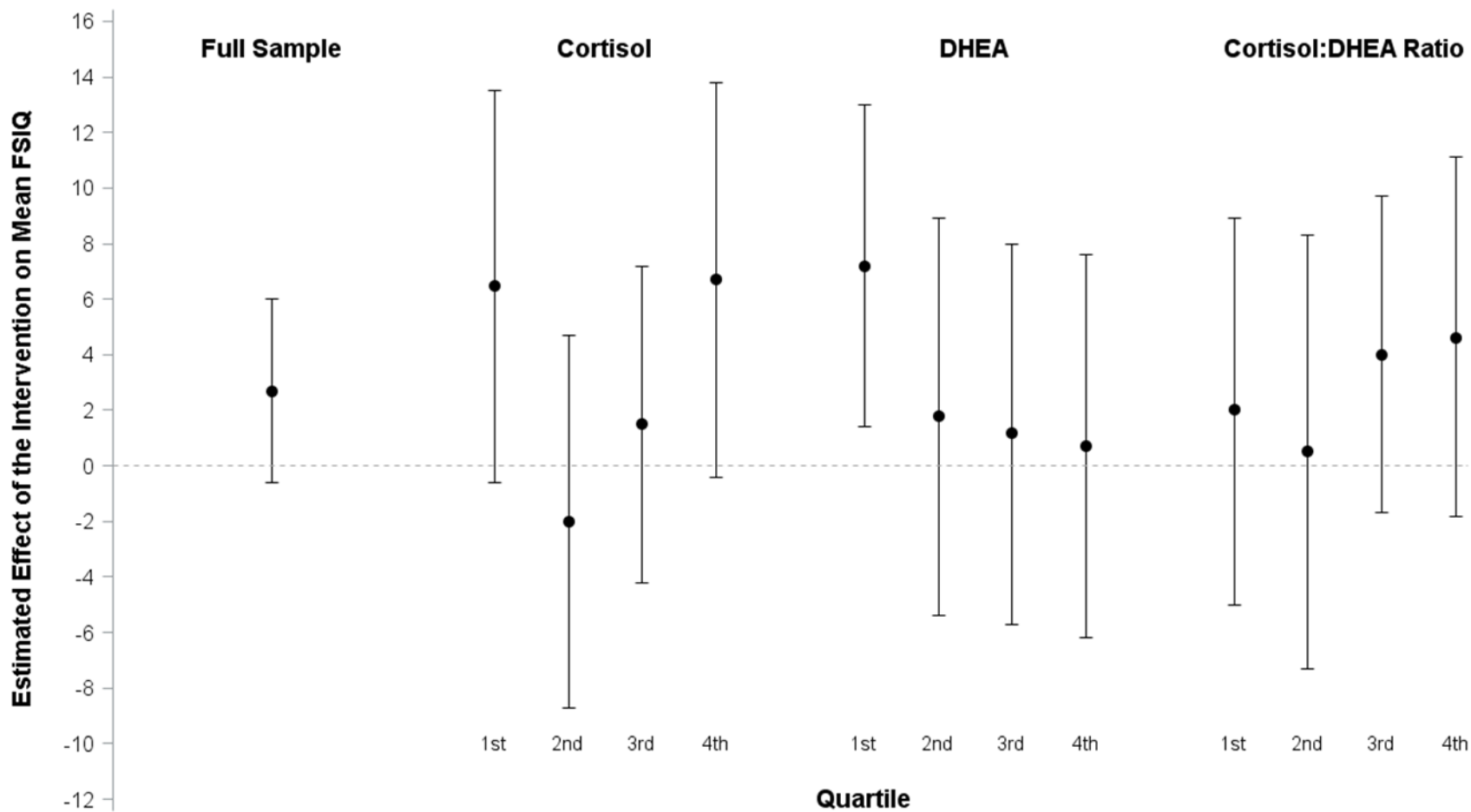
Table B.3. Phi coefficients of correlations between binary effect modifiers

	Enrollment in October-March	Vitamin intake in early pregnancy	Maternal education at baseline	Household income at baseline	Gestational age at enrollment	Child's sex	Maternal matrix reasoning raw score	Cortisol concentration in early pregnancy	DHEA concentration in early pregnancy	C/D ratio in early pregnancy	PSS-4 score in early pregnancy
Enrollment in October-March											
Vitamin intake in early pregnancy	0.04 (N=370)										
Maternal education at baseline	0.12* (N=357)	0.17** (N=346)									
Household income at baseline	-0.13* (N=378)	0.09 (N=366)	0.14* (N=354)								
Gestational age at enrollment	-0.03 (363)	-0.09 (N=351)	0.06 (N=343)	0.11* (N=358)							
Child's sex	-0.07 (N=383)	0.03 (N=370)	0.03 (N=357)	0.02 (N=378)	0.03 (N=363)						
Maternal matrix reasoning raw score	0.08 (N=363)	0.02 (N=350)	0.04 (N=338)	0.14 (N=358)	0.06 (N=343)	-0.08 (N=293)					
Cortisol concentration in early pregnancy	-0.07 (N=293)	0.00 (N=287)	-0.06 (N=271)	0.03 (N=289)	-0.04 (N=275)	0.01 (N=293)	0.07 (N=282)				
DHEA concentration in early pregnancy	-0.03 (N=0.56)	-0.04 (N=287)	0.11 (N=271)	0.02 (N=289)	-0.06 (N=275)	-0.06 (N=293)	-0.10 (N=282)	0.02 (N=293)			
C/D ratio in early pregnancy	0.04 (N=293)	-0.02 (N=287)	-0.04 (N=271)	0.07 (N=289)	-0.04 (N=275)	0.04 (N=293)	0.03 (N=282)	0.02 (N=293)	0.05 (N=293)		
PSS-4 score in early pregnancy	0.09 (N=378)	-0.03 (N=365)	0.10 (N=353)	0.03 (N=373)	-0.01 (N=358)	-0.01 (N=378)	-0.05 (N=358)	0.06 (N=291)	-0.10 (N=291)	0.08 (N=291)	

*P≤0.05
**P≤0.01
DHEA = dehydroepiandrosterone
PSS-4 = Four-question perceived stress scale

Table B.4. Estimated effects of the air cleaner intervention on mean full-scale IQ (FSIQ), stratified by potential effect modifiers after excluding 102 women who reported hair treatment (N = 281).

Effect Modifier	Stratum	N	Mean (SD) FSIQ		Estimated Effect of the Intervention on Mean FSIQ				Interaction p-value
			Control	Intervention	Effect Estimate	Lower 95%	Upper 95%	p-value	
	All	281	98.0 (15.0)	100.4 (13.5)	2.7	-0.7	6.0	0.12	-----
Gestational age at enrollment	< 11 weeks	129	97.2 (14.6)	100.9 (13.7)	3.7	-1.2	8.6	0.14	0.51
	≥ 11 weeks	138	97.9 (15.7)	99.3 (13.5)	1.4	-3.5	6.3	0.57	
Enrollment season	October-March	182	97.6 (14.6)	99.9 (13.6)	2.3	-1.8	6.4	0.27	0.79
	April-September	99	98.3 (15.7)	101.5 (13.6)	3.2	-2.6	9.1	0.27	
Vitamin intake in early pregnancy	No	65	94.1 (16.2)	99.7 (11.8)	5.6	-1.5	12.6	0.12	0.27
	Yes	208	99.5 (14.4)	100.6 (14.1)	1.1	-2.8	5.0	0.58	
Monthly household income at baseline	< 1,200,000 MNT	146	95.6 (13.9)	101.0 (12.4)	5.3	1.0	9.7	0.01	0.07
	≥ 1,200,000 MNT	132	100.8 (15.9)	99.9 (14.7)	-0.8	-6.1	4.5	0.76	
Maternal education at baseline	Did not complete university	34	94.5 (8.6)	101.1 (10.1)	6.6	-0.1	13.2	0.05	0.41
	Completed university	229	98.5 (15.8)	100.5 (14.2)	2.0	-1.9	5.9	0.30	
Maternal intelligence[a]	≤Median	131	95.3 (13.8)	99.7 (13.1)	4.4	-0.3	9.1	0.06	0.47
	>Median	134	99.9 (15.7)	101.4 (13.8)	1.5	-3.5	6.6	0.54	

		N	Score[a]	Score[a]	Difference			p	p
Maternal hair cortisol concentration in early pregnancy	Middle tertile	77	100.7 (14.2)	97.3 (12.6)	-3.4	-9.5	2.7	0.27	
	Bottom or top tertile	141	96.6 (15.4)	102.6 (13.5)	6.0	1.2	10.8	0.02	0.02
Maternal hair DHEA concentration in early pregnancy	≤Median	115	98.4 (15.3)	103.2 (12.1)	4.9	-0.2	10.0	0.06	0.23
	>Median	103	97.6 (14.7)	97.9 (14.2)	0.3	-5.4	6.0	0.91	
Cortisol / DHEA hair concentration ratio in early pregnancy	≤Median	106	98.3 (16.0)	100.2 (15.3)	1.9	-4.2	7.9	0.54	0.70
	>Median	112	97.6 (14.0)	101.0 (11.6)	3.4	-1.4	8.2	0.17	
Perceived stress score[b] in early pregnancy	≤Median	152	97.5 (15.6)	99.9 (14.0)	2.4	-2.4	7.1	0.32	0.97
	>Median	125	98.5 (13.9)	101.0 (13.3)	2.5	-2.3	7.3	0.31	
Child's sex	Female	130	101.1 (15.4)	105.4 (12.4)	4.3	-0.5	9.1	0.08	0.35
	Male	151	94.9 (14.0)	96.2 (13.1)	1.2	-3.1	5.6	0.57	

[a]Wechsler Abbreviated Scale of Intelligence (WASI) matrix reasoning raw score
[b]Four-question perceived stress scale (PSS-4) score

Table B.5. Effects of the air cleaner intervention on mean FSIQ estimated from separate multiple regression models with an intervention x modifier interaction term after excluding 62 women who reported hair treatment (N = 180).

Effect modifier	Group that benefitted most	Estimated between-group difference in the intervention's effect on mean FSIQ	Lower 95%	Upper 95%	Interaction p-value
Maternal vitamin intake in early pregnancy	No vitamin intake	8.6	-0.9	18.1	0.08
Maternal hair DHEA concentration in early pregnancy	Hair DHEA below the median	5.4	-2.7	13.5	0.19
Maternal hair cortisol concentration in early pregnancy	Hair cortisol in bottom or top tertile	4.7	-3.8	13.2	0.28
Household income	Household income below the median	4.2	-4.2	12.5	0.33
Child's sex	Female children	4.1	-4.2	12.3	0.33
Maternal intelligence[a]	Maternal intelligence score below the median	3.3	-4.6	11.2	0.41
Enrollment season	Enrolled October-March	1.9	-6.9	10.6	0.67
Gestational age at enrollment	Women who enrolled at 11 weeks gestation or later	1.8	-6.5	10.2	0.66
Maternal perceived stress score in early pregnancy[b]	Perceived stress above the median	0.5	-7.8	8.8	0.90
Maternal education	Did not complete university	0.1	-13.7	13.9	0.99

[a]Wechsler Abbreviated Scale of Intelligence (WASI) matrix reasoning raw score
[b]Four-question perceived stress scale (PSS-4) score

Table B.6. Heterogeneity in the intervention's effect on mean full-scale IQ (FSIQ) estimated from parsimonious regression models containing main effects and variable x intervention interactions for the modifier of interest and variables correlated with the modifier of interest (phi correlation with p<0.20).

Effect modifier	Group that benefitted more	Estimated between-group difference in the intervention's effect on mean FSIQ	Lower 95%	Upper 95%	Interaction P-value	Variables included in the model[a]
Maternal hair cortisol concentration in early pregnancy	Hair cortisol in bottom or top tertile	7.9	1.0	14.8	0.02	Hair cortisol[b]
Maternal hair DHEA concentration in early pregnancy	Hair DHEA below the median	5.0	-2.0	12.0	0.16	Maternal hair DHEA Maternal education Maternal perceived
Maternal education	Did not complete university	4.8	-6.5	16.0	0.40	Maternal education Maternal vitamin intake
Maternal vitamin intake in early pregnancy	No vitamin intake	4.2	-3.3	11.7	0.28	Maternal hair Maternal vitamin intake Monthly household income

[a]All models also included intervention status and variable x intervention interactions for all variables.
[b]No variables were correlated with cortisol (phi correlation coefficient with p<0.20).

Appendix C. Supplemental material for chapter four

Table C.1. Comparison of characteristics for dyads in which children did (N = 382) and did not (N = 92) participate in WPPSI-IV testing.

	Participated in WPPSI-IV testing (N=382)	Did not participate in WPPSI-IV testing (N=92)
	Median (25th, 75th percentile) or N (%)	Median (25th, 75th percentile) or N (%)
Intervention status		
Intervention	201 (52.6)	41 (44.6)
Control	181 (47.4)	51 (55.4)
Maternal age at enrollment	29.0 (25.0, 33.0)	27 .0 (24.0, 32.0)
Not reported, N (%)	10 (2.6)	2 (2.2)
Maternal pre-pregnancy BMI	21.5 (19.2, 24.2)	21.5 (19.6, 23.1)
Not reported, N (%)	26 (6.8)	3 (3.3)
Enrollment season		
Winter	112 (29.6)	35 (38.0)
Spring	110 (28.8)	27 (29.35)
Summer	49 (12.8)	6 (6.5)
Fall	110 (28.80)	24 (26.1)
Lived with a smoker at enrollment		
Yes	173 (45.3)	45 (48.9)
No	200 (52.4)	44 (47.8)
Not reported, N (%)	9 (2.4)	3 (3.3)
Maternal education		
Completed university	309 (80.9)	70 (76.1)
Did not complete university	47 (12.3)	13 (14.1)
Not reported, N (%)	26 (6.8)	9 (9.8)
Monthly household income		
<800,000 Tugrik	71 ((18.6)	19 (20.7)
800,000 – 1,190,000 Tugrik	127 (44.2)	26 (26.3)
≥1,200,000 Tugrik	169 (44.2)	43 (46.7)
Not reported, N (%)	15 (3.9)	4 (4.4)
Maternal alcohol consumption		
Yes	193 (50.5)	41 (44.6)
No	175 (45.8)	47 (51.1)
Not reported, N (%)	14 (3.7)	4 (4.4)
Maternal vitamin intake at enrollment	281 (73.6)	63 (68.5)
Yes	88 (23.0)	25 (27.2)
No	13 (3.4)	4 (4.4)
Not reported, N (%)		
Maternal blood cadmium concentration	0.2 (0.1, 0.3)	0.3 (0.2, 0.4)
Not measured, N (%)	61 (16.0)	42 (45.7)
Maternal blood lead concentration	1.4 (1.2, 1.8)	1.5 (1.2, 1.9)
Not measured, N (%)	61 (16.0)	42 (45.7)
Parity		
0	131 (34.3)	21 (22.8)
1	148 (38.7)	32 (34.8)
≥2	101 (26.4)	11 (12.0)
Not reported, N (%)	2 (0.5)	28 (30.4)
Child's sex		
Boy	198 (51.8)	38 (41.3)
Girl	184 (48.2)	35 (38.0)

Not reported, N (%)	0 (0.0)	19 (20.7)
Maternal intelligence (WASI Matrix Reason Score)	16.0 (12.0, 19.0)	17.0 (15.0, 19.0)
Not measured, N (%)	20 (5.2)	71 (76.0)
Maternal intelligence (WASI Vocabulary Score)	35.0 (32.0, 39.0)	39.0 (31.0, 41.0)
Not measured, N (%)	20 (5.2)	71 (76.0)
Breasted Infants		
Never	9 (2.4)	2 (2.2)
< 12 months	91 (23.8)	5 (5.4)
≥ 12 months	277 (72.5)	17 (18.5)
Not reported, (N %)	5 (1.3)	68 (73.9)
HOME Score	31.0 (298.0, 33.0)	30.0 (28.0, 32.0)
Not measured, N (%)	81 (21.2)	71 ()
Child blood lead concentration	2.6 (1.8, 3.5)	2.1 (1.4, 4.1)
Not measured, N (%)	72 (18.8)	76 (77.2)
PM$_{2.5}$ concentration during full pregnancy in μg/m^3	28.2 (24.2, 33.8)	29.5 (25.8, 34.4)
Not measured, N (%)	0 (0.0)	19 (20.7)
PM$_{2.5}$ concentration during first trimester in μg/m^3	29.5 (20.4, 40.0)	33.8 (20.9, 45.8)
Not measured, N (%)	0 (0.0)	19 (20.7)
PM$_{2.5}$ concentration during second trimester in μg/m^3	27.2 (17.9, 39.5)	28.2 (22.0, 41.5)
Not measured, N (%)	0 (0.0)	19 (20.7)
PM$_{2.5}$ concentration during third trimester in μg/m^3	21.6 (16.6, 29.7)	21.2 (15.7, 29.5)
Not measured, N (%)	0 (0.0)	19 (20.7)

HOME= Home Observation Measurement of the Environment.

WPPSI-IV = Wechsler Preschool and Primary Scale of Intelligence. Fourth Edition

Table C.2. Estimated changes in mean full-scale IQ (FSIQ) per interquartile range (IQR) contrast in indoor PM$_{2.5}$ concentration (N=475) from different regression models.

Exposure Period	Model	Effect Estimate	95% Confidence Interval
Full pregnancy	Primary	-1.1	-3.7, 1.5
	Secondary	-0.6	-3.2, 1.9
	Primary + maternal blood cadmium	-0.8	-3.4, 1.8
	Primary + maternal blood lead	-1.1	-3.7, 1.5
First trimester	Primary	-3.6	-6.6, -0.7
	Secondary	-3.5	-6.7, -0.3
	Primary + maternal blood cadmium	-4.0	-7.5, -0.6
	Primary + maternal blood lead	-3.6	-6.6, -0.7
Second trimester	Primary	-0.4	-4.4, 3.6
	Secondary	1.7	-2.9, 6.3
	Primary + maternal blood cadmium	-0.6	-4.6, 3.4
	Primary + maternal blood lead	-0.4	-4.3, 3.6
Third trimester	Primary	2.4	-0.2, 4.9
	Secondary	1.3	-1.4, 4.1
	Primary + maternal blood cadmium	2.4	-0.2, 5.1
	Primary + maternal blood lead	2.5	-0.1, 5.1

Primary model: The regression models were adjusted for intervention group, monthly family income at enrollment (<800,000, 800,000 to 1,199,999, and ≥ 1,200,000 tugriks), mother's education (< or ≥ university degree), enrollment season, household smoking status at enrollment (yes/no) and child's sex. Trimester-specific models were also adjusted for PM2.5 concentrations in other trimesters

Secondary model: The regression models were adjusted for variables in the primary model and mother's pre-pregnancy BMI, mother's intelligence (WASI matrix reasoning and vocabulary raw scores), parity (0, 1, ≥2), mother's age at enrollment, mother's multivitamin intake at enrollment (yes/no), mother's alcohol consumption during pregnancy (yes/no), breastfeeding status (never, <12 months, ≥12 months), HOME score when child was one year old, and child's blood lead level at age two (log-2 transformed).

Table C.3. Estimated changes in mean full-scale IQ (FSIQ) per interquartile range (IQR) contrast in indoor PM2.5 concentration (N=475), stratified by household smoking status at enrollment

	Smoking Households (N = 227)		Non-Smoking Households (N = 248)	
	Estimate	95% CI	Estimate	95% CI
Full pregnancy	0.7	-2.9, 4.3	-1.7	-5.2, 1.7
First trimester	-1.3	-5.9, 3.2	-5.6	-10.1, -1.2
Second trimester	-0.7	-7.1, 5.7	5.1	-1.0, 11.1
Third trimester	4.5	0.5, 8.5	-2.0	-5.8, 1.8

Figure C.1. Directed acyclic graph showing assumed relationships between indoor concentration PM2.5 during pregnancy, FSIQ at four years of age, and other variables.
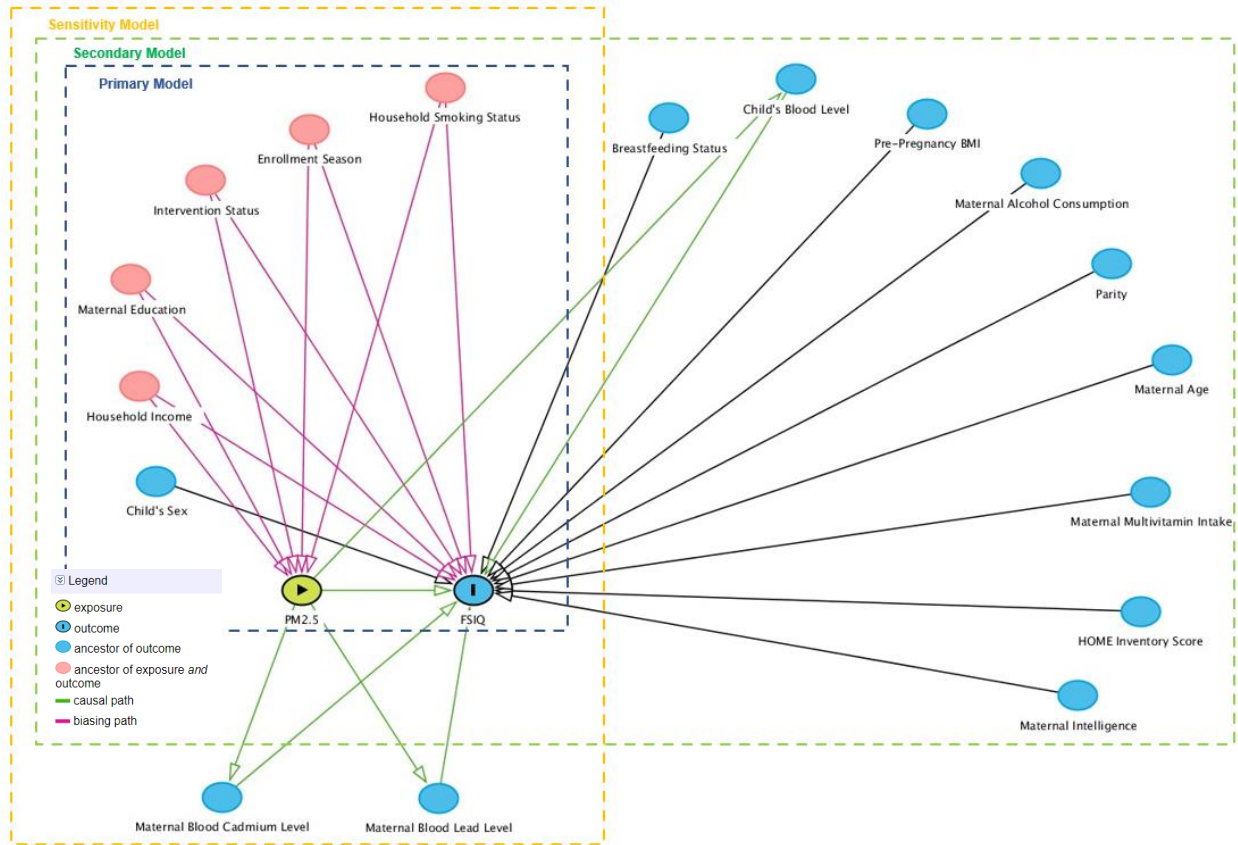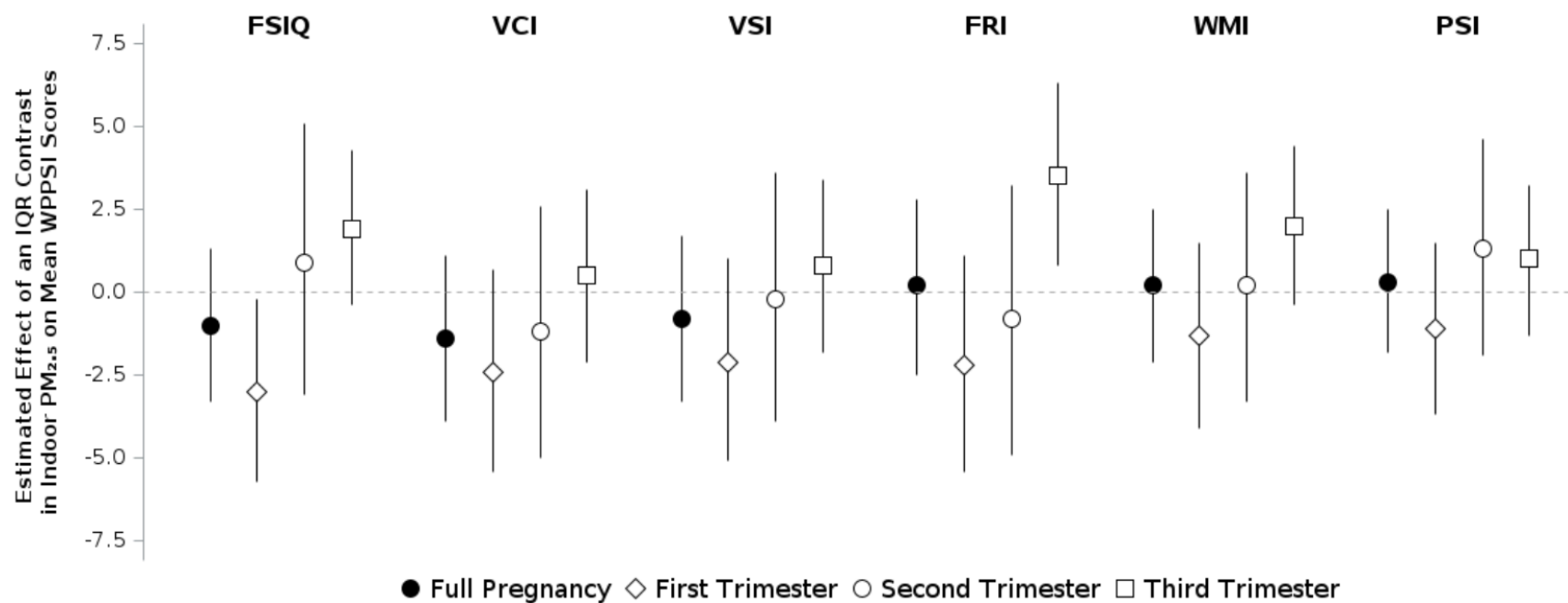
Figure C.2. Estimated changes in mean WPPSI-IV composite indices per interquartile range (IQR) contrast in indoor PM$_{2.5}$ concentration (N=382)

Primary model: The regression models were adjusted for intervention group, monthly family income at enrollment (<800,000, 800,000 to 1,199,999, and ≥ 1,200,000 tugriks), mother's education (< or ≥ university degree), enrollment season, household smoking status at enrollment (yes/no) and child's sex. Trimester-specific models were also adjusted for PM$_{2.5}$ concentrations in other trimesters.

NOTE: Full pregnancy indoor PM$_{2.5}$ exposure IQR contract = 9.4 μg/m^3, 1st trimester indoor PM$_{2.5}$ exposure IQR contract = 20.7 μg/m^3, 2nd trimester indoor PM$_{2.5}$ exposure IQR contract = 21.2 μg/m^3, 3rd trimester indoor PM$_{2.5}$ exposure IQR contract = 13.3 μg/m^3.

FSIQ = full-scale IQ, VCI = verbal comprehension index, VSI = visual spatial index, FRI = fluid reasoning index, WMI = working memory index, PSI = processing speed index.