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Joint Effects of Air Pollution Mixtures and Psychosocial Factors on Child Psychopathology in a South African Birth Cohort

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An abstract of
A dissertation submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of
Doctor in Philosophy
in Epidemiology
2023

Abstract

Joint Effects of Air Pollution Mixtures and Psychosocial Factors on Child Psychopathology in a South African Birth Cohort

By Grace M. Christensen

Risk of childhood psychopathology is complex and includes both environmental and social risk factors. A majority of the current literature on psychosocial stress and air pollution's effect on child psychopathology focuses on outdoor air pollution exposure and stress in high-income countries with relatively low exposures. Very little is known about the effects of indoor air pollution (IAP), especially in low- and middle-income countries where many children and pregnant women are exposed to high levels of IAP as well as psychosocial stressors.

The overarching goal of this dissertation is to investigate the individual and joint effects of prenatal and early-life exposure to IAP mixtures and psychosocial factors (PF) on child psychopathology. We leverage data from a unique birth cohort from South Africa, the Drakenstein Child Health Study.

AIM 1: We investigated the effect of prenatal exposure to IAP and PFs on trajectories of childhood psychopathology symptoms at 24, 42, and 60 months. We found externalizing behavior trajectory was associated with particulate matter and smoking, while internalizing behavior trajectory was associated with volatile organic compounds.

AIM 2: We investigated the pre- and early postnatal periods as sensitive periods of exposure to IAP and PFs on childhood psychopathology at 6.5 years. Prenatal exposure to IAP and PFs, as well as the total prenatal mixture was associated with increased psychopathology. Analyses also indicated that the prenatal period is a sensitive period for IAP exposure, while PFs, including depression and alcohol, were associated with childhood psychopathology in both periods.

AIM 3: We investigated inflammation during infancy as a potential mediator of the association between prenatal exposure to IAP and PFs and childhood psychopathology. IAPs were associated with increased inflammation, while the association with PFs did not have a consistent pattern. We did not find evidence of mediation by inflammatory markers, possibly due to the small sample size and evidence of effect modification by HIV status and ancestry.

Overall, our findings add evidence that prenatal exposure to IAPs and PFs are associated with psychopathology during childhood. These findings can be used to target interventions to reduce exposure to IAPs and PFs and prevent childhood psychopathology.

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Acknowledgements

First and foremost, I would like to thank the participants of the Drakenstein Child Health Study and their families for their involvement in this research project. Without their commitment to this study, this work would not be possible.

To my dissertation committee, thank you for your mentorship during this process. To Anke, thank you for your support and dedication throughout the doctoral program. You were always encouraging me in all aspects of this process. To Michele, thank you for your guidance and thoughtful feedback. Together you and Anke were a co-chair dream team. To Shakira, thank you for inspiring helpful discussion around the psychosocial aspects of this research. Howard, thank you for lending your knowledge of environmental mixtures and methodology, especially when these new methods did not work as planned. To Dan, thank you for your thoughtful comments and expertise with psychiatry and the DCHS. It was a pleasure to work with you and the DCHS team. To all of you, together you made an excellent committee.

I also want to thank my colleagues at the University of Cape Town including, Marilyn Lake, Aneesa Vanker, Susan Malcolm-Smith, Pieter Naudé, and Heather Zar. Thank you all for your support in writing these manuscripts and dissertation documents.

Thank you to all Emory University Department of Epidemiology PhD students, faculty, and staff. Thank you all for creating a positive and welcoming environment in which I could learn, ask questions, and complete this work. Thank you to Stephanie Eick for your knowledge and guidance around environmental mixtures. To the Huels lab, thank you for providing help and feedback on this dissertation and countless other projects.

To Katie Campbell, Sanjana Pampati, Laura Englund, Carol Liu, Chrystelle Kiang, and Chang Liu, thank you from the bottom of my heart for being the best cohort I could ask for. I will only be submitting this dissertation once, while looking at my Elmo mug.

To my family (my parents, Kim Turgeon and Bill Christensen, and my brother, Sam Christensen), thank you for your support and encouragement throughout my life and academic journey. To my friends, thank you for your advice and for listening to me talk about my work the past few years. To Zack Graves, thank you for your unwavering support and laughing with me throughout this process.

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Chapter 1 : Introduction and Background

Overarching Goal and Specific Aims

Childhood psychopathology, including emotional and behavioral problems, affect parents, teachers, and most importantly the child, and can follow children into adulthood[1]. Risk factors for childhood psychopathology are complex and include both environmental and social factors. Air pollutants from road traffic and second hand smoke exposure during pregnancy and early life, have been shown to impact childhood behavioral problems over time [2–7]. However, the majority of research in this area has been conducted in high income countries and focuses on children's exposure to outdoor air pollution or environmental tobacco smoke. Very little is known about the effects of indoor air pollution on child psychopathology and the few studies that exist use proxies for air pollutants such as smoking or cooking habits. More precise air pollution measurements and advanced statistical modelling are needed to determine which pollutants specifically affect psychopathology. An especially vulnerable window for these exposures is the perinatal period because this is a critical time for brain development[8].

Adverse early life events, including parental intimate partner violence, parental substance use, and other psychosocial stressors have also been shown to increase risk of child psychopathology[9–12]. Few studies have looked at both environmental and psychosocial exposures, but one study found that prenatal exposure to polycyclic aromatic hydrocarbons magnified the effect of early life stress on child behavior[13]. Co-occurrence of environmental and social stressors is common, and it is hypothesized that both air pollution and psychosocial stress affect psychopathology through inflammatory mechanisms[14–16]. Research into joint effects of environmental and social risk factors is necessary because in a 'real-world' setting these exposures occur together, and research studies should not investigate exposures in a vacuum. Using only single exposure models does not adequately represent the true exposure.

Determining risk factors for childhood psychopathology is an important step in reducing child emotional and behavioral problems, especially when exposure can be prevented or reduced.

The **overarching goal** of this dissertation was to investigate the joint effects of prenatal and early-life exposure to air pollution mixtures and psychosocial factors on child psychopathology. This dissertation used data from the Drakenstein Child Health Study, a South African birth cohort with extensive indoor air pollution and psychosocial exposure measurements. We will leverage existing data on exposure measurements taken during the 2nd trimester of pregnancy and in early life, as well as repeated measurements of childhood psychopathology using the Childhood Behavior Checklist (CBCL). CBCL measurements using the pre-school age scale (2 to 5 years old) will provide insights into early-life trajectories of child behavior, while the school-age scale (6.5 years old) can provide insights into neuropsychiatric disorders, which are easier to diagnose at school age. This dissertation will use state-of-the-art exposure mixture modeling methods such as Self-Organizing Maps and Bayesian Kernel Machine Regression to model joint and individual effects of exposures. Utilizing multiple methods to analyze exposure mixtures will allow for a holistic assessment of mixture effects.

Aim 1: Assess joint effects of air pollution and psychosocial factors on early-life trajectories of child psychopathology. Examine trajectories of CBCL score at 2, 3.5, and 5 years in association with in utero exposure mixtures of air pollution and psychosocial factors.

Aim 2: Investigate prenatal and early-life exposure to joint effects of air pollution and psychosocial factors in association with child psychopathology at school age. a) Examine the joint effect of air pollution and psychosocial factor exposure mixtures during the pre- and postnatal periods separately on CBCL score at 6.5 years. **b)** Determine critical periods of exposure to air pollutants and psychosocial factors on CBCL score at 6.5 years using a structured life course approach.

Aim 3: Investigate the role of inflammation as a potential mediator. a) Estimate the joint effects of in utero air pollution and psychosocial factors exposure during pregnancy on inflammation in the child in early life. **b)** Investigate inflammation as a potential mediator for the joint effects of air pollution and psychosocial factors on CBCL score at 6.5 years using causal mediation analysis.

Overall, this dissertation will provide insight into how joint effects of environmental and social exposures impact childhood psychopathology, as well as identify sensitive periods of exposure.

Background

Childhood Psychopathology

Childhood psychopathology, including anxiety, attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder, and depression, cause problems for children in all aspects of life[18]. A systematic review found that experiencing mental health problems before the age of 14 years was associated with increased risk of adult mental disorders. Additionally, the authors found that elevated symptoms rather than an actual diagnosis in childhood was more strongly associated with adult disorders[19]. Since a majority of mental health services are targeted at adults, there is a large gap in knowledge in prevention of psychopathology in children[19]. Bridging this gap in research on modifiable risk factors has potential to reduce burden of mental health problems in childhood. This will in turn increase quality of life by promoting greater educational attainment, improved social functioning, and prevention of adult psychopathology[18].

Psychopathology presents in a variety of ways and is characteristically split into two categories of disorders, internalizing and externalizing. Externalizing behaviors are displayed outwardly and reflect the behavior towards the environment. Examples of externalizing behaviors include aggression, delinquency, and hyperactivity[20]. In contrast, internalizing behavior is directed inward and reflect the child's emotional and psychological state. Internalizing behaviors include depression, anxiety, somatic complaints, and suicidal ideation[21]. There is overlap between

internalizing and externalizing behaviors as a child's internalizing behavior may negatively affect the people around them including parents, siblings, peers, and teachers. Co-morbidity between internalizing and externalizing disorders is also common[20,21].

A large majority of research on childhood psychopathology is conducted in high income countries, yet almost 80% of children live in low to middle income countries (LMICs). Compared to high income countries and the global average, LMICs fare worse in social indicators for children, including the human development index, primary school enrollment ratio, under five malnutrition, among others. These social indicators are known to be associated with childhood mental health[22]. This dissertation will focus on a South African study population. In 2008 the first nationally representative study of psychiatric disorders was conducted in South Africa and indicated high burden of illness. The study found 16.5% of the population had a psychiatric disorder in the past 12 months, and 30.3% had a lifetime occurrence, though the study was only conducted in adults[23]. As prevalence of risk factors for childhood psychopathology are higher in LMICs it is important to study childhood psychopathology in these populations. Childhood psychopathology can be impacted by both social and environmental factors, and joint effects of these exposures are poorly understood. Understanding and identifying particularly dangerous combinations of these exposures may improve interventions to reduce burden of childhood psychopathology. Additionally, these exposures may impact future psychopathology differently during particular developmental periods like gestation and early life. Understanding sensitive periods of exposure will also improve interventions to reduce disease burden.

Indoor Air Pollution

Indoor air pollution is a well-known contributor to the global burden of disease, accounting for about for 4% of the global burden of disease and an estimated 2 million deaths annually[24,25]. LMICs, like South Africa, typically have higher levels of indoor air pollution compared to high income countries. Common causes of indoor air pollution include tobacco smoke, use of

kerosene or biomass cooking and heating appliances, and cleaning supplies, pesticides, or other sovents[26]. Women and children are most at risk for exposure to indoor air pollution because they typically spend more time indoors and are more involved in food preparation and cooking[24].

Animal studies have shown air pollutants affect the central nervous system (CNS) and elements of behavior [14,27]. Epidemiologic studies in humans have also shown that exposure to outdoor air pollutants during pregnancy and early life affects child psychopathology[3,13,28]. Though, little is known about the effects of indoor air pollution, which is the main source of air pollution in low income countries[29]. A Korean study found environmental tobacco smoke exposure in early life and maternal smoking during pregnancy associated with adverse Childhood Behavior Checklist (CBCL) score at 5 years[2]. Additionally, indoor air pollutants from maternal cooking during pregnancy were associated with hyperactive behaviors in children, though the study did not measure individual air pollutants, only proxy measures[5]. Indoor air pollution is most often measured using survey-based proxy measures e.g. cooking practices, smoking, etc. As the scientific community is already aware of the sources of indoor air pollution[29], it is important to look at individual pollutants to pinpoint what exactly is causing health problems and the biological mechanisms involved.

This dissertation will focus on the following indoor air pollutants; Carbon Monoxide, Particulate Matter 10 microns in diameter, Nitrogen Dioxide, Sulfur Dioxide, and Volatile Organic Compounds.

Carbon Monoxide (CO)

Carbon monoxide (CO) is a product of incomplete combustion. Indoor sources of CO can include car exhaust from attached garages, tobacco smoke, and gas cooking and heating appliances[26]. CO is an odorless, colorless, and non-irritating gas. CO poisoning can occur with acute and well as chronic exposure and has neurological effects. CO is a neurotoxin and patients with CO poisoning can suffer from brain injury, with neurocognitive symptoms like

impaired memory, cognitive decline, depression and anxiety, as well as motor defects[30]. Low levels of chronic exposure have also been seen to cause neurological damage[31]. CO can affect the brain by reducing oxygen availability in red blood cells and increasing inflammation, producing an ischemic and anoxic brain injury[30]. Additionally, CO can cross the placenta and is of particular concern to pregnant women[32].

There are few studies examining the effect of pre- and postnatal CO exposure on child psychopathology, as many studies use the source of CO as the exposure. One study found CO exposure during the 3rd trimester from woodsmoke to be associated with decreased performance on several neurobehavioral tests at 6-7 years old. Researchers found CO exposure was significantly associated with visuo-spatial integration, short-term memory recall, long-term memory recall, and fine motor performance[33].

Particulate Matter (PM)

Particulate matter (PM) is a mixture of organic and inorganic chemicals which include organic carbon and elemental carbon. As PM ranges in size, this dissertation will focus on PM less than 10 microns in diameter (PM_{10}). Sources of indoor PM_{10} include, smoking, cooking from kerosene and biomass fuels, wood stoves and furnaces, and infiltration from outside sources (e.g. car traffic)[26]. Ultrafine (0.1 micron) and fine (2.5 microns) PM are the most neurotoxic as they are small enough to translocate out of the lungs and nasal olfactory and into the brain tissue[27]. One hypothesis for the mechanism of toxicity is that PM induces proinflammatory cytokines, which in turn harm microglial cells in the brain[27].

Indoor PM_{10} exposure during pregnancy was associated with decreased neurodevelopment at 2 years old in the Drakenstein Child Health Study, the cohort studied in this dissertation[34]. Additional studies have also found associations between prenatal and early life exposure to outdoor or ambient PM_{10} and neurodevelopment[35–37]. A systematic review into outdoor PM_{10} exposure during pregnancy and psychopathology like autism spectrum disorder (ASD) or

attention deficit and hyperactivity disorder (ADHD) have shown mixed results, though this may be due to differential exposure and outcome assessment methods[38]. A study from the United States found no association between outdoor PM_{10} exposure during pregnancy and early life and childhood behavior checklist (CBCL) scores[39].

Nitrogen Dioxide (NO_2)

Nitrogen Dioxide (NO_2) is a by-product of combustion, indoor sources include gas and kerosene cooking and heating. Infiltration by outdoor sources can also increase indoor air pollution[26]. Exposure to NO_2 during pregnancy can increase inflammation and oxidative stress, and disrupt the blood brain barrier, causing damage to the brain. These neurotoxic effects of NO_2 exposure can affect child psychopathology[40].

Few epidemiologic studies have assessed the effects of prenatal or early life exposure to NO_2 on child psychopathology, and none assess indoor exposure. One study from Japan measured outdoor levels of NO_2 during pregnancy found an association between NO_2 level and aspects of the Childhood Behavior Checklist (Japanese Edition) (CBCL) at 8 years old[41]. A Chinese study, found outdoor NO_2 concentrations in the first trimester were significantly associated with increased total difficulties at 3-4 years old measured by the Strengths and Difficulties questionnaire (SDQ)[42]. Furthermore, a Spanish study found pre- and postnatal exposure to outdoor NO_2 negatively affected attention function at 4-5 years old[43]. Another study, from Taiwan, found a significant association between outdoor NO_2 levels in early childhood and Autism Spectrum Disorder (ASD) diagnosis[44].

Sulfur Dioxide (SO_2)

Sulfur Dioxide (SO_2) is a product of combustion from sulfur containing fuels including diesel, kerosene, and coal. Indoor sources include cooking and heating appliances using sulfur containing fuels, as well as infiltration from outdoor sources like diesel exhaust[26]. To assess neurotoxicity of SO_2, an animal study found chronic exposure in rats reduced neurological

functioning and increase inflammatory cytokines. Indicating long term exposure to SO_2 can produce neurobiological changes[45].

Similar to NO_2, few epidemiologic studies have evaluated the behavioral cognitive effects of prenatal or early life exposure to SO_2. The Chinese study mentioned above[42] also estimated the effect of outdoor SO_2 during pregnancy on SDQ scores, they found a significant association between SO_2 exposure in the first trimester and total difficulties[42]. A Taiwanese study found early childhood exposure to SO_2 increased risk of ASD diagnosis[44].

Volatile Organic Compounds (VOCs)

Volatile organic compounds (VOCs) are emitted from sources through combustion and evaporation. Indoor sources of VOCs include cigarette smoking, solvents, home renovation materials, household products, and pesticides. VOCs typically found in homes includes benzene, toluene, ethylbenzene, and xylenes[26]. An animal study evaluating the neurotoxic mechanisms of VOCs, including benzene, toluene, and xylene, found mice exposed to low-doses of the VOC mixture had impaired learning and memory capacity. Additionally, they found VOC exposed mice had increased levels of reactive oxygen species (ROS)[46].

Very few epidemiologic studies have investigated VOC exposure and neurodevelopment or cognitive outcomes. As of this review, there are no epidemiologic studies estimating the effect of prenatal exposure to VOCs and neurocognitive outcomes. A Japanese study evaluating the effect of early childhood exposure to VOCs on neurodevelopment found exposure to m,p-xylene and o-xylene at 3 years old was associated with reduced score on the Ages and Stages Questionnaire[47].

Maternal Psychosocial Factors

Exposure to psychosocial factors during pregnancy also affects child behavioral development and psychopathology. Animal studies have shown prenatal stress affects behavior in rats [48–50],

and there is growing epidemiological evidence for prenatal psychosocial stress' effects on child cognitive development[51]. Stressful life events during pregnancy, family income below poverty line, and mother not finishing high school were associated with increased CBCL t-scores from age 2-14 years. Adverse prenatal environment was associated with increased levels of behavior problems in childhood and problematic mental health trajectories[52,53]. Mood and anxiety disorders during pregnancy are the most common health conditions suffered by women of reproductive age[54]. Research from primarily high income countries indicates that between 10-20% of pregnant women experience a diagnosed mental disorder (e.g. anxiety, depression) during their pregnancy[55,56], and the prevalence of undiagnosed mental disorders is likely much higher. Additionally, in LMICs, where little research is done on psychosocial stress, prevalence of depression and exposure to violence is even higher[57]. Prevention of psychosocial stress through clinical interventions and social support could not only prevent and reduce morbidity of maternal stress, but also reduce the downstream effects on child psychopathology.

In this dissertation, psychosocial factors were evaluated using multiple measures from the following domains; threat and trauma, deprivation, substance use and abuse, and psychological distress and psychiatric disorders.

Deprivation

Stress from deprivation can come from food insecurity, material deprivation, lack of adequate housing, or low socioeconomic status (SES). A meta-analysis of studies in the United States found aspects of SES including low family income, low subjective SES, low parental education, poverty status, and receipt of public assistance were associated with childhood psychopathology. Researchers also found that SES was more strongly associated with externalizing behaviors than internalizing behaviors[58].

Threat and Trauma

Stress from threat and trauma can come from intimate partner (IPV) or domestic violence (DV), including physical violence, emotional violence, and sexual violence. In 2011, violence against women was declared an urgent public health priority by the WHO[59]. A systematic review found mixed results in studies assessing the effect or prenatal exposure to IPV and DV on child neurodevelopment, though seven of eleven studies found an association. This limited number of studies indicates a need for further research[59].

Stressful life events such as divorce and death or sickness of family members are also a source of stress and trauma. Few studies have examined stressful life events in relation to child neurodevelopment and psychopathology. One study from 1990 found mothers of children with ASD had experienced more family discord than mothers of children without ASD[60]. A more recent study found stressful events during pregnancy was associated with both ADHD and ASD behaviors as measured by the CBCL[61]. A study from the Drakenstein Child Health Study in South Africa found that maternal PTSD was associated with poorer fine motor development and adaptive behavior in children[62].

Substance Use and Abuse

Alcohol and tobacco use during pregnancy have been well known to cause neurological deficits in offspring and are a major reason for campaigns against prenatal use of tobacco and alcohol. Alcohol is a known teratogen that disrupts fetal development. Fetal alcohol spectrum disorder (FASD) has a wide range of both physical and neurological symptoms including, growth deficiency, abnormal brain growth, and cognitive and behavioral impairments[63]. Tobacco use during pregnancy is well known to be associated with decreased neurodevelopment and child behavior problems, and cigarettes are the most commonly used substance during pregnancy[64]. Prenatal tobacco exposure has been seen to affect inattention, oppositional behavior, emotional

instability, and physical aggression[64]. In a previous study done in the Drakenstein Child Heath Study prenatal tobacco use was associated with decreased adaptive behavior[34].

Psychological Distress and Psychiatric Disorders

Maternal depression is a global public health concern and rates of depression have been found to be up to 74% in LMICs. The relationship between maternal depression and child psychopathology has been well established, and maternal depression is a distinct early life stress for the child that shapes the child's stress response[65]. Results from a birth cohort measuring the effects of depression in mothers on immune markers and child psychopathology found that children of depressed mothers exhibited higher immune markers and greater social withdrawal. They also found that depressed mothers had higher cortisol and immune makers, and displayed more negative parenting behaviors[65]. A Spanish study found mothers with a mental disorder had higher odds of offspring presenting with a mental disorder than mothers without a mental disorder[66].

Joint Effects of Air Pollution and stress

Environmental and social exposures co-occur, but are often researched separately. The NIEHS designated investigating environmental mixtures a priority[17], this idea must extend to social factors as well. Synergistic effects of environmental and social factors are probable, and have been demonstrated in previous research[67]. It is important to investigate joint and potentially synergistic effects of exposures because it will identify especially vulnerable subgroups, in which the disease burden is likely to be larger than in the general population. As discussed above, both indoor air pollution and psychosocial factors are risk factors for child psychopathology. In one previous study, prenatal exposure to polyaromatic hydrocarbons increased the effect of exposure to psychosocial stress on CBCL score [13]. Synergy is probable because air pollutants and stress act on the brain in similar mechanisms through inflammation [27,68].

Biological Pathways and Inflammation

Understanding the mechanism through which exposure to air pollutants and psychosocial stress during pregnancy affects child psychopathology is important to determine causality. Thus far, most studies exploring the mechanism between air pollution, stress, and psychopathology have been done in animal models. It is important to extend the knowledge we learn from animal studies to human studies. Using causal mediation techniques on prospective human cohorts can help us understand these biological mechanisms in humans.

As previously discussed, alcohol and tobacco are well known to cause neurological deficits in offspring. Alcohol is a known teratogen, and crosses through the placenta to disrupt formation of the CNS in the fetus[69]. There are several proposed mechanisms of alcohol teratogenicity, one mechanism proposes alcohol consumption can generate free radicals as by-products of CYP2E1 metabolism. The free radicals target polyunsaturated fatty acids side chains in brain tissue membranes, causing fetal brain tissue damage during organogenesis which manifests as CNS dysfunction in the offspring after delivery[69]. Nicotine is also a known teratogen, though a mechanism remains unclear[64].

It is hypothesized that air pollution affects the central nervous system (CNS) through mechanisms of neuroinflammation and oxidative stress[8,16,27,70,71]. Animal models show air pollutants cause a systemic inflammatory response, including inside the brain. Both the physical air pollutant particle, and the toxic components absorbed on the particle can create an inflammatory response. Translocation of air pollutant nanoparticles from the lungs and nasal pathways to other areas of the body cause damage to the body and brain. Microglia respond to this damage by releasing inflammatory cytokines like TNF-α, IL-1β, and IL-6, and reactive oxygen species (ROS). Chronic activation of the microglia and over production of inflammatory markers and ROS can cause neuronal cell death[27].

It is hypothesized that inflammation may also play a role in how stress impacts the CNS[68,71,72]. Early life stress has been associated with chronic peripheral inflammation in both cross-sectional and longitudinal studies[16]. A meta-analysis found low SES is associated with higher levels of systemic inflammation, including higher levels of interlukin-6 (IL-6), which is also associated with neuroinflammation[73]. Inflammatory response from the microglia during gestation and early life periods can affect brain development through microglial involvement in pruning and shaping of the neuronal synapses[68,71]. This inflammatory pathway is one potential biological mechanism that is common between social and environmental factors, which is why we focus on it in this dissertation. Psychosocial exposures may impact child mental health through additional pathways such as parent-child attachment.

Critical Periods of Exposure

It is important to examine sensitive time windows of exposure, like gestation and early life. Pregnancy and early life are critical periods of brain development. The CNS begins to develop as early as the first month of gestation[74]. Throughout pregnancy, processes such as proliferation, differentiation, migration, synaptogenesis, apoptosis, and myelination create the brain. After birth, postnatal synaptogenesis, apoptosis, and neuronal pruning further shape the neuronal synapses. Disruption or dysregulation of these processes can lead to functional abnormalities which can lead to psychopathology[32].

During the 2nd and 3rd week of gestation folding and fusion of the ectoderm begins to create the neural tube. By week 5 neuronal proliferation begins and neuroblasts are rapidly reproducing within the ventricular zone. Around week 8 the neuroblasts begin to differentiate into specific neuronal cell types or macroglia. Neuronal migration begins by week 12 and peaks between week 12 and 20, completing by weeks 26-29[75]. The number of neurons peaks around week 28 and apoptosis culls excess neurons starting by week 18. During this time, synaptogenesis is also occurring. In the 3rd trimester, around week 34, there is a period of peak synaptogenesis

which continues into early postnatal life. During this peak almost 40,000 new synapses are formed every second[75]. Myelination of neurons begins around week 29, and by week 40 almost 5% of white matter is myelinated. During this time disruptions of myelination from environmental toxins, drugs, nutritional deficiencies, and preterm birth are thought to predispose infants to poor cognitive and neuropsychiatric outcomes[75].

In the postnatal period, the infant brain is around 36% of the size of an adult brain by week 2-4. Neuronal migration, synaptogenesis, and apoptosis are still occurring during this period. Expansion of glia and myelination are responsible for the bulk of brain growth in newborns and toddlers[75]. By 1 year old the brain will be about 70% of its adult size. Synaptic pruning through apoptosis is an important part of postnatal brain development. Synaptic density peaks between 4-12 months, at 140-150% of adult density[75]. Pruning begins in late gestation and increases postnatally[75].

Data Source

This research will leverage existing data from the Drakenstein Child Health Study (DCHS), a unique multidisciplinary birth cohort based in South Africa. Pregnant women (N=1,141) were recruited from 2012-2015, follow-up with mother-child pairs has been conducted at least annually thereafter. Exposure data on social and environmental risk factors were collected during the 2nd trimester and postnatally in the early life of the child [57,76,77] . Childhood psychopathology was measured using the Child Behavior Checklist (CBCL) at 2, 3.5, 5, and 6.5 years old. Data access was approved for this project by DCHS PIs Dr. Heather Zar and Dr. Dan Stein.

Chapter 2 : Joint Effects of Indoor Air Pollution and Maternal Psychosocial Factors During Pregnancy on Trajectories of Early Childhood Psychopathology

This chapter addresses specific aim 1, assessing joint effects of air pollution and psychosocial factors on early-life trajectories of psychopathology. The version of the manuscript presented in this dissertation is currently under review at the *American Journal of Epidemiology*.

Abstract

Background: Prenatal indoor air pollution and maternal psychosocial factors have been associated with adverse psychopathology. We used environmental exposure mixture methodology to investigate joint effects of both exposure classes on child behavior trajectories.

Methods: For 360 children from the South African Drakenstein Child Health Study, we created trajectories of Child Behavior Checklist scores (24, 42, 60 months) using latent class linear mixed effects models. Indoor air pollutants and psychosocial factors were measured during pregnancy (2nd trimester). After adjusting for confounding, single-exposure effects (per natural log-1 unit increase) were assessed using polytomous logistic regression models; joint effects using self-organizing maps (SOM), and principal component (PC) analysis.

Results: Three externalizing trajectories were chosen for both internalizing and externalizing problems, and can be categorized as ‘high’, ‘medium’, and ‘low’ problems. High externalizing trajectory was associated with increased particulate matter (PM10) exposure (OR [95%-CI]: 1.25 [1.01,1.55]) and SOM exposure profile most associated with smoking (2.67 [1.14,6.27]). Medium internalizing trajectory was associated with increased emotional intimate partner violence (2.66 [1.17,5.57]), increasing trajectory with increased benzene (1.24 [1.02,1.51]) and toluene (1.21 [1.02,1.44]) and the PC most correlated with benzene and toluene (1.25 [1.02, 1.54]).

Conclusions: Prenatal exposure to environmental pollutants and psychosocial factors was associated with internalizing and externalizing child behavior trajectories. Understanding joint effects of adverse exposure mixtures will facilitate targeted interventions to prevent childhood psychopathology.

Introduction

Childhood psychopathology, including emotional and behavioral problems, affect parents, teachers, and most importantly the child, and can persist into adulthood[1]. Experiencing mental health problems before age 14 is associated with increased risk of adult psychopathology. Psychopathology is characteristically split into two categories of disorders, internalizing and externalizing. Externalizing behaviors reflect the behavior towards the environment, whereas internalizing behaviors are reflected inward. Externalizing conditions include attention-deficit/hyperactivity disorder (ADHD) and oppositional defiant, and internalizing conditions include anxiety and depression[20,21].

Pregnancy is a sensitive period of brain development, as the central nervous system begins to develop as early as the first month of gestation[74]. Investigating modifiable risk factors of childhood psychopathology during pregnancy has the potential to reduce the burden of mental health problems in both children and adults[18].

Indoor air pollution is a ubiquitous and well-known contributor to the global burden of disease [24,25]. Animal studies have shown exposure to air pollutants during pregnancy affects the central nervous system of the fetus and elements of behavior in adulthood[14,27]. Epidemiologic studies in humans have also shown that exposure to outdoor air pollutants during pregnancy and early life affects child psychopathology[3,13,28]. A Korean study found maternal smoking during pregnancy was associated with adverse Childhood Behavior Checklist (CBCL) total problems score at 5 years[2]. Additionally, indoor air pollutants from maternal cooking during pregnancy associated with hyperactive behaviors in children at 3 years old, though the study did not measure individual air pollutants, and instead used survey information on cooking fuel as a proxy measure[5].

Exposure to adverse psychosocial factors during pregnancy also negatively affects child development and mental health. Animal studies have shown prenatal stress affects behavior[48–50], and there is growing epidemiological evidence that prenatal psychosocial stressors are associated with impaired child cognitive development[51]. The Australian Raine study found stressful life events during pregnancy, family income below poverty line, and mother not finishing high school were associated with increased CBCL t-scores from age 2-14 years[52]. Additionally, stressful events during pregnancy, including death of a relative, and financial problems, was associated with increased levels of behavior problems in childhood and problematic mental health trajectories in the Raine study[52,53].

Childhood psychopathology can be impacted by both psychosocial and environmental factors, and joint effects of these exposures are poorly understood[78], as they are usually researched separately. Joint effects of environmental and psychosocial factors are probable, and have been demonstrated in previous research on birth outcomes like birthweight and gestational age[67,78–80]. It is important to investigate joint effects of environmental and psychosocial factors because it may help to identify especially vulnerable subgroups, in which the disease burden is likely to be larger than in the general population. So far, very few studies have investigated joint effects of air pollution and psychosocial factors on childhood psychopathology. One epidemiologic study conducted in New York City, USA, found that prenatal exposure to polyaromatic hydrocarbons increased the effect of exposure to psychosocial stress on CBCL score in school-age children [13]. Another study, conducted in Boston, USA, found Black Carbon exposure during pregnancy was significantly associated with lower attention concentration index scores in boys with high exposure to prenatal stress[81]. However, both of these studies only used one air pollutant and one psychosocial factor when investigating joint effects of air pollution and psychosocial stress on child psychology instead of an exposure mixture. This does not reflect real life exposure as

people are exposed to many pollutants and psychosocial factors at the same time[78]. Additionally, both of these studies were conducted in the USA, a high-income country.

A majority of research on childhood psychopathology is conducted in high income countries, yet almost 80% of children live in low to middle income countries[22]. Indoor air pollution is an important source of air pollution in low to middle income countries, where many homes rely on alternate fuel sources for household energy and particularly affects women who through traditional gender norms generally spend more time indoors and are more involved in food preparation and cooking[24,29]. Additionally, in lot to middle income countries, prevalence of perinatal depression and exposure to violence is even higher than in high income countires[57]. Therefore, pregnant women in low to middle income countries may be uniquely susceptible to the joint effects of indoor air pollution and psychosocial factors.

We aim to investigate the individual and joint effects of prenatal exposure to indoor air pollution and maternal psychosocial factors on trajectories of psychopathology in early childhood in a South African birth cohort. This study uses traditional single-exposure polytomous logistic regression modeling to investigate the effects of indoor air pollutants and psychosocial factors during pregnancy individually, as well as exposure mixture methods, such as self-organizing maps, principal components analysis, and quantile g-computation to investigate joint effects of exposures.

Methods

Data Source

This study uses data from a subset of participants enrolled in the Drakenstein Child Health Study (DCHS), a multi-disciplinary population-based pregnancy cohort based in South Africa. Pregnant women were recruited in their 2nd trimester of pregnancy from 2012-2015, follow-up with mother-child pairs has been conducted annually thereafter. Pregnant women seeking care

at two public sector primary healthcare clinics, who were at least 18 years of age, were within 20-28 weeks gestation, and had no intention of moving away from the district were eligible for enrollment. Recruitment for DCHS has been described elsewhere[57,82]. The full cohort includes N=1,141 mother-child pairs, among which a subset (n=819) were selected for indoor air pollution measurement. Mother-child pairs with indoor air pollution measurements, and complete child behavior checklist measurements at 24, 42, and 60 months of age were included in this analysis (n=360). The DCHS was approved by the Human Research Ethics Committee of the Faculty of Health Sciences, University of Cape Town, by Stellenbosch University and the Western Cape Provincial Research committee. Written informed consent was provided by the mothers for herself and her child and is renewed annually.

Indoor Air Pollution Assessment

Indoor air pollution measurements were taken during participants' 2nd trimester of pregnancy. Pollutants measured include particulate matter <10 microns in diameter (PM_{10}), carbon monoxide (CO), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and Volatile Organic Compounds (VOCs) benzene and toluene. Particulate Matter (PM_{10}) was collected over 24 hours with a personal air sampling pump (SKC AirChek 52®), using a gravimetrically pre-weighted filter. Carbon monoxide (CO) was collected over 24 hours using an Altair® carbon monoxide single gas detection unit, electrochemical sensor detection of gas at 10-minute intervals were collected. Sulphur dioxide (SO_2) and nitrogen dioxide (NO_2) were collected over 2 weeks using Radiello® absorbent filters in polyethylene diffusive body. Volatile organic compounds, including benzene and toluene, were collected over 2 weeks using Markes® thermal desorption tubes[83]. Information on type of home, distance from major road, size of home, number of inhabitants, access to basic amenities, fuels used for cooking and heating, ventilation within homes, and pesticides and cleaning materials used in the home was collected at home visits[83].

Assessment of Psychosocial Factors

Psychosocial factors were collected via questionnaire in the 2nd trimester of pregnancy and included multiple dimensions of psychosocial stress. Employment, education, household income, household assets, marital status, number of dependents, and financial activities were included as indicators of socioeconomic status. Perceived household food insecurity was assessed using an adapted version of the USDA Household Food Security Scale[84]. Intimate partner violence was assessed using the IPV Questionnaire adapted from the WHO multi-country study and the Women's Health Study in Zimbabwe[85,86]. The IPV questionnaire assesses lifetime and recent (past year) exposure to emotional, physical, and sexual violence. The World Mental Health Life Events Questionnaire (LEQ) was used to measure trauma and resilience. Use of alcohol and tobacco were assessed using the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST). Additionally, tobacco smoke exposure was assessed via urinary cotinine and questionnaire. The Self Reporting Questionnaire (SRQ-20), a measure endorsed by the WHO, was used to measure psychological distress[87,88]. The Edinburgh Postnatal Depression Scale (EPDS) was used to measure depressive symptoms[89].

Outcome Assessment

Parent-reported child psychopathology was assessed using the pre-school version of the Child Behavior Checklist (CBCL) administered at 24, 42, and 60 months old[90]. Child behavior was assessed using a 3-point Likert scale (0 = not true; 2 = often or very true) to create a score, consisting of 113 questions, which can be divided into internalizing and externalizing sub scores. The internalizing scale combines the scores from the anxious/depressed, withdrawn/depressed, and somatic complaints syndromic scales. The externalizing scale combines the rule-breaking and aggressive behavior syndromic scales[90]. Higher CBCL scores indicate increased problematic behavior, indicative of child psychopathology. CBCL scores

show good associations with psychopathology diagnoses from the DSM-5 including, anxiety, oppositional defiant disorder, attention deficit/hyperactivity disorder, among others[91]. Standardized CBCL scores, or T-scores, for externalizing and internalizing behavior were used as outcomes in our analyses.

Statistical Analysis

Multiple imputation of missing values

While there were no missing values in any of the outcome variables or covariates in our final analysis sample, some participants are missing indoor air pollution or psychosocial measurements **(Table 2-1)**. We assume these missing exposure variables are missing at random based on inspections of missingness patterns **(Figure 2-1)**. To increase the sample size, we used multiple imputation to impute these missing exposure values. Using the R package *Hmisc*, indoor air pollution and psychosocial factor variables were imputed using predictive mean matching, with models that include indoor air pollutants, house characteristics, and psychosocial factor measures. Five seed numbers were created using a random number generator, each seed resulted in its own set of multiple imputed variables. One imputed set, from the 5 sets, from each seed was randomly chosen to use for analyses. The seed with the highest R^2 values, a measure used to explain how well the missing variable was predicted, was selected for primary analysis. R^2 values for each multiple imputed exposure variable differed between seeds. Analyses using complete cases and the other imputation seeds were conducted as a sensitivity analysis.

***Table 2-1**: Proportion of missing prenatal exposure data in analysis sample.*

Exposure	# missing	% missing	n	total N*
PM_{10}	38	11%	322	360
CO	74	21%	286	360
benzene	49	14%	311	360
toluene	49	14%	311	360
NO_2	43	12%	317	360
SO_2	43	12%	317	360
maternal smoking (cotinine)	10	3%	350	360
food insecurity	29	8%	331	360
SRQ	45	13%	315	360
IPV - emotional	44	12%	316	360
IPV - physical	44	12%	316	360
IPV - sexual	44	12%	316	360
LEQ	52	14%	308	360
EPDS	44	12%	316	360
ASSIST - tobacco	49	14%	311	360
ASSIST - alcohol	49	14%	311	360
SES assets	0	0%	360	360

Abbreviations: Particulate Matter (PM10); Carbon monoxide (CO); Nitrogen dioxide (NO2); Sulfur dioxide (SO2); Socioeconomic Status (SES); Self-Reporting Questionnaire (SRQ-20); Edinburgh Postnatal Depression Scale (EPDS); Life Experiences Questionnaire (LEQ); Intimate Partner Violence (IPV); Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST)

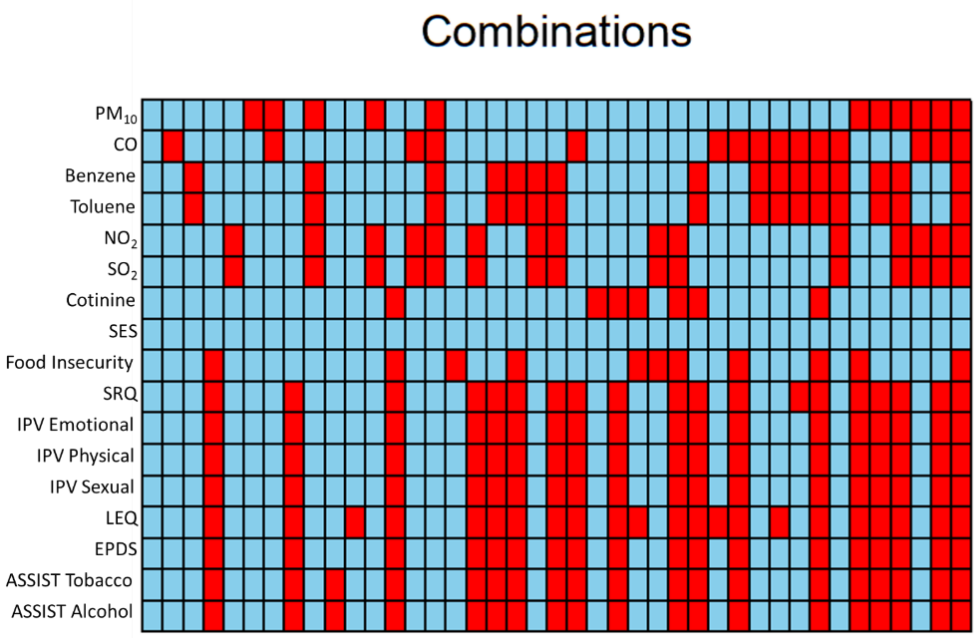


Figure 2-1: *Combinations of missingness patterns of exposure variables. Each row is a missingness pattern where red indicates that variable is missing, and blue indicates not missing.*

Assessment of CBCL Trajectories

The outcome used in this study was trajectory of CBCL score from 24, 42, and 60 months old children. Participants with CBCL measurements at all time points (n=360) were included. Trajectories were created using Latent Class Linear Mixed Effects Models (LCMM). LCMM models for log-transformed CBCL t-scores were used to create latent classes, using child sex as a fixed effect covariate and age in months at CBCL measurement as a random effect covariate. Using the R package *lcmm*, LCMM defines a number of 'typical' trajectories of CBCL scores, which then were assigned to participants and used as the outcome in the subsequent polytomous logistic regression analyses (described below)[92]. One to five latent classes were evaluated in LCMM models, the final model was selected based on measures of model fit such as Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), sample-size-adjusted BIC (SABIC), and entropy **(Table 2-2)**. Trajectories for CBCL externalizing and internalizing sub scales were created.

Table 2-2: *Latent Class Mixed Effects Models (LCMM) model comparison statistics used to determine number of classes used in analysis. Bolded models were used in exposure-outcome analyses.*

Model Type	G	AIC	BIC	SABIC	entropy	% class1	% class2	% class3	% class4	% class5
Externalizing Problems										
-	1	-45.14	17.08	-33.68	1.00	100.00				
A	2	-50.47	31.20	-35.43	0.56	44.04	55.96			
B	2	-59.27	18.51	-44.94	0.61	48.20	51.80			
C	2	-57.78	23.88	-42.74	0.61	52.63	47.37			
A	3	-79.80	21.31	-61.18	0.82	26.04	52.08	21.88		
B	3	-79.80	21.31	-61.18	0.82	52.08	26.04	21.88		
C	**3**	**-94.63**	**6.48**	**-76.00**	**0.85**	**48.48**	**22.71**	**28.81**		
A	4	-69.81	50.75	-47.60	0.86	51.80	26.04	22.16	0.00	
B	4	-95.08	25.48	-72.87	0.85	39.34	11.63	23.27	25.76	
C	4	-96.11	24.45	-73.90	0.80	28.25	23.27	26.87	21.61	
A	5	-104.14	35.86	-78.35	0.83	24.65	27.70	14.40	23.55	9.70
B	5	-104.14	35.86	-78.35	0.83	9.70	23.55	24.65	27.70	14.40
C	5	-127.27	12.72	-101.49	0.87	8.03	21.05	21.05	28.81	21.05
Internalizing Problems										
-	1	175.18	237.40	186.64	1.00	100.00				
A	2	120.85	202.51	135.89	0.77	61.22	38.78			
B	2	142.62	224.28	157.66	0.72	54.02	45.98			
C	2	120.84	202.51	135.89	0.77	38.78	61.22			
A	3	87.92	189.03	106.54	0.84	24.65	31.30	44.04		
B	3	87.60	188.71	106.23	0.82	24.65	31.58	43.77		
C	**3**	**87.60**	**188.71**	**106.23**	**0.82**	**24.65**	**43.77**	**31.58**		
A	4	79.24	199.80	101.45	0.83	35.73	24.93	19.39	19.94	
B	4	84.57	205.13	106.78	0.73	32.41	25.21	29.64	12.74	
C	4	79.24	199.80	101.45	0.83	19.39	19.94	24.93	35.73	
A	5	107.92	247.92	133.70	0.89	0.00	31.30	44.04	24.65	0.00
B	5	83.40	223.40	109.18	0.76	24.65	26.59	9.97	19.11	19.67
C	5	69.52	209.52	95.30	0.79	11.08	27.98	20.78	22.99	17.17

Model Type A: Initial value generated from maximum likelihood estimates of a G=1 model; B: Initial value generated randomly from the asymptotic distribution of the estimates of the G=1 model; C: Initial value is found by a grid search run from 30 iterations from 100 random vectors. Abbreviations: Number of classes (G), Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), sample-size-adjusted BIC (SABIC), Percentage of participants in class (%class).

Single-exposure models

Adjusted polytomous logistic regression models were used to estimate single air pollutant and psychosocial factor effects on CBCL trajectory. Confounding was assessed using directed acyclic graphs (DAGs) informed by prior research and literature reviews **(Figure 2-3)**. To control for confounding, each model was adjusted for maternal age at baseline, maternal HIV status, child ancestry, and socioeconomic status (when not used as the exposure of interest). In individual models, all exposures were natural log-transformed for modeling. To account for confounding by psychosocial factors, models with indoor air pollutants as the main exposure were additionally adjusted for psychosocial factors, and vice versa. The model estimating the effect of socioeconomic status was adjusted air pollution exposures. To avoid oversaturation of the linear regression models, and as the exposures within each exposure group (air pollution exposure and psychosocial factors) were highly correlated, the first principal components of each group were used as confounders instead of the original variables. To create these principal components, we conducted a principal component analysis (PCA) for each exposure group separately (more details can be found in the supplementary methods). In a sensitivity analysis to account for seasonality of indoor air pollution measurement, we adjusted the air pollution exposure models for season of indoor air pollution measurement along with previously mentioned confounders.

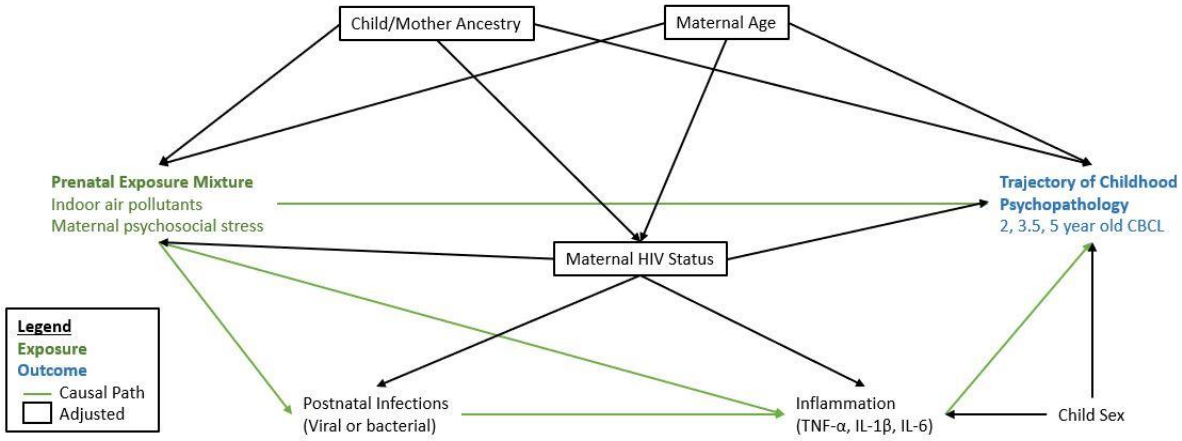


***Figure 2-2:**. DAG of underlying causal pathways between prenatal exposure to indoor air pollutants and psychosocial factors including socioeconomic status, and trajectories of childhood psychopathology.*

Joint effects models

We used two complementary mixture methods to examine joint effects of indoor air pollution and psychosocial factors: PCA and self-organizing maps (SOM). While PCA was not developed as an exposure mixture method, using the first few PCs explains a percentage of the total variance in the data using a smaller number of variables. In addition, PCs are continuous, orthogonal and uncorrelated, which can increase the statistical power to detect associations in comparison to categorical variables. PCs were calculated based on centered and scaled indoor air pollution and psychosocial exposure variables. PCs of the exposure mixture (combination of indoor air pollution and psychosocial exposure variables) were created and added as exposure variables to the polytomous logistic regression model to investigate the joint effect of indoor air pollution and psychosocial factors on CBCL trajectories. The number of PCs added to the model was determined by proportion of variance contributed as seen in an 'elbow plot' **(Figure 2-4)**, resulting in five PCs that explained 55% of the total variance. Polytomous logistic regression models were adjusted for maternal age at baseline, maternal HIV status, and child ancestry.

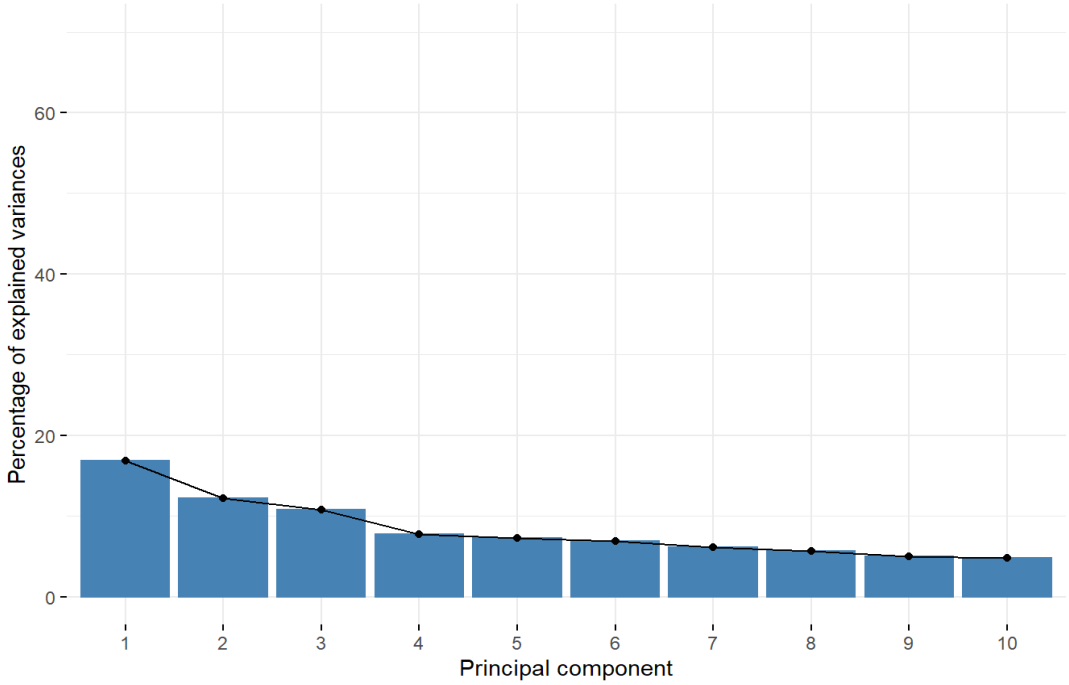


Figure 2-3: *Scree (elbow) plot describing the proportion of variance explained by each principal component analysis of indoor air pollutant and psychosocial factor exposures.*

SOM was used to examine the effects of certain exposure profiles on CBCL trajectory. The SOM algorithm identifies exposure cluster profiles with exposure levels homogenous within the cluster and heterogeneous between clusters. The advantage of SOM over PCA is interpretability of the exposure profile clusters. However, with smaller sample sizes there can be low numbers of participants in some clusters. The number of clusters chosen for analyses was based on multiple statistical measures identifying group structure, including AIC, and adjusted R^2, as well as visual inspection of the clusters for interpretability and suitable number of participants in each cluster, resulting in four SOM clusters to represent prenatal exposure profiles. Indoor air pollution and psychosocial factor variables were centered and scaled before running the SOM clustering algorithm. The effect of these exposure clusters on CBCL trajectory was assessed using adjusted polytomous logistic regression. Adjusted models were adjusted for maternal age, maternal HIV status, and child ancestry. We used the SOM R package as implemented in https://github.com/johnlpearce/ECM.

Finally, we used quantile g-computation to estimate the overall effect of our exposure mixture on a dichotomized version of the CBCL trajectories[93]. Quantile g-computation cannot analyze a 3-level outcome variable, so high and medium trajectories were combined and contrasted with low trajectories. Using the *qgcomp* R package, an overall mixture effect and partial effect contributions from each exposure were calculated for high/medium vs low CBCL trajectory adjusted for maternal age, maternal HIV status, and ancestry. The adjusted model was fit using binomial regression and fitted for 10 deciles of exposure and 200 bootstrapped samples. All analyses were performed using R version 3.6.1 (R Core Team, Vienna, Austria).

Results

Study Population

The final sample for this analysis consisted of 360 mother-child pairs. The mean maternal age during pregnancy was 26.9 (SD = 5.6) years. Nearly a quarter of mothers (n=78; 21.7%) were HIV positive at baseline. Half of the children were male (n=190; 52.8%). In this sample 50.3% (n=181) of mothers identified their children as having mixed ancestry, the other half identified as having black African ancestry (n=179; 49.7%) **(Table 2-3)**. **Table 2-4** compares demographic and exposure characteristics in the full cohort, the indoor air pollution subsample, and the analysis sample. Demographic characteristics and psychosocial factor scores are similar across samples. Indoor air pollutant exposure concentrations in the analysis sample are slightly lower than in the full cohort, except for PM_{10} (analysis sample median: 41.46 µg/m^3 vs full cohort: 33.45 µg/m^3) and cotinine (analysis sample median: 61.34 ng/mL vs full cohort: 43.00 ng/mL) which are higher than in the full cohort.

***Table 2-3**: Drakenstein Child Health Study (DCHS) population characteristics.*

N	360
Maternal Age (mean (SD))	26.87 (5.61)
Male Child (%)	190 (52.8)
Child Ancestry (%)	
Black African	179 (4.97)
Mixed Ancestry	181 (50.3)
Mother HIV Positive (%)	78 (21.7)
CBCL Externalizing Trajectory (%)	
1 (Medium)	175 (48.6)
2 (Low)	80 (22.2)
3 (High)	105 (29.2)
CBCL Internalizing Trajectory (%)	
1 (Increasing)	89 (24.7)
2 (Decreasing)	158 (43.9)
3 (Medium)	113 (31.4)
PM10 µg/m3 (median [IQR])	40.72 [14.03, 69.07]
CO mg/m3 (median [IQR])	0.00 [0.00, 60.00]
Benzene µg/m3 (median [IQR])	3.28 [1.11, 8.63]
Toluene µg/m3 (median [IQR])	15.42 [5.93, 42.94]
NO2 µg/m3 (median [IQR])	5.90 [2.66, 11.14]
SO2 µg/m3 (median [IQR])	0.00 [0.00, 0.18]
Urine Cotinine ng/ml (median [IQR])	58.95 [13.67, 500.00]
SES Asset Sum (median [IQR])	7.00 [5.00, 8.00]
Food Insecurity Total Score (median [IQR])	0.00 [0.00, 2.00]
SRQ-20 Total Score (median [IQR])	4.00 [1.00, 7.00]
EPDS Total Score (median [IQR])	9.00 [6.00, 12.00]
LEQ Total Score (median [IQR])	1.00 [0.00, 3.00]
Emotional IPV Score (median [IQR])	5.00 [4.00, 7.00]
Physical IPV Score (median [IQR])	6.00 [5.00, 8.00]
ASSIST Tobacco Score (median [IQR])	0.00 [0.00, 18.00]
ASSIST Alcohol Score (median [IQR])	0.00 [0.00, 0.00]

Abbreviations: Human Immunodeficiency Virus (HIV); Childhood Behavior Checklist (CBCL); Particulate Matter (PM10); Carbon monoxide (CO); Nitrogen dioxide (NO2); Sulfur dioxide (SO2); Socioeconomic Status (SES); Self-Reporting Questionnaire (SRQ-20); Edinburgh Postnatal Depression Scale (EPDS); Life Experiences Questionnaire (LEQ); Intimate Partner Violence (IPV); Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST)

Table 2-4: *Comparison of demographic and exposure characteristics between the full DCHS cohort, the subsample with indoor air pollution measurements, and the analysis sample.*

	Full DCHS Cohort	IAP Subsample	Analysis Sample
n	1143	819	360
Maternal Age (mean (SD))	26.60 (5.68)	26.60 (5.67)	26.87 (5.61)
Male Child (%)	586 (51.3)	422 (51.5)	190 (52.8)
Mixed Ancestry (%)	510 (44.7)	379 (46.3)	181 (50.3)
Mother HIV Positive (%)	248 (21.7)	171 (20.9)	78 (21.7)
PM10 µg/m3 (median [IQR])	33.37 [12.49, 64.80]	33.45 [12.49, 65.43]	41.46 [14.42, 69.71]
CO mg/m3 (median [IQR])	0.00 [0.00, 102.50]	0.00 [0.00, 120.00]	0.00 [0.00, 0.00]
Benzene µg/m3 (median [IQR])	4.28 [1.75, 11.29]	4.34 [1.75, 11.50]	3.21 [1.05, 8.47]
Toluene µg/m3 (median [IQR])	16.79 [7.04, 44.24]	16.94 [7.09, 44.79]	15.51 [5.80, 44.47]
NO2 µg/m3 (median [IQR])	7.13 [3.33, 12.69]	7.19 [3.34, 12.70]	5.75 [2.63, 11.21]
SO2 µg/m3 (median [IQR])	0.00 [0.00, 0.28]	0.00 [0.00, 0.28]	0.00 [0.00, 0.17]
Urine Cotinine ng/ml (median [IQR])	43.00 [10.70, 500.00]	43.35 [10.70, 500.00]	61.35 [14.33, 500.00]
SES Asset Sum (median [IQR])	7.00 [5.00, 8.00]	7.00 [5.00, 8.00]	7.00 [5.00, 8.00]
Food Insecurity Total Score (median [IQR])	0.00 [0.00, 2.00]	0.00 [0.00, 2.00]	0.00 [0.00, 2.00]
SRQ-20 Total Score (median [IQR])	4.00 [1.00, 7.00]	4.00 [1.50, 7.00]	3.00 [1.00, 6.00]
EPDS Total Score (median [IQR])	9.00 [6.00, 12.00]	9.00 [6.00, 13.00]	9.00 [6.00, 12.00]
LEQ Total Score (median [IQR])	1.00 [0.00, 3.00]	1.00 [0.00, 3.00]	1.00 [0.00, 3.00]
Emotional IPV Score (median [IQR])	4.00 [4.00, 7.00]	5.00 [4.00, 7.00]	5.00 [4.00, 7.00]
Physical IPV Score (median [IQR])	5.00 [5.00, 7.00]	5.00 [5.00, 7.00]	6.00 [5.00, 8.00]
ASSIST Tobacco Score (median [IQR])	0.00 [0.00, 13.00]	0.00 [0.00, 14.00]	0.00 [0.00, 18.00]
ASSIST Alcohol Score (median [IQR])	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]

Abbreviations: Indoor Air Pollution (IAP); Human Immunodeficiency Virus (HIV); Particulate Matter (PM10); Carbon monoxide (CO); Nitrogen dioxide (NO2); Sulfur dioxide (SO2); Socioeconomic Status (SES); Self-Reporting Questionnaire (SRQ-20); Edinburgh Postnatal Depression Scale (EPDS); Life Experiences Questionnaire (LEQ); Intimate Partner Violence (IPV); Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST)

Trajectories

At each time period, CBCL internalizing and externalizing sub scores were highly correlated (24 months: Pearson r = 0.71; 42 months: r = 0.7; 60 months: r = 0.82; **Table 2-5**).

Table 2-5: *Pearson correlation coefficients among CBCL Total Problems, Externalizing Problems, and Internalizing Problems T-scores at each time point.*

	24 Months CBCL T-Score		
	Total Problems	Externalizing	Internalizing
Total Problems	1	0.91	0.90
Externalizing	0.91	1	0.71
Internalizing	0.90	0.71	1
	42 Months CBCL T-Score		
	Total Problems	Externalizing	Internalizing
Total Problems	1	0.92	0.86
Externalizing	0.92	1	0.70
Internalizing	0.86	0.70	1
	60 Months CBCL T-Score		
	Total Problems	Externalizing	Internalizing
Total Problems	1	0.93	0.93
Externalizing	0.93	1	0.82
Internalizing	0.93	0.82	1

Three trajectories were chosen for CBCL externalizing problems and internalizing problems **(Table 2-2)**. Trajectories for externalizing problems were categorized as ‘high’, ‘medium’, and ‘low’ trajectories, as they correspond to relatively high, medium, and low scores across time points **(Figure 2-5A, Table 2-6)**. Latent class 1, the ‘medium’ trajectory decreased slightly over time but scores were always between the ‘high’ and ‘low’ trajectory. Latent class 2 had the lowest CBCL externalizing scores over the study period. In contrast, latent class 3 always had the highest CBCL externalizing score over the study period. In all regression analyses the ‘low’ trajectory was used as the reference group.

Table 2-6: *Median (IQR) CBCL T-score at 24, 42, and 60 months for each CBCL trajectory.*

		Median (IQR) CBCL T- Score		
	N	24 Months	42 Months	60 Months
Externalizing Problems				
1 (Medium)	175	46.0 (15.0)	40.0 (6.0)	39.0 (12.0)
2 (Low)	80	43.0 (13.8)	28.0 (0.0)	38.0 (13.0)
3 (High)	105	50.0 (17.0)	55.0 (8.0)	43.0 (16.0)
Internalizing Problems				
1 (Increasing)	89	51.0 (17.0)	41.0 (16.0)	61.0 (7.0)
2 (Decreasing)	158	43.0 (20.0)	37.0 (12.00	29.0 (4.0)
3 (Medium)	113	47.0 (21.0)	37.0 (18.0)	43.0 (6.0)

CBCL internalizing problems score trajectories were categorized as, having ‘decreasing’, ‘medium’ and ‘increasing’ trajectories., For the internalizing problems scores, all three trajectories slightly decreased between 24 and 42 months and diverged from 42 to 60 months **(Figure 2-5B, Table 2-6)**. The CBCL internalizing problems trajectory shown in latent class 1 is characterized as having sharply increasing CBCL internalizing score after 42 months, this trajectory is described as the ‘increasing’ trajectory. In contrast, latent class 2 shows a decreasing trajectory over the time period and will be described as the ‘decreasing’ trajectory. Latent class 3 is stable over time and scores are between the increasing and decreasing trajectories, therefore will be described as the ‘medium’ trajectory. In all regression analyses the ‘decreasing’ trajectory was used as the reference group.

Single-exposure models

PM_{10} was associated with high externalizing problems trajectory (1.25; 1.01, 1.55) **(Figure 2-6A, Table 2-7)**. Benzene and toluene were associated with high internalizing problems trajectory (benzene: 1.24; 1.02, 1.51; Toluene: 1.21; 1.02, 1.44). Emotional intimate partner violence score was associated with higher odds of the medium internalizing trajectory (2.66; 1.27, 5.57) **(Figure 2-6B, Table 2-7)**.

Joint effects models

The five PCs selected to be included in joint effects modeling have differential loadings that represent directions of correlations in the data **(Figure 2-7)**. PC1 is explained by high positive correlation with adverse psychosocial factors such as cotinine level, intimate partner violence, and ASSIST tobacco and alcohol scores. PC2 is uncorrelated with psychosocial factors, and is characterized by increased indoor air pollution, particularly benzene and toluene. PC3 is negatively correlated with most adverse psychosocial factors, except for a positive correlation with smoking and alcohol. PC4 is characterized primarily by high CO and NO_2 and low SES. PC5 is characterized by low SES, high food insecurity and intimate partner violence. In adjusted polytomous logistic regression models using externalizing CBCL trajectory, PC1 was associated with both high (1.25; 1.02, 1.54) and medium (1.27; 1.04, 1.54) trajectories and PC3 was significantly associated with the medium (1.33; 1.04, 171) trajectory compared to the low trajectory. Both PC1 and 3 are explained by high cotinine level and high ASSIST Tobacco and Alcohol scores. The more robust association with PC1 reflects that externalizing CBCL trajectory is associated with both smoking related exposures and high psychosocial stressors **(Figure 2-7A, Table 2-8)**. Increasing internalizing CBCL trajectory was associated with PC2 (1.22; 1.02, 1.48), the PC mostly explained by high benzene and toluene levels in adjusted polytomous regression models **(Figure 2-7B, Table 2-8)**.

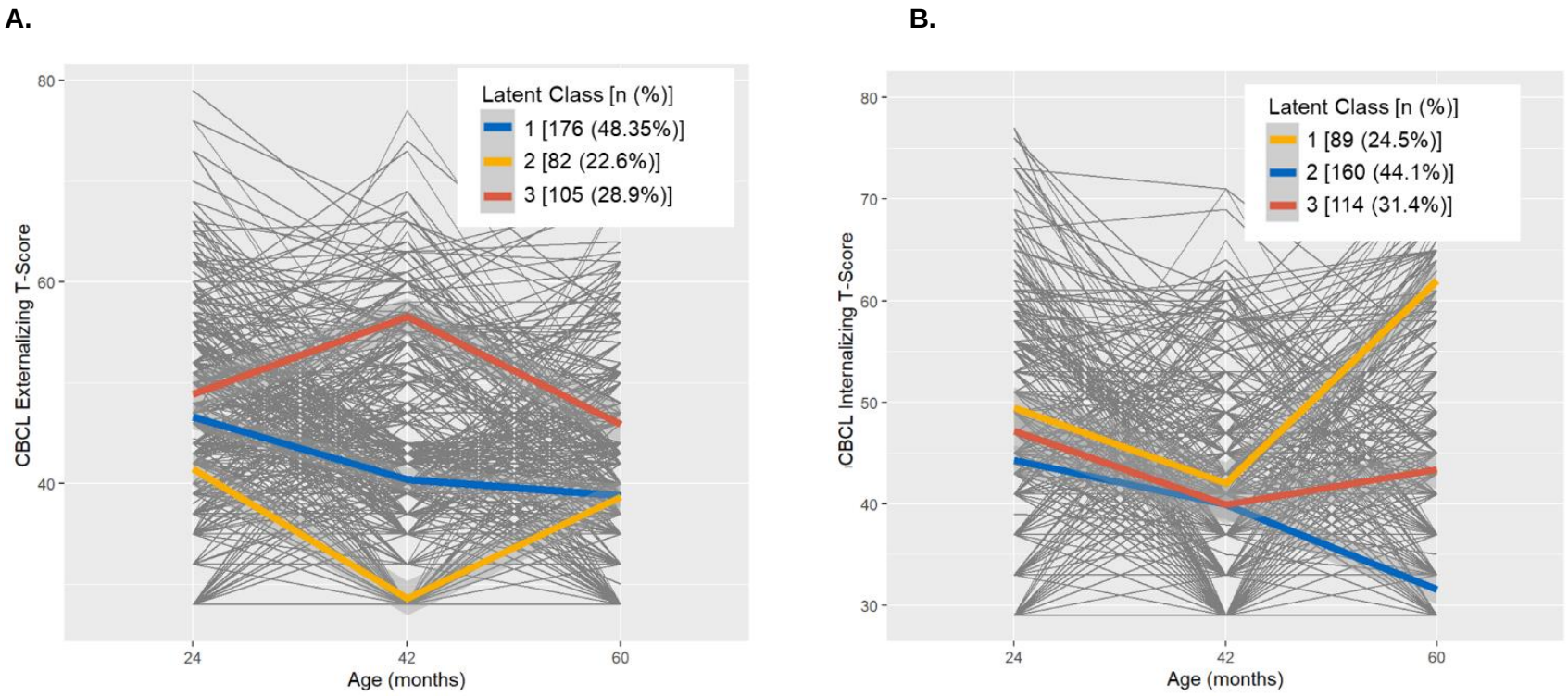
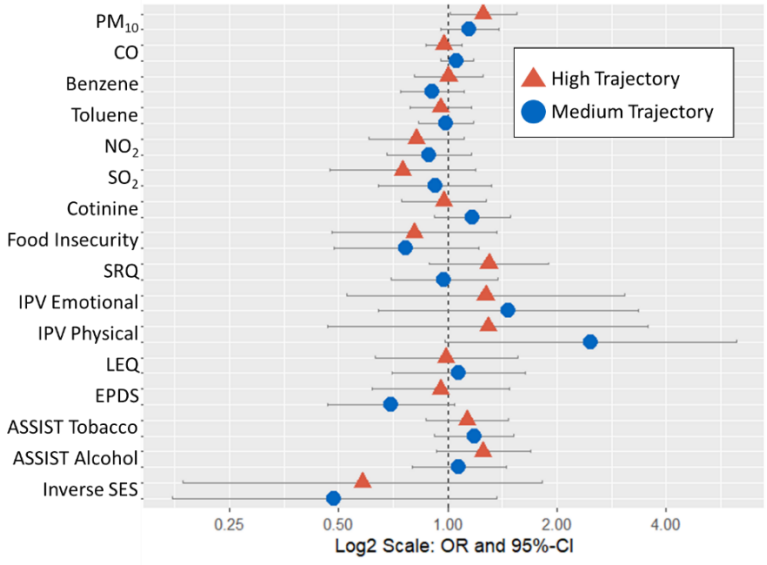


Figure 2-4: *Latent Class Mixed Model (LCMM) trajectories. Child Behavior Checklist (CBCL) T-score trajectories modeled using LCMM, adjusted for child sex and age in months at CBCL assessment in the DCHS.* ***A.*** *CBCL externalizing problems T-score.* ***B.*** *CBCL Internalizing problems T score.*

A.



B.

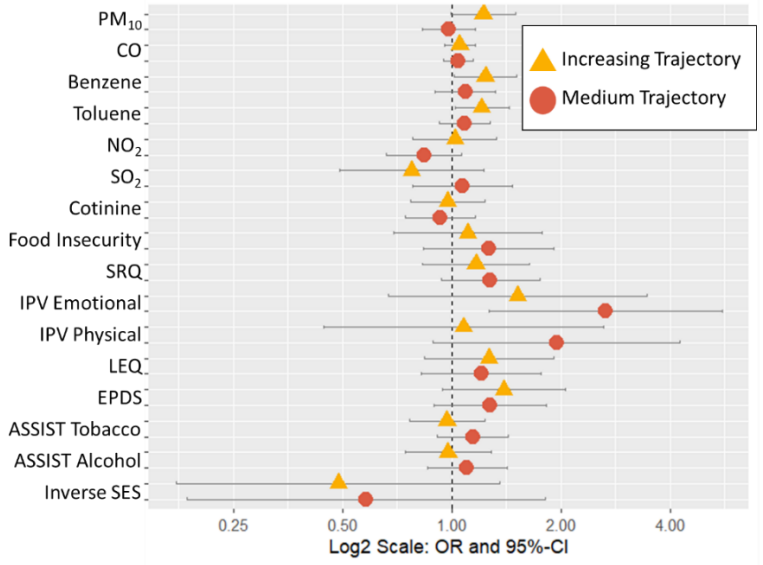


Figure 2-5*: Results from single-exposure polytomous logistic regression models, adjusted for maternal age, maternal HIV status, and ancestry, in the DCHS (N=360).* ***A.*** *CBCL Externalizing Problems.* ***B.*** *CBCL Internalizing Problems. Odds ratios are presented on a log2 scale to improve readability of effect estimates.*

Table 2-7: *Odds ratios and 95% CIs for individual exposure adjusted polytomous logistic regression models. Polytomous logistic regression models were adjusted for maternal HIV status, maternal age, and ancestry. Models using indoor air pollutant exposures were additionally adjusted for socioeconomic status, and principal components of psychosocial factors, and vice versa. Tables shows results from complete case models as well as multiple imputation (MI) models using 5 different random seeds (MI1 to MI5). MI4 models were presented in the main analysis.*

	Complete Case N	Complete Case	MI1	MI2	MI3	MI4 (Main results)	MI5
				Externalizing Problems			
PM10, high	186	1.31 (0.95, 1.81)	1.17 (0.95, 1.45)	**1.31 (1.05, 1.63)**	**1.32 (1.07, 1.64)**	**1.25 (1.01, 1.55)**	**1.25 (1.01, 1.55)**
PM10, medium		1.11 (0.84, 1.47)	1.04 (0.86, 1.24)	1.1 (0.92, 1.33)	1.13 (0.94, 1.35)	1.15 (0.95, 1.38)	1.09 (0.91, 1.3)
CO, high	186	1.05 (0.89, 1.23)	1 (0.89, 1.12)	1.03 (0.92, 1.14)	0.98 (0.88, 1.1)	0.98 (0.87, 1.1)	1.04 (0.93, 1.16)
CO, medium		1.09 (0.93, 1.27)	1.05 (0.95, 1.16)	1.03 (0.93, 1.14)	1.03 (0.93, 1.14)	1.06 (0.96, 1.17)	1.05 (0.95, 1.16)
Benzene, high	186	1.05 (0.77, 1.43)	0.94 (0.76, 1.16)	1.01 (0.8, 1.27)	1.04 (0.84, 1.29)	1 (0.81, 1.25)	0.94 (0.75, 1.17)
Benzene, medium		0.99 (0.74, 1.32)	0.84 (0.68, 1.02)	0.9 (0.73, 1.12)	0.94 (0.76, 1.15)	0.91 (0.74, 1.11)	0.94 (0.77, 1.16)
Toluene, high	186	0.86 (0.66, 1.13)	0.91 (0.75, 1.1)	0.94 (0.78, 1.14)	0.97 (0.81, 1.17)	0.96 (0.79, 1.16)	0.92 (0.75, 1.11)
Toluene, medium		0.97 (0.77, 1.24)	0.99 (0.83, 1.17)	0.97 (0.82, 1.15)	0.97 (0.82, 1.15)	0.99 (0.83, 1.17)	1.03 (0.86, 1.22)
NO2, high	186	0.81 (0.53, 1.24)	0.81 (0.6, 1.1)	0.92 (0.69, 1.22)	0.88 (0.65, 1.19)	0.82 (0.6, 1.11)	0.84 (0.62, 1.13)
NO2, medium		0.93 (0.63, 1.38)	0.97 (0.74, 1.27)	0.97 (0.75, 1.26)	0.92 (0.71, 1.21)	0.89 (0.68, 1.16)	0.93 (0.71, 1.21)
SO2, high	186	0.73 (0.39, 1.37)	0.85 (0.52, 1.38)	0.75 (0.45, 1.23)	0.84 (0.52, 1.36)	0.75 (0.47, 1.19)	0.81 (0.49, 1.33)
SO2, medium		0.86 (0.51, 1.43)	1.01 (0.68, 1.49)	0.97 (0.67, 1.41)	1.14 (0.78, 1.66)	0.92 (0.64, 1.32)	1 (0.68, 1.48)
Cotinine, high	186	0.99 (0.63, 1.55)	0.96 (0.74, 1.24)	0.99 (0.76, 1.28)	1 (0.76, 1.3)	0.98 (0.75, 1.28)	1.08 (0.84, 1.39)

Cotinine, medium		1.2 (0.79, 1.83)	1.16 (0.92, 1.47)	1.09 (0.86, 1.38)	1.15 (0.91, 1.47)	1.17 (0.92, 1.49)	1.21 (0.96, 1.52)
Food Insecurity, high	184	0.76 (0.35, 1.66)	0.86 (0.52, 1.45)	0.68 (0.4, 1.15)	0.8 (0.48, 1.33)	0.81 (0.48, 1.36)	0.87 (0.52, 1.46)
Food Insecurity, medium		0.8 (0.4, 1.6)	0.7 (0.44, 1.11)	0.68 (0.43, 1.08)	0.74 (0.47, 1.16)	0.77 (0.49, 1.21)	0.79 (0.5, 1.24)
SQR, high	186	1.37 (0.77, 2.42)	1.27 (0.87, 1.84)	1.27 (0.87, 1.85)	1.28 (0.89, 1.84)	1.3 (0.89, 1.9)	1.2 (0.82, 1.75)
SRQ, medium		0.95 (0.57, 1.58)	1.05 (0.75, 1.47)	1.01 (0.72, 1.4)	1.01 (0.73, 1.4)	0.98 (0.7, 1.37)	1.02 (0.72, 1.42)
IPV Emotional, high	186	1.61 (0.44, 5.88)	1.14 (0.48, 2.7)	1.2 (0.5, 2.87)	1.47 (0.61, 3.56)	1.27 (0.52, 3.08)	0.95 (0.4, 2.26)
IPV Emotional, medium		1.41 (0.41, 4.9)	1.09 (0.48, 2.47)	1.23 (0.55, 2.74)	1.3 (0.57, 2.99)	1.47 (0.65, 3.35)	1.2 (0.54, 2.67)
IPV Physical, high	186	2.51 (0.52, 12.17)	1.18 (0.43, 3.2)	1.41 (0.51, 3.88)	1.87 (0.68, 5.15)	1.29 (0.47, 3.56)	1.24 (0.47, 3.31)
IPV Physical, medium		3.56 (0.78, 16.15)	1.94 (0.78, 4.83)	2.46 (0.98, 6.2)	**2.65 (1.03, 6.82)**	2.47 (0.98, 6.24)	1.92 (0.78, 4.72)
LEQ, high	181	1.11 (0.57, 2.16)	1.02 (0.65, 1.6)	0.78 (0.49, 1.24)	1.14 (0.72, 1.8)	0.99 (0.63, 1.56)	1.08 (0.68, 1.7)
LEQ, medium		1.21 (0.65, 2.26)	1.12 (0.74, 1.7)	0.84 (0.55, 1.28)	1.11 (0.73, 1.71)	1.07 (0.7, 1.63)	1.1 (0.72, 1.68)
EPDS, high	186	0.82 (0.4, 1.68)	0.96 (0.63, 1.47)	1.03 (0.69, 1.54)	0.98 (0.65, 1.47)	0.96 (0.62, 1.47)	1.01 (0.65, 1.57)
EPDS, medium		0.52 (0.26, 1.03)	0.67 (0.46, 0.99)	0.82 (0.57, 1.19)	0.87 (0.6, 1.28)	0.7 (0.47, 1.04)	0.7 (0.47, 1.05)
ASSIST Tobacco, high	181	1.05 (0.66, 1.65)	1.19 (0.91, 1.56)	1.13 (0.89, 1.44)	1.11 (0.86, 1.42)	1.13 (0.87, 1.47)	1.1 (0.85, 1.42)
ASSIST Tobacco, medium		0.94 (0.62, 1.45)	1.18 (0.91, 1.52)	1.23 (0.98, 1.55)	1.23 (0.97, 1.56)	1.18 (0.92, 1.52)	1.2 (0.94, 1.53)
ASSIST Alcohol, high	181	0.84 (0.55, 1.29)	1.15 (0.86, 1.54)	1.16 (0.87, 1.55)	1.16 (0.86, 1.56)	1.25 (0.93, 1.69)	1.07 (0.82, 1.4)
ASSIST Alcohol, medium		0.71 (0.47, 1.09)	0.98 (0.73, 1.31)	1 (0.75, 1.33)	1.08 (0.81, 1.45)	1.07 (0.8, 1.45)	0.88 (0.67, 1.15)
SES, high	186	1.32 (0.27, 6.51)	0.62 (0.2, 1.92)	0.53 (0.17, 1.66)	0.63 (0.21, 1.93)	0.58 (0.19, 1.82)	0.57 (0.18, 1.77)

SES, medium		0.78 (0.18, 3.32)	0.51 (0.18, 1.41)	0.53 (0.19, 1.46)	0.56 (0.21, 1.54)	0.49 (0.17, 1.36)	0.51 (0.19, 1.42)
				Internalizing Problems			
PM10, increasing	186	1.24 (0.92, 1.66)	1.13 (0.93, 1.39)	1.21 (0.98, 1.5)	**1.24 (1.01, 1.53)**	1.22 (1, 1.5)	1.13 (0.92, 1.38)
PM10, medium		0.93 (0.73, 1.18)	0.9 (0.76, 1.06)	0.91 (0.77, 1.08)	0.92 (0.78, 1.08)	0.98 (0.83, 1.16)	0.94 (0.79, 1.11)
CO, increasing	186	1.04 (0.91, 1.18)	1.05 (0.96, 1.16)	1.04 (0.95, 1.15)	1.05 (0.95, 1.16)	1.05 (0.95, 1.16)	1.05 (0.95, 1.15)
CO, medium		1.05 (0.92, 1.19)	1.02 (0.92, 1.12)	1 (0.91, 1.1)	1.07 (0.97, 1.17)	1.04 (0.95, 1.15)	1.04 (0.95, 1.14)
Benzene, increasing	186	1.06 (0.82, 1.37)	1.08 (0.88, 1.31)	1.15 (0.93, 1.41)	1.16 (0.94, 1.42)	**1.24 (1.02, 1.51)**	1.09 (0.88, 1.33)
Benzene, medium		0.96 (0.74, 1.23)	1.06 (0.88, 1.28)	1.09 (0.89, 1.33)	1.15 (0.95, 1.38)	1.09 (0.9, 1.32)	1.11 (0.91, 1.34)
Toluene, increasing	186	1.1 (0.88, 1.37)	1.14 (0.97, 1.36)	**1.21 (1.02, 1.43)**	1.14 (0.97, 1.35)	**1.21 (1.02, 1.44)**	1.18 (0.99, 1.4)
Toluene, medium		1.01 (0.81, 1.25)	1.13 (0.96, 1.31)	1.16 (0.99, 1.36)	1.12 (0.96, 1.31)	1.08 (0.92, 1.27)	1.16 (0.99, 1.36)
NO2, increasing	186	0.99 (0.7, 1.42)	0.95 (0.73, 1.25)	0.94 (0.73, 1.22)	0.97 (0.74, 1.26)	1.02 (0.78, 1.33)	1.02 (0.78, 1.32)
NO2, medium		0.83 (0.6, 1.16)	0.84 (0.66, 1.07)	0.84 (0.67, 1.07)	0.83 (0.65, 1.06)	0.84 (0.66, 1.07)	0.86 (0.68, 1.09)
SO2, increasing	186	0.75 (0.42, 1.36)	0.82 (0.53, 1.28)	0.77 (0.49, 1.21)	0.82 (0.53, 1.29)	0.78 (0.49, 1.23)	0.84 (0.54, 1.33)
SO2, medium		0.91 (0.59, 1.41)	0.94 (0.66, 1.32)	0.93 (0.66, 1.29)	1.15 (0.86, 1.53)	1.07 (0.78, 1.47)	1.02 (0.73, 1.42)
Cotinine, increasing	186	1.22 (0.84, 1.77)	0.98 (0.78, 1.24)	1.01 (0.8, 1.27)	0.94 (0.74, 1.2)	0.97 (0.77, 1.24)	1.05 (0.84, 1.32)
Cotinine, medium		0.98 (0.69, 1.4)	0.91 (0.73, 1.13)	0.92 (0.74, 1.14)	0.87 (0.7, 1.09)	0.93 (0.75, 1.16)	0.91 (0.74, 1.13)
Food Insecurity, increasing	184	1.49 (0.76, 2.91)	1.3 (0.81, 2.08)	1.08 (0.67, 1.74)	1.1 (0.69, 1.75)	1.11 (0.69, 1.77)	1.19 (0.75, 1.89)
Food Insecurity, medium		1.58 (0.85, 2.94)	1.4 (0.92, 2.14)	1.21 (0.8, 1.84)	1.24 (0.82, 1.87)	1.26 (0.84, 1.91)	1.2 (0.79, 1.82)

SQR, increasing	186	1.23 (0.76, 1.99)	1.3 (0.92, 1.82)	1.26 (0.9, 1.77)	1.36 (0.98, 1.91)	1.17 (0.83, 1.64)	1.4 (0.99, 1.98)
SRQ, medium		1.38 (0.87, 2.18)	1.28 (0.94, 1.74)	1.29 (0.95, 1.75)	1.28 (0.94, 1.73)	1.28 (0.93, 1.75)	**1.38 (1.01, 1.9)**
IPV Emotional, increasing	186	1.6 (0.5, 5.15)	1.54 (0.69, 3.48)	1.54 (0.69, 3.45)	1.3 (0.57, 2.97)	1.52 (0.67, 3.46)	1.89 (0.85, 4.22)
IPV Emotional, medium		**4.74 (1.66, 13.55)**	**2.56 (1.21, 5.42)**	**2.34 (1.12, 4.87)**	**2.58 (1.22, 5.46)**	**2.66 (1.27, 5.57)**	**2.78 (1.32, 5.84)**
IPV Physical, increasing	186	0.85 (0.24, 2.97)	1.16 (0.47, 2.82)	1.24 (0.52, 2.97)	1.13 (0.46, 2.76)	1.08 (0.44, 2.63)	1.11 (0.46, 2.66)
IPV Physical, medium		2.15 (0.74, 6.22)	1.96 (0.88, 4.39)	1.72 (0.78, 3.82)	2 (0.9, 4.45)	1.95 (0.89, 4.27)	1.9 (0.87, 4.17)
LEQ, increasing	181	1.46 (0.82, 2.59)	**1.51 (1, 2.27)**	1.12 (0.74, 1.71)	1.44 (0.94, 2.19)	1.27 (0.84, 1.92)	1.25 (0.82, 1.89)
LEQ, medium		1.07 (0.63, 1.82)	1.23 (0.84, 1.8)	1.16 (0.79, 1.71)	1.15 (0.78, 1.7)	1.21 (0.82, 1.77)	1 (0.68, 1.48)
EPDS, increasing	186	1.59 (0.9, 2.81)	1.24 (0.86, 1.8)	1.27 (0.87, 1.84)	1.47 (0.99, 2.17)	1.39 (0.94, 2.06)	**1.63 (1.08, 2.46)**
EPDS, medium		1.25 (0.77, 2.03)	1.09 (0.78, 1.53)	1.05 (0.76, 1.46)	1.18 (0.84, 1.66)	1.28 (0.89, 1.83)	1.23 (0.86, 1.76)
ASSIST Tobacco, increasing	181	1.06 (0.72, 1.55)	1.01 (0.79, 1.29)	1.02 (0.82, 1.27)	1 (0.79, 1.26)	0.97 (0.77, 1.23)	0.95 (0.75, 1.2)
ASSIST Tobacco, medium		1.14 (0.79, 1.64)	1.25 (0.99, 1.58)	1.09 (0.88, 1.34)	1.17 (0.95, 1.46)	1.14 (0.91, 1.44)	1.15 (0.92, 1.43)
ASSIST Alcohol, increasing	181	0.75 (0.5, 1.12)	0.88 (0.66, 1.16)	0.96 (0.73, 1.27)	1 (0.77, 1.32)	0.98 (0.75, 1.28)	0.98 (0.75, 1.29)
ASSIST Alcohol, medium		0.96 (0.67, 1.37)	1.08 (0.84, 1.38)	1.08 (0.84, 1.38)	1.1 (0.85, 1.42)	1.1 (0.86, 1.42)	1.2 (0.95, 1.52)
SES, increasing	186	0.4 (0.1, 1.61)	0.51 (0.18, 1.41)	0.53 (0.19, 1.46)	0.56 (0.21, 1.54)	0.49 (0.17, 1.36)	0.51 (0.19, 1.42)
SES, medium		0.61 (0.17, 2.15)	0.62 (0.2, 1.92)	0.53 (0.17, 1.66)	0.63 (0.21, 1.93)	0.58 (0.19, 1.82)	0.57 (0.18, 1.77)

Abbreviations: Particulate Matter (PM10); Carbon monoxide (CO); Nitrogen dioxide (NO2); Sulfur dioxide (SO2); Socioeconomic Status (SES); Self-Reporting Questionnaire (SRQ-20); Edinburgh Postnatal Depression Scale (EPDS); Life Experiences Questionnaire (LEQ); Intimate Partner Violence (IPV); Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST)

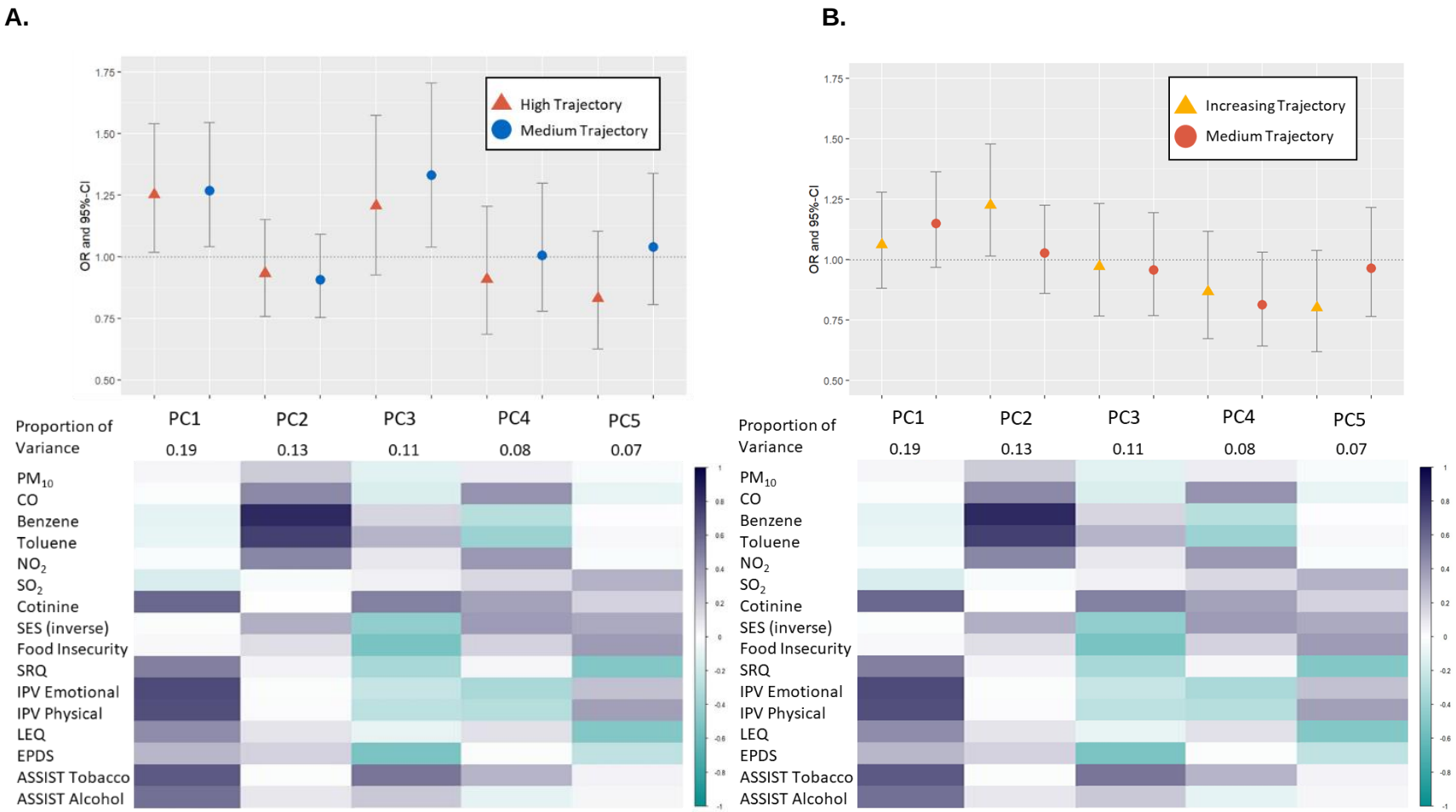


Figure 2-6: *Top panels show results of polytomous logistic regression modeling using principal components of exposure mixture, adjusted for maternal age, maternal HIV status, ancestry in the DCHS. Bottom panels show a correlation matrix between individual air pollutant and psychosocial factor exposures and each principal component. Purple indicates higher positive correlation, while teal indicated higher negative correlation in the DCHS.* ***A.*** *CBCL Externalizing Problems.* ***B.*** *CBCL Internalizing Problems.*

Table 2-8: *Joint exposure models using PCA to create Principal Components (PCs) of indoor air pollutant and psychosocial factor variables. The first five or 16 PCs were used as a joint exposure variable in polytomous logistic regression modeling. OR and 95% CI from adjusted polytomous logistic regression models. Polytomous logistic regression models adjusted for maternal HIV status, maternal age, and ancestry.*

	OR (95% CI)
	Externalizing Problems
PC1, High	**1.25 (1.02, 1.54)**
PC1, Medium	**1.27 (1.04, 1.54)**
PC2, High	0.93 (0.76, 1.15)
PC2, Medium	0.91 (0.75, 1.09)
PC3, High	1.21 (0.93, 1.57)
PC3, Medium	**1.33 (1.04, 1.71)**
PC4, High	0.91 (0.69, 1.21)
PC4, Medium	1 (0.78, 1.3)
PC5, High	0.83 (0.63, 1.1)
PC5, Medium	1.04 (0.81, 1.34)
	Internalizing Problems
PC1, increasing	1.06 (0.88, 1.28)
PC1, medium	1.15 (0.97, 1.36)
PC2, increasing	**1.22 (1.01, 1.48)**
PC2, medium	1.03 (0.86, 1.22)
PC3, increasing	0.97 (0.77, 1.23)
PC3, medium	0.96 (0.77, 1.19)
PC4, increasing	0.87 (0.67, 1.12)
PC4, medium	0.81 (0.64, 1.03)
PC5, increasing	0.8 (0.62, 1.04)
PC5, medium	0.96 (0.76, 1.21)

The four clusters identified by the SOM algorithm represent exposure profiles seen in this population **(Table 2-9)**. Participants with a cluster 1 exposure profile have relatively low exposure to all environmental and adverse psychosocial exposures, while participants with a cluster 2 exposure profile have high exposure to indoor air pollutants, low socioeconomic status, and depression. The cluster 3 exposure profile represents participants with smoking and alcohol use. Finally, the cluster 4 exposure profile has high exposure to most adverse psychosocial

factors and PM_{10}. In SOM analyses with externalizing problems trajectory, the cluster associated with high cotinine level and ASSIST tobacco and alcohol scores (cluster 3), indicative of tobacco and alcohol use, was associated with the high trajectory (2.67; 1.14, 6.27), compared to the low exposure cluster (cluster 1) **(Figure 2-8, Table 2-10)**, in line with the PCA analysis. No SOM exposure cluster was associated with CBCL internalizing problems trajectories.

***Table 2-9**: Descriptive statistics (Median (IQR)) of indoor air pollutant and psychosocial factor exposures in Self-Organizing Map (SOM) exposure clusters.*

	SOM Cluster			
	1	**2**	**3**	**4**
N (%)	66 (18.3)	147 (40.8)	74 (20.6)	73 (20.3)
PM10 µg/m3 (median [IQR])	29.06 [10.69, 58.50]	38.63 [16.29, 65.70]	39.39 [13.39, 68.55]	39.70 [14.10, 73.82]
CO mg/m3 (median [IQR])	0.00 [0.00, 0.00]	120.00 [0.00, 1050.00]	0.00 [0.00, 120.00]	0.00 [0.00, 60.00]
Benzene µg/m3 (median [IQR])	2.82 [0.95, 5.00]	35.44 [12.66, 97.14]	4.65 [2.55, 9.28]	2.84 [1.30, 6.64]
Toluene µg/m3 (median [IQR])	10.67 [4.70, 21.48]	53.72 [23.91, 255.05]	18.69 [9.31, 46.87]	13.57 [4.68, 24.37]
NO2 µg/m3 (median [IQR])	5.05 [2.09, 9.28]	12.84 [7.28, 20.48]	8.37 [4.24, 13.18]	5.90 [3.44, 9.38]
SO2 µg/m3 (median [IQR])	0.00 [0.00, 0.26]	0.00 [0.00, 0.64]	0.00 [0.00, 0.26]	0.00 [0.00, 0.00]
Urine Cotinine ng/ml (median [IQR])	16.50 [10.00, 50.88]	21.50 [10.00, 47.00]	500.00 [500.00, 500.00]	431.00 [32.22, 500.00]
SES Asset Sum (median [IQR])	7.00 [6.00, 8.00]	6.00 [4.00, 7.00]	8.00 [7.00, 8.00]	7.00 [5.00, 8.00]
Food Insecurity Total Score (median [IQR])	0.00 [0.00, 1.00]	1.00 [0.00, 4.00]	0.00 [0.00, 0.00]	0.00 [0.00, 3.00]
SRQ-20 Total Score (median [IQR])	3.00 [1.00, 6.00]	3.00 [1.00, 5.00]	4.00 [2.00, 7.00]	6.00 [4.00, 10.00]
EPDS Total Score (median [IQR])	8.00 [6.00, 12.00]	10.00 [8.00, 13.00]	8.00 [5.00, 12.00]	11.00 [8.00, 15.00]
LEQ Total Score (median [IQR])	1.00 [0.00, 2.00]	1.00 [0.00, 2.00]	2.00 [1.00, 3.00]	3.00 [1.00, 5.00]
Emotional IPV Score (median [IQR])	4.00 [4.00, 5.00]	4.00 [4.00, 6.00]	4.00 [4.00, 6.00]	11.00 [9.00, 13.00]
Physical IPV Score (median [IQR])	5.00 [5.00, 6.00]	5.00 [5.00, 7.00]	5.50 [5.00, 6.75]	11.50 [9.00, 15.00]
ASSIST Tobacco Score (median [IQR])	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	23.00 [17.00, 24.75]	0.00 [0.00, 24.00]
ASSIST Alcohol Score (median [IQR])	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 10.00]	0.00 [0.00, 14.25]

Abbreviations: Particulate Matter (PM10); Carbon monoxide (CO); Nitrogen dioxide (NO2); Sulfur dioxide (SO2); Socioeconomic Status (SES); Self-Reporting Questionnaire (SRQ-20); Edinburgh Postnatal Depression Scale (EPDS); Life Experiences Questionnaire (LEQ); Intimate Partner Violence (IPV); Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST)

Table 2-10*: Joint exposure models using SOM clusters as a joint exposure variable, OR and 95% CIs from adjusted polytomous regression models. Polytomous logistic regression models adjusted for maternal HIV status, maternal age, and ancestry.*

	OR (95% CI)
	Externalizing Problems
Cluster 1, high	REF
Cluster 1, Medium	REF
Cluster 2, High	1.08 (0.46, 2.53)
Cluster 2, Medium	0.8 (0.38, 1.69)
Cluster 3, High	**2.67 (1.14, 6.27)**
Cluster 3, Medium	1.88 (0.82, 4.28)
Cluster 4, High	1.57 (0.64, 3.85)
Cluster 4, Medium	1.67 (0.74, 3.76)
	Internalizing Problems
Cluster 1, increasing	REF
Cluster 1, medium	REF
Cluster 2, increasing	1.91 (0.89, 4.1)
Cluster 2, medium	1.21 (0.59, 2.47)
Cluster 3, increasing	1.81 (0.85, 3.82)
Cluster 3, medium	1.18 (0.56, 2.47)
Cluster 4, increasing	1.2 (0.52, 2.79)
Cluster 4, medium	1.75 (0.86, 3.59)

In quantile g-computation models, the overall mixture was not significantly associated with high/medium compared to low externalizing (mixture OR: 1.42; p-value: 0.50) or internalizing (mixture OR: 1.59; p-value: 0.29) trajectories. Though not statistically significant, there is a slight positive trend in odds of both high/medium externalizing and internalizing trajectory as deciles of the exposure mixture increase **(Figure 2-9)**.

Sensitivity analyses

Results from sensitivity analysis models comparing complete case and imputed exposures were similar to the main results presented above. In internalizing problems models, toluene was also associated with the increasing trajectory in one other imputation model, but ORs were

consistent across all models. Similarly for benzene, the association with increasing trajectory was not significant for other models, but the ORs consistent across all models **(Table 2-7)**.

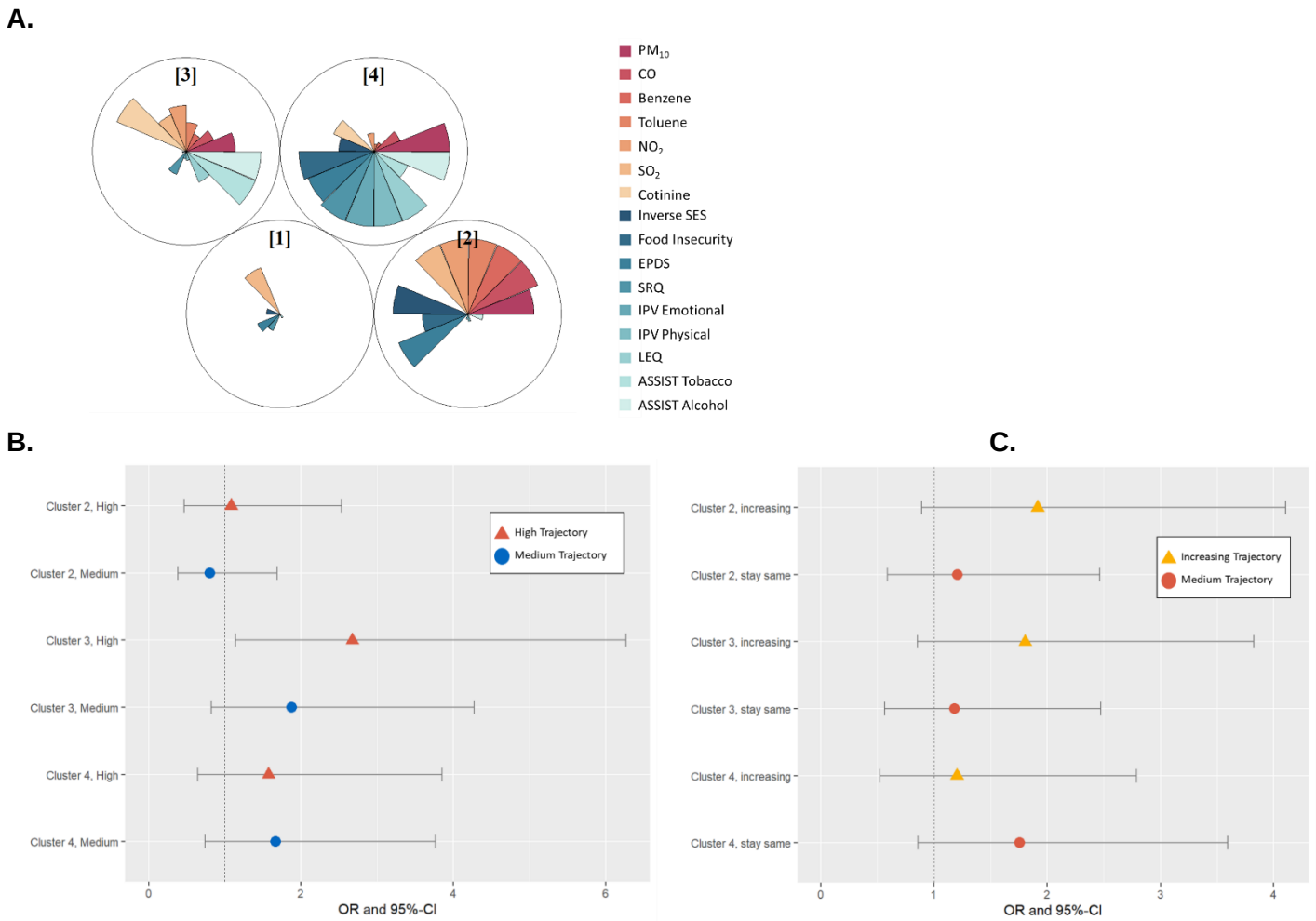


Figure 2-7: *SOM analysis investigating associations between clusters of indoor air pollution and psychosocial factors on CBCL trajectories.* ***A.*** *SOM cluster star plot, slices represent median values of the mixture component, each circle is a SOM cluster. Red/orange slices represent indoor air pollutants while blue slices represent psychosocial factors.* ***B.*** *Results from adjusted polytomous logistic regression model for Externalizing Problems trajectory, using cluster 1 as the reference group. Model adjusted for maternal age, maternal HIV status, and ancestry.* ***C.*** *Results from adjusted polytomous logistic regression model for Internalizing Problems trajectory, using cluster 1 as the reference group. Model adjusted for maternal age, maternal HIV status, and ancestry.*

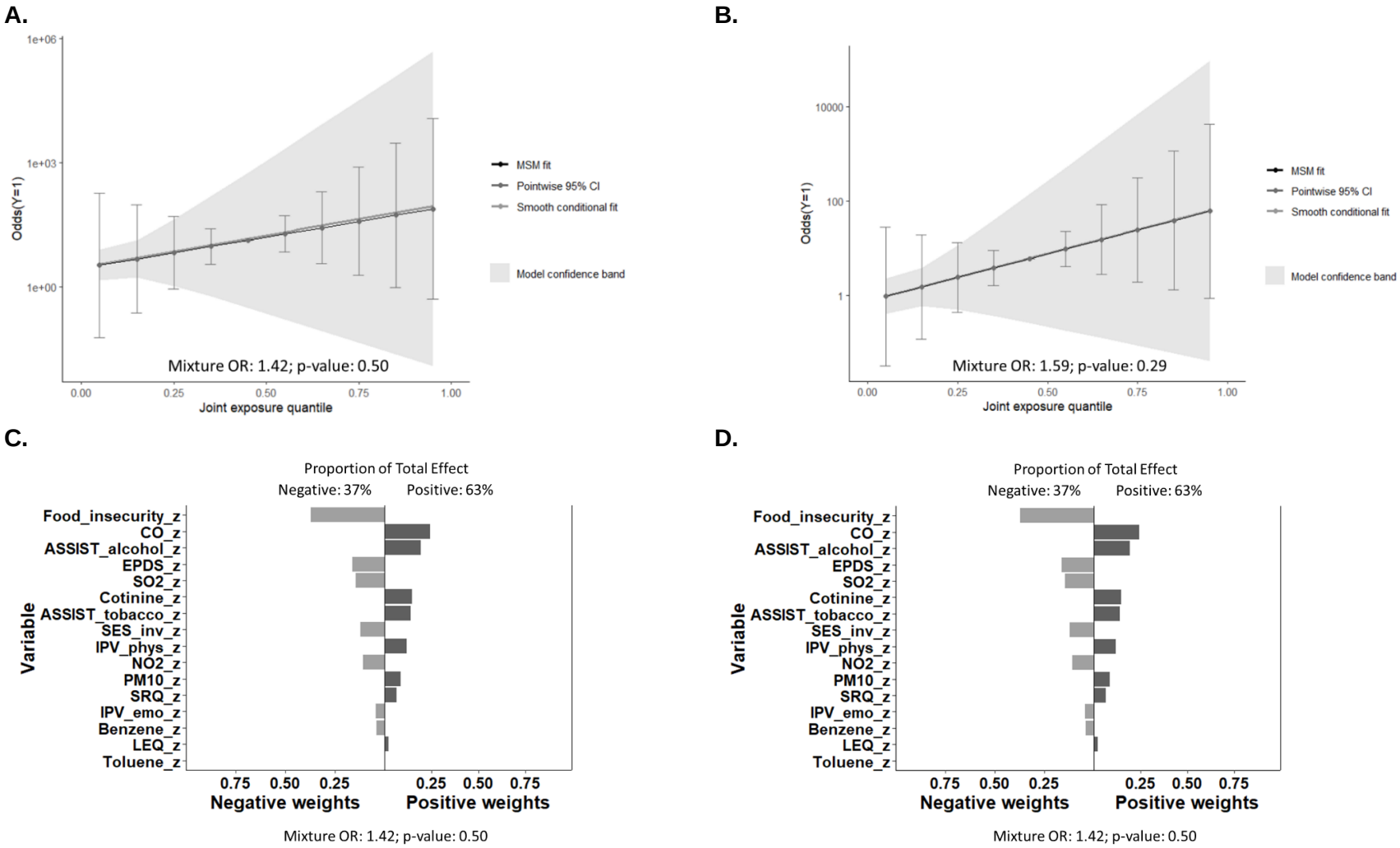


Figure 2-8*: Total mixture effect estimates from quantile G-computation models, adjusted for maternal age, maternal HIV status, and ancestry. Weight of each exposure mixture component from quantile G-computation models, adjusted for maternal age, maternal HIV status, and ancestry. Weights from models were the total mixture effect was not significant should not be interpreted.* ***A.*** *Total mixture effect on binary externalizing trajectory (low vs. medium/high).* ***B.*** *Total mixture effect on binary internalizing trajectory (low vs. medium/high).* ***C.*** *Weights from externalizing model.* ***D.*** *Weights from internalizing model.*

Discussion

In this analysis of mother-child pairs from a South African birth cohort, trajectories of internalizing and externalizing child behavior at 24, 42, and 60 months were differentially associated with prenatal indoor air pollution and psychosocial exposures. Internalizing problems trajectory was individually associated with both exposures to indoor air pollution and adverse psychosocial factors, while the externalizing problems trajectory was mostly associated with smoking related exposures. This analysis indicates that different exposures might differently affect internalizing and externalizing problem trajectories.

We observed that externalizing problems trajectory was most associated with prenatal smoking behaviors and PM_{10}, a by-product of cigarette smoke. This has been observed in a previous study from the DCHS[94]. In other prior studies investigating PM_{10} exposure during pregnancy and autism spectrum disorder, a condition that exhibits externalizing behaviors, results have been mixed. Only one study found a significant harmful effect of PM_{10}[95], the rest found a null association[38]. Other studies investigating smoking during pregnancy have found associations with externalizing behaviors, including inattention and impulsivity[96–98].

The internalizing problems trajectory was associated with emotional intimate partner violence. Few studies have investigated the association between intimate partner violence before and during pregnancy and childhood psychopathology. One study found intimate partner violence during pregnancy was correlated with borderline or clinical internalizing problems, externalizing problems and total problems using the CBCL in children 18 months-18 years old[99]. However, results from our study may not be directly comparable as that study did not separate different types of intimate partner violence, and did not adjust for confounding. More epidemiology studies investigating prenatal exposure to intimate partner violence and their association with

child behavior are needed. Our study also found individual and joint associations with volatile organic compounds, specifically benzene and toluene, and internalizing problems trajectory.

To our knowledge, our study is the first to investigate the association between prenatal volatile organic compounds exposure and childhood psychopathology. One prior study has investigated volatile organic compounds and neurodevelopmental outcomes, though they measured exposure in early childhood, and found m,p-xylene and o-xylene were associated with decreased scores in the ages and stages questionnaire, which screens young children for developmental delays[47]. Continued epidemiologic research on prenatal volatile organic compound exposure is necessary to examine the relationship between volatile organic compounds and child psychopathy.

In analyses using PCs and SOM, high air pollution exposure coupled with low socioeconomic status was associated with internalizing behavior trajectories. This finding indicates that pregnant women with low SES could benefit from indoor air pollution interventions to reduce childhood psychopathology. In support of our findings, prior studies investigating neurodevelopmental or psychopathological outcomes at one time period found an interaction between air pollutants and adverse psychosocial factors. However, these studies did not use environmental mixture methods and instead used interaction terms between one air pollutant and one psychosocial factor[13,81,100,101]. Studies using other health outcomes have also found joint effects of prenatal air pollution and psychosocial factor exposure. A recent review article found several studies showing prenatal psychosocial factors modifying the effect of ambient and traffic related air pollution on adverse birth and childhood outcomes such a birthweight, gestational age and asthma[78].

Synergy is probable because air pollutants and stress caused by psychosocial factors may impact similar brain mechanisms, including inflammation [27,68]. It is hypothesized that air pollution affects the central nervous system (CNS) via neuroinflammation and oxidative stress[8,16,27,70,71].

Animal models show that air pollutants cause a systemic inflammatory response, including neuroinflammation inside the brain. Both the physical air pollutant particle, and the toxic components absorbed on the particle can create an inflammatory response. Translocation of air pollutant nanoparticles from the lungs and nasal pathways to other areas of the body, including the placenta[102], cause damage to the mother's body and fetus. Microglia respond to this damage by releasing inflammatory cytokines like TNF-α, IL-1β, and IL-6, and reactive oxygen species (ROS), inducing oxidative stress. Chronic activation of the microglia and over production of inflammatory markers and ROS can cause neuronal cell death[27]. A range of research also documents that adverse psychosocial factors are associated with neuroinflammation and oxidative stress[68,71,72].

Several strengths of this study deserve emphasis. First, this analysis used measurements of multiple indoor air pollution exposures. Indoor air pollution in LMICs is most often measured using survey-based proxy measures e.g. cooking practices, smoking, etc. Given the well-known harmful effects of indoor air pollution[29], it is important to measure individual pollutants to pinpoint which chemical, or combination of chemicals, is causing health problems and the biological mechanisms involved. Second, this study leverages a unique prospective birth cohort with repeated measurements of psychopathology across time periods. And finally, the traditional single-exposure analysis is complemented with two environmental mixtures methods, PCA and SOM. These methods allow us to explore joint-effects of environmental and social exposure profiles that are associated with psychopathology trajectory. Estimating joint effects can identify vulnerable subgroups to target for interventions to reduce childhood psychopathology.

Several limitations deserve emphasis. First, we were unable to investigate the effect of the total mixture on trajectories or psychopathology. Currently, environmental mixture methods that estimate a total mixture effect (e.g. Bayesian kernel machine regression (BKMR), weighted quantile sum regression, etc.) can only accommodate linear or logistic regression, and not

polytomous logistic regression. We created a dichotomized trajectory variable (high/medium vs low) to estimate an overall mixture effect using quantile g-computation, however collapsing trajectory categories led to a loss of information which consequently reduced the statistical power to detect associations with the overall mixture. An additional limitation is that we were unable to investigate interaction between exposures (synergy/antagonism). Alternative methods like BKMR can estimate interactions between exposures on binary or continuous outcomes. However, BKMR works best with a smaller number of exposures and a larger sample size, especially if the goal is to look at pairwise interactions between exposures. In contrast, one advantage of the SOM methods that we used is that the SOM profiles are based on how exposures co-occur in real life. These profiles can be used for more practical interventions (e.g. highlighting vulnerable subgroups of people who are exposed to both air pollution and depression) than looking at pairwise synergy/antagonism which may not correspond to exposures that appear in real life. As methods to investigate environmental exposure mixtures advance this may be an option for future studies Second, the lack of fine ($PM_{2.5}$) and ultrafine PM measurements. $PM_{2.5}$ measurement was not collected because, at the time, personal $PM_{2.5}$ monitoring was not easily available for this large of a study. Additionally, this study uses indoor air pollution measurements from one point (24 hours or two-week average, depending on pollutant) in the 2nd trimester and in early life to characterize exposure for the whole period. Psychosocial measures were administered at one time in the 2nd trimester. This could create some misclassification of the exposure by either over- or under-estimating a participant's exposure during pregnancy. Furthermore, by only collecting exposure data in the 2nd trimester of pregnancy we may be missing important effects of pollutants and psychosocial factors in early pregnancy, or effects of exposure more proximal to the outcome. Nevertheless, prior research in the DCHS has found associations between exposures in the 2nd trimester and several outcomes[57,58], including neurodevelopment[59]. Other limitations include biases from residual confounding, and selection bias, though this cohort was selected to be population

based and representative of peri-urban populations in South Africa and other low income countries. While this study had a relatively small sample size, few studies have such detailed exposure information and repeated outcomes, especially in a low to middle income country.

Chapter 3 : Sensitive periods for exposure to indoor air pollutants and psychosocial factors in association with symptoms of psychopathology at school-age in a South African birth cohort

This chapter addresses specific aim 2, investigating prenatal and early-life exposure to joint effects of air pollution and psychosocial factors in association with child psychopathology at school age. The version of the manuscript presented in this dissertation is currently under review at *Environmental Health Perspectives*.

Abstract

Background: Gestation and the first few months of life are important periods for brain development. During these periods, exposure to environmental toxicants and psychosocial stressors are particularly harmful and may impact brain development. Specifically, exposure to indoor air pollutants (IAP) and psychosocial factors (PF) during these sensitive periods has been shown to predict childhood psychopathology.

Objectives: This study aims to investigate sensitive periods for the individual and joint effects of IAP and PF on childhood psychopathology at 6.5 years.

Methods: We analyzed data from the Drakenstein Child Health Study (N=599), a South African birth cohort. Exposure to IAP and PF was measured during the second trimester of pregnancy and 4 months postpartum. The outcome of childhood psychopathology was assessed at 6.5 years old using the Childhood Behavior Checklist (CBCL). We investigated individual effects of either pre- or postnatal exposure to IAP and PF on CBCL scores using adjusted linear regression models, and joint effects of these exposures using quantile g-computation and self-organizing maps (SOM). To identify possible sensitive periods, we used a structured life course modeling approach (SLCMA) as well as exposure mixture methods (quantile g-computation and SOM).

Results: Prenatal exposure to IAP or PFs, as well as the total prenatal mixture assessed using quantile g-computation, were associated with increased psychopathology. SLCMA and SOM models also indicated that the prenatal period is a sensitive period for IAP exposure on childhood psychopathology. Depression and alcohol were associated in both the pre- and postnatal period, while CO was associated with the postnatal period.

Conclusions: Pregnancy may be a sensitive period for the effect of indoor air pollution on childhood psychopathology. Exposure to maternal depression and alcohol in both periods was

also associated with psychopathology. Determining sensitive periods of exposure is vital to ensure effective interventions to reduce childhood psychopathology.

Introduction

Childhood psychopathology, including anxiety, attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder, and depression, can cause problems for children in all aspects of life[18]. Previous studies have found that children who experience elevated symptoms of psychopathology are at a higher risk of developing mental health problems as adults[19]. The two major categories of psychopathology symptoms and disorders are internalizing and externalizing. Externalizing behaviors, such as aggression, delinquency, and hyperactivity are displayed outwardly and reflect the behavior towards the environment[20]. In contrast, internalizing behaviors, such as depression, anxiety, somatic complaints, and suicidal ideation, are directed inward and reflect the child's emotional and psychological state[21].There is a gap in knowledge on how to prevent psychopathology in children[19]. Bridging this gap through identification of modifiable risk factors has potential to reduce the burden of mental health problems in childhood.

Air pollution may be one modifiable risk factor, shown in both animal experiments and human observational studies to affect the central nervous system (CNS) and elements of behavior and psychopathology[3,13,14,27,28]. Additionally, exposure to psychosocial factors and their determinants which may induce stress, such as socioeconomic status, substance use, violence, and psychological distress, also affects child behavioral development and psychopathology. Animal studies have shown prenatal stress affects behavior in rats [48–50], and there is growing epidemiological evidence for pre- and postnatal psychosocial stress' effects on child cognitive development[51]. However, few studies have examined the combined association of air pollutants and psychosocial factors on psychopathology.

While exposure to both indoor air pollution and psychosocial factors have been associated with childhood psychopathology separately[37,51,103,104]. Joint effects of these exposures are probable and have been seen previously in research on childhood psychopathology[13,100,101,105]. As

exposure to indoor air pollutants and psychosocial factors co-occur and often cluster around socioeconomic status, it is important to consider joint effects of these risk factors. Investigating joint effects will also help to identify and target subgroups that are especially vulnerable to developing childhood psychopathology. However, a limitation of current studies is that they typically focus on exposure at one time period (i.e., exposure during pregnancy). Exposure to both indoor air pollution and psychosocial factors can be reduced through interventions. Understanding the role of these exposures and their joint effects, as well as the timing of exposure, in developing psychopathology will allow for targeted interventions with the goal of reducing incidence and symptoms of childhood psychopathology.

Pregnancy and early life may be particularly important time periods to explore the individual and joint effects of air pollution and psychosocial stress on brain health. The central nervous system begins to develop as early as the first month of gestation[74] and key milestones in brain development occur throughout pregnancy. After birth, postnatal synaptogenesis, apoptosis, and neuronal pruning further shape the neuronal synapses. Disruption or dysregulation of these processes can lead to functional abnormalities which can lead to psychopathology[32]. Therefore, brain development in pre- and early postnatal time periods may be especially sensitive to indoor air pollutants and psychosocial stressors.

Literature on sensitive periods for the effects of exposure to air pollution on childhood psychopathology are mixed. For example, a German study found that prenatal exposure to environmental tobacco smoke was more strongly associated with behavioral problems at 10 years old[103], as measured by the Strengths and Difficulties Questionnaire (SDQ),as opposed to early life tobacco exposure. However, a study of French children found postnatal environmental tobacco exposure, alone or in combination with prenatal exposure, was associated with adverse SDQ scores[104]. Additionally, a Chinese study investigating pre- and postnatal exposure to $PM_{2.5}$

and PM_{10} were more strongly associated with adverse neurodevelopment at 2 years old than prenatal exposure[37].

Few studies have compared how psychosocial factors experienced during pregnancy and early life of the child impact later childhood psychopathology. A systematic review on childhood maltreatment and psychopathology found no consensus on sensitive periods among available epidemiology studies[106]. One study from the United States found prenatal depressive symptoms, as measured by the Edinburgh Postpartum Depression Scale (EPDS), was associated with poorer behavioral development in mid-childhood[107]. This study found postpartum symptoms were not associated with any behavioral outcomes after adjustment for prenatal symptoms[107]. Another study from the United States found prenatal stressful life events and intimate partner violence were associated with externalizing Childhood Behavior Checklist (CBCL) score[108].

Another limitation of the current literature is that a majority of studies are focused on children in high-income countries (HICs). Pregnant women and children in low- and middle-income countries (LMICs) are particularly impacted by indoor air pollution and psychosocial factors. LMICs typically have higher levels of indoor air pollution, compared to HICs, partially due to fuels used while cooking and heating the home[26] Women and children are most at risk for exposure to indoor air pollution because they tend to spend more time indoors and are more involved in food preparation and cooking[24]. Compared to HICs and the global average, LMICs also fare worse in social indicators for children, including the human development index, primary school enrollment ratio, under five malnutrition, among others[22]. These social indicators are known to be associated with childhood mental health[22].

We aimed to address these limitations by leveraging data from the South African Drakenstein Child Health Study (DCHS). Our goal was to examine the individual and joint effects of indoor air pollutants and psychosocial factors in pregnancy and early childhood on childhood

psychopathology. This study examines how individual and joint exposure during pregnancy and early life impact childhood psychopathology by investigating each period separately. We additionally use a life course modeling approach to determine sensitive periods for separate exposures. Finally, we investigate sensitive periods of joint exposure effects.

Methods

Study Population

Participants came from the Drakenstein Child Health Study (DCHS), a population-based birth cohort from outside Cape Town, South Africa. As previously described in greater detail, pregnant women were recruited between March 2012 and March 2015 from two public sector healthcare clinics. Enrollment criteria were that participants were at least 18 years of age, within 20-28 weeks gestation, and were not planning on moving away from the district. Detailed recruitment information for the DCHS has been described elsewhere[57,76]. The DCHS conducts follow-up visits with mother-child pairs frequently; 6 visits in the first year of life and 6 monthly visits thereafter. The full cohort includes N=1,141 mother-child pairs; we selected a subset for analysis based on availability of indoor air pollution and CBCL measurements (n=599; **Figure 3-1**). The DCHS was approved by the Human Research Ethics Committee of the Faculty of Health Sciences, University of Cape Town, by Stellenbosch University and the Western Cape Provincial Research committee. Written informed consent was provided by the mothers for herself and her child and is renewed annually.

Exposure Assessment

Indoor Air Pollution

Indoor air pollution measurements were taken during participants' 2nd trimester of pregnancy and postnatally at 4 months. As described previously[83,105], pollutants measured include

particulate matter (PM_{10}), carbon monoxide (CO), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and Volatile Organic Compounds (VOCs) benzene and toluene. PM_{10} was collected over 24 hours with a personal air sampling pump (SKC AirChek 52®), using a gravimetrically pre-weighted filter. CO was collected over 24 hours using an Altair® carbon monoxide single gas detection unit, electrochemical sensor detection of gas at 10-minute intervals were collected. SO_2 and NO_2 were collected over 2 weeks using Radiello® absorbent filters in polyethylene diffusive body. VOCs, including benzene and toluene, were collected over 2 weeks using Markes® thermal desorption tubes[83]. Information on household information including type of home, distance from major road, size of home, number of inhabitants, access to basic amenities, fuels used for cooking and heating, ventilation within homes, and pesticides and cleaning materials used in the home was collected at home visits[83].

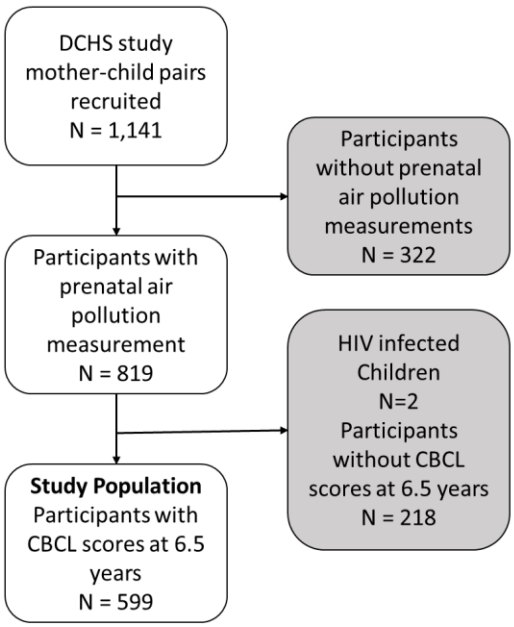


***Figure 3-1**: Study population flow diagram.*

Psychosocial Factors and Their Determinants

Psychosocial factors and their determinants were collected via questionnaire in the 2nd trimester of pregnancy and at 6-10 weeks postnatal, designed to capture multiple dimensions of the psychosocial landscape. *Socioeconomic status* was collected as a sum of indicators of assets owned and utilized by the household (e.g. electricity in the home, etc.). The USDA Household Food Security Scale was used to measure perceived *food insecurity*[84]. *Emotional, physical, and sexual intimate partner violence* (IPV) was assessed using the IPV Questionnaire adapted from the World Health Organization (WHO) multi-country study and the Women's Health Study in Zimbabwe[85,86]. Only emotional and physical IPV were used in further analyses because few women (<10%) experienced sexual IPV. The World Mental Health Life Events Questionnaire (LEQ) was used to measure *traumatic life experiences and resilience*. Use of *alcohol and tobacco* were assessed using the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST). Few women (at most 2%) reported use of other substances (e.g., marijuana) and those questionnaires were not included in further analysis. Additionally, tobacco smoke exposure was assessed via urinary cotinine, but only in the prenatal period. The WHO endorsed measure, Self-Reporting Questionnaire (SRQ-20), was used to measure *psychological distress*[87,88]. Finally, the Edinburgh Postnatal Depression Scale (EPDS) was used to measure *depressive symptoms*[89]. These factors were chosen for this study because they have been shown to be risk factors for childhood psychopathology[106–108].

All exposures were natural-log transformed for linear regression modeling and additionally centered and scaled to have a mean at 0 and standard deviation of 1 before mixture modeling.

Outcome Assessment

Parent-reported child psychopathology was assessed using the school version of the Child Behavior Checklist (CBCL) at 6.5 years of age[90]. The CBCL, consisting of 113 questions,

assesses child behavior using a Likert scale (0 = absent; 1= occurs sometimes; 2 = occurs often) to create a score, defined as total problems score. These questions can be sub divided into internalizing and externalizing sub scales. The internalizing scale includes questions from the anxious/depressed, withdrawn/depressed, and somatic complaints syndromic scales. The externalizing scale includes the rule-breaking and aggressive behavior syndromic scales[90]. CBCL total problems, internalizing problems, and externalizing problems scores were right skewed and were therefore natural log-transformed to be used in modeling approaches described below.

Statistical Analysis

Multiple imputation of missing values

There were no missing values in our outcome or covariates. However, some participants were missing indoor air pollution or psychosocial measurements in either the pre- or postnatal period **(Table 3-1)**. We assume these values are missing at random based on inspections of the missingness patterns **(Figure 3-2)**. To increase sample size and retain statistical power we used multiple imputation, as implemented by the *hmisc* R package, to impute missing exposure variables. Pre- and postnatal indoor air pollution and psychosocial factor variables were imputed using predictive mean matching. Separate imputation models were used for each time period and included indoor air pollutants, household characteristics, and psychosocial factor measurements. For each time period, five seed numbers were created using a random number generator. Each seed resulted in its own set (k = 10) of multiple imputed variables, and one imputed set of was randomly chosen to use for analyses Pooling of the k imputed values was not compatible with methods used in the statistical analysis. Finally, the seed with the highest R^2 values, a measure used to explain how well the missing variable was predicted, was selected

for primary analysis and results. Sensitivity analyses using complete cases and the other imputation seeds were conducted.

	Prenatal Measurement				Postnatal Measurement			
Exposure	**# missing**	**% missing**	**n**	**total N**	**# missing**	**% missing**	**n**	**total N**
PM_{10}	59	10%	540	599	253	42%	346	599
CO	115	19%	484	599	292	49%	307	599
benzene	67	11%	532	599	285	48%	314	599
toluene	67	11%	532	599	285	48%	314	599
NO_2	64	11%	535	599	238	40%	361	599
SO_2	64	11%	535	599	236	39%	363	599
maternal smoking (cotinine)*	17	3%	582	599	-	-	-	-
food insecurity	49	8%	550	599	119	20%	480	599
SRQ	54	9%	545	599	197	33%	402	599
IPV - emotional	53	9%	546	599	196	33%	403	599
IPV - physical	53	9%	546	599	196	33%	403	599
LEQ	67	11%	532	599	198	33%	401	599
EPDS	54	9%	545	599	197	33%	402	599
ASSIST - tobacco	58	10%	541	599	196	33%	403	599
ASSIST - alcohol	58	10%	541	599	196	33%	403	599
SES assets	0	0%	599	599	122	20%	477	599

*Cotinine was only measured in the prenatal period

Abbreviations: Particulate Matter (PM_{10}); Carbon monoxide (CO); Nitrogen dioxide (NO_2); Sulfur dioxide (SO_2); Socioeconomic Status (SES); Self-Reporting Questionnaire (SRQ-20); Edinburgh Postnatal Depression Scale (EPDS); Life Experiences Questionnaire (LEQ); Intimate Partner Violence (IPV); Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST)

Table 3-1: *Proportion of missing pre- and postnatal exposure data in analysis sample.*

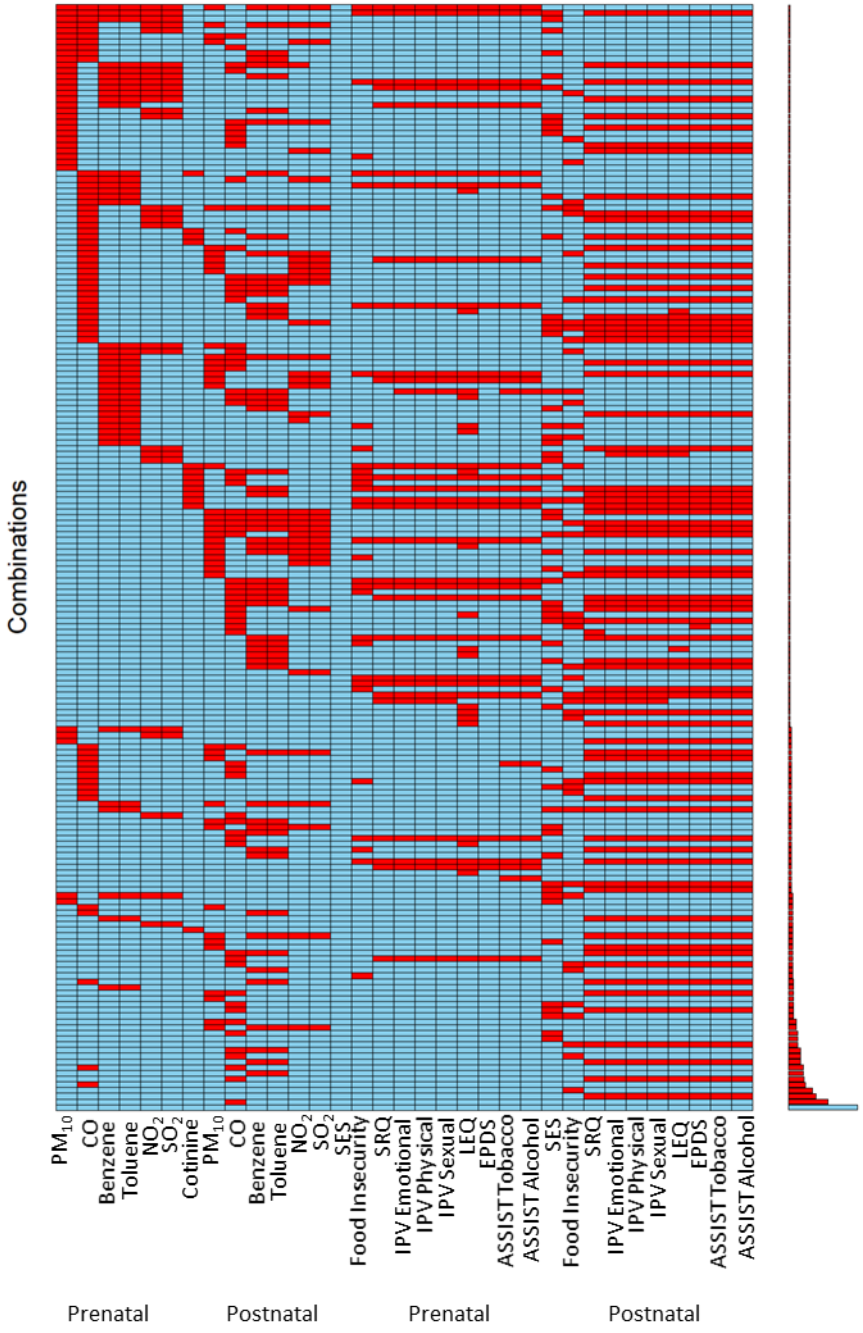


Figure 3-2: *Combinations of missingness patterns of exposure variables. Each row is a missingness pattern where red indicates that variable is missing, and blue indicates not missing. Abbreviations: Particulate Matter (PM_{10}); Carbon monoxide (CO); Nitrogen dioxide (NO_2); Sulfur dioxide (SO_2); Socioeconomic Status (SES); Self-Reporting Questionnaire (SRQ-20); Edinburgh Postnatal Depression Scale (EPDS); Life Experiences Questionnaire (LEQ); Intimate Partner Violence (IPV); Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST).*

Association analyses

This study aims to investigate both individual and joint effects of indoor air pollutants and psychosocial factors at two time periods, pre- and postnatal, on CBCL score at 6.5 years including externalizing, and internalizing subscales. The analysis workflow consists of two parts, 1) single exposure period exposure-outcome modeling, where pre- and postnatal exposures are investigated separately, and 2) Exposure modeling of sensitive periods. In our single exposure period approach, we first used linear regression to examine individual exposure-outcome effects, and next two environmental mixture methods (Quantile G-Computation and Self-Organizing Maps) to investigate joint effects of multiple exposures (exposure mixture). To investigate sensitive periods of exposure for individual exposures we used a Structured Life Course Modeling Approach and for the exposure mixture we used Self-Organizing Maps as described below.

Pre- and Postnatal exposure-outcome modeling

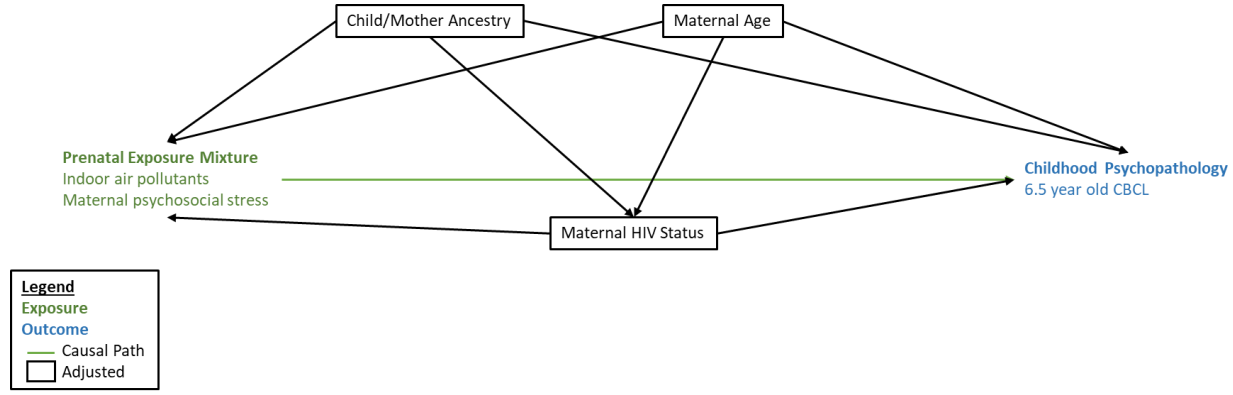
To investigate the association between each individual prenatal exposure and CBCL scores at 6.5 years we used linear regression. Confounding was assessed using directed acyclic graphs (DAGs) **(Figure 3-3A-C)**. All models were minimally adjusted for a set of confounders including maternal HIV status, maternal age, ancestry (Black African versus mixed ancestry), and socioeconomic status (when not used as the exposure of interest). In sensitivity analyses an extended confounder set was used to additionally adjust for confounding from psychosocial factors in air pollutant exposure models and vice versa. In the air pollutant exposure models, psychosocial confounders were summarized as principal components (using Principal Components Analysis), as opposed to individual variables, to avoid instability in estimation because psychosocial factors were highly correlated. In these extended confounder set models the first four principal components of psychosocial factors were included as confounders.

Similarly, the models investigating socioeconomic status or psychosocial stressors as the main exposures were adjusted for the first four principal components of indoor air pollution.

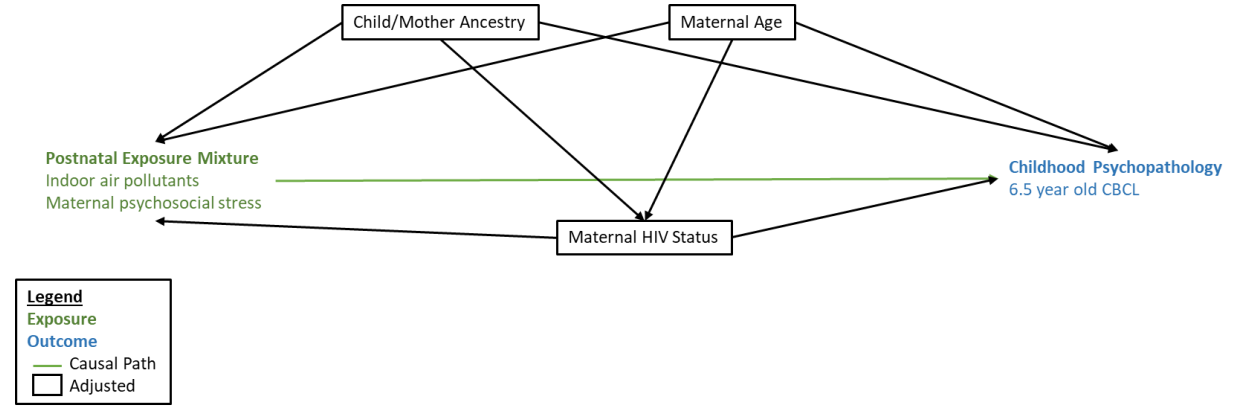
Two environmental mixture modeling approaches were used to investigate joint effects of the prenatal mixture of indoor air pollutants and psychosocial factors on CBCL: quantile g-Computation, and self-organizing maps (SOM). Quantile g-computation provides an overall mixture effect estimate as well as relative contributions of each exposure in the mixture[93]. Quantile g-computation uses g-computation to estimate the total effect of our mixture as each exposure increases by one quantile simultaneously. Additionally, the partial effect of each exposure is calculated as positive or negative weights[93]. Quantile G-Computation models using the imputed analysis sample data were adjusted for maternal age, maternal HIV status, and ancestry. The adjusted model was fitted for deciles of exposure and 200 bootstrapped samples. All quantile g-computation analyses were conducted using the *qgcomp* package in R (ver. 4.1.2).

SOM was used to create and examine profiles of exposure to indoor air pollution and psychosocial factors on CBCL scores. The SOM algorithm identifies clusters, or profiles, of an exposure mixture. Clusters have exposure levels that are homogenous within the cluster and heterogenous between clusters[109,110]. The number of clusters chosen for further analysis was determined by multiple statistical measures assessing group structure, including Akaike information criterion (AIC), and adjusted R^2, additionally visual inspection of the clusters for interpretability and appropriate distribution of participants among clusters. To investigate the joint effect of indoor air pollutants and psychosocial factors on CBCL, SOM clusters were then assigned to participants and treated as a categorical exposure variable in linear regression analysis. The linear regression model using SOM cluster as the exposure was adjusted for maternal age, maternal HIV status, and ancestry. We used the SOM R package as implemented in https://github.com/johnlpearce/ECM.

A.



B.



C.

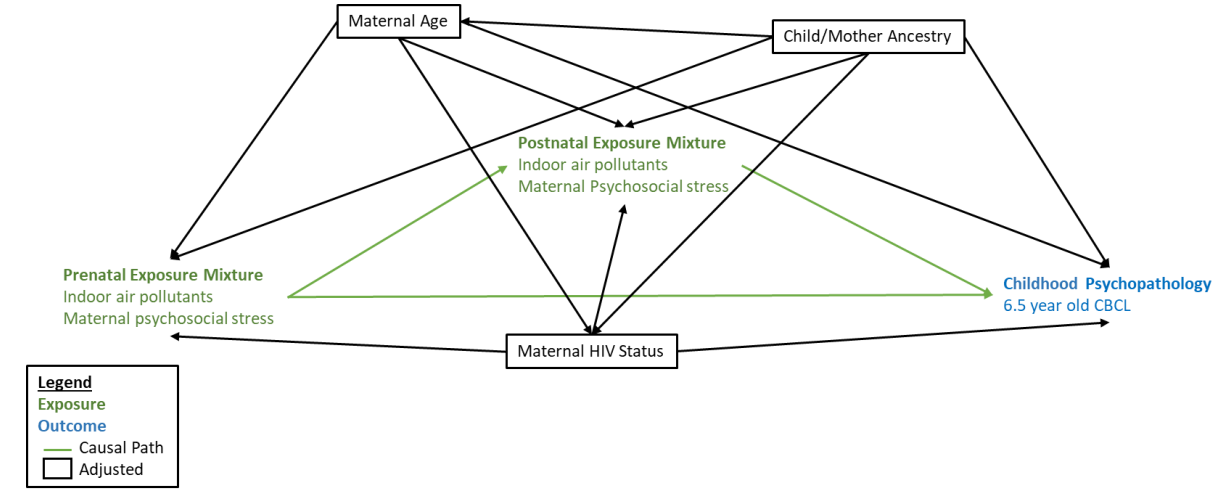


Figure 3-3*: DAGs of underlying causal pathways between pre- and postnatal exposure to indoor air pollutants and psychosocial factors including socioeconomic status, and childhood psychopathology at 6.5 years.* ***A.*** *DAG for prenatal exposure only.* ***B.*** *DAG for postnatal exposure only.* ***C.*** *DAG for pre- and postnatal exposure.*

The effect of postnatal exposures to indoor air pollution and psychosocial factors on CBCL at 6.5 years was also assessed using single-exposure linear regression models, Quantile G-Computation, and SOM. Postnatal single-exposure models were conducted and adjusted for confounding in the same way as prenatal single-exposure models, using maternal age and HIV status at baseline, ancestry and SES. Including principal components of the other group of exposures (indoor air pollutants or psychosocial factors) as confounders was also done as a sensitivity analysis. Postnatal mixture modeling (Quantile G-Computation and SOM) was also conducted and adjusted for confounding the same way as prenatal models.

Sensitive Periods of Exposure

To investigate sensitive periods of exposure to individual indoor air pollutants and psychosocial factors (prenatal vs. postnatal) we used the structured life course modeling approach (SLCMA)[111]. SLCMA is an established approach that can compare multiple competing theoretical models of life course modeling[112–114]. SLCMA uses least angle regression variable selection, a type of least absolute shrinkage and selection operator (LASSO) to determine which a priori determined life course hypothesis is most associated with an outcome. Based on the number of exposure periods and exploratory nature of this study, we investigated four life course hypotheses: sensitive periods (prenatal versus postnatal), accumulation of exposure over the pre- and postnatal periods, and interaction between pre- and postnatal period exposures. All single-exposure SLCMA models were adjusted for maternal age, maternal HIV status, ancestry, and SES (except for when SES was the exposure of interest).

To investigate sensitive periods of the indoor air pollution and psychosocial factor exposure mixture, we used SOM. As opposed to SLCMA which is a structured approach comparing a priori hypotheses, SOM is an unstructured approach that can compare ad hoc hypotheses. As discussed above, SOM creates and compares profiles of exposure mixtures. Using this method

in addition to SLCMA enhances our analysis because SOM compares pre- and postnatal exposure profiles experienced by our participants. To create SOM clusters identifying profiles of pre- and postnatal exposure, we added both pre- and postnatal exposures to the SOM algorithm at the same time. These SOM clusters represent combined pre- and postnatal exposure profiles. The SOM clusters were assigned to each participant and used as a categorical exposure variable in linear regression analysis. The linear regression model was adjusted for maternal HIV status and maternal age at baseline, and ancestry.

Results

Study Population Characteristics

Among our study population of n=599 participants, the average maternal age was 26.85 years (SD: 5.68), with nearly a quarter of mothers (n=134, 22.4%) HIV-infected at enrolment. Among the children, half were male (n=309, 51.6%), **(Table 3-2).** Median IAP exposures were higher in the prenatal period compared to the postnatal period. Median SES was slightly higher and food insecurity was lower in the postnatal period. Other psychosocial factor averages were similar in prenatal and postnatal periods **(Table 3-2)**. Indoor air pollutants were not highly correlated within or between time periods; psychosocial factors were moderately correlated within and between time periods **(Figure 3-4)**. At 6.5 years of age, the CBCL total problems score was highly correlated with both externalizing (Pearson rho = 0.91) and internalizing (Pearson Rho = 0.73) sub scales. Externalizing and internalizing sub scales were moderately correlated with each other (Pearson Rho = 0.48; **Table 3-3**).

Table 3-2: *Drakenstein Child Health Study (DCHS) population characteristics.*

n	599	
Maternal Age (mean (SD))	26.85 (5.68)	
Male Child (%)	309 (51.6)	
Child Ancestry (%)		
Black African	326 (54.4)	
Mixed Ancestry	273 (45.6)	
Mother HIV Positive (%)	134 (22.4)	
CBCL at 6.5 years		
Total Problems Score (median [IQR])	7.00 [3.00, 13.50]	
Externalizing Problems Score (median [IQR])	3.00 [1.00, 6.00]	
Internalizing Problems Score (median [IQR])	1.00 [0.00, 2.00]	
Exposures	Prenatal	Postnatal
PM10 µg/m3 (median [IQR])	35.59 [12.49, 69.14]	29.29 [12.52, 56.37]
CO mg/m3 (median [IQR])	0.00 [0.00, 85.00]	0.00 [0.00, 0.00]
Benzene µg/m3 (median [IQR])	4.34 [1.86, 11.39]	2.72 [0.92, 7.52]
Toluene µg/m3 (median [IQR])	17.63 [8.07, 50.15]	16.20 [6.62, 51.29]
NO2 µg/m3 (median [IQR])	7.43 [3.61, 13.23]	6.09 [2.94, 14.32]
SO2 µg/m3 (median [IQR])	0.00 [0.00, 0.30]	0.00 [0.00, 0.00]
Urine Cotinine ng/ml (median [IQR])	44.40 [10.85, 500.00]	-
SES Asset Sum (median [IQR])	7 [6, 8]	8 [6, 9]
Food Insecurity Total Score (median [IQR])	0 [0, 2]	0 [0, 0]
SRQ-20 Total Score (median [IQR])	4 [1, 6]	2 [0, 4]
Emotional IPV Score (median [IQR])	5 [4, 7]	4 [4, 6]
Physical IPV Score (median [IQR])	5 [5, 7]	5 [5, 7]
LEQ Total Score (median [IQR])	1 [0, 3]	1 [0, 2]
EPDS Total Score (median [IQR])	9 [6, 13]	8 [4, 12]
ASSIST Tobacco Score (median [IQR])	0 [0, 14]	0 [0, 21]
ASSIST Alcohol Score (median [IQR])	0 [0, 0]	0 [0, 0]

Abbreviations: Human Immunodeficiency Virus (HIV); Childhood Behavior Checklist (CBCL); Particulate Matter (PM10); Carbon monoxide (CO); Nitrogen dioxide (NO2); Sulfur dioxide (SO2); Socioeconomic Status (SES); Self-Reporting Questionnaire (SRQ-20); Edinburgh Postnatal Depression Scale (EPDS); Life Experiences Questionnaire (LEQ); Intimate Partner Violence (IPV); Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST)

Table 3-3: *Pearson Correlation between CBCL sub-scores at 6.5 years old.*

	Total Problems	Externalizing Problems	Internalizing Problems
Total Problems	1	0.91	0.73
Externalizing Problems	0.91	1	0.48
Internalizing Problems	0.73	0.48	1

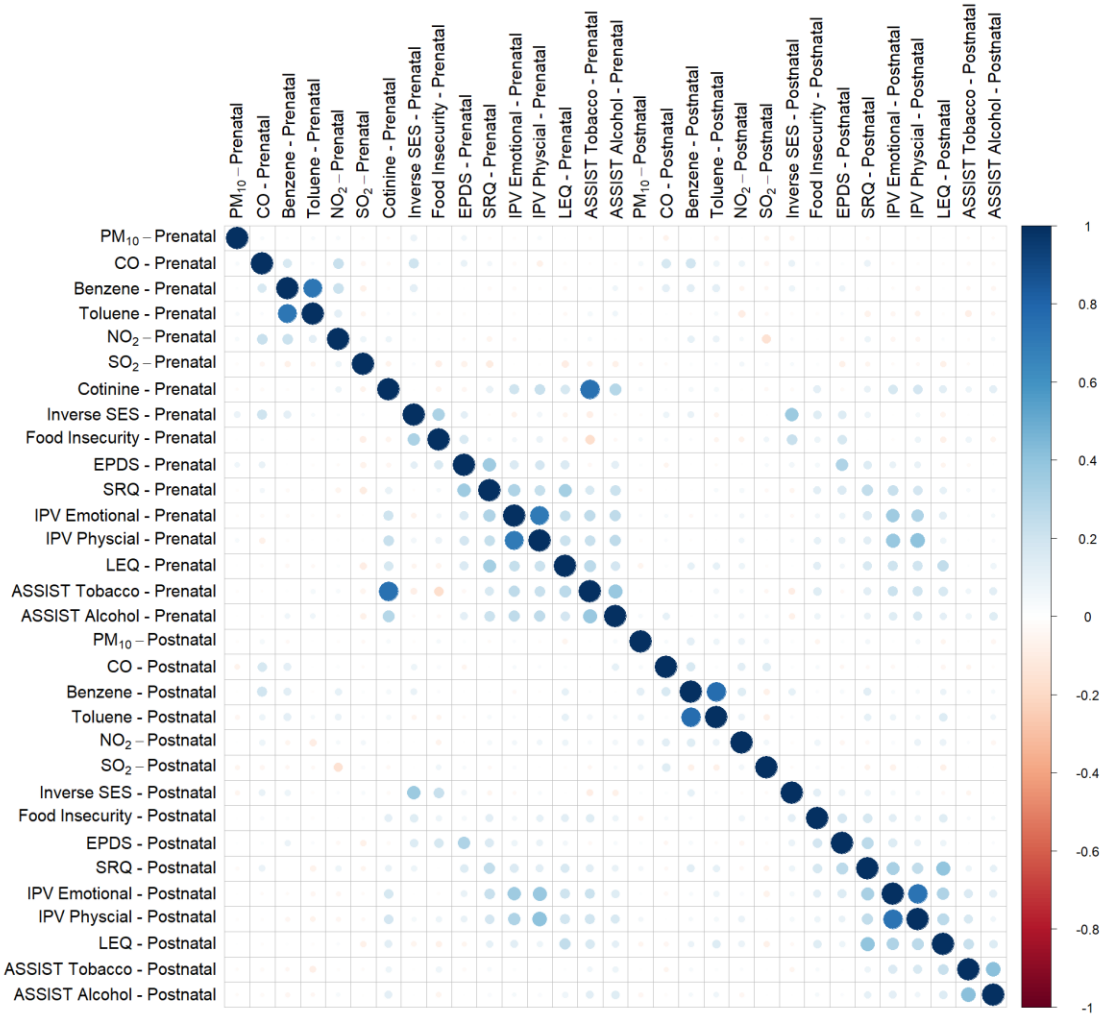


Figure 3-4: *Pearson correlation matrix with pre- and postnatal exposure measurements.*

Prenatal Exposure Analyses

In adjusted single-exposure linear regression models for the prenatal exposures a one-unit increase in log-transformed PM_{10} (beta: 0.08; 95% CI: 0.03, 0.13), psychological distress (SRQ) (beta: 0.10; 95% CI: 0.00, 0.20), Physical IPV (beta: 0.29; 95% CI: 0.03, 0.55), depression (EPDS) (beta: 0.16; 95% CI: 0.04, 0.28), and ASSIST Alcohol (beta: 0.11; 95% CI: 0.03, 0.19) were associated with an increase in the CBCL total problems score **(Table 3-4, Figure 3-5A)**. Adjusted single-exposure models investigating CBCL externalizing problems found associations between a one-unit increase in log-transformed prenatal Toluene (beta: 0.05; 95% CI: 0.00, 0.10), and ASSIST Alcohol (beta:0.11; 95% CI: 0.04, 0.18; **Table 3-4, Figure 3-5C)**. For CBCL

internalizing problems, we found associations with a one-unit increase in log-transformed prenatal PM_{10} (beta: 0.04; 95% CI: 0.00, 0.08), SRQ (beta: 0.09; 95% CI: 0.02, 0.17), and ASSIST Alcohol (beta: 0.07; 95% CI: 0.01, 0.13; **Table 3-4, Figure 3-5E)**. Results were similar in the complete cases analyses and when using other imputation seeds **(Table 3-4)**. Results were similar when single-exposure linear regression models were additionally adjusted for PCs of the other exposure group (IAP or PF). The only difference between the two adjustment sets was that in the extended models, NO_2 was associated with CBCL total problems and physical IPV was associated with CBCL externalizing problems.

Adjusted quantile g-computation models showed that the prenatal mixture was significantly associated with higher CBCL total scores (Psi beta: 0.32; p-value: 0.013) and externalizing (Psi beta: 0.35; p-value: 0.003) problems, and not with internalizing (Psi beta: 0.14; p-value: 0.19) problems **(Figure 3-6A-C)**. Prenatal ASSIST Alcohol score had the largest partial effect in both total and externalizing problems models **(Figure 3-7A-B)**.

Table 3-4: *Beta estimates and 95% CIs for individual prenatal exposure adjusted linear regression models. The common confounder linear regression models were adjusted for maternal HIV status, maternal age, ancestry, and socioeconomic status. Extended confounder set models using indoor air pollutant exposures were additionally adjusted principal components of psychosocial factors, and vice versa. Tables shows results from complete case models as well as multiple imputation (MI) models using 5 different random seeds (MI1 to MI5). MI5 models were presented in the main analysis.*

		Complete Case	MI1	MI2	MI3	MI4	MI5 (Analysis Sample)
		CBCL Total Problems					
PM_{10}	Extended Confounder Set	**0.08 (0.01, 0.16)**	**0.06 (0.01, 0.11)**	**0.06 (0.01, 0.11)**	**0.06 (0.01, 0.11)**	0.05 (0, 0.1)	**0.08 (0.03, 0.13)**
	Common Confounders	**0.08 (0.01, 0.16)**	**0.06 (0.01, 0.12)**	**0.06 (0.01, 0.11)**	**0.06 (0.01, 0.12)**	0.05 (0, 0.11)	**0.08 (0.03, 0.13)**
CO	Extended Confounder Set	0.01 (-0.03, 0.05)	0.01 (-0.02, 0.04)	0.01 (-0.02, 0.04)	0.01 (-0.02, 0.04)	0.02 (-0.01, 0.04)	0.01 (-0.01, 0.04)
	Common Confounders	0.01 (-0.02, 0.05)	0.01 (-0.02, 0.04)	0.01 (-0.02, 0.03)	0.01 (-0.02, 0.04)	0.02 (-0.01, 0.05)	0.01 (-0.01, 0.04)
Benzene	Extended Confounder Set	0.03 (-0.05, 0.11)	0.03 (-0.03, 0.09)	0.03 (-0.03, 0.08)	0.04 (-0.02, 0.09)	0.04 (-0.02, 0.1)	0.03 (-0.02, 0.09)
	Common Confounders	0.03 (-0.04, 0.11)	0.03 (-0.03, 0.09)	0.03 (-0.03, 0.08)	0.03 (-0.02, 0.09)	0.03 (-0.02, 0.09)	0.03 (-0.02, 0.09)
Toluene	Extended Confounder Set	0.04 (-0.02, 0.11)	0.03 (-0.02, 0.08)	0.03 (-0.02, 0.08)	0.04 (-0.01, 0.09)	0.02 (-0.03, 0.08)	0.04 (-0.01, 0.1)
	Common Confounders	0.04 (-0.02, 0.11)	0.03 (-0.02, 0.08)	0.03 (-0.02, 0.08)	0.04 (-0.02, 0.09)	0.02 (-0.03, 0.07)	0.04 (-0.01, 0.1)
NO_2	Extended Confounder Set	**0.11 (0.01, 0.22)**	**0.09 (0.01, 0.17)**	0.07 (-0.01, 0.14)	**0.08 (0, 0.16)**	**0.09 (0.02, 0.17)**	**0.08 (0.01, 0.16)**
	Common Confounders	0.1 (-0.01, 0.2)	0.08 (0, 0.15)	0.06 (-0.02, 0.14)	0.07 (-0.01, 0.15)	**0.09 (0.01, 0.16)**	0.08 (0, 0.16)
SO_2	Extended Confounder Set	0.12 (-0.05, 0.29)	-0.05 (-0.15, 0.06)	-0.05 (-0.16, 0.07)	0 (-0.13, 0.12)	-0.03 (-0.15, 0.09)	-0.02 (-0.14, 0.1)
	Common Confounders	0.09 (-0.07, 0.26)	-0.07 (-0.18, 0.04)	-0.07 (-0.18, 0.04)	-0.03 (-0.15, 0.09)	-0.05 (-0.17, 0.06)	-0.04 (-0.16, 0.08)

Cotinine	Extended Confounder Set	-0.1 (-0.2, -0.01)	-0.02 (-0.08, 0.04)	-0.03 (-0.09, 0.04)	-0.02 (-0.08, 0.05)	-0.03 (-0.09, 0.04)	-0.03 (-0.09, 0.04)
	Common Confounders	-0.08 (-0.16, -0.01)	0 (-0.06, 0.06)	0 (-0.06, 0.06)	0 (-0.06, 0.06)	0 (-0.06, 0.05)	0 (-0.06, 0.06)
Food Insecurity	Extended Confounder Set	-0.03 (-0.22, 0.15)	0.07 (-0.07, 0.21)	0.04 (-0.09, 0.18)	0.02 (-0.11, 0.16)	0.05 (-0.08, 0.18)	0.03 (-0.1, 0.17)
	Common Confounders	-0.05 (-0.24, 0.13)	0.07 (-0.06, 0.21)	0.05 (-0.09, 0.18)	0.03 (-0.11, 0.16)	0.05 (-0.08, 0.18)	0.03 (-0.1, 0.17)
SRQ	Extended Confounder Set	**0.14 (0, 0.28)**	**0.14 (0.04, 0.24)**	**0.12 (0.02, 0.22)**	**0.13 (0.03, 0.23)**	**0.13 (0.03, 0.23)**	**0.11 (0.01, 0.22)**
	Common Confounders	0.12 (-0.02, 0.25)	**0.13 (0.03, 0.23)**	**0.11 (0.01, 0.21)**	**0.12 (0.02, 0.22)**	**0.12 (0.02, 0.22)**	**0.1 (0, 0.2)**
IPV Emotional	Extended Confounder Set	0.11 (-0.21, 0.44)	0.18 (-0.06, 0.43)	0.16 (-0.08, 0.4)	0.16 (-0.08, 0.41)	0.14 (-0.11, 0.38)	0.16 (-0.09, 0.4)
	Common Confounders	0.07 (-0.26, 0.39)	0.18 (-0.06, 0.42)	0.16 (-0.08, 0.4)	0.16 (-0.08, 0.4)	0.14 (-0.1, 0.38)	0.16 (-0.08, 0.4)
IPV Physical	Extended Confounder Set	0.14 (-0.23, 0.5)	0.28 (0.01, 0.55)	0.21 (-0.06, 0.48)	0.24 (-0.03, 0.5)	0.16 (-0.11, 0.42)	0.29 (0.02, 0.55)
	Common Confounders	0.13 (-0.23, 0.49)	0.27 (0.01, 0.54)	0.23 (-0.04, 0.49)	0.23 (-0.03, 0.49)	0.16 (-0.1, 0.42)	0.29 (0.03, 0.55)
LEQ	Extended Confounder Set	0.07 (-0.09, 0.24)	0.05 (-0.07, 0.18)	0.04 (-0.08, 0.16)	0.03 (-0.09, 0.15)	0.08 (-0.04, 0.19)	0.07 (-0.05, 0.19)
	Common Confounders	0.07 (-0.1, 0.23)	0.05 (-0.07, 0.17)	0.04 (-0.08, 0.16)	0.02 (-0.1, 0.14)	0.07 (-0.04, 0.19)	0.07 (-0.05, 0.19)
EPDS	Extended Confounder Set	0.1 (-0.06, 0.26)	**0.17 (0.05, 0.29)**	**0.12 (0, 0.25)**	**0.14 (0.02, 0.26)**	**0.16 (0.04, 0.28)**	**0.16 (0.03, 0.28)**
	Common Confounders	0.11 (-0.06, 0.27)	**0.17 (0.05, 0.29)**	**0.13 (0.01, 0.25)**	**0.14 (0.02, 0.26)**	**0.16 (0.04, 0.28)**	**0.16 (0.04, 0.28)**
ASSIST Tobacco	Extended Confounder Set	0.01 (-0.13, 0.14)	-0.03 (-0.11, 0.05)	-0.01 (-0.1, 0.08)	0 (-0.09, 0.09)	0.02 (-0.08, 0.11)	0.02 (-0.08, 0.11)
	Common Confounders	-0.06 (-0.15, 0.03)	-0.01 (-0.08, 0.05)	0.01 (-0.06, 0.07)	0.01 (-0.06, 0.07)	0.01 (-0.05, 0.08)	0.02 (-0.04, 0.09)
ASSIST Alcohol	Extended Confounder Set	**0.14 (0.03, 0.25)**	**0.12 (0.03, 0.2)**	**0.12 (0.04, 0.2)**	**0.11 (0.03, 0.19)**	**0.11 (0.03, 0.19)**	**0.11 (0.03, 0.19)**

Inverse SES	Common Confounders	**0.11 (0, 0.22)**	**0.12 (0.04, 0.2)**	**0.12 (0.04, 0.2)**	**0.1 (0.03, 0.18)**	**0.11 (0.03, 0.19)**	**0.11 (0.03, 0.19)**
	Extended Confounder Set	0.15 (-0.28, 0.58)	-0.01 (-0.32, 0.3)	-0.01 (-0.32, 0.3)	0.01 (-0.31, 0.32)	0.02 (-0.29, 0.33)	-0.02 (-0.33, 0.29)
	Common Confounders	0.21 (-0.21, 0.62)	0.05 (-0.24, 0.35)	0.05 (-0.24, 0.35)	0.05 (-0.24, 0.35)	0.05 (-0.24, 0.35)	0.05 (-0.24, 0.35)
				CBCL Externalizing Problems			
PM_{10}	Extended Confounder Set	0.03 (-0.04, 0.1)	0.02 (-0.03, 0.07)	0.03 (-0.02, 0.08)	0.03 (-0.02, 0.08)	0.02 (-0.03, 0.07)	0.04 (0, 0.09)
	Common Confounders	0.03 (-0.04, 0.1)	0.03 (-0.02, 0.07)	0.03 (-0.02, 0.08)	0.03 (-0.02, 0.08)	0.02 (-0.03, 0.07)	0.04 (-0.01, 0.09)
CO	Extended Confounder Set	0.03 (-0.01, 0.06)	0.02 (-0.01, 0.04)	0.01 (-0.02, 0.03)	0.02 (-0.01, 0.04)	0.02 (-0.01, 0.04)	0.02 (-0.01, 0.05)
	Common Confounders	0.03 (-0.01, 0.06)	0.02 (-0.01, 0.04)	0.01 (-0.02, 0.03)	0.02 (-0.01, 0.04)	0.02 (-0.01, 0.04)	0.02 (-0.01, 0.05)
Benzene	Extended Confounder Set	0.05 (-0.02, 0.12)	0.04 (-0.01, 0.1)	0.04 (-0.01, 0.09)	**0.06 (0, 0.11)**	**0.06 (0.01, 0.11)**	0.05 (0, 0.1)
	Common Confounders	0.05 (-0.02, 0.12)	0.04 (-0.01, 0.1)	0.04 (-0.01, 0.09)	**0.05 (0, 0.11)**	**0.06 (0, 0.11)**	0.05 (0, 0.1)
Toluene	Extended Confounder Set	0.05 (-0.01, 0.11)	0.04 (-0.01, 0.09)	0.04 (-0.01, 0.08)	**0.05 (0, 0.1)**	0.04 (-0.01, 0.08)	0.05 (0, 0.09)
	Common Confounders	0.05 (-0.01, 0.11)	0.04 (-0.01, 0.09)	0.04 (-0.01, 0.09)	**0.05 (0, 0.1)**	0.04 (-0.01, 0.08)	**0.05 (0, 0.1)**
NO_2	Extended Confounder Set	0.08 (-0.02, 0.17)	0.05 (-0.02, 0.13)	0.04 (-0.03, 0.11)	0.06 (-0.01, 0.13)	0.05 (-0.03, 0.12)	0.05 (-0.03, 0.12)
	Common Confounders	0.06 (-0.03, 0.16)	0.04 (-0.03, 0.12)	0.03 (-0.04, 0.1)	0.05 (-0.02, 0.12)	0.04 (-0.03, 0.11)	0.04 (-0.03, 0.11)
SO_2	Extended Confounder Set	0.09 (-0.06, 0.25)	-0.02 (-0.12, 0.09)	-0.03 (-0.14, 0.08)	0.01 (-0.1, 0.12)	-0.01 (-0.12, 0.1)	-0.01 (-0.12, 0.1)
	Common Confounders	0.08 (-0.07, 0.23)	-0.03 (-0.13, 0.07)	-0.05 (-0.15, 0.06)	0 (-0.11, 0.11)	-0.03 (-0.14, 0.08)	-0.02 (-0.13, 0.09)
Cotinine	Extended Confounder Set	-0.1 (-0.19, -0.02)	-0.02 (-0.08, 0.04)	-0.02 (-0.08, 0.04)	-0.03 (-0.08, 0.03)	-0.03 (-0.09, 0.03)	-0.03 (-0.09, 0.03)

	Common Confounders	-0.08 (-0.15, -0.01)	-0.01 (-0.06, 0.04)	0 (-0.06, 0.05)	-0.01 (-0.06, 0.04)	-0.01 (-0.06, 0.05)	0 (-0.06, 0.05)
Food Insecurity	Extended Confounder Set	-0.03 (-0.2, 0.15)	0.04 (-0.08, 0.17)	0.03 (-0.1, 0.15)	0 (-0.13, 0.12)	0.04 (-0.08, 0.17)	0.02 (-0.11, 0.14)
	Common Confounders	-0.05 (-0.22, 0.13)	0.05 (-0.08, 0.17)	0.03 (-0.09, 0.15)	0 (-0.12, 0.13)	0.04 (-0.08, 0.17)	0.02 (-0.11, 0.14)
SRQ	Extended Confounder Set	0.11 (-0.02, 0.24)	**0.1 (0.01, 0.19)**	**0.09 (0, 0.19)**	0.1 (0, 0.19)	0.09 (0, 0.18)	0.08 (-0.02, 0.17)
	Common Confounders	0.1 (-0.03, 0.23)	0.09 (0, 0.18)	0.09 (-0.01, 0.18)	0.09 (0, 0.18)	0.08 (-0.01, 0.17)	0.07 (-0.02, 0.16)
IPV Emotional	Extended Confounder Set	0.12 (-0.18, 0.43)	0.16 (-0.07, 0.38)	0.14 (-0.08, 0.37)	0.12 (-0.1, 0.35)	0.12 (-0.11, 0.34)	0.15 (-0.08, 0.37)
	Common Confounders	0.07 (-0.23, 0.37)	0.15 (-0.08, 0.37)	0.14 (-0.08, 0.36)	0.11 (-0.11, 0.33)	0.1 (-0.12, 0.32)	0.14 (-0.08, 0.37)
IPV Physical	Extended Confounder Set	0.14 (-0.2, 0.48)	0.23 (-0.02, 0.47)	0.17 (-0.08, 0.42)	0.19 (-0.06, 0.43)	0.12 (-0.13, 0.36)	**0.24 (0, 0.49)**
	Common Confounders	0.11 (-0.22, 0.45)	0.21 (-0.03, 0.45)	0.17 (-0.07, 0.41)	0.16 (-0.08, 0.4)	0.1 (-0.14, 0.33)	0.24 (0, 0.48)
LEQ	Extended Confounder Set	0.08 (-0.08, 0.23)	0.02 (-0.09, 0.13)	-0.01 (-0.12, 0.11)	0.02 (-0.09, 0.13)	0.07 (-0.04, 0.17)	0.04 (-0.07, 0.16)
	Common Confounders	0.07 (-0.08, 0.23)	0.01 (-0.1, 0.13)	-0.01 (-0.12, 0.1)	0.01 (-0.1, 0.12)	0.06 (-0.05, 0.17)	0.04 (-0.07, 0.15)
EPDS	Extended Confounder Set	0.05 (-0.1, 0.2)	**0.12 (0.01, 0.24)**	0.09 (-0.03, 0.2)	0.1 (-0.02, 0.21)	**0.12 (0.01, 0.23)**	0.11 (0, 0.22)
	Common Confounders	0.05 (-0.1, 0.21)	**0.12 (0.01, 0.23)**	0.09 (-0.02, 0.2)	0.09 (-0.02, 0.2)	**0.11 (0, 0.22)**	0.11 (0, 0.22)
ASSIST Tobacco	Extended Confounder Set	-0.01 (-0.14, 0.11)	-0.03 (-0.11, 0.04)	-0.02 (-0.11, 0.06)	-0.01 (-0.1, 0.07)	0.01 (-0.08, 0.1)	0.01 (-0.08, 0.1)
	Common Confounders	-0.07 (-0.16, 0.01)	-0.02 (-0.08, 0.04)	-0.01 (-0.07, 0.05)	-0.01 (-0.07, 0.05)	0.01 (-0.06, 0.07)	0.01 (-0.05, 0.07)
ASSIST Alcohol	Extended Confounder Set	**0.14 (0.04, 0.24)**	**0.11 (0.03, 0.19)**	**0.11 (0.03, 0.18)**	**0.1 (0.03, 0.18)**	**0.11 (0.03, 0.18)**	**0.11 (0.04, 0.19)**
	Common Confounders	**0.11 (0.01, 0.2)**	**0.11 (0.03, 0.18)**	**0.1 (0.03, 0.18)**	**0.1 (0.03, 0.17)**	**0.1 (0.03, 0.18)**	**0.11 (0.04, 0.18)**

Inverse SES	Extended Confounder Set	0.08 (-0.32, 0.48)	-0.01 (-0.29, 0.28)	-0.01 (-0.3, 0.27)	0 (-0.29, 0.29)	0.03 (-0.25, 0.32)	-0.02 (-0.31, 0.26)
	Common Confounders	0.1 (-0.28, 0.48)	0.02 (-0.25, 0.3)	0.02 (-0.25, 0.3)	0.02 (-0.25, 0.3)	0.02 (-0.25, 0.3)	0.02 (-0.25, 0.3)
		CBCL Internalizing Problems					
PM_{10}	Extended Confounder Set	0.05 (-0.01, 0.1)	0.04 (0, 0.08)	0.04 (0, 0.08)	0.04 (0, 0.08)	0.03 (-0.01, 0.07)	**0.04 (0, 0.08)**
	Common Confounders	0.05 (-0.01, 0.1)	**0.04 (0, 0.08)**	0.04 (0, 0.08)	**0.04 (0, 0.08)**	0.03 (-0.01, 0.07)	**0.04 (0, 0.08)**
CO	Extended Confounder Set	0 (-0.02, 0.03)	-0.01 (-0.03, 0.01)	0 (-0.02, 0.02)	-0.01 (-0.03, 0.01)	-0.01 (-0.03, 0.01)	0 (-0.03, 0.02)
	Common Confounders	0 (-0.02, 0.03)	-0.01 (-0.03, 0.01)	0 (-0.02, 0.02)	-0.01 (-0.03, 0.02)	0 (-0.03, 0.02)	0 (-0.02, 0.02)
Benzene	Extended Confounder Set	-0.01 (-0.07, 0.05)	-0.02 (-0.06, 0.03)	-0.02 (-0.06, 0.03)	-0.01 (-0.05, 0.03)	-0.02 (-0.06, 0.03)	-0.01 (-0.05, 0.04)
	Common Confounders	-0.01 (-0.06, 0.05)	-0.01 (-0.06, 0.03)	-0.01 (-0.06, 0.03)	-0.01 (-0.05, 0.03)	-0.02 (-0.06, 0.03)	0 (-0.05, 0.04)
Toluene	Extended Confounder Set	-0.02 (-0.07, 0.03)	-0.01 (-0.05, 0.02)	-0.02 (-0.06, 0.02)	-0.01 (-0.05, 0.02)	-0.02 (-0.06, 0.02)	0 (-0.04, 0.03)
	Common Confounders	-0.02 (-0.07, 0.03)	-0.01 (-0.05, 0.03)	-0.01 (-0.05, 0.02)	-0.01 (-0.05, 0.03)	-0.02 (-0.06, 0.02)	0 (-0.04, 0.04)
NO_2	Extended Confounder Set	0.06 (-0.01, 0.14)	0.04 (-0.02, 0.1)	0.01 (-0.05, 0.06)	0.02 (-0.03, 0.08)	0.04 (-0.02, 0.1)	0.03 (-0.03, 0.09)
	Common Confounders	0.06 (-0.02, 0.13)	0.03 (-0.03, 0.09)	0 (-0.05, 0.06)	0.02 (-0.04, 0.07)	0.03 (-0.02, 0.09)	0.03 (-0.03, 0.08)
SO_2	Extended Confounder Set	0.11 (-0.01, 0.23)	-0.02 (-0.1, 0.06)	-0.01 (-0.1, 0.08)	0 (-0.09, 0.09)	-0.01 (-0.1, 0.08)	-0.01 (-0.1, 0.07)
	Common Confounders	0.09 (-0.04, 0.21)	-0.04 (-0.12, 0.04)	-0.03 (-0.11, 0.06)	-0.02 (-0.11, 0.07)	-0.02 (-0.11, 0.06)	-0.03 (-0.12, 0.06)
Cotinine	Extended Confounder Set	-0.02 (-0.09, 0.05)	0 (-0.05, 0.05)	-0.01 (-0.06, 0.04)	0 (-0.04, 0.05)	0 (-0.05, 0.05)	0 (-0.05, 0.05)
	Common Confounders	-0.01 (-0.07, 0.05)	0.01 (-0.04, 0.05)	0.01 (-0.04, 0.05)	0.01 (-0.03, 0.05)	0 (-0.04, 0.04)	0.01 (-0.04, 0.05)

Food Insecurity	Extended Confounder Set	-0.01 (-0.15, 0.13)	0.07 (-0.03, 0.17)	0.05 (-0.05, 0.15)	0.05 (-0.05, 0.15)	0.03 (-0.06, 0.13)	0.07 (-0.03, 0.17)
	Common Confounders	-0.02 (-0.16, 0.12)	0.07 (-0.03, 0.17)	0.05 (-0.05, 0.15)	0.05 (-0.05, 0.16)	0.03 (-0.06, 0.13)	0.07 (-0.03, 0.17)
SRQ	Extended Confounder Set	**0.13 (0.03, 0.23)**	**0.11 (0.03, 0.18)**	**0.08 (0.01, 0.16)**	**0.1 (0.03, 0.18)**	**0.1 (0.03, 0.18)**	**0.1 (0.02, 0.17)**
	Common Confounders	**0.11 (0.01, 0.21)**	**0.1 (0.03, 0.17)**	**0.08 (0, 0.15)**	**0.1 (0.02, 0.17)**	**0.1 (0.03, 0.17)**	**0.09 (0.02, 0.17)**
IPV Emotional	Extended Confounder Set	-0.08 (-0.32, 0.17)	-0.01 (-0.19, 0.17)	-0.01 (-0.19, 0.17)	-0.01 (-0.19, 0.17)	0.01 (-0.17, 0.19)	0 (-0.18, 0.19)
	Common Confounders	-0.08 (-0.32, 0.16)	0 (-0.18, 0.18)	0 (-0.18, 0.18)	0 (-0.18, 0.18)	0.01 (-0.17, 0.19)	0.01 (-0.17, 0.19)
IPV Physical	Extended Confounder Set	0.08 (-0.19, 0.35)	0.09 (-0.11, 0.29)	0.09 (-0.11, 0.29)	0.12 (-0.07, 0.32)	0.07 (-0.13, 0.26)	0.15 (-0.05, 0.34)
	Common Confounders	0.11 (-0.16, 0.37)	0.1 (-0.09, 0.3)	0.11 (-0.09, 0.3)	0.13 (-0.06, 0.32)	0.07 (-0.12, 0.26)	0.15 (-0.04, 0.35)
LEQ	Extended Confounder Set	0.01 (-0.11, 0.14)	0 (-0.09, 0.09)	0.01 (-0.08, 0.1)	-0.02 (-0.11, 0.07)	-0.02 (-0.11, 0.07)	0 (-0.09, 0.09)
	Common Confounders	0.02 (-0.11, 0.14)	0 (-0.09, 0.09)	0.01 (-0.08, 0.1)	-0.02 (-0.11, 0.07)	-0.01 (-0.1, 0.07)	0 (-0.09, 0.09)
EPDS	Extended Confounder Set	0.04 (-0.08, 0.16)	0.05 (-0.04, 0.14)	0.04 (-0.05, 0.13)	0.05 (-0.04, 0.15)	0.07 (-0.02, 0.16)	0.06 (-0.03, 0.15)
	Common Confounders	0.05 (-0.07, 0.17)	0.05 (-0.04, 0.14)	0.04 (-0.05, 0.14)	0.06 (-0.03, 0.15)	0.07 (-0.02, 0.16)	0.06 (-0.03, 0.15)
ASSIST Tobacco	Extended Confounder Set	0 (-0.1, 0.1)	-0.01 (-0.07, 0.05)	-0.01 (-0.08, 0.06)	-0.02 (-0.09, 0.05)	-0.02 (-0.09, 0.05)	-0.02 (-0.09, 0.05)
	Common Confounders	0 (-0.07, 0.06)	0 (-0.05, 0.05)	0 (-0.05, 0.05)	0 (-0.05, 0.05)	0 (-0.05, 0.05)	0 (-0.05, 0.05)
ASSIST Alcohol	Extended Confounder Set	**0.1 (0.02, 0.18)**	**0.07 (0.01, 0.13)**	**0.07 (0.01, 0.13)**	**0.07 (0.01, 0.13)**	**0.07 (0.01, 0.14)**	**0.07 (0.01, 0.13)**
	Common Confounders	**0.09 (0.01, 0.17)**	**0.07 (0.01, 0.13)**	**0.07 (0.01, 0.13)**	**0.07 (0.02, 0.13)**	**0.07 (0.01, 0.13)**	**0.07 (0.01, 0.13)**
Inverse SES	Extended Confounder Set	0.02 (-0.3, 0.34)	0.01 (-0.22, 0.24)	0.02 (-0.22, 0.25)	0.02 (-0.21, 0.26)	0.04 (-0.19, 0.27)	0.03 (-0.2, 0.26)

Common Confounders	0.09 (-0.21, 0.4)	0.06 (-0.16, 0.28)	0.06 (-0.16, 0.28)	0.06 (-0.16, 0.28)	0.06 (-0.16, 0.28)	0.06 (-0.16, 0.28)

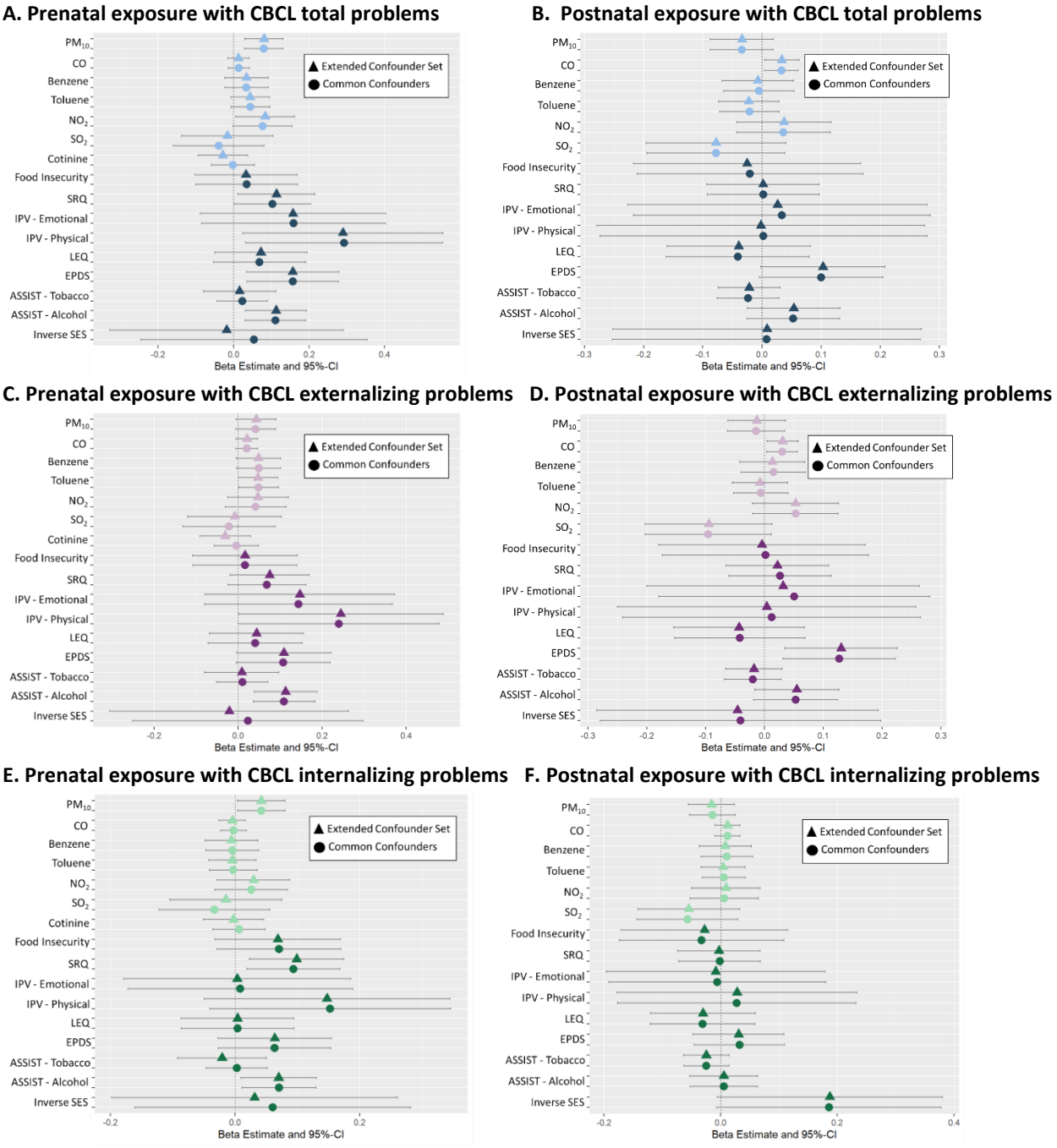
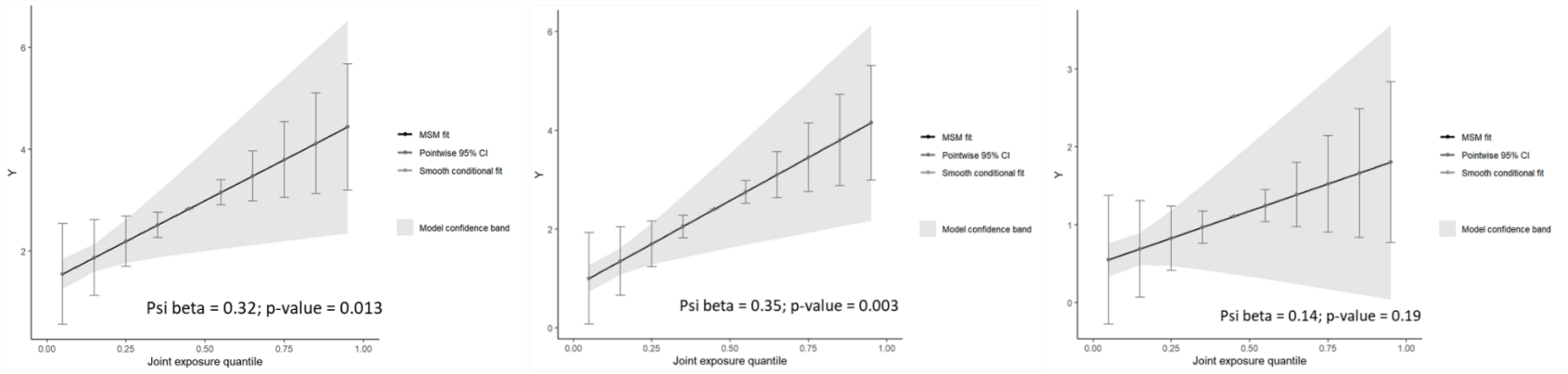


Figure 3-5: *Results from single-exposure linear regression models. Common confounder models adjusted for maternal age, maternal HIV status, ancestry, and SES (when SES is not the main exposure). In extended confounder models, indoor air pollutant models are additionally adjusted for principal components of psychosocial exposures, and vice versa.* ***A.*** *Associations between prenatal exposures and CBCL total problems.* ***B.*** *Associations between postnatal exposures and CBCL total problems.* ***C.*** *Associations between prenatal exposures and CBCL externalizing problems.* ***D.*** *Associations between postnatal exposures and CBCL externalizing problems.* ***E.*** *Associations between prenatal exposures and CBCL internalizing problems.* ***F.*** *Associations between postnatal exposures and CBCL internalizing problems.*

A. Prenatal exposure with total problems. **B. Prenatal exposure with externalizing problems.** **C. Prenatal exposure with internalizing problems**



D. Postnatal exposure with total problems. **E. Postnatal exposure with externalizing problems.** **F. Postnatal exposure with internalizing problems**

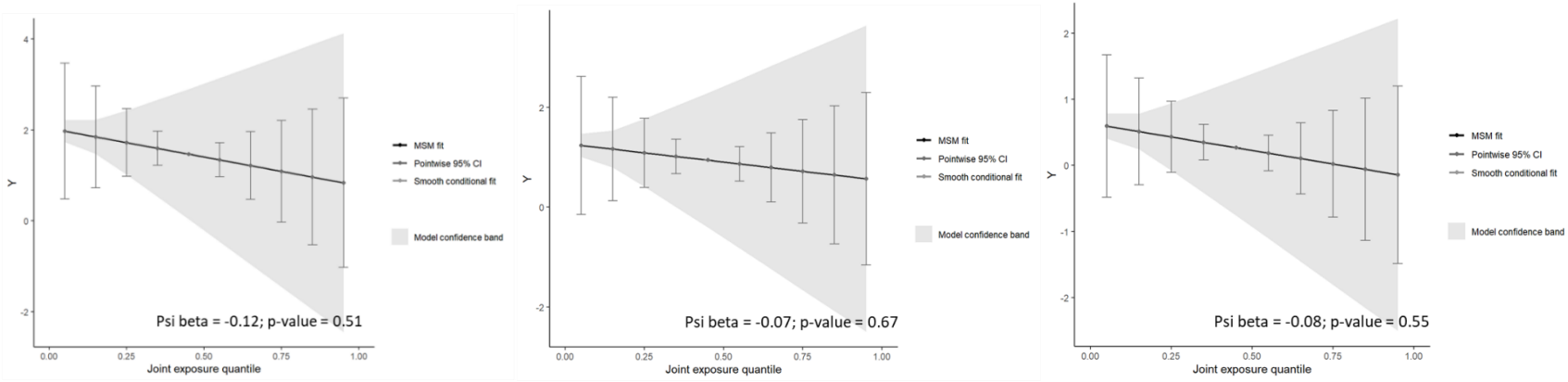
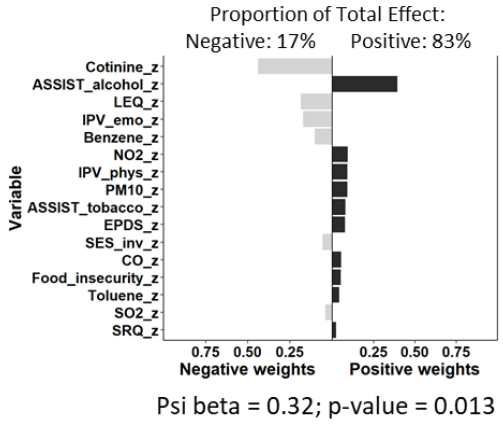


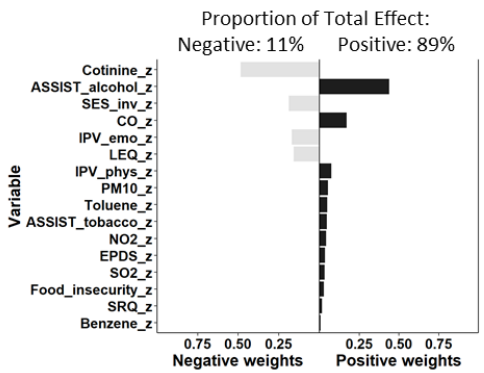
Figure 3-6: *Total mixture effect estimates from quantile G-computation models, adjusted for maternal age, maternal HIV status, and ancestry.* ***A.*** *association between prenatal exposure and CBCL total problems.* ***B.*** *Association between prenatal exposure mixture and CBCL externalizing problems.* ***C.*** *Association between prenatal exposure mixture and CBCL internalizing problems.* ***D.*** *Association between postnatal exposure mixture and CBCL total problems.* ***E.*** *Association between prenatal exposure mixture and CBCL externalizing problems.* ***F.*** *Association between postnatal exposure mixture and CBCL internalizing problems.*

A. Prenatal exposure with total problems.



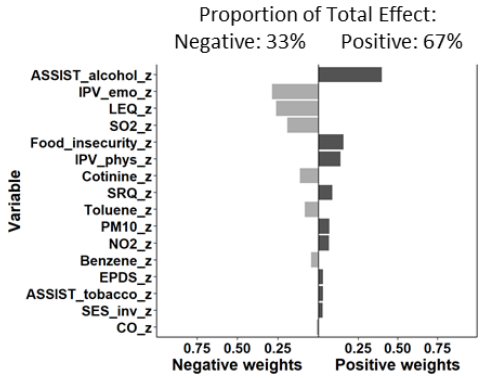
Psi beta = 0.32; p-value = 0.013

B. Prenatal exposure with externalizing problems.



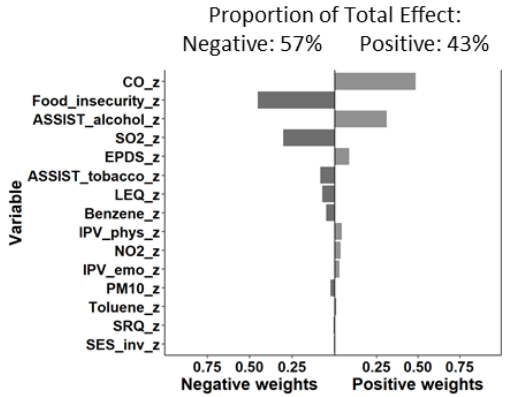
Psi beta = 0.35; p-value = 0.003

C. Prenatal exposure with internalizing problems



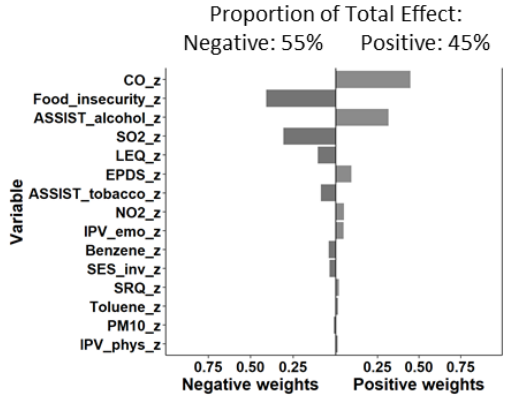
Psi beta = 0.14; p-value = 0.19

D. Postnatal exposure with total problems.



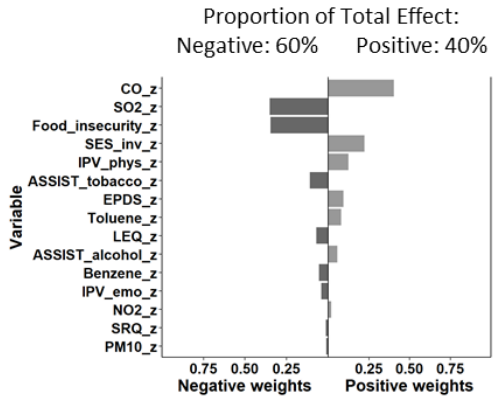
Psi beta = -0.12; p-value = 0.51

E. Postnatal exposure with externalizing problems.



Psi beta = -0.07; p-value = 0.67

F. Postnatal exposure with internalizing problems



Psi beta = -0.08; p-value = 0.55

Figure 3-7: *Weight of each exposure mixture component from quantile G-computation models, adjusted for maternal age, maternal HIV status, and ancestry. Weights from models were the total mixture effect was not significant should not be interpreted.* ***A.*** *Association between prenatal exposure mixture and CBCL total problems.* ***B.*** *Association between prenatal exposure mixture and CBCL externalizing problems.* ***C.*** *Association between prenatal exposure mixture and CBCL internalizing problems.* ***D.*** *Association between postnatal exposure mixture and CBCL total problems.* ***E****. Association between postnatal exposure mixture and CBCL externalizing problems.* ***F****. Association between postnatal exposure mixture and CBCL internalizing problems.*

SOM analysis using prenatal exposures grouped our study population in 4 exposure profile clusters. Cluster 3 was selected as the reference cluster because it had the lowest exposure to all pollutants and psychosocial factors, except for SO2 **(Table 3-5, Figure 3-8A)**. Using SOM cluster indicator as categorical exposure in adjusted linear regression model, cluster 2 (beta: 0.24; 95% CI: 0.10, 0.58), which was reflective of smoking and alcohol exposures (high cotinine level and ASSIST Tobacco and Alcohol scores) was associated with increasing CBCL total problems score, compared to the reference cluster 3. Additionally, cluster 4 (beta: 0.31; 95% CI: 0.07, 0.55), the cluster reflective of high levels of most psychosocial factors, was associated with increasing CBCL total problems score, compared to the reference cluster 3 **(Table 3-6, Figure 3-8B)**. Similarly, cluster 2 (beta: 0.27; 95% CI: 0.05, 0.50) and cluster 4 (beta: 0.26; 95% CI: 0.04, 0.48) were associated with increasing CBCL externalizing problems score, compared to the reference cluster 3 **(Table 3-6, Figure 3-8C)**. No SOM cluster was significantly associated with CBCL internalizing problems, though all were negatively associated compared to cluster 3 **(Table 3-6, Figure 3-8D)**.

Table 3-5: *Descriptive statistics (Median (IQR)) of prenatal indoor air pollutant and psychosocial factor exposures in prenatal Self-Organizing Map (SOM) exposure clusters.*

	SOM Cluster			
	1	**2**	**3**	**4**
n (%)	129 (21.5)	122 (20.4)	246 (41.1)	102 (17.0)
Maternal Age (mean (SD))	28.06 (5.94)	25.38 (5.12)	26.76 (5.65)	27.29 (5.70)
Male Child (%)	64 (49.6)	72 (59.0)	122 (49.6)	51 (50.0)
Mixed Ancestry (%)	32 (24.8)	108 (88.5)	65 (26.4)	68 (66.7)
Mother HIV Positive (%)	48 (37.2)	13 (10.7)	55 (22.4)	18 (17.6)
PM10 µg/m3 (median [IQR])	38.70 [15.32, 67.16]	49.06 [13.39, 73.10]	30.01 [12.09, 62.48]	34.12 [13.13, 70.24]
CO mg/m3 (median [IQR])	60.00 [0.00, 850.00]	0.00 [0.00, 187.50]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]
Benzene µg/m3 (median [IQR])	36.15 [11.95, 94.02]	5.25 [2.74, 10.97]	2.75 [0.90, 4.73]	3.13 [1.41, 8.24]
Toluene µg/m3 (median [IQR])	61.16 [27.01, 400.55]	18.29 [9.42, 54.46]	10.96 [4.36, 20.50]	14.21 [5.92, 40.09]
NO2 µg/m3 (median [IQR])	12.68 [6.69, 19.82]	9.23 [4.76, 13.17]	5.40 [2.28, 9.88]	7.12 [4.34, 11.66]
SO2 µg/m3 (median [IQR])	0.00 [0.00, 0.43]	0.00 [0.00, 0.26]	0.00 [0.00, 0.26]	0.00 [0.00, 0.23]
Urine Cotinine ng/ml (median [IQR])	24.80 [10.00, 58.10]	500.00 [500.00, 500.00]	17.00 [10.00, 50.88]	500.00 [37.47, 500.00]
SES Asset Sum (median [IQR])	6.00 [5.00, 7.00]	8.00 [7.00, 8.00]	8.00 [6.00, 8.00]	7.50 [6.00, 8.00]
Food Insecurity Total Score (median [IQR])	1.00 [0.00, 4.00]	0.00 [0.00, 0.00]	0.00 [0.00, 1.00]	0.00 [0.00, 2.75]
SRQ-20 Total Score (median [IQR])	2.00 [1.00, 5.00]	4.00 [2.00, 7.00]	3.00 [1.00, 6.00]	5.50 [4.00, 9.00]
Emotional IPV Score (median [IQR])	4.00 [4.00, 5.00]	5.00 [4.00, 6.00]	4.00 [4.00, 5.00]	10.00 [8.00, 13.00]
Physical IPV Score (median [IQR])	5.00 [5.00, 6.00]	5.00 [5.00, 6.00]	5.00 [5.00, 6.00]	11.00 [9.00, 14.00]

LEQ Total Score (median [IQR])	1.00 [0.00, 2.00]	2.00 [1.00, 4.00]	1.00 [0.00, 2.00]	3.00 [1.00, 5.00]
EPDS Total Score (median [IQR])	10.00 [7.00, 12.00]	9.00 [5.00, 12.00]	9.00 [6.00, 12.00]	11.00 [8.00, 15.00]
ASSIST Tobacco Score (median [IQR])	0.00 [0.00, 0.00]	24.00 [17.25, 25.00]	0.00 [0.00, 0.00]	7.50 [0.00, 24.00]
ASSIST Alcohol Score (median [IQR])	0.00 [0.00, 0.00]	0.00 [0.00, 6.25]	0.00 [0.00, 0.00]	0.00 [0.00, 15.00]

Abbreviations: Particulate Matter (PM10); Carbon monoxide (CO); Nitrogen dioxide (NO2); Sulfur dioxide (SO2); Socioeconomic Status (SES); Self-Reporting Questionnaire (SRQ-20); Edinburgh Postnatal Depression Scale (EPDS); Life Experiences Questionnaire (LEQ); Intimate Partner Violence (IPV); Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST)

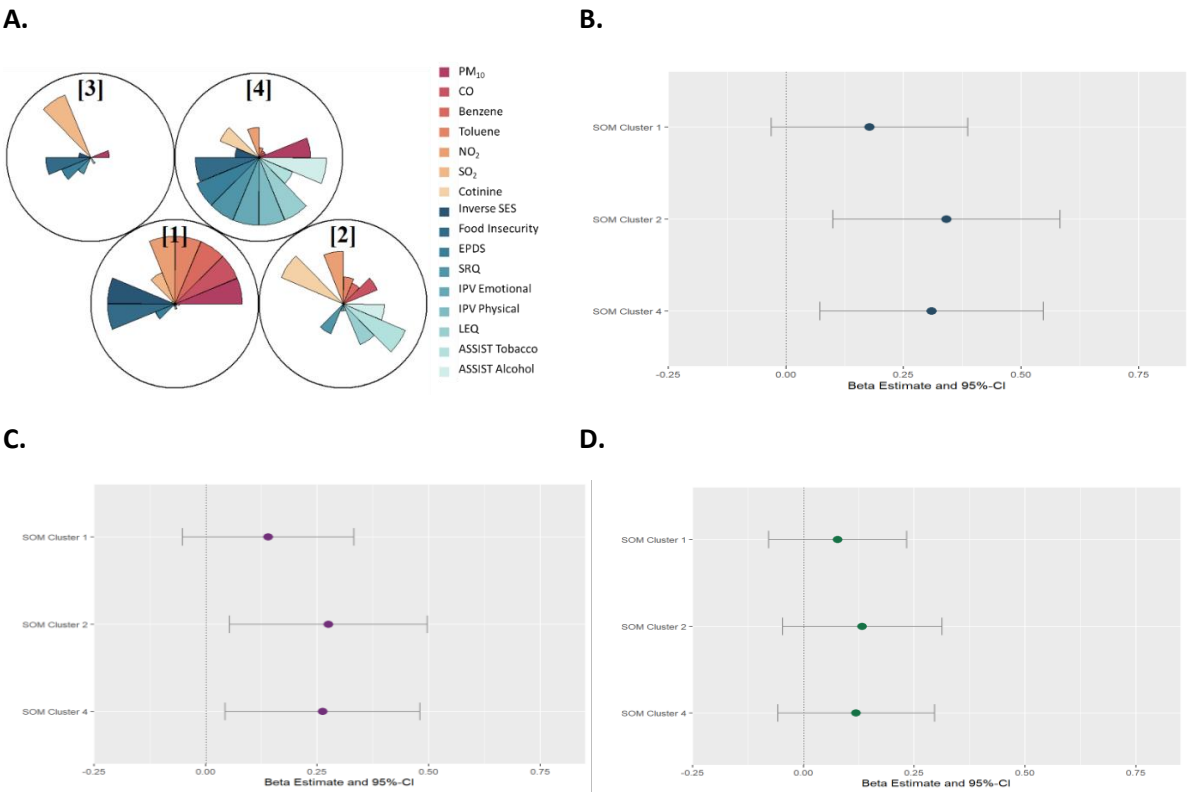


Figure 3-8: *Results from self-organizing map (SOM) analysis using prenatal indoor air pollutants and psychosocial factors.* ***A.*** *SOM clusters created using pre- natal indoor air pollutants and psychosocial factors****. B.*** *Associations between SOM clusters and CBCL total problems, adjusted by maternal age, maternal HIV status, and ancestry. SOM cluster 3 is used as the reference group.* ***C.*** *Associations between SOM clusters and CBCL externalizing problems, adjusted by maternal age, maternal HIV status, and ancestry. SOM cluster 3 is used as the reference group.* ***D.*** *Associations between SOM clusters and CBCL internalizing problems, adjusted by maternal age, maternal HIV status, and ancestry. SOM cluster 3 is used as the reference group.*

Table 3-6: *Joint exposure models using prenatal exposure SOM clusters as a joint exposure variable, OR and 95% CIs from adjusted linear regression models. Linear regression models adjusted for maternal HIV status, maternal age, and ancestry.*

	Total Problems
	Beta (95% CI)
Cluster 1	0.18 (-0.03, 0.39)
Cluster 2	**0.34 (0.10, 0.58)**
Cluster 3	REF
Cluster 4	**0.31 (0.07, 0.55)**
	Externalizing Problems
	Beta (95% CI)
Cluster 1	0.14 (-0.05, 0.33)
Cluster 2	**0.27 (0.05, 0.50)**
Cluster 3	REF
Cluster 4	**0.26 (0.04, 0.48)**
	Internalizing Problems
	Beta (95% CI)
Cluster 1	0.08 (-0.08, 0.23)
Cluster 2	0.09 (-0.05, 0.31)
Cluster 3	REF
Cluster 4	0.09 (-0.06, 0.30)

Postnatal Exposure Analyses

In adjusted single-exposure models for the postnatal exposures, only a one-unit increase in log-transformed CO (beta: 0.03; 95% CI: 0.00, 0.06) was associated with CBCL total problems **(Table 3-7, Figure 3-5B)**. A one-unit increase in log-transformed CO (beta: 0.03; 95% CI: 0.00, 0.06) and EPDS (beta: 0.13; 95% CI: 0.03, 0.23) were associated with CBCL externalizing problems **(Table 3-7, Figure 3-5D)**. No postnatal exposures were significantly associated with CBCL internalizing problems in adjusted single-exposure models **(Table 3-7, Figure 3-5F)**. Results were similar in the complete cases analyses and when using other imputation seeds **(Table 3-7).**

The postnatal exposure mixture was not significantly associated with any CBCL outcome in quantile g-computation model **(Figure 3-6D-F, Figure 3-7D-F)**.

SOM analysis using postnatal exposures grouped our study population in 4 exposure profile clusters, which differed from prenatal clusters **(Table 3-8, Figure 3-9A)**. For linear regression modeling, cluster 3 was again used as the reference group as it had the lowest exposure medians for all exposures **(Table 3-8)**. No postnatal exposure cluster, compared to the reference cluster 3, was significantly associated with any CBCL outcome **(Table 3-9, Figure 3-9B-D)**.

Sensitive Period Analyses

Single-exposure SLCMA analysis for CBCL total problems score confirmed the prenatal sensitive period as the most likely life course model for PM10, psychological distress (SRQ) and Physical IPV, and the postnatal sensitive period for CO. However, an accumulation life course model was most supported for depression (EPDS) and ASSIST Alcohol. Additionally, an interaction life course model was most supported for Emotional IPV. Similar patterns were seen for CBCL internalizing and externalizing problems **(Table 3-10)**.

SOM analysis with both prenatal and postnatal exposures grouped our study population in 6 exposure profile clusters. Custer 6 was selected as the reference group for regression analyses because it has the lowest median exposure values for most exposures **(Table 3-1, Figure 3-10A)**. Adjusted linear regression models using SOM cluster as the exposure found cluster 1 (beta: 0.38; 95% CI: 0.14, 0.62), characterized by low SES, high EPDS and food insecurity scores in both pre- and postnatal periods as well as high prenatal indoor air pollution, was significantly associated with CBCL total problems, compared to the reference cluster 6 **(Table 3-2, Figure 3-10B)**. Cluster 1 (beta: 0.29; 95% CI: 0.07, 0.51) was also associated with CBCL externalizing problems, compared to the reference cluster 6 **(Table 3-2, Figure 3-10C)**. No SOM cluster was associated with CBCL internalizing problems score **(Table 3-2, Figure 3-10D)**.

Table 3-7: *Beta estimates and 95% CIs for individual postnatal exposure adjusted linear regression models. The common confounders linear regression models were adjusted for maternal HIV status, maternal age, ancestry, and socioeconomic status. Extended confounder set models using indoor air pollutant exposures were additionally adjusted principal components of psychosocial factors, and vice versa. Tables shows results from complete case models as well as multiple imputation (MI) models using 5 different random seeds (MI1 to MI5). MI5 models were presented in the main analysis.*

		Complete Case	MI1	MI2	MI3	MI4	MI5 (Analysis Sample)
		CBCL Total Problems					
PM_{10}	Extended Confounder Set	0.05 (-0.09, 0.18)	-0.02 (-0.07, 0.03)	-0.01 (-0.06, 0.04)	-0.01 (-0.06, 0.05)	-0.03 (-0.08, 0.02)	-0.03 (-0.09, 0.02)
	Common Confounders	0.04 (-0.1, 0.17)	-0.02 (-0.07, 0.03)	-0.01 (-0.06, 0.04)	0 (-0.06, 0.05)	-0.03 (-0.08, 0.02)	-0.03 (-0.09, 0.02)
CO	Extended Confounder Set	0.06 (-0.01, 0.14)	0.03 (0, 0.05)	**0.03 (0, 0.06)**	**0.04 (0.01, 0.07)**	0.02 (-0.01, 0.05)	**0.03 (0, 0.06)**
	Common Confounders	0.06 (-0.02, 0.13)	0.03 (0, 0.05)	**0.03 (0, 0.06)**	**0.03 (0.01, 0.06)**	0.02 (-0.01, 0.05)	**0.03 (0, 0.06)**
Benzene	Extended Confounder Set	-0.07 (-0.24, 0.1)	0 (-0.06, 0.05)	-0.02 (-0.07, 0.04)	-0.05 (-0.11, 0.01)	-0.03 (-0.1, 0.03)	-0.01 (-0.07, 0.05)
	Common Confounders	-0.06 (-0.23, 0.1)	0 (-0.06, 0.05)	-0.01 (-0.07, 0.04)	-0.04 (-0.1, 0.02)	-0.03 (-0.09, 0.03)	-0.01 (-0.06, 0.05)
Toluene	Extended Confounder Set	-0.04 (-0.17, 0.09)	0 (-0.04, 0.05)	0 (-0.05, 0.05)	-0.02 (-0.07, 0.03)	-0.02 (-0.07, 0.03)	-0.02 (-0.07, 0.03)
	Common Confounders	-0.05 (-0.18, 0.08)	0 (-0.05, 0.05)	0 (-0.05, 0.05)	-0.01 (-0.06, 0.04)	-0.02 (-0.07, 0.03)	-0.02 (-0.07, 0.03)
NO_2	Extended Confounder Set	-0.01 (-0.25, 0.23)	0 (-0.09, 0.09)	0.01 (-0.08, 0.09)	0.04 (-0.04, 0.13)	-0.02 (-0.1, 0.06)	0.04 (-0.04, 0.12)
	Common Confounders	0 (-0.23, 0.23)	0 (-0.09, 0.09)	0.01 (-0.08, 0.09)	0.05 (-0.03, 0.13)	-0.01 (-0.09, 0.06)	0.04 (-0.04, 0.12)
SO_2	Extended Confounder Set	-0.11 (-0.56, 0.34)	-0.05 (-0.19, 0.09)	-0.06 (-0.2, 0.08)	-0.11 (-0.22, -0.01)	-0.08 (-0.21, 0.05)	-0.08 (-0.2, 0.04)
	Common Confounders	-0.06 (-0.49, 0.37)	-0.05 (-0.18, 0.09)	-0.07 (-0.21, 0.07)	-0.12 (-0.22, -0.02)	-0.08 (-0.21, 0.04)	-0.08 (-0.19, 0.04)

Food Insecurity	Extended Confounder Set	0.01 (-0.57, 0.59)	-0.06 (-0.26, 0.14)	-0.02 (-0.22, 0.18)	0.04 (-0.15, 0.23)	0.04 (-0.15, 0.23)	-0.02 (-0.22, 0.17)
	Common Confounders	-0.05 (-0.57, 0.47)	-0.06 (-0.25, 0.14)	-0.03 (-0.23, 0.18)	0.03 (-0.16, 0.22)	0.04 (-0.14, 0.23)	-0.02 (-0.21, 0.17)
SRQ	Extended Confounder Set	0.2 (-0.08, 0.48)	0.04 (-0.06, 0.14)	**0.1 (0, 0.19)**	0.04 (-0.06, 0.14)	0.05 (-0.04, 0.15)	0 (-0.09, 0.1)
	Common Confounders	0.19 (-0.08, 0.46)	0.04 (-0.06, 0.14)	**0.1 (0.01, 0.2)**	0.03 (-0.06, 0.13)	0.05 (-0.04, 0.15)	0 (-0.09, 0.1)
IPV Emotional	Extended Confounder Set	0 (-0.76, 0.76)	-0.03 (-0.27, 0.22)	0.17 (-0.08, 0.43)	0.08 (-0.14, 0.29)	0.06 (-0.19, 0.31)	0.03 (-0.23, 0.28)
	Common Confounders	0.01 (-0.73, 0.74)	-0.03 (-0.27, 0.21)	0.18 (-0.07, 0.44)	0.07 (-0.15, 0.29)	0.05 (-0.2, 0.29)	0.03 (-0.22, 0.28)
IPV Physical	Extended Confounder Set	0.15 (-0.76, 1.07)	-0.01 (-0.29, 0.27)	0.09 (-0.21, 0.39)	0.09 (-0.17, 0.35)	0.17 (-0.1, 0.44)	0 (-0.28, 0.28)
	Common Confounders	0.2 (-0.67, 1.07)	-0.01 (-0.29, 0.27)	0.1 (-0.2, 0.39)	0.08 (-0.18, 0.34)	0.15 (-0.12, 0.42)	0 (-0.27, 0.28)
LEQ	Extended Confounder Set	0.02 (-0.39, 0.43)	0.02 (-0.1, 0.15)	**0.14 (0.01, 0.27)**	0.11 (-0.02, 0.24)	0.08 (-0.05, 0.21)	-0.04 (-0.16, 0.08)
	Common Confounders	0.02 (-0.37, 0.41)	0.02 (-0.1, 0.15)	**0.14 (0.02, 0.27)**	0.11 (-0.02, 0.23)	0.08 (-0.05, 0.21)	-0.04 (-0.16, 0.08)
EPDS	Extended Confounder Set	0.27 (-0.11, 0.64)	0.08 (-0.03, 0.19)	**0.15 (0.04, 0.26)**	**0.14 (0.03, 0.24)**	0.09 (-0.02, 0.2)	0.1 (0, 0.21)
	Common Confounders	0.28 (-0.09, 0.64)	0.08 (-0.03, 0.19)	**0.15 (0.05, 0.26)**	**0.14 (0.03, 0.24)**	0.09 (-0.01, 0.19)	0.1 (0, 0.2)
ASSIST Tobacco	Extended Confounder Set	-0.16 (-0.38, 0.06)	0 (-0.06, 0.07)	0.01 (-0.06, 0.08)	0.03 (-0.07, 0.12)	0 (-0.07, 0.08)	-0.02 (-0.07, 0.03)
	Common Confounders	-0.16 (-0.38, 0.05)	0 (-0.06, 0.07)	0.01 (-0.06, 0.08)	0.03 (-0.06, 0.12)	0 (-0.07, 0.08)	-0.02 (-0.08, 0.03)
ASSIST Alcohol	Extended Confounder Set	-0.16 (-0.38, 0.06)	0.01 (-0.06, 0.08)	0 (-0.06, 0.06)	0.03 (-0.07, 0.12)	0.01 (-0.08, 0.1)	0.05 (-0.02, 0.13)
	Common Confounders	-0.16 (-0.38, 0.05)	0.01 (-0.06, 0.08)	0 (-0.06, 0.06)	0.03 (-0.06, 0.12)	0.01 (-0.08, 0.1)	0.05 (-0.03, 0.13)
Inverse SES	Extended Confounder Set	0.1 (-0.71, 0.9)	-0.03 (-0.3, 0.24)	0.08 (-0.19, 0.34)	-0.06 (-0.33, 0.21)	-0.12 (-0.37, 0.13)	0.01 (-0.25, 0.27)

	Common Confounders	0.11 (-0.67, 0.89)	-0.03 (-0.29, 0.24)	0.08 (-0.19, 0.34)	-0.06 (-0.32, 0.21)	-0.11 (-0.36, 0.14)	0.01 (-0.25, 0.27)
		CBCL Externalizing Problems					
PM_{10}	Extended Confounder Set	0.02 (-0.1, 0.13)	-0.01 (-0.06, 0.04)	0 (-0.05, 0.05)	0 (-0.05, 0.05)	-0.01 (-0.05, 0.04)	-0.01 (-0.06, 0.04)
	Common Confounders	0 (-0.11, 0.12)	-0.01 (-0.06, 0.04)	0 (-0.05, 0.05)	0 (-0.05, 0.05)	-0.01 (-0.05, 0.04)	-0.01 (-0.06, 0.03)
CO	Extended Confounder Set	0.06 (-0.01, 0.12)	**0.03 (0.01, 0.06)**	**0.03 (0.01, 0.06)**	**0.03 (0, 0.06)**	0.02 (-0.01, 0.04)	**0.03 (0, 0.06)**
	Common Confounders	0.05 (-0.01, 0.12)	**0.03 (0.01, 0.05)**	**0.03 (0.01, 0.06)**	**0.03 (0, 0.06)**	0.02 (-0.01, 0.04)	**0.03 (0, 0.06)**
Benzene	Extended Confounder Set	-0.03 (-0.17, 0.12)	0.01 (-0.04, 0.06)	-0.01 (-0.06, 0.04)	-0.03 (-0.08, 0.03)	-0.01 (-0.07, 0.04)	0.01 (-0.04, 0.07)
	Common Confounders	-0.01 (-0.15, 0.14)	0.01 (-0.04, 0.06)	-0.01 (-0.06, 0.05)	-0.02 (-0.08, 0.03)	-0.01 (-0.06, 0.05)	0.02 (-0.04, 0.07)
Toluene	Extended Confounder Set	-0.01 (-0.12, 0.11)	0.02 (-0.02, 0.06)	0.01 (-0.03, 0.06)	-0.01 (-0.06, 0.04)	-0.01 (-0.06, 0.04)	-0.01 (-0.05, 0.04)
	Common Confounders	0 (-0.11, 0.11)	0.02 (-0.03, 0.06)	0.01 (-0.03, 0.06)	0 (-0.05, 0.05)	-0.01 (-0.05, 0.04)	-0.01 (-0.05, 0.04)
NO_2	Extended Confounder Set	0.02 (-0.19, 0.22)	0.02 (-0.06, 0.1)	0.02 (-0.06, 0.09)	0.07 (0, 0.15)	-0.01 (-0.08, 0.06)	0.05 (-0.02, 0.13)
	Common Confounders	0.05 (-0.14, 0.25)	0.02 (-0.06, 0.1)	0.01 (-0.06, 0.09)	0.08 (0, 0.15)	-0.01 (-0.08, 0.06)	0.05 (-0.02, 0.13)
SO_2	Extended Confounder Set	-0.29 (-0.67, 0.08)	-0.1 (-0.23, 0.03)	-0.13 (-0.27, 0)	-0.09 (-0.18, 0)	-0.1 (-0.22, 0.02)	-0.09 (-0.2, 0.01)
	Common Confounders	-0.31 (-0.67, 0.06)	-0.1 (-0.22, 0.03)	-0.14 (-0.27, -0.01)	-0.09 (-0.19, 0)	-0.1 (-0.22, 0.01)	-0.1 (-0.2, 0.01)
Food Insecurity	Extended Confounder Set	-0.27 (-0.75, 0.21)	-0.04 (-0.22, 0.14)	0.02 (-0.16, 0.21)	0.02 (-0.16, 0.19)	0.05 (-0.12, 0.22)	0 (-0.18, 0.17)
	Common Confounders	-0.41 (-0.85, 0.02)	-0.04 (-0.23, 0.14)	0.01 (-0.17, 0.2)	0.02 (-0.16, 0.19)	0.05 (-0.12, 0.22)	0 (-0.17, 0.18)
SRQ	Extended Confounder Set	0.18 (-0.05, 0.41)	0.04 (-0.05, 0.13)	0.08 (-0.01, 0.17)	0.04 (-0.05, 0.13)	0.04 (-0.05, 0.13)	0.02 (-0.07, 0.11)

IPV Emotional	Common Confounders	0.16 (-0.07, 0.39)	0.04 (-0.05, 0.13)	0.09 (0, 0.17)	0.04 (-0.05, 0.12)	0.04 (-0.05, 0.13)	0.03 (-0.06, 0.11)
	Extended Confounder Set	-0.01 (-0.65, 0.62)	-0.02 (-0.24, 0.2)	0.1 (-0.13, 0.34)	0.07 (-0.13, 0.27)	0.02 (-0.2, 0.25)	0.03 (-0.2, 0.26)
IPV Physical	Common Confounders	0.01 (-0.62, 0.64)	-0.02 (-0.24, 0.2)	0.12 (-0.11, 0.35)	0.06 (-0.14, 0.26)	0.02 (-0.21, 0.25)	0.05 (-0.18, 0.28)
	Extended Confounder Set	-0.17 (-0.93, 0.59)	-0.06 (-0.31, 0.2)	0.06 (-0.21, 0.34)	0.05 (-0.19, 0.28)	0.1 (-0.15, 0.35)	0 (-0.25, 0.26)
LEQ	Common Confounders	-0.07 (-0.82, 0.67)	-0.06 (-0.31, 0.2)	0.08 (-0.19, 0.35)	0.04 (-0.2, 0.28)	0.08 (-0.17, 0.33)	0.01 (-0.24, 0.27)
	Extended Confounder Set	-0.04 (-0.38, 0.29)	-0.03 (-0.14, 0.09)	0.08 (-0.03, 0.2)	0.05 (-0.07, 0.17)	0.05 (-0.07, 0.17)	-0.04 (-0.15, 0.07)
	Common Confounders	-0.06 (-0.39, 0.28)	-0.03 (-0.14, 0.09)	0.09 (-0.03, 0.2)	0.04 (-0.07, 0.16)	0.04 (-0.08, 0.16)	-0.04 (-0.15, 0.07)
EPDS	Extended Confounder Set	0.18 (-0.13, 0.5)	**0.11 (0.01, 0.21)**	**0.14 (0.04, 0.24)**	**0.14 (0.04, 0.23)**	**0.1 (0, 0.2)**	**0.13 (0.03, 0.23)**
	Common Confounders	0.2 (-0.11, 0.52)	**0.11 (0.01, 0.21)**	**0.14 (0.05, 0.24)**	**0.14 (0.04, 0.23)**	**0.1 (0.01, 0.2)**	**0.13 (0.03, 0.22)**
ASSIST Tobacco	Extended Confounder Set	-0.08 (-0.26, 0.11)	0.01 (-0.05, 0.07)	0.01 (-0.05, 0.08)	0.03 (-0.05, 0.12)	0.02 (-0.05, 0.08)	-0.02 (-0.07, 0.03)
	Common Confounders	-0.08 (-0.26, 0.11)	0.01 (-0.05, 0.07)	0.02 (-0.05, 0.08)	0.04 (-0.05, 0.12)	0.02 (-0.05, 0.09)	-0.02 (-0.07, 0.03)
ASSIST Alcohol	Extended Confounder Set	-0.08 (-0.26, 0.11)	0.01 (-0.05, 0.08)	0 (-0.05, 0.06)	0.03 (-0.05, 0.12)	0.02 (-0.06, 0.11)	0.05 (-0.02, 0.13)
	Common Confounders	-0.08 (-0.26, 0.11)	0.01 (-0.05, 0.08)	0.01 (-0.05, 0.06)	0.04 (-0.05, 0.12)	0.03 (-0.06, 0.11)	0.05 (-0.02, 0.12)
Inverse SES	Extended Confounder Set	-0.53 (-1.19, 0.13)	-0.03 (-0.28, 0.21)	0.01 (-0.24, 0.25)	-0.13 (-0.38, 0.11)	-0.14 (-0.37, 0.09)	-0.05 (-0.28, 0.19)
	Common Confounders	-0.49 (-1.15, 0.17)	-0.04 (-0.28, 0.2)	0 (-0.24, 0.25)	-0.13 (-0.38, 0.12)	-0.13 (-0.36, 0.1)	-0.04 (-0.28, 0.2)
		CBCL Internalizing Problems					
PM_{10}	Extended Confounder Set	0.09 (-0.03, 0.2)	0.01 (-0.03, 0.04)	0.03 (-0.01, 0.07)	0.01 (-0.03, 0.05)	0.01 (-0.03, 0.05)	-0.02 (-0.05, 0.02)

CO	Common Confounders	0.09 (-0.02, 0.19)	0.01 (-0.03, 0.04)	0.03 (-0.01, 0.07)	0.01 (-0.03, 0.05)	0.01 (-0.03, 0.05)	-0.01 (-0.05, 0.03)
	Extended Confounder Set	0.04 (-0.02, 0.11)	0.01 (-0.01, 0.03)	0 (-0.02, 0.02)	0.01 (-0.01, 0.03)	0 (-0.02, 0.02)	0.01 (-0.01, 0.03)
Benzene	Common Confounders	0.04 (-0.02, 0.1)	0.01 (-0.01, 0.03)	0 (-0.02, 0.02)	0.01 (-0.01, 0.03)	0 (-0.02, 0.02)	0.01 (-0.01, 0.03)
	Extended Confounder Set	0 (-0.14, 0.14)	-0.02 (-0.06, 0.03)	-0.01 (-0.05, 0.03)	-0.03 (-0.07, 0.02)	-0.02 (-0.07, 0.02)	0.01 (-0.04, 0.05)
Toluene	Common Confounders	-0.01 (-0.15, 0.13)	-0.02 (-0.06, 0.03)	-0.01 (-0.05, 0.04)	-0.02 (-0.07, 0.02)	-0.02 (-0.07, 0.02)	0.01 (-0.03, 0.05)
	Extended Confounder Set	0.03 (-0.08, 0.14)	-0.02 (-0.05, 0.02)	0 (-0.04, 0.04)	-0.01 (-0.05, 0.03)	0 (-0.04, 0.04)	0 (-0.03, 0.04)
NO_2	Common Confounders	0.02 (-0.09, 0.12)	-0.02 (-0.05, 0.02)	0 (-0.04, 0.04)	-0.01 (-0.04, 0.03)	0 (-0.04, 0.04)	0.01 (-0.03, 0.04)
	Extended Confounder Set	0.09 (-0.11, 0.29)	0 (-0.06, 0.07)	0 (-0.07, 0.06)	0.01 (-0.05, 0.08)	-0.02 (-0.07, 0.04)	0.01 (-0.05, 0.07)
SO_2	Common Confounders	0.05 (-0.14, 0.24)	0 (-0.06, 0.07)	0 (-0.06, 0.06)	0.02 (-0.04, 0.08)	-0.01 (-0.07, 0.04)	0.01 (-0.05, 0.06)
	Extended Confounder Set	-0.14 (-0.51, 0.23)	-0.06 (-0.16, 0.04)	-0.01 (-0.11, 0.1)	-0.06 (-0.14, 0.01)	-0.04 (-0.14, 0.05)	-0.05 (-0.14, 0.03)
Food Insecurity	Common Confounders	-0.08 (-0.44, 0.28)	-0.06 (-0.16, 0.04)	-0.01 (-0.12, 0.1)	-0.06 (-0.14, 0.01)	-0.04 (-0.13, 0.05)	-0.06 (-0.14, 0.03)
	Extended Confounder Set	0.27 (-0.21, 0.74)	-0.07 (-0.21, 0.08)	-0.08 (-0.23, 0.07)	0.04 (-0.11, 0.18)	0 (-0.14, 0.13)	-0.03 (-0.17, 0.11)
SRQ	Common Confounders	0.16 (-0.27, 0.59)	-0.08 (-0.23, 0.06)	-0.08 (-0.23, 0.06)	0.02 (-0.12, 0.16)	-0.01 (-0.14, 0.13)	-0.03 (-0.17, 0.11)
	Extended Confounder Set	0.03 (-0.2, 0.26)	0.04 (-0.03, 0.11)	0.04 (-0.03, 0.12)	0.02 (-0.05, 0.1)	-0.01 (-0.08, 0.07)	0 (-0.07, 0.07)
IPV Emotional	Common Confounders	0.03 (-0.19, 0.26)	0.03 (-0.04, 0.1)	0.05 (-0.02, 0.12)	0.02 (-0.05, 0.09)	-0.01 (-0.08, 0.07)	0 (-0.07, 0.07)
	Extended Confounder Set	-0.12 (-0.74, 0.51)	-0.03 (-0.21, 0.15)	0.06 (-0.13, 0.25)	0.01 (-0.15, 0.17)	-0.03 (-0.21, 0.16)	-0.01 (-0.2, 0.18)
	Common Confounders	-0.08 (-0.68, 0.53)	-0.02 (-0.2, 0.15)	0.07 (-0.12, 0.25)	0.02 (-0.14, 0.18)	-0.02 (-0.2, 0.17)	-0.01 (-0.19, 0.18)

IPV Physical	Extended Confounder Set	0.21 (-0.54, 0.96)	0.06 (-0.15, 0.27)	0.11 (-0.11, 0.33)	0.07 (-0.13, 0.26)	0.12 (-0.08, 0.32)	0.03 (-0.18, 0.23)
	Common Confounders	0.24 (-0.48, 0.96)	0.05 (-0.16, 0.26)	0.1 (-0.12, 0.32)	0.07 (-0.12, 0.26)	0.13 (-0.07, 0.33)	0.03 (-0.18, 0.23)
LEQ	Extended Confounder Set	0.04 (-0.3, 0.37)	0.04 (-0.05, 0.14)	0.07 (-0.02, 0.17)	0.07 (-0.03, 0.16)	0.02 (-0.07, 0.12)	-0.03 (-0.12, 0.06)
	Common Confounders	0.01 (-0.31, 0.33)	0.04 (-0.06, 0.13)	0.07 (-0.02, 0.17)	0.06 (-0.04, 0.15)	0.02 (-0.08, 0.11)	-0.03 (-0.12, 0.06)
EPDS	Extended Confounder Set	0.11 (-0.2, 0.43)	-0.01 (-0.09, 0.07)	0.05 (-0.03, 0.12)	0.06 (-0.02, 0.14)	0.04 (-0.04, 0.11)	0.03 (-0.05, 0.11)
	Common Confounders	0.12 (-0.19, 0.43)	-0.01 (-0.09, 0.07)	0.05 (-0.03, 0.13)	0.05 (-0.02, 0.13)	0.03 (-0.04, 0.11)	0.03 (-0.05, 0.11)
ASSIST Tobacco	Extended Confounder Set	-0.08 (-0.26, 0.11)	-0.02 (-0.06, 0.03)	-0.01 (-0.06, 0.04)	-0.01 (-0.08, 0.06)	-0.02 (-0.08, 0.03)	-0.02 (-0.06, 0.01)
	Common Confounders	-0.08 (-0.26, 0.09)	-0.02 (-0.06, 0.03)	-0.01 (-0.06, 0.04)	-0.01 (-0.08, 0.06)	-0.02 (-0.08, 0.03)	-0.02 (-0.06, 0.01)
ASSIST Alcohol	Extended Confounder Set	-0.08 (-0.26, 0.11)	-0.02 (-0.07, 0.04)	-0.03 (-0.07, 0.02)	-0.01 (-0.08, 0.06)	-0.03 (-0.09, 0.04)	0.01 (-0.05, 0.06)
	Common Confounders	-0.08 (-0.26, 0.09)	-0.02 (-0.07, 0.04)	-0.03 (-0.07, 0.02)	-0.01 (-0.08, 0.06)	-0.02 (-0.09, 0.04)	0.01 (-0.05, 0.06)
Inverse SES	Extended Confounder Set	0.63 (-0.02, 1.28)	0.12 (-0.07, 0.32)	0.21 (0.02, 0.41)	0.15 (-0.05, 0.35)	0.05 (-0.14, 0.24)	0.19 (-0.01, 0.38)
	Common Confounders	0.61 (-0.03, 1.24)	0.11 (-0.08, 0.31)	0.19 (-0.01, 0.38)	0.14 (-0.05, 0.34)	0.05 (-0.13, 0.24)	0.19 (-0.01, 0.38)

Table 3-8: *Descriptive statistics (Median (IQR)) of postnatal indoor air pollutant and psychosocial factor exposures in postnatal Self-Organizing Map (SOM) exposure clusters.*

	SOM Cluster			
	1	**2**	**3**	**4**
n (%)	47 (7.8)	117 (19.5)	309 (51.6)	126 (21.0)
Maternal Age (mean (SD))	27.46 (5.55)	26.65 (5.81)	26.53 (5.64)	27.58 (5.67)
Male Child (%)	22 (46.8)	63 (53.8)	150 (48.5)	74 (58.7)
Mixed Ancestry (%)	13 (27.7)	74 (63.2)	122 (39.5)	64 (50.8)
Mother HIV Positive (%)	11 (23.4)	25 (21.4)	66 (21.4)	32 (25.4)
PM10 µg/m3 (median [IQR])	41.20 [14.95, 82.34]	29.28 [13.39, 57.33]	25.35 [11.12, 51.32]	35.13 [14.54, 68.44]
CO mg/m3 (median [IQR])	60.00 [0.00, 485.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 505.00]
Benzene µg/m3 (median [IQR])	1.97 [0.69, 6.34]	2.69 [0.91, 5.45]	1.79 [0.72, 3.75]	32.39 [10.86, 108.78]
Toluene µg/m3 (median [IQR])	10.95 [6.02, 27.07]	15.89 [6.52, 35.33]	11.03 [4.67, 22.65]	189.77 [55.45, 530.56]
NO2 µg/m3 (median [IQR])	9.24 [5.05, 14.61]	6.19 [3.42, 13.90]	4.75 [2.45, 11.09]	11.92 [4.75, 18.36]
SO2 µg/m3 (median [IQR])	7.93 [3.69, 12.62]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]
SES Asset Sum (median [IQR])	8.00 [6.00, 9.00]	8.00 [5.00, 9.00]	8.00 [6.00, 9.00]	8.00 [6.00, 9.00]
Food Insecurity Total Score (median [IQR])	0.00 [0.00, 0.00]	0.00 [0.00, 1.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]
SRQ-20 Total Score (median [IQR])	0.00 [0.00, 2.00]	5.00 [2.00, 9.00]	1.00 [0.00, 2.00]	3.00 [1.00, 5.00]
Emotional IPV Score (median [IQR])	4.00 [4.00, 4.00]	9.00 [7.00, 12.00]	4.00 [4.00, 4.00]	4.00 [4.00, 6.00]
Physical IPV Score (median [IQR])	5.00 [5.00, 7.00]	11.00 [7.00, 13.00]	5.00 [5.00, 5.00]	5.00 [5.00, 6.00]
LEQ Total Score (median [IQR])	0.00 [0.00, 1.00]	2.00 [1.00, 4.00]	0.00 [0.00, 2.00]	1.00 [0.00, 3.00]
EPDS Total Score (median [IQR])	8.00 [5.00, 10.00]	11.00 [7.00, 16.00]	7.00 [4.00, 10.00]	8.00 [5.00, 13.00]
ASSIST Tobacco Score (median [IQR])	0.00 [0.00, 21.00]	16.00 [0.00, 26.00]	0.00 [0.00, 16.00]	3.00 [0.00, 23.25]
ASSIST Alcohol Score (median [IQR])	0.00 [0.00, 0.00]	0.00 [0.00, 3.00]	0.00 [0.00, 0.00]	0.00 [0.00, 3.00]

Abbreviations: Particulate Matter (PM10); Carbon monoxide (CO); Nitrogen dioxide (NO2); Sulfur dioxide (SO2); Socioeconomic Status (SES); Self-Reporting Questionnaire (SRQ-20); Edinburgh Postnatal Depression Scale (EPDS); Life Experiences Questionnaire (LEQ); Intimate Partner Violence (IPV); Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST)

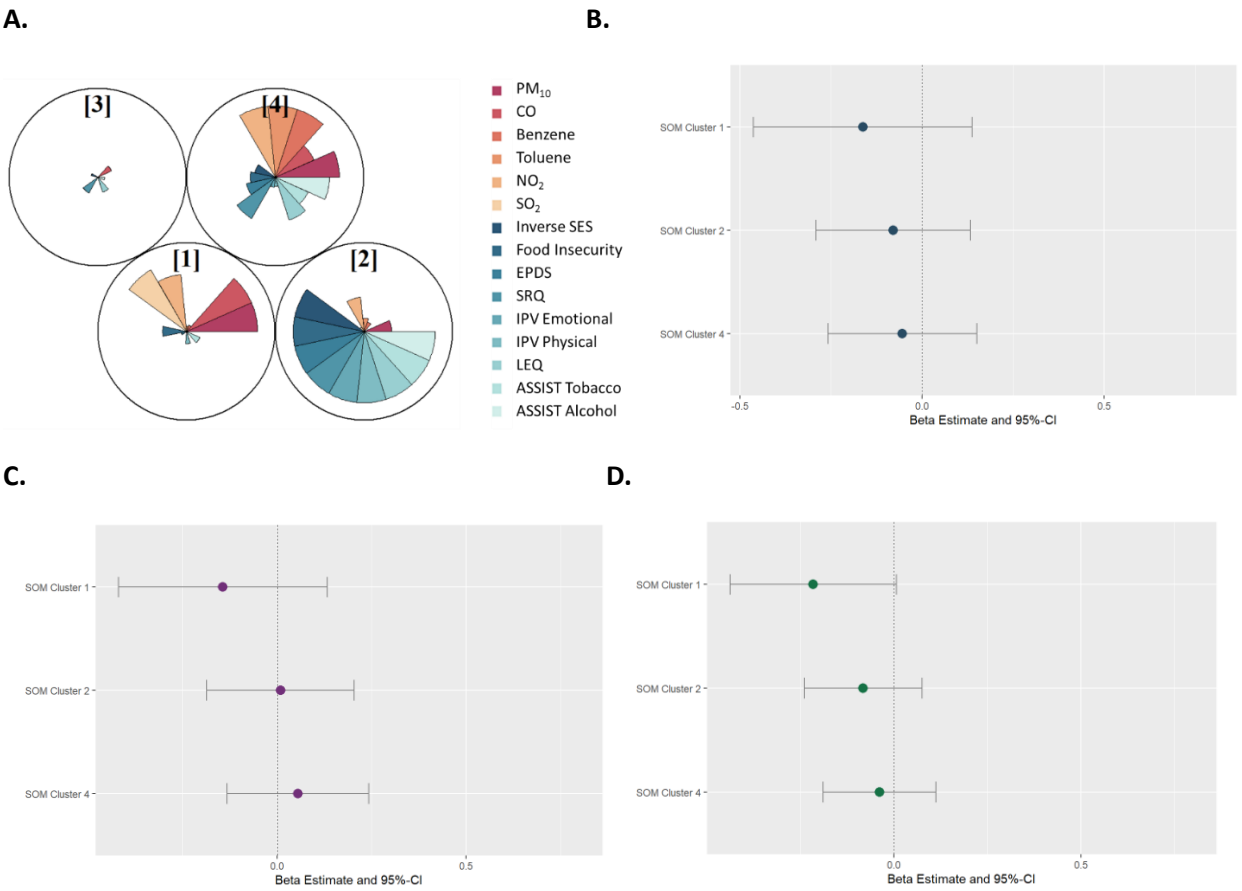


Figure 3-9. *Results from self-organizing map (SOM) analysis using postnatal indoor air pollutants and psychosocial factors. A. SOM clusters created using postnatal indoor air pollutants and psychosocial factors. B. Associations between SOM clusters and CBCL total problems, adjusted by maternal age, maternal HIV status, and ancestry. SOM cluster 3 is used as the reference group. C. Associations between SOM clusters and CBCL externalizing problems, adjusted by maternal age, maternal HIV status, and ancestry. SOM cluster 3 is used as the reference group. D. Associations between SOM clusters and CBCL internalizing problems, adjusted by maternal age, maternal HIV status, and ancestry. SOM cluster 3 is used as the reference group.*

Table 3-9: *Joint exposure models using postnatal exposure SOM clusters as a joint exposure variable, OR and 95% CIs from adjusted linear regression models. linear regression models adjusted for maternal HIV status, maternal age, and ancestry.*

	Total Problems
	Beta (95% CI)
Cluster 1	-0.16 (-0.46, 0.14)
Cluster 2	-0.08 (-0.29, 0.13)
Cluster 3	REF
Cluster 4	0.05 (0.26, 0.15)
	Externalizing Problems
	Beta (95% CI)
Cluster 1	-0.14 (-0.42, 0.13)
Cluster 2	0.01 (-0.19, 0.20)
Cluster 3	REF
Cluster 4	0.06 (-0.13, 0.24)
	Internalizing Problems
	Beta (95% CI)
Cluster 1	-0.22 (-0.44, 0.01)
Cluster 2	-0.08 (-0.24, 0.08)
Cluster 3	REF
Cluster 4	-0.04 (-0.19, 0.11)

***Table 3-10**: Results from single-exposure structured life course modeling approach (SLCMA) analyses. Single-exposure SLCMA models adjusted for maternal age, maternal HIV status, ancestry, and socioeconomic status (when not the exposure of interest).*

	Total Problems				
	Relaxed LASSO Inference				
Exposure	1st selection in LASSO	R2	Coef	CI low	CI up
PM_{10}	**Prenatal**	**0.016**	**0.123**	**0.044**	**0.201**
CO	**Postnatal**	**0.008**	**0.089**	**0.011**	**0.168**
Benzene	Interaction	0.005	-0.066	-0.142	0.010
Toluene	Prenatal	0.005	0.069	-0.010	0.147
NO_2	Accumulation	0.006	0.054	0.000	0.108
SO_2	Accumulation	0.003	-0.038	-0.093	0.017
SES Inverse	Prenatal	0.001	-0.191	-0.664	0.256
Food Insecurity	Prenatal	0.000	0.022	-0.065	0.110
SRQ	**Prenatal**	**0.007**	**0.082**	**0.002**	**0.162**
IPV Emotional	**Interaction**	**0.009**	**-0.069**	**-0.128**	**-0.012**
IPV Physical	**Prenatal**	**0.008**	**0.089**	**0.010**	**0.168**
LEQ	Interaction	0.002	-0.044	-0.121	0.033
EPDS	**Accumulation**	**0.012**	**0.080**	**0.021**	**0.140**
ASSIST Tobacco	Postnatal	0.001	-0.035	-0.113	0.044
ASSIST Alcohol	**Accumulation**	**0.013**	**0.076**	**0.023**	**0.131**
	Externalizing Problems				
	Relaxed LASSO Inference				
Exposure	1st selection in LASSO	R2	Coef	CI low	CI up
PM_{10}	Prenatal	0.005	0.064	-0.008	0.136
CO	**Accumulation**	**0.01**	**0.06**	**0.013**	**0.108**
Benzene	Prenatal	0.006	0.068	-0.005	0.14
Toluene	**Prenatal**	**0.007**	**0.074**	**0.002**	**0.146**
NO_2	Accumulation	0.005	0.0449	-0.005	0.095
SO_2	Postnatal	0.005	-0.065	-0.137	0.008
SES Inverse	Interaction	0.002	-0.031	-0.092	0.03
Food Insecurity	Prenatal	0	0.011	-0.07	0.092
SRQ	**Prenatal**	**0.004**	**0.054**	**-0.019**	**0.128**
IPV Emotional	**Interaction**	**0.007**	**-0.055**	**-0.108**	**-0.001**
IPV Physical	**Prenatal**	**0.006**	**0.073**	**0.0002**	**0.145**
LEQ	Postnatal	0.001	-0.028	-0.102	0.046
EPDS	**Accumulation**	**0.014**	**0.0799**	**0.023**	**0.134**
ASSIST Tobacco	Interaction	0.004	0.058	-0.0136	0.13
ASSIST Alcohol	**Accumulation**	**0.015**	**0.076**	**0.0256**	**0.126**
	Internalizing Problems				
	Relaxed LASSO Inference				
Exposure	1st selection in LASSO	R2	Coef	CI low	CI up

PM_{10}	**Prenatal**	**0.008**	**0.0645**	**0.0064**	**0.122**
CO	Postnatal	0.002	0.0321	-0.026	0.09
Benzene	Interaction	0.002	-0.028	-0.084	0.029
Toluene	Interaction	0	0.0158	-0.042	0.074
NO_2	Prenatal	0.001	0.0256	-0.032	0.084
SO_2	Accumulation	0.003	-0.029	-0.0699	0.011
SES Inverse	Postnatal	0.005	0.057	-0.055	0.119
Food Insecurity	Prenatal	0.003	0.0459	-0.019	0.111
SRQ	**Prenatal**	**0.1**	**0.074**	**0.015**	**0.133**
IPV Emotional	**Interaction**	**0.013**	**-0.062**	**-0.105**	**-0.019**
IPV Physical	Prenatal	0.004	0.0462	-0.0123	0.105
LEQ	Interaction	0.007	-0.058	-0.115	-0.001
EPDS	Prenatal	0.003	0.063	-0.026	0.154
ASSIST Tobacco	Postnatal	0.003	-0.037	-0.095	0.021
ASSIST Alcohol	**Prenatal**	**0.009**	**0.072**	**0.011**	**0.132**

Footnotes: Relaxed LASSO results are not adjusted for multiple testing nor for lasso selection. Bolded values indicate statistical significance.
Abbreviations: Human Immunodeficiency Virus (HIV); Childhood Behavior Checklist (CBCL); Particulate Matter (PM10); Carbon monoxide (CO); Nitrogen dioxide (NO2); Sulfur dioxide (SO2); Socioeconomic Status (SES); Self-Reporting Questionnaire (SRQ-20); Edinburgh Postnatal Depression Scale (EPDS); Life Experiences Questionnaire (LEQ); Intimate Partner Violence (IPV); Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST)

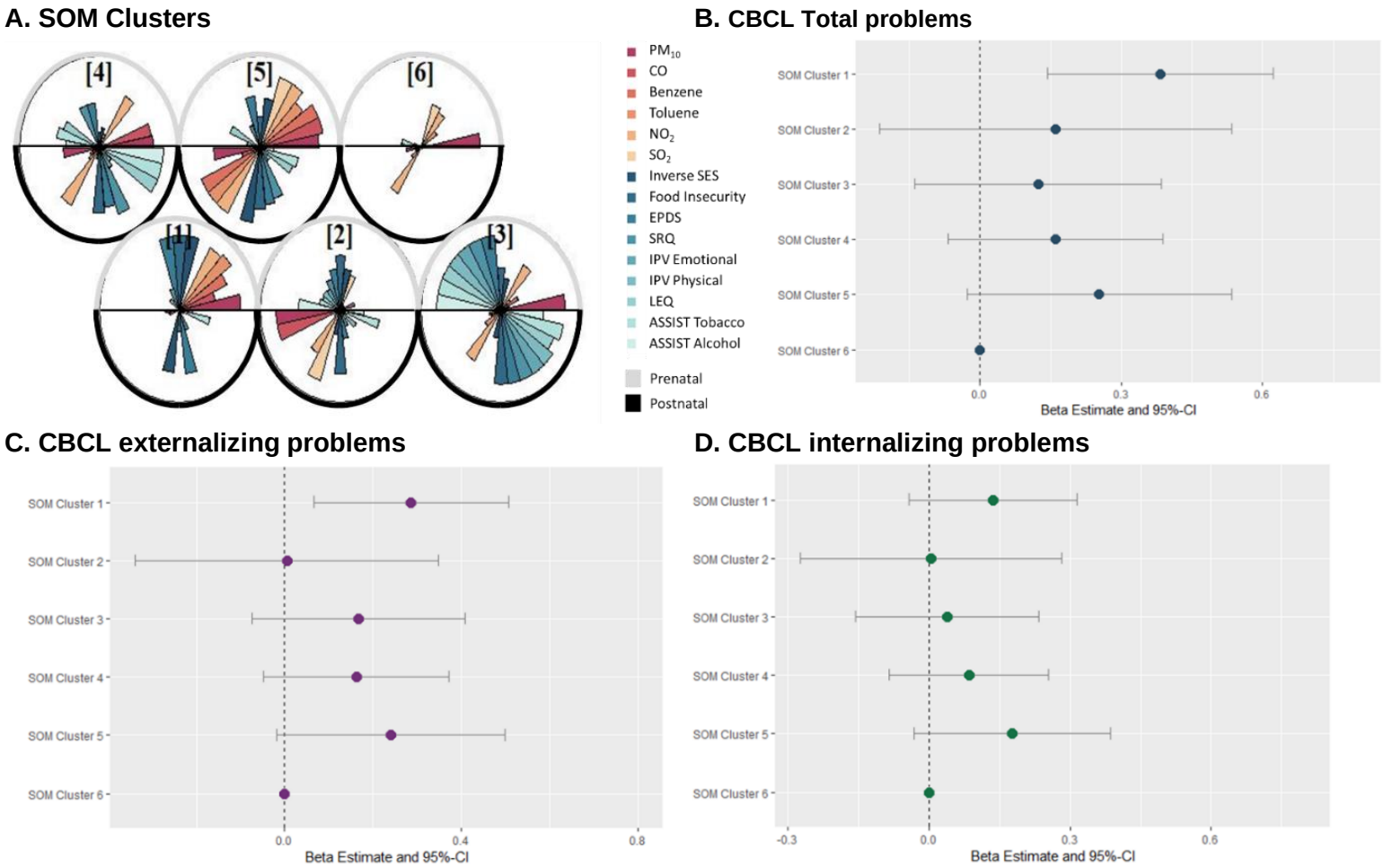


Figure 3-10*: Results from self-organizing map (SOM) analysis combining pre- and postnatal indoor air pollutants and psychosocial factors.* ***A.*** *SOM clusters created using pre- and postnatal indoor air pollutants and psychosocial factors.* ***B****. Associations between SOM clusters and CBCL total problems, adjusted by maternal age, maternal HIV status, and ancestry. SOM cluster 6 is used as the reference group.* ***C.*** *Associations between SOM clusters and CBCL externalizing problems, adjusted by maternal age, maternal HIV status, and ancestry. SOM cluster 6 is used as the reference group****. D.*** *Associations between SOM clusters and CBCL internalizing problems, adjusted by maternal age, maternal HIV status, and ancestry. SOM cluster 6 is used as the reference group.*

Table 3-11: *Descriptive statistics (Median (IQR)) of prenatal and postnatal indoor air pollutant and psychosocial factor exposures in prenatal and postnatal Self-Organizing Map (SOM) exposure clusters.*

	SOM Cluster					
	1	**2**	**3**	**4**	**5**	**6**
N (%)	129 (21.5)	32 (5.3)	86 (14.4)	134 (22.4)	69 (11.5)	149 (24.9)
Maternal Age (mean (SD))	26.84 (6.02)	26.98 (5.63)	26.69 (5.65)	25.97 (5.65)	28.14 (5.74)	27.11 (5.35)
Male Child (%)	59 (45.7)	16 (50.0)	45 (52.3)	82 (61.2)	38 (55.1)	69 (46.3)
Mixed Ancestry (%)	15 (11.6)	9 (28.1)	64 (74.4)	85 (63.4)	23 (33.3)	77 (51.7)
Mother HIV Positive (%)	42 (32.6)	10 (31.2)	14 (16.3)	21 (15.7)	25 (36.2)	22 (14.8)
Prenatal Exposures						
PM10 µg/m3 (median [IQR])	41.57 [16.63, 69.29]	14.86 [3.72, 62.53]	40.30 [15.29, 72.11]	41.07 [10.04, 71.14]	32.10 [16.58, 67.16]	32.08 [12.07, 67.95]
CO mg/m3 (median [IQR])	0.00 [0.00, 360.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 315.00]	0.00 [0.00, 500.00]	0.00 [0.00, 0.00]
Benzene µg/m3 (median [IQR])	9.16 [3.18, 35.82]	1.91 [0.44, 7.65]	3.32 [1.55, 9.62]	3.78 [1.57, 6.90]	5.48 [3.11, 40.58]	3.42 [1.28, 7.00]
Toluene µg/m3 (median [IQR])	30.19 [14.16, 108.27]	13.91 [3.47, 41.38]	16.06 [5.92, 48.55]	12.59 [5.36, 27.66]	19.15 [9.47, 57.44]	14.58 [6.54, 41.59]
NO2 µg/m3 (median [IQR])	9.25 [4.08, 16.63]	3.50 [0.00, 6.43]	7.54 [4.56, 11.38]	8.05 [3.75, 13.80]	9.28 [4.34, 15.70]	6.70 [3.04, 11.00]
SO2 µg/m3 (median [IQR])	0.00 [0.00, 0.00]	0.00 [0.00, 0.50]	0.00 [0.00, 0.18]	0.00 [0.00, 0.20]	0.16 [0.00, 0.96]	0.00 [0.00, 0.28]
SES Asset Sum (median [IQR])	6.00 [5.00, 7.00]	7.00 [5.75, 8.00]	7.00 [5.00, 8.00]	8.00 [7.00, 8.00]	7.00 [5.00, 8.00]	8.00 [7.00, 9.00]
Food Insecurity Total Score (median [IQR])	3.00 [0.00, 4.00]	1.00 [0.00, 3.25]	0.00 [0.00, 2.00]	0.00 [0.00, 0.00]	0.00 [0.00, 2.00]	0.00 [0.00, 0.00]
SRQ-20 Total Score (median [IQR])	3.00 [1.00, 6.00]	4.00 [1.75, 6.00]	6.00 [4.00, 9.00]	5.00 [3.00, 7.00]	4.00 [1.00, 6.00]	2.00 [0.00, 3.00]
Emotional IPV Score (median [IQR])	4.00 [4.00, 5.00]	6.00 [4.00, 7.25]	10.00 [8.00, 13.00]	5.00 [4.00, 6.00]	4.00 [4.00, 6.00]	4.00 [4.00, 5.00]

Physical IPV Score (median [IQR])	5.00 [5.00, 7.00]	6.00 [5.00, 10.00]	11.00 [9.00, 14.00]	5.00 [5.00, 6.00]	5.00 [5.00, 6.00]	5.00 [5.00, 6.00]
LEQ Total Score (median [IQR])	1.00 [0.00, 1.00]	1.00 [0.00, 3.00]	3.00 [2.00, 5.00]	2.00 [1.00, 4.00]	2.00 [1.00, 3.00]	1.00 [0.00, 2.00]
EPDS Total Score (median [IQR])	11.00 [9.00, 13.00]	10.00 [6.75, 12.00]	12.00 [9.00, 16.00]	10.00 [7.00, 13.00]	9.00 [7.00, 12.00]	6.00 [3.00, 9.00]
ASSIST Tobacco Score (median [IQR])	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	18.50 [0.00, 24.00]	0.00 [0.00, 23.00]	0.00 [0.00, 0.00]	0.00 [0.00, 3.00]
ASSIST Alcohol Score (median [IQR])	0.00 [0.00, 0.00]	0.00 [0.00, 0.50]	0.00 [0.00, 14.75]	0.00 [0.00, 3.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]
Postnatal Exposures						
PM10 µg/m3 (median [IQR])	25.35 [13.80, 51.05]	46.77 [25.77, 78.41]	25.76 [11.60, 48.31]	34.89 [16.37, 61.53]	35.88 [15.03, 75.36]	24.89 [5.48, 55.72]
CO mg/m3 (median [IQR])	0.00 [0.00, 60.00]	60.00 [0.00, 482.50]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 600.00]	0.00 [0.00, 0.00]
Benzene µg/m3 (median [IQR])	1.31 [0.49, 4.31]	1.80 [0.99, 3.36]	3.47 [0.91, 7.78]	3.72 [1.60, 6.55]	95.14 [40.91, 169.71]	1.89 [0.81, 3.83]
Toluene µg/m3 (median [IQR])	10.05 [3.15, 18.29]	10.19 [5.65, 26.44]	19.74 [9.53, 44.14]	20.04 [9.92, 47.56]	405.47 [112.98, 873.22]	11.33 [5.89, 34.10]
NO2 µg/m3 (median [IQR])	3.58 [2.05, 7.13]	6.02 [3.89, 14.60]	6.45 [3.96, 15.77]	7.93 [3.52, 14.69]	10.58 [3.11, 20.46]	6.09 [3.16, 13.97]
SO2 µg/m3 (median [IQR])	0.00 [0.00, 0.00]	9.32 [7.54, 18.29]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]
SES Asset Sum (median [IQR])	7.00 [5.00, 9.00]	8.00 [6.00, 8.00]	8.00 [6.00, 9.00]	8.00 [7.00, 9.00]	7.00 [5.00, 9.00]	8.00 [7.00, 9.00]
Food Insecurity Total Score (median [IQR])	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 1.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]
SRQ-20 Total Score (median [IQR])	1.00 [0.00, 3.00]	0.00 [0.00, 2.25]	4.00 [2.00, 6.75]	3.00 [2.00, 6.00]	3.00 [1.00, 5.00]	0.00 [0.00, 1.00]
Emotional IPV Score (median [IQR])	4.00 [4.00, 5.00]	4.00 [4.00, 5.00]	9.00 [7.00, 12.00]	5.00 [4.00, 6.75]	4.00 [4.00, 6.00]	4.00 [4.00, 4.00]
Physical IPV Score (median [IQR])	5.00 [5.00, 6.00]	5.50 [5.00, 8.00]	11.00 [7.00, 13.00]	5.00 [5.00, 7.00]	5.00 [5.00, 7.00]	5.00 [5.00, 5.00]

LEQ Total Score (median [IQR])	0.00 [0.00, 1.00]	0.50 [0.00, 1.00]	2.00 [0.25, 4.00]	2.00 [1.00, 3.00]	1.00 [0.00, 3.00]	0.00 [0.00, 1.00]
EPDS Total Score (median [IQR])	9.00 [7.00, 12.00]	7.50 [3.50, 10.00]	10.00 [7.00, 14.00]	9.00 [5.00, 12.75]	8.00 [5.00, 13.00]	4.00 [1.00, 8.00]
ASSIST Tobacco Score (median [IQR])	0.00 [0.00, 25.00]	0.00 [0.00, 23.00]	5.50 [0.00, 25.75]	6.00 [0.00, 24.00]	0.00 [0.00, 24.00]	0.00 [0.00, 2.00]
ASSIST Alcohol Score (median [IQR])	0.00 [0.00, 0.00]	0.00 [0.00, 0.75]	0.00 [0.00, 3.00]	0.00 [0.00, 6.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]

Abbreviations: Particulate Matter (PM10); Carbon monoxide (CO); Nitrogen dioxide (NO2); Sulfur dioxide (SO2); Socioeconomic Status (SES); Self-Reporting Questionnaire (SRQ-20); Edinburgh Postnatal Depression Scale (EPDS); Life Experiences Questionnaire (LEQ); Intimate Partner Violence (IPV); Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST)

Table 3-12: *Joint exposure models using combined pre- and postnatal exposure SOM clusters as a joint exposure variable, OR and 95% CIs from adjusted linear regression models. Linear regression models adjusted for maternal HIV status, maternal age, and ancestry.*

	Total Problems
	Beta (95% CI)
Cluster 1	**0.38 (0.14, 0.62)**
Cluster 2	0.16 (-0.21, 0.53)
Cluster 3	0.12 (-0.14, 0.39)
Cluster 4	0.16 (-0.07, 0.39)
Cluster 5	0.25 (-0.03, 0.53)
Cluster 6	REF
	Externalizing Problems
	Beta (95% CI)
Cluster 1	**0.29 (0.07, 0.51)**
Cluster 2	0.01 (-0.34, 0.35)
Cluster 3	0.17 (-0.07, 0.41)
Cluster 4	0.16 (-0.05, 0.37)
Cluster 5	0.24 (-0.02, 0.5)
Cluster 6	REF
	Internalizing Problems
	Beta (95% CI)
Cluster 1	0.14 (-0.04, 0.31)
Cluster 2	0 (-0.27, 0.28)
Cluster 3	0.04 (-0.16, 0.23)
Cluster 4	0.08 (-0.09, 0.25)
Cluster 5	0.18 (-0.03, 0.39)
Cluster 6	REF

Discussion

This study of mother-child pairs in the South African Drakenstein Child Health Study found prenatal exposure to indoor air pollution, as opposed to postnatal, was most strongly associated with childhood psychopathology at 6.5 years. This result was seen in both traditional single-exposure, single-period modeling, as well as in methods using environmental mixture and structured life course approaches. Only CO in the postnatal period had stronger associations with child psychopathology, as compared to the prenatal period. We also found exposure to psychosocial factors including depression, ASSIST Alcohol score, and psychological distress in the prenatal period to be most strongly associated with child psychopathology. This was observed in single-exposure, single-time period models as well as single-time period environmental mixtures modeling approaches Additionally, the SOM model combining pre- and postnatal exposures found the cluster with high depression scores in both periods, along with high prenatal indoor air pollution, was associated with CBCL scores.

PM_{10} exposure during pregnancy was found to be especially harmful to childhood psychopathology at age 6.5 years. This extends our previous work in the DCHS, in which indoor PM_{10} exposure in the prenatal period was also associated with impaired neurodevelopment at 2 years, by showing adverse associations with cognitive outcomes not only in early childhood but also at school-age[34]. A systematic review of prenatal exposure to outdoor PM_{10} and psychopathology, like autism spectrum disorder (ASD) or attention deficit and hyperactivity disorder (ADHD), found inconsistent results which may be due to differential exposure and differing outcome assessments between studies[38]. Further research is necessary to elucidate the association of prenatal PM_{10} exposure and psychopathology. When investigating sensitive periods of exposure, a Chinese study investigating ambient PM exposure during pregnancy and the first 2 years postnatal found both pre- and postnatal exposure to PM_{10} and $PM_{2.5}$ were

associated with adverse Chinese revision of Bayley Scale of Infant Development (BSID-CR) scores. However, in that study postnatal exposure was more strongly associated with BSID-CR scores than prenatal exposure[37], which is the opposite of our findings. Differences in findings could be due to differences in exposure measurement and concentrations. In the Chinese study, authors investigated ambient PM exposure as opposed to indoor PM, and the exposure concentrations were much higher in the Chinese study. Their minimum ambient prenatal PM_{10} concentration was 97.93 μg/m^3, which is much larger than our median indoor PM_{10} concentration of 35.59 μg/m^3. They also investigated postnatal PM_{10} exposure for 2 years after birth, compared to 4 months in our study[37]. Another study investigating sensitive periods of air pollution exposure and cognitive functioning found ambient PM_{10} exposure in the 22nd-29th weeks of pregnancy, and not postnatal exposure, was associated with cognitive function in boys at 5-6 years old[115]. However, this study used postnatal exposure at 60 months, which is much later than in our study[115]. Most research on air pollution exposure focuses on one single time period, as shown in a recent review[116]. Additionally there are few epidemiological studies that investigate early life or childhood exposure to air pollution and childhood psychopathology[116]. Most studies explore exposure and psychopathology in adulthood, or only prenatal exposure on childhood psychopathology[116].

Postnatal, but not prenatal, CO exposure was associated with childhood psychopathology at 6.5 years old. There are very few studies examining the effect of pre- and postnatal CO exposure on child psychopathology. One study by Dix-Cooper, et al. found CO exposure during the 3rd trimester from woodsmoke to be associated with decreased performance on several neurobehavioral tests at 6-7 years old. Exposure to CO as an infant (0-9 months) was not associated with neurobehavioral tests at 6-7 years[33]. Differential findings could be due to low sample size (n = 20 in prenatal, n = 39 in postnatal) in their study, as well as measurement of CO exposure and neurobehavioral outcome measures. Their study used the average of

personal (wearable) measurement devices, while our study measured CO in the main living area of the home[33]. Based on these findings, there is a need for more research on how CO exposure in early life and childhood impacts childhood psychopathology.

Our study found prenatal maternal smoking was associated with childhood psychopathology,. Maternal tobacco use during pregnancy is well known to be associated with decreased neurodevelopment and child behavior problems[64] One hypothesized pathway linking prenatal tobacco use and neurodevelopment and psychopathology is through low birthweight and decreased in-utero brain growth[117]. In support of our findings, prenatal tobacco use has been seen to affect inattention, oppositional behavior, emotional instability, and physical aggression[64]. In a previous study done in the DCHS prenatal, but not postnatal, tobacco use was associated with decreased adaptive behavior[34] . Studies investigating environmental tobacco smoke (ETS) exposure during the pre- and postnatal periods have mixed findings regarding sensitive periods. A German study investigating ETS exposure during pregnancy and early life found prenatal exposure was more strongly associated with SDQ score at 10 years old[103] than postnatal exposure, which is in line with our findings. However, a French study found postnatal ETS exposure, alone or associated with prenatal exposure, was associated with adverse SDQ scores[104]. Additional research is needed to fully clarify sensitive periods of ETS exposure.

We also found associations between pre- and postnatal maternal alcohol and childhood psychopathology. Single-exposure, single-period models found associations between ASSIST Alcohol score and psychopathology in the prenatal period, but not in the postnatal period. However, SLCMA modeling found accumulation of ASSIST alcohol score in the pre- and postnatal periods impacted psychopathology. These results indicate that alcohol exposure during pregnancy is more strongly associated with childhood psychopathology, but that maternal drinking behaviors postnatally may also contribute to psychopathology. Alcohol is a known teratogen that disrupts fetal development. Fetal alcohol spectrum disorder (FASD) has a

wide range of both physical and neurological symptoms including, growth deficiency, abnormal brain growth, and cognitive and behavioral impairments[63]. The teratogenic effects of alcohol on the developing fetal brain may explain the stronger association with prenatal exposure and CBCL score in single-time period analyses in this study. However, a systematic review found mixed associations between alcohol consumption during pregnancy and childhood ADHD incidence, an externalizing psychopathology[118]. While alcohol use after pregnancy is not neurotoxic to the child in the same way as to the fetus, maternal alcohol use may impact the child through other pathways, such as parenting skills.

Most psychosocial factors investigated were not associated with childhood psychopathology in either time period. However, pre- and postnatal depression was also associated with childhood psychopathology. The relationship between maternal depression and child psychopathology has been well established, and maternal depression is a distinct early life stress for the child that shapes the child's stress response[65]. Results from a birth cohort measuring the effects of postnatal depression in mothers on immune markers and child psychopathology found that children of depressed mothers exhibited higher immune markers and greater social withdrawal. They also found that depressed mothers had higher cortisol and immune makers, and displayed more negative parenting behaviors[65]. It is difficult to investigate sensitive periods of exposure to psychosocial factors, like depression, because unlike with pollutants these factors may vary less over this small time interval. Consequently, one major limitation of this analysis is the lack of participants with low psychosocial factor exposure during one period, and high exposure in another period. In our study, pre- and postnatal measurements were taken less than 1 year apart and exposure to these factors did not change very much between time periods. This limits comparisons of sensitive periods of exposure, as we cannot compare high/low and low/high groups.

Joint effects of indoor air pollution and psychosocial factors occurred, primarily in the prenatal period. Quantile g-computation analysis found increases in the total prenatal exposure mixture were associated with increased CBCL scores. This is in line with our previous in the DCHS, which found joint effects of prenatal exposure to indoor air pollution and psychosocial factors on trajectories of childhood psychopathology from 2 to 5 years old [105]. Other studies using interaction terms between individual pollutants and psychosocial factors instead of environmental mixture methodology, have also found joint effects of environmental and psychosocial exposures on childhood psychopathology[13,100]. A New York City, USA, based study found interactions between prenatal polycyclic aromatic hydrocarbons (PAH) and early life stress on CBCL attention and thought scores[13]. That same cohort also found interactions between prenatal PAH exposure and prenatal/childhood hardship on ADHD behavior problems[100]. Synergy between indoor air pollutants and psychosocial factors may derive from mechanisms involving inflammation and oxidative stress[27,68]. Exposure to both air pollution[8,16,27,70,71] and stress associated with psychosocial factors[68,71,72] have been associated with inflammation and oxidative stress. Inflammation and oxidative stress can damage neurons and the CNS, which may impact psychopathology later in life[27]. Future studies should investigate these factors as mediators between exposure to air pollution and psychosocial factors and childhood psychopathology.

This study has several limitations. First, exposure measurements for fine ($PM_{2.5}$) and ultrafine PM measurements were not collected in this cohort because, at the time, personal $PM_{2.5}$ monitoring was not easily available for a study of this size. PM smaller than PM_{10} is hypothesized to be more harmful to the CNS because its smaller size allows for particles to travel throughout the body and brain[27]. Additionally, each air pollutant measurement was only collected once in each time period. There could be some misclassification of the exposure, though prior DCHS studies have also found associations between indoor air pollutants and

several neurodevelopmental and psychopathological outcomes[34,105], as well as respiratory outcomes[119]. Another small limitation in our study is the lack of postnatal maternal cotinine measurements. In the prenatal period our study used urine cotinine measurements, which measure exposure to nicotine from both first and secondhand smoking. Maternal cotinine measurement was not available in the postnatal period, so we could not use it as a measure of maternal smoking. Child cotinine measurements were available in this period, though those would reflect exposure to tobacco smoke from anyone in the household and would not be in concordance with maternal ASSIST Tobacco measurements. Additionally, our methods did not account for variation due to imputation because we were unable to pool imputed datasets. There are also limitations regarding biases from residual confounding, selection bias and generalizability. The DCHS cohort was created to be population based and representative of peri-urban populations in South Africa, and other LMICs, which decreases the likelihood of selection bias. However, these results may not be generalizable to populations outside of peri-urban populations in LMICs.

There are also several strengths of this study worth highlighting. First, the DCHS is a unique multidisciplinary cohort from an underrepresented population in mental health research, children from a LMIC. The DCHS also has repeated measures of indoor air pollutants and psychosocial factor exposures, allowing for comparison of time-period effects on childhood psychopathology and estimation of joint effects of both exposure groups. This cohort also has measures from many domains of psychosocial factors including, threat and trauma, deprivation, substance use, and psychological distress and psychiatric disorders, which allows for a well-rounded view of psychosocial factors and their determinants. This rich dataset allowed us to use both traditional single-exposure linear regression analyses as well as newer environmental mixture methods such as quantile g-computation, SOM, and ECM to examine joint effects of exposures.

Additionally, the repeated exposure measurements allowed for testing of sensitive periods of both individual and joint exposure effects using SLCMA and SOM.

This study identified the prenatal period as a particularly vulnerable period for exposure to indoor air pollution and psychosocial factors and later childhood psychopathology. Prenatal exposure to indoor air pollution was seen to be more strongly associated in the prenatal period, while psychosocial factors such as depression and alcohol use were associated with psychopathology in both periods, but had stronger associations in the prenatal period. Interventions aimed at reducing incidence and symptoms of childhood psychopathology should focus on reducing exposure from air pollutants and smoking particularly in the prenatal period. Interventions and mental health services for mother with depression and substance use could be beneficial in both the pre- and postnatal periods. Future studies should investigate additional pollutants such as fine and ultrafine PM, sensitive time periods during pregnancy, and interventions for reducing exposure to indoor air pollutants and psychosocial factors.

Chapter 4 : Joint Effects of Prenatal Exposure to Indoor Air Pollution and Psychosocial Factors on Early Life Inflammation

This chapter addresses specific AIM 3a, estimating joint effects of in utero air pollution and psychosocial factors exposure during pregnancy on inflammation in the child in early life. The version of the manuscript presented in this dissertation will be submitted to *Environmental Research.*

Abstract

Background: It is hypothesized that air pollution and stress impact the central nervous system through neuroinflammatory mechanisms. However, few studies have investigated the association between prenatal exposure to indoor air pollution and psychosocial factors on inflammatory markers in infancy. This study investigates the individual and joint effects of prenatal exposure to indoor air pollution and psychosocial factors on early life inflammation (interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α)).

Methods: We analyzed data from the South African Drakenstein Child Health Study (N=225). Indoor air pollution and psychosocial factor measurements were taken in the 2nd trimester of pregnancy. Circulating inflammatory markers (IL-1β, Il-6, and TNF-α) were measured in serum in the infants at 6 weeks postnatal. Linear regression models were used to investigate associations between individual exposures and inflammatory markers. To investigate joint effects of environmental and psychosocial factors, Self-Organizing Maps (SOM) were used to create exposure profile clusters. These clusters were added to linear regression models to investigate the associations between exposure profiles and inflammatory markers. All models were adjusted for maternal age, maternal HIV status, and ancestry to control for confounding.

Results: Most indoor air pollutants were positively associated with inflammatory markers, particularly benzene and TNF-α in single pollutant models. No consistent patterns were found for psychosocial factors in single-exposure linear regression models. In joint effects analyses, the SOM profile with high indoor air pollution, low SES, and high maternal depressive symptoms were associated with higher inflammation.

Conclusions: Indoor air pollutants were consistently associated with increased inflammation in both individual and joint effects models, particularly in combination with low SES and maternal depressive symptoms. The trend for individual psychosocial factors was not as clear, with

mainly null associations. As we have observed pro- and anti-inflammatory effects, future research should investigate joint effects of these exposures on inflammation and their health effects.

Introduction

During everyday life pregnant individuals are exposed to a variety of environmental and psychosocial stressors, from indoor air pollution to violence and food insecurity. Many of these exposures have been associated with child neurodevelopment and psychopathology, though the mechanism through which they are associated remains unclear[38,40,52,53,59,105,120]. One prevalent hypothesis is that environmental and psychosocial stressors activate neuroinflammatory processes, which may impact the central nervous system and the developing brain[71].

It is hypothesized that air pollution affects the central nervous system (CNS) through mechanisms of neuroinflammation[8,16,27,70,71]. Animal models have shown that air pollutants cause a systemic inflammatory response, including neuroinflammation[27]. Both the physical air pollutant particle, and the toxic components absorbed on the particle can create an inflammatory response. Translocation of air pollutant particles from the lungs and nasal pathways to other areas of the body cause damage to the body and brain[27]. Air pollution particles have also been shown to cross the placenta and directly reach the developing fetal body and brain[121]. Microglia, the resident immune cells of the brain, respond to the invading particle damage by releasing inflammatory cytokines such as TNF-α, IL-1β, and IL-6, and reactive oxygen species (ROS)[27]. Chronic activation of the microglia and over production of inflammatory markers and ROS can cause neuronal damaging effects[27]. Impaired neuronal cell functioning may contribute to CNS disease pathology and development of clinical neurological disorders[27]. Inflammatory response from the microglia during gestation and early life periods can also affect brain development through microglial involvement in pruning and shaping of the neuronal synapses[68,71]. However, there are few studies in humans investigating how prenatal exposure to air pollutants impacts inflammatory response in the infant.

It is hypothesized that inflammation may also play a role in how stress impacts the CNS, but this association been a more recent area of research[68,71,72]. Childhood stress has been associated with chronic peripheral inflammation in both cross-sectional and longitudinal studies[16]. A meta-analysis found low adulthood SES was associated with higher levels of systemic inflammation in adults, including higher levels of interlukin-6 (IL-6)[73]. However, there is little epidemiologic research on how psychological stress during pregnancy impacts inflammation in the child. The few epidemiology studies available show mixed pro- and anti-inflammatory results[122,123]

As pregnant individuals are often exposed to both air pollution and stress-inducing psychosocial factors, joint effects are likely and have been seen in prior studies investigating other health effects[78,79,105]. As of this writing, only one epidemiology study has investigated joint effects of prenatal exposure to air pollution and psychosocial factors on infant inflammation. Hahn et al. investigated effect modification of the association between prenatal fine particulate matter ($PM_{2.5}$) exposure and inflammatory markers in cord blood by maternal depression. They found no significant effect modification of the association[124]. More epidemiological studies are needed to investigate both the individual and joint effects of prenatal exposure to air pollution and psychosocial factors on markers of inflammation.

Our study leverages data from a South African birth cohort to investigate how individual and joint prenatal exposure to indoor air pollution and psychosocial factors are associated with inflammatory markers, specifically interleukin-1β, interleukin-6, and tumor necrosis factor-α, in the infant at 6 weeks postnatal. This population from a low- to middle-income country is highly exposed to both indoor air pollution as well as psychosocial stressors, which makes joint effects of these exposure likely[57,83,105]. Individual and joint effects of these exposures on neurobehavioral outcomes have been previously observed in this cohort[49,94,105,120]. We use self-organizing maps to create exposure profiles of prenatal exposure to indoor air pollutants and

psychosocial factors. Then we investigate the association between prenatal exposure profile and infant inflammatory markers.

Methods

Study Population

This study is based on a subset of participants from the Drakenstein Child Health Study (DCHS). The DCHS is a multi-disciplinary population-based pregnancy cohort based in South Africa. Recruited during the 2nd trimester of pregnancy, women 18 years and older were enrolled from 2012-2015. Follow-up with mother-child pairs was conducted at multiple points in the child's first year of life and annually thereafter. More detailed recruitment and follow up information can be found elsewhere[57,76]. Of the N = 1,141 mother-child pairs recruited, a subset of n = 225 were included in this analysis. The primary reason for the reduction in sample size is that only a small subset of infants were selected for measurement of inflammatory markers at 6 weeks old. The subset of DCHS participants selected for measurement of inflammatory markers was enriched with HIV infected mothers and an equal number of non-infected mothers **(Table 4-1)**. To be included in this analysis participants had indoor air pollution measurements in the second trimester of pregnancy, infants were not HIV infected and had valid measurements of inflammation at 6 weeks old. Due to infection prevention efforts, only two children were born with HIV. HIV infected children were excluded from this analysis sample **(Figure 4-1)**. The DCHS was approved by the Human Research Ethics Committee (HREC) of the University of Cape Town (HREC 401/2009), Stellenbosch University (N12/02/0002) and Western Cape Provincial Health Research Committee (2011RP45). Written informed consent was provided by each mother for herself and her child and is renewed annually.

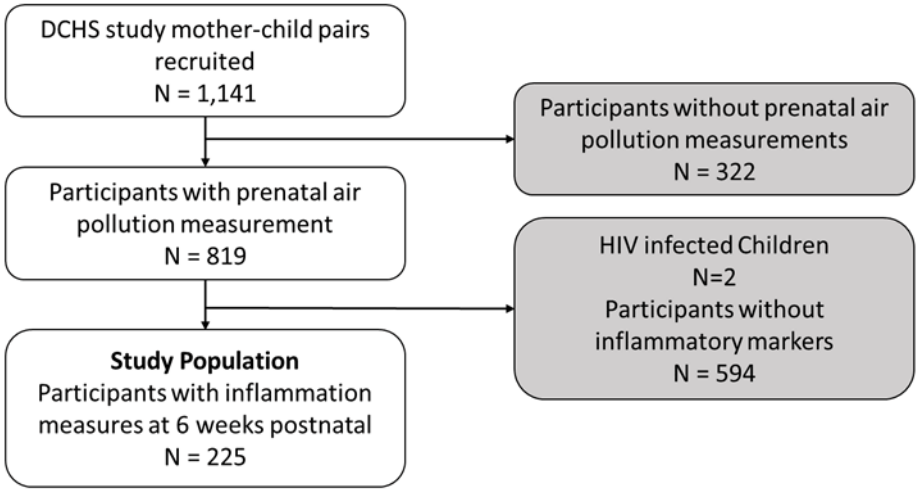


Figure 4-1: *Study population flow diagram.*

Indoor Air Pollution Assessment

As described previously [76,83,105], indoor air pollution measurements were taken during participants' 2nd trimester of pregnancy. Pollutants measured include particulate matter <10 microns in diameter (PM_{10}), carbon monoxide (CO), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and Volatile Organic Compounds (VOCs) benzene and toluene. Particulate Matter (PM_{10}) was collected over 24 hours with a personal air sampling pump (SKC AirChek 52®), using a gravimetrically pre-weighted filter. Carbon monoxide (CO) was collected over 24 hours using an Altair® carbon monoxide single gas detection unit, electrochemical sensor detection of gas at 10-minute intervals were collected. Sulphur dioxide (SO_2) and nitrogen dioxide (NO_2) were collected over 2 weeks using Radiello® absorbent filters in polyethylene diffusive body. Volatile organic compounds, including benzene and toluene, were collected over 2 weeks using Markes® thermal desorption tubes[83]. Additional information on factors that could impact indoor air pollution (e.g., type of home, distance from major road, size of home, number of inhabitants, access to basic amenities, fuels used for cooking and heating, ventilation within homes, and pesticides and cleaning materials used in the home) was collected at home visits[83].

Assessment of Psychosocial Factors

Assessment of psychosocial factors was conducted via self-reported questionnaire in the 2nd trimester of pregnancy. Employment, education, household income, household assets, marital status, number of dependents, and financial activities were included as indicators of socioeconomic status. Perceived household food insecurity was assessed using an adapted version of the USDA Household Food Security Scale[84]. Intimate partner violence (IPV) was assessed using the IPV Questionnaire adapted from the World Health Organization (WHO)'s multi-country study and the Women's Health Study in Zimbabwe[85,86]. The IPV questionnaire assesses lifetime and recent (past year) exposure to emotional, physical, and sexual violence. The World Mental Health Life Events Questionnaire (LEQ) was used to measure trauma and resilience. Use of alcohol and tobacco were assessed using the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST). Additionally, tobacco smoke exposure was assessed via urinary cotinine. The Self Reporting Questionnaire (SRQ-20), a measure endorsed by the WHO, was used to measure psychological distress[87,88]. The Edinburgh Postnatal Depression Scale (EPDS) was used to measure depressive symptoms[89].

Assessment of Inflammatory Markers

Peripheral blood serum samples from the infants at 6 weeks old were collected as previously described[76]. Pro-inflammatory immune markers (IL-1β, IL-6, and TNF-α) are analyzed with a Milliplex® Luminex premix 13-plex kit (HSTCMAG28SPMX13; Merck)[76]. IL-1β, IL-6, TNF-α were selected *a priori* as inflammatory markers for these analyses as they are commonly reported in literature on their associations with neuroinflammation[16,27].

IL-1β, IL-6 and TNF-α had a skewed distribution and were natural log-transformed in all statistical analyses.

Table 4-1: *Comparison of demographic and exposure characteristics between the full DCHS cohort, the subsample with indoor air pollution measurements, and the analysis sample with inflammatory marker measurements.*

	Full DCHS Cohort	IAP Subsample	Analysis Sample
N	1143	819	225
Maternal Age (mean (SD))	26.60 (5.68)	26.60 (5.67)	27.65 (5.98)
Male Child (%)	586 (51.3)	422 (51.5)	130 (57.8)
Mixed Ancestry (%)	510 (44.7)	379 (46.3)	90 (40.0)
Mother HIV Positive (%)	248 (21.7)	171 (20.9)	95 (42.2)
Indoor air pollutants			
PM10 µg/m3 (median [IQR])	33.37 [12.49, 64.80]	33.45 [12.49, 65.43]	39.01 [14.97, 69.62]
CO mg/m3 (median [IQR])	0.00 [0.00, 102.50]	0.00 [0.00, 120.00]	0.00 [0.00, 120.00]
Benzene µg/m3 (median [IQR])	4.28 [1.75, 11.29]	4.34 [1.75, 11.50]	4.34 [1.91, 12.72]
Toluene µg/m3 (median [IQR])	16.79 [7.04, 44.24]	16.94 [7.09, 44.79]	16.02 [6.61, 45.02]
NO2 µg/m3 (median [IQR])	7.13 [3.33, 12.69]	7.19 [3.34, 12.70]	6.05 [3.10, 11.27]
SO2 µg/m3 (median [IQR])	0.00 [0.00, 0.28]	0.00 [0.00, 0.28]	0.00 [0.00, 0.14]
Psychosocial Factors			
Urine Cotinine ng/ml (median [IQR])	43.00 [10.70, 500.00]	43.35 [10.70, 500.00]	52.70 [14.60, 500.00]
SES Asset Sum (median [IQR])	7.00 [5.00, 8.00]	7.00 [5.00, 8.00]	7.00 [5.00, 8.00]
Food Insecurity Total Score (median [IQR])	0.00 [0.00, 2.00]	0.00 [0.00, 2.00]	0.00 [0.00, 3.00]
SRQ-20 Total Score (median [IQR])	4.00 [1.00, 7.00]	4.00 [1.50, 7.00]	4.00 [2.00, 8.00]
EPDS Total Score (median [IQR])	9.00 [6.00, 12.00]	9.00 [6.00, 13.00]	10.00 [7.00, 14.00]
LEQ Total Score (median [IQR])	1.00 [0.00, 3.00]	1.00 [0.00, 3.00]	2.00 [1.00, 3.00]
Emotional IPV Score (median [IQR])	4.00 [4.00, 7.00]	5.00 [4.00, 7.00]	5.00 [4.00, 7.00]
Physical IPV Score (median [IQR])	5.00 [5.00, 7.00]	5.00 [5.00, 7.00]	6.00 [5.00, 8.00]
ASSIST Tobacco Score (median [IQR])	0.00 [0.00, 13.00]	0.00 [0.00, 14.00]	0.00 [0.00, 15.00]
ASSIST Alcohol Score (median [IQR])	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]
Inflammatory Markers			
IL-1β (median [IQR])	-	-	1.05 [0.48, 1.76]
IL-6 (median [IQR])	-	-	1.93 [0.69, 4.08]
TNF-α (median [IQR])	-	-	19.57 [14.48, 28.23]

Statistical Analysis

Multiple Imputation of Missing Values

While there were no missing values in the outcome or covariates, some participants were missing exposure data including certain indoor air pollutants and psychosocial factors **(Table 4-2)**. Based on inspections of missingness patterns, we assume these values are missing at random **(Figure 4-2)**. Using the *hmisc* R package, multiple imputation was preformed to impute missing exposure variables. Exposure variables were imputed using predictive mean matching, models included pre- and postnatal (4 months) measurements of indoor air pollution, psychosocial factors, and household characteristics. Five seed numbers were created using a random number generator, each seed resulted in its own set (k=10) of variables with missing values imputed. One of the k sets was randomly selected to use for analyses as pooling of the k sets was not compatible with one method used in the statistical analysis. The seed with the highest R^2 values, a measure available within *hmisc* used to explain how well missing values were predicted, was selected for use in primary analyses and results. Sensitivity analyses with complete cases and other imputation seeds were also conducted.

Table 4-2: *Proportion of missing prenatal exposure data in analysis sample.*

Exposure	# missing	% missing	n	Total N
PM_{10}	20	9%	205	225
CO	43	19%	182	225
Benzene	26	12%	199	225
Toluene	26	12%	199	225
NO_2	22	10%	203	225
SO_2	22	10%	203	225
Maternal smoking (cotinine)	3	1%	222	225
SES assets	0	0%	225	225
food insecurity	12	5%	213	225
SRQ	13	6%	212	225
IPV - emotional	13	6%	212	225
IPV - physical	13	6%	212	225
IPV - sexual	13	6%	212	225
LEQ	18	8%	207	225
EPDS	14	6%	211	225
ASSIST - tobacco	14	6%	211	225
ASSIST - alcohol	14	6%	211	225

Abbreviations: Matter (PM10); Carbon monoxide (CO); Nitrogen dioxide (NO2); Sulfur dioxide (SO2); Socioeconomic Status (SES); Self-Reporting Questionnaire (SRQ-20); Edinburgh Postnatal Depression Scale (EPDS); Life Experiences Questionnaire (LEQ); Intimate Partner Violence (IPV); Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST)

Association Analyses

To investigate the association between prenatal exposure to indoor air pollution and psychosocial factors with inflammation at 6 weeks old, we used both single-exposure and environmental mixture methodology. Traditional single-exposure linear regression modeling techniques were used to estimate the associations of all exposures individually with inflammation. Next, using Self-Organizing Maps (SOM) we estimated joint effects of indoor air pollution and psychosocial factor exposures on inflammation. These joint effects estimated by the SOM can highlight exposure profiles of our population that have the greatest impact on inflammation in the infant.

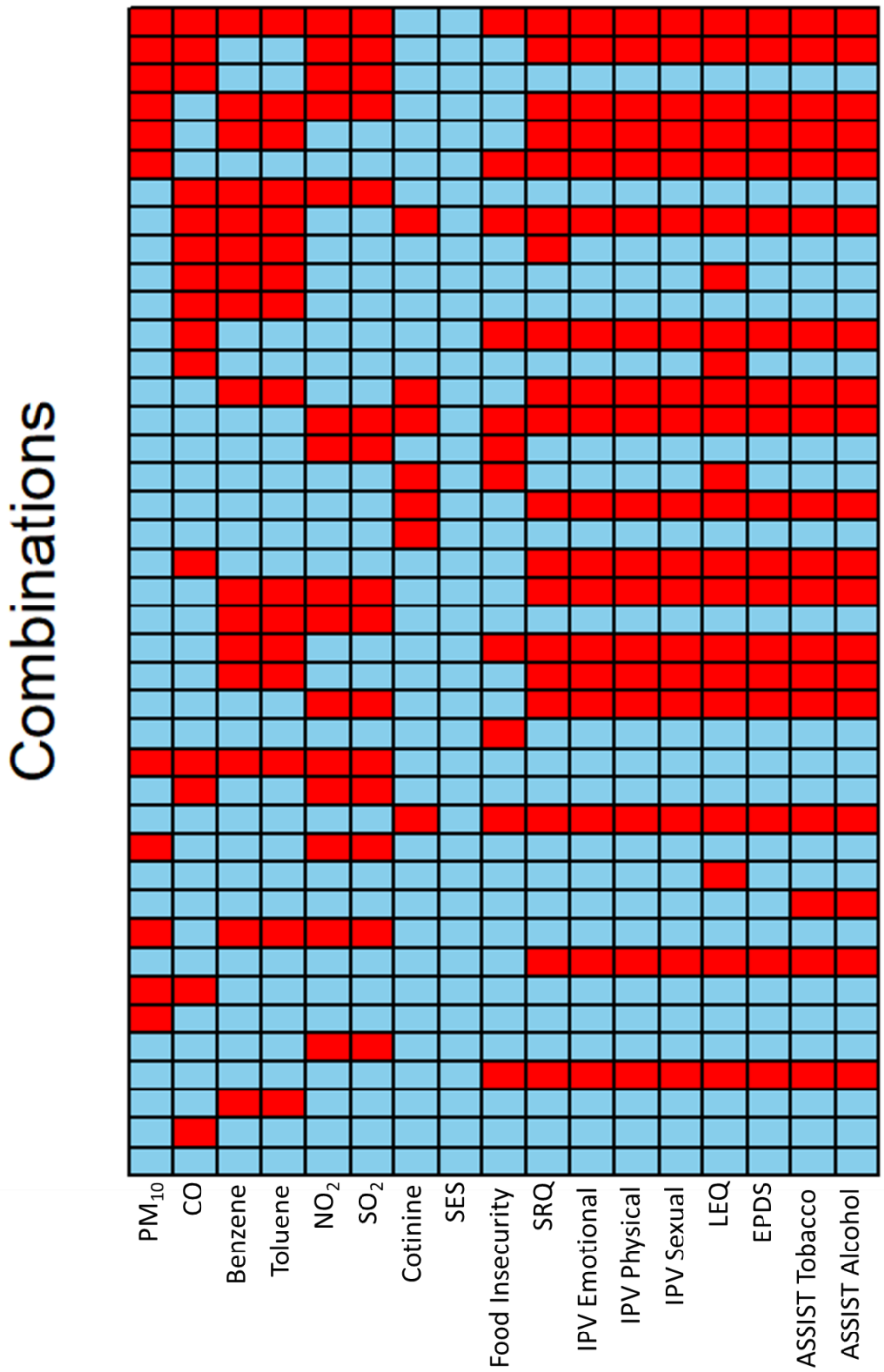


Figure 4-2*: Combinations of missingness patterns of exposure variables. Each row is a missingness pattern where red indicates that variable is missing, and blue indicates not missing.*

Single-Exposure Models

To investigate how individual prenatal indoor air pollutant and psychosocial factors are associated with inflammation at 6 weeks old we used single-exposure linear regression models. All exposures were right skewed and natural log-transformed for linear regression analyses. Each exposure was used in its own linear regression model adjusted for the minimal set of confounders, which included maternal age, maternal HIV status, ancestry, and socioeconomic status (except when the exposure of interest). Confounders were determined using a directed acyclic graph (DAG; **Figure 4-3**). In sensitivity analyses, single-exposure models were additionally adjusted for principal components (PCs) of the other group of exposures (indoor air pollutants or psychosocial factors). We used PCs as confounding variables, created by principal components analysis (PCA), as opposed to the individual variables to include information on many correlated variables but avoid over adjustment of the model. In these models the first 4 PCs of indoor air pollutants or psychosocial stressors, respectively, were included in the models as confounders.

We explored effect modification by ancestry (Black African vs Mixed Ancestry), and maternal HIV status. Ancestry was chosen as an effect modifier because there are noted differences in socioeconomic as well as psychosocial risk factors by ancestry in the DCHS[57]. HIV status was also investigated as an effect modifier because of the known connection with inflammation[125] and the high burden in this population.

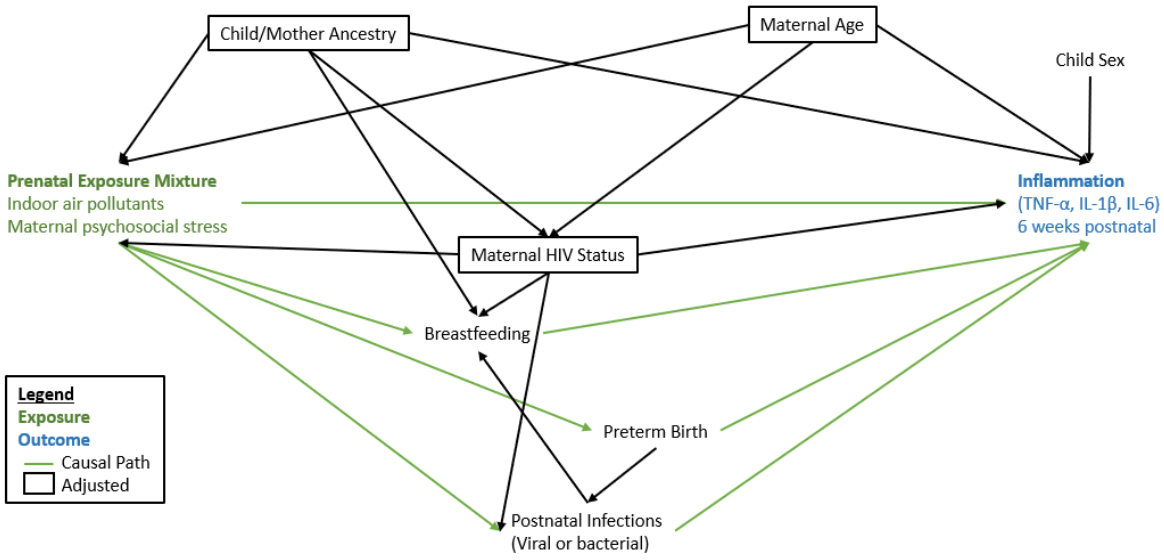


***Figure 4-3**: Directed Acyclic Graph (DAG) of underlying causal pathways between prenatal exposure to indoor air pollutants and psychosocial factors including socioeconomic status, and inflammatory markers at 6 weeks old.*

Self-Organizing Maps

Self-organizing maps (SOM) is an unsupervised algorithm that creates profiles of exposure. SOM was used to create profiles of prenatal exposure to indoor air pollution and psychosocial factors. SOM identifies clusters of exposure, or profiles of exposure, that are homogeneous within cluster and heterogeneous between clusters[109,126]. To prepare for the SOM algorithm, exposures were natural log-transformed and scaled to have a mean of 0 and a standard deviation of 1. The number of clusters chosen for association analyses was based on statistical measures of group structure, including Akaike information criterion (AIC), and adjusted R^2. As has been done previously, visual inspection of the clusters for interpretability and appropriate distribution of participants among clusters was also used to select the number of clusters. To investigate the association between the SOM clusters and inflammation, SOM clusters were assigned to participants and added to linear regression models as a categorical exposure variable. The linear regression model using SOM clusters as the exposure was adjusted for

maternal age, maternal HIV status, and ancestry. We used the SOM R package as implemented in https://github.com/johnlpearce/ECM.

All analyses were performed using R version 4.1.2 (R Core Team, Vienna, Austria).

Results

On average, mothers in our study population of n=225 mother-child pairs were 27.7 years old (SD: 5.98). Over 40% of mothers were infected with HIV. About half (57.8%) of the children included in this analysis were male **(Table 4-3).** Indoor air pollutants were not highly correlated, while psychosocial factors were moderately correlated with each other. Indoor air pollutants and psychosocial factors were not correlated with each other **(Figure 4-4)**. There was low to moderate correlation (ρ = 0.05 – 0.39) among inflammatory markers **(Table 4-4)**.

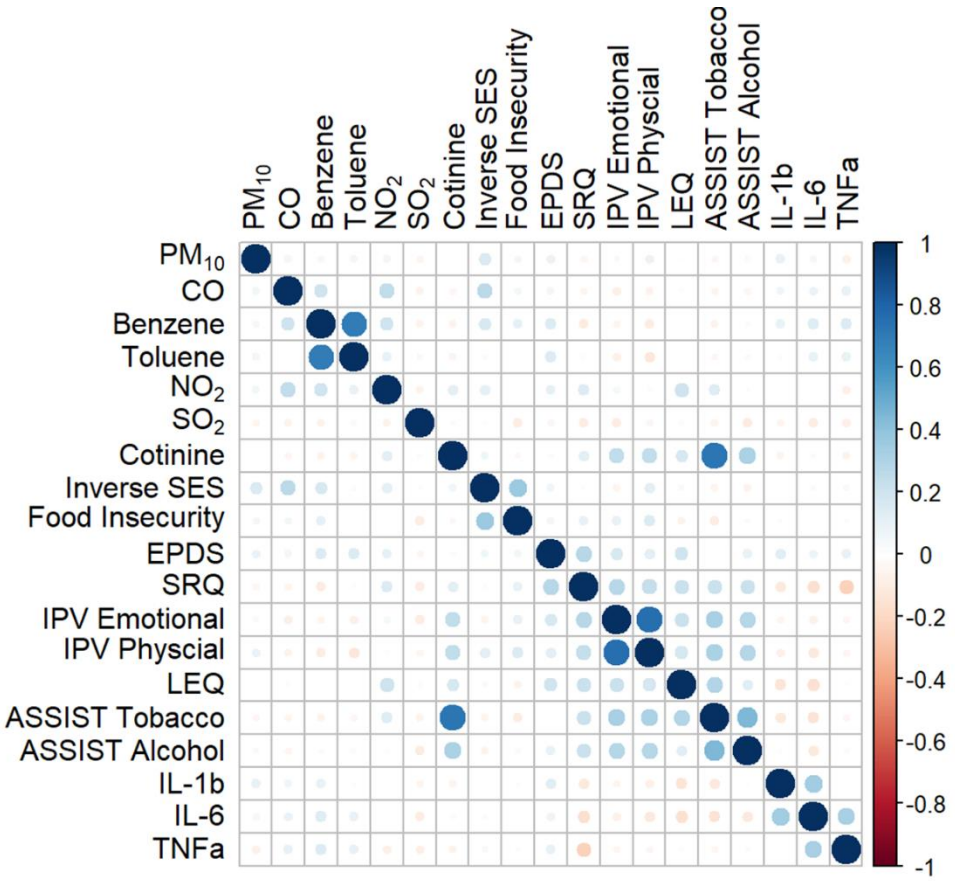


Figure 4-4*: Pearson correlation matrix with prenatal exposure measurements.*

Table 4-3: *Descriptive characteristics of the study population.*

N	225
Maternal Age (mean (SD))	27.65 (5.98)
Male Child (%)	130 (57.8)
Ancestry	
Black African Ancestry (5)	135 (60.0)
Mixed Ancestry (%)	90 (40.0)
Mother HIV-infected (%)	95 (42.2)
Indoor Air Pollutants	
PM10 µg/m3 (median [IQR])	39.01 [14.97, 69.62]
CO mg/m3 (median [IQR])	0.00 [0.00, 120.00]
Benzene µg/m3 (median [IQR])	4.34 [1.91, 12.72]
Toluene µg/m3 (median [IQR])	16.02 [6.61, 45.02]
NO2 µg/m3 (median [IQR])	6.05 [3.10, 11.27]
SO2 µg/m3 (median [IQR])	0.00 [0.00, 0.14]
Psychosocial Factors	
Urine Cotinine ng/ml (median [IQR])	52.70 [14.60, 500.00]
SES Asset Sum (median [IQR])	7.00 [5.00, 8.00]
Food Insecurity Total Score (median [IQR])	0.00 [0.00, 3.00]
SRQ-20 Total Score (median [IQR])	4.00 [2.00, 8.00]
Emotional IPV Score (median [IQR])	5.00 [4.00, 7.00]
Physical IPV Score (median [IQR])	6.00 [5.00, 8.00]
LEQ Total Score (median [IQR])	2.00 [1.00, 3.00]
EPDS Total Score (median [IQR])	10.00 [7.00, 14.00]
ASSIST Tobacco Score (median [IQR])	0.00 [0.00, 15.00]
ASSIST Alcohol Score (median [IQR])	0.00 [0.00, 0.00]
Inflammatory Markers	
IL-1β (median [IQR])	1.05 [0.48, 1.76]
IL-6 (median [IQR])	1.93 [0.69, 4.08]
TNF-α (median [IQR])	19.57 [14.48, 28.23]

Abbreviations: Particulate Matter (PM10); Carbon monoxide (CO); Nitrogen dioxide (NO2); Sulfur dioxide (SO2); Socioeconomic Status (SES); Self-Reporting Questionnaire (SRQ-20); Edinburgh Postnatal Depression Scale (EPDS); Life Experiences Questionnaire (LEQ); Intimate Partner Violence (IPV); Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST); Interleukin 1β (IL-1β); Interleukin 6 (IL-6); Tumor Necrosis Factor-α (TNF-α).

Table 4-4: *Spearman correlation between inflammatory markers at 6 weeks old.*

	IL-1β	IL-6	TNF-α
IL-1β	1	0.39	0.05
IL-6	0.39	1	
TNF-α	0.05	0.26	1

Single-Exposure Analyses

In single-exposure linear regression models adjusted for confounders, there were consistent positive associations between most indoor air pollutants and inflammatory markers. For example, a one-unit increase in benzene was associated with higher TNF-α levels ([beta: 0.06; 95% CI: 0.00, 0.12]; **Table 4-5, Figure 4-5C)**. SO_2 was the only air pollutant which was associated with lower inflammation, though these associations were not statistically significant **(Table 4-5, Figure 4-5).**

No consistent patterns were found for psychosocial factors in single-exposure linear regression models. A majority of psychosocial factors were not associated with any inflammatory marker. Psychological distress (SRQ) was consistently associated with lower inflammation (IL-6: beta: -0.13; 95% CI: -0.25, -0.01; TNF-α: beta: -0.16; 95% CI: -0.25, -0.07). A one unit increase in adverse life experiences (LEQ) (beta: -0.16; 95% CI: -0.33, -0.00) was also associated with lower IL-6 levels **(Table 4-5, Figure 4-5)**. Depression symptoms (EPDS) were consistently associated with higher inflammation, though none of these effect estimates were statistically significant. Results were similar in sensitivity analyses when additionally adjusting for PCs of the other exposure group **(Table 4-6)**, and in sensitivity analyses using complete cases and when using other MI seeds in the multiple imputation **(Table 4-5)**.

Table 4-5: *Beta estimates and 95% CIs for individual exposure adjusted linear regression models. The linear regression models were adjusted for maternal HIV status, maternal age, ancestry, and socioeconomic status. Tables shows results from complete case models as well as multiple imputation (MI) models using 5 different random seeds (MI1 to MI5). MI4 models were presented in the main analysis.*

	Complete Case	MI1	MI2	MI3	MI4 (Analysis Sample)	MI5
			IL-1β			
PM10 Common Confounders	0 (-0.07, 0.06)	0.03 (-0.01, 0.07)	0.03 (-0.01, 0.07)	0.02 (-0.02, 0.07)	0.03 (-0.01, 0.07)	0.04 (-0.01, 0.08)
CO Common Confounders	0.02 (-0.01, 0.04)	0.01 (-0.01, 0.03)	0.01 (-0.01, 0.03)	0.01 (-0.01, 0.03)	0.01 (-0.01, 0.03)	0.02 (0, 0.04)
Benzene Common Confounders	0.03 (-0.03, 0.09)	0.02 (-0.02, 0.06)	0.02 (-0.02, 0.07)	0.01 (-0.03, 0.05)	0.03 (-0.01, 0.07)	0.02 (-0.03, 0.06)
Toluene Common Confounders	0.01 (-0.04, 0.06)	0 (-0.03, 0.04)	0 (-0.03, 0.04)	0 (-0.03, 0.04)	0 (-0.03, 0.04)	0 (-0.04, 0.04)
SO2 Common Confounders	0 (-0.16, 0.17)	-0.02 (-0.12, 0.09)	-0.04 (-0.15, 0.08)	-0.05 (-0.16, 0.06)	-0.04 (-0.15, 0.07)	-0.03 (-0.15, 0.08)
NO2 Common Confounders	0.01 (-0.08, 0.09)	0 (-0.05, 0.06)	-0.01 (-0.07, 0.05)	0 (-0.06, 0.06)	0.01 (-0.05, 0.07)	0.01 (-0.05, 0.07)
Cotinine Common Confounders	0.01 (-0.04, 0.07)	-0.01 (-0.06, 0.03)	-0.01 (-0.05, 0.04)	-0.01 (-0.05, 0.03)	-0.01 (-0.05, 0.03)	0 (-0.04, 0.04)
ASSIST Tobacco Common Confounders	0 (-0.06, 0.07)	-0.03 (-0.08, 0.02)	-0.04 (-0.09, 0.01)	-0.03 (-0.08, 0.02)	-0.04 (-0.09, 0.01)	-0.04 (-0.09, 0.01)
ASSIST Alcohol Common Confounders	0 (-0.08, 0.07)	0 (-0.05, 0.06)	-0.02 (-0.07, 0.04)	0 (-0.06, 0.06)	-0.01 (-0.06, 0.05)	-0.01 (-0.06, 0.05)
EPDS Common Confounders	0.15 (0.01, 0.29)	0.11 (0.01, 0.21)	0.12 (0.02, 0.22)	0.1 (0.01, 0.2)	0.1 (0, 0.2)	0.1 (0, 0.21)
SRQ Common Confounders	-0.08 (-0.18, 0.03)	-0.03 (-0.1, 0.05)	-0.05 (-0.12, 0.02)	-0.03 (-0.1, 0.04)	-0.06 (-0.13, 0.01)	-0.04 (-0.11, 0.03)
IPV Physical Common Confounders	-0.05 (-0.3, 0.21)	-0.03 (-0.22, 0.15)	-0.05 (-0.24, 0.13)	-0.05 (-0.24, 0.13)	-0.1 (-0.28, 0.08)	-0.04 (-0.23, 0.14)
IPV Emotional Common Confounders	-0.06 (-0.31, 0.19)	0.01 (-0.17, 0.18)	-0.01 (-0.19, 0.16)	-0.04 (-0.21, 0.13)	-0.06 (-0.23, 0.11)	-0.04 (-0.21, 0.13)

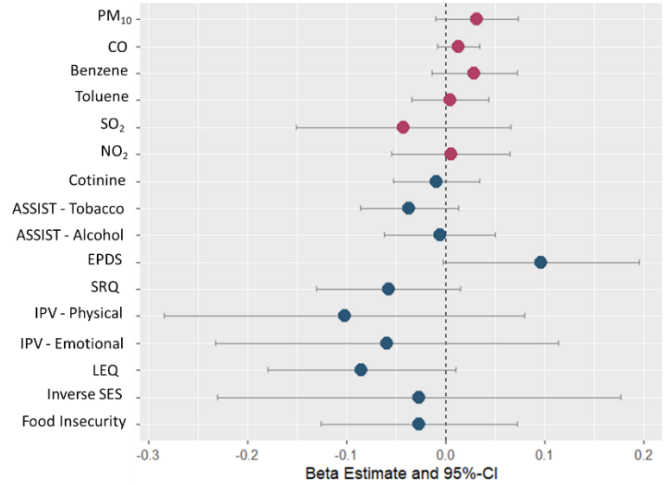
LEQ Common Confounders	-0.03 (-0.16, 0.11)	-0.05 (-0.15, 0.05)	-0.09 (-0.19, 0.01)	-0.07 (-0.17, 0.03)	-0.08 (-0.18, 0.01)	-0.07 (-0.16, 0.03)
SES Common Confounders	0 (-0.29, 0.29)	-0.03 (-0.23, 0.18)	-0.03 (-0.23, 0.18)	-0.03 (-0.23, 0.18)	-0.03 (-0.23, 0.18)	-0.03 (-0.23, 0.18)
Food Insecurity Common Confounders	0.01 (-0.13, 0.14)	-0.02 (-0.12, 0.08)	-0.01 (-0.11, 0.09)	-0.02 (-0.12, 0.08)	-0.03 (-0.13, 0.07)	0 (-0.1, 0.1)
			IL-6			
PM10 Common Confounders	0.02 (-0.09, 0.14)	0.05 (-0.01, 0.12)	0.05 (-0.02, 0.12)	0.05 (-0.02, 0.12)	0.03 (-0.04, 0.1)	0.05 (-0.02, 0.12)
CO Common Confounders	0.02 (-0.03, 0.07)	0.04 (0.01, 0.07)	0.02 (-0.01, 0.06)	0.01 (-0.03, 0.05)	0.03 (-0.01, 0.07)	0.03 (-0.01, 0.06)
Benzene Common Confounders	0.06 (-0.05, 0.16)	0.08 (0.01, 0.15)	0.06 (-0.02, 0.13)	0.02 (-0.05, 0.09)	0.07 (0, 0.14)	0.06 (-0.01, 0.13)
Toluene Common Confounders	0.05 (-0.04, 0.14)	0.04 (-0.02, 0.11)	0.02 (-0.04, 0.09)	0.02 (-0.05, 0.08)	0.05 (-0.02, 0.11)	0.04 (-0.02, 0.11)
SO2 Common Confounders	-0.05 (-0.34, 0.23)	-0.14 (-0.32, 0.04)	-0.14 (-0.33, 0.05)	-0.15 (-0.34, 0.04)	-0.15 (-0.34, 0.04)	-0.17 (-0.36, 0.02)
NO2 Common Confounders	0 (-0.15, 0.15)	-0.01 (-0.11, 0.09)	-0.01 (-0.11, 0.09)	-0.01 (-0.11, 0.09)	0.01 (-0.09, 0.12)	0 (-0.1, 0.1)
Cotinine Common Confounders	0.02 (-0.08, 0.12)	0.03 (-0.05, 0.1)	0.03 (-0.05, 0.1)	0.03 (-0.04, 0.11)	0.03 (-0.04, 0.11)	0.05 (-0.03, 0.12)
ASSIST Tobacco Common Confounders	-0.11 (-0.23, 0.01)	-0.05 (-0.14, 0.04)	-0.06 (-0.15, 0.02)	-0.06 (-0.14, 0.03)	-0.06 (-0.14, 0.03)	-0.06 (-0.15, 0.02)
ASSIST Alcohol Common Confounders	-0.12 (-0.25, 0.01)	-0.06 (-0.15, 0.04)	-0.08 (-0.17, 0.02)	-0.05 (-0.15, 0.05)	-0.06 (-0.15, 0.04)	-0.07 (-0.17, 0.02)
EPDS Common Confounders	0.08 (-0.17, 0.33)	0.12 (-0.05, 0.28)	0.12 (-0.04, 0.29)	0.11 (-0.06, 0.27)	0.08 (-0.09, 0.25)	0.09 (-0.09, 0.27)
SRQ Common Confounders	-0.16 (-0.34, 0.02)	-0.08 (-0.2, 0.04)	-0.11 (-0.24, 0.01)	-0.1 (-0.22, 0.02)	-0.13 (-0.25, -0.01)	-0.09 (-0.21, 0.03)
IPV Physical Common Confounders	-0.23 (-0.68, 0.21)	-0.12 (-0.44, 0.2)	-0.13 (-0.45, 0.18)	-0.09 (-0.41, 0.22)	-0.2 (-0.51, 0.12)	-0.12 (-0.44, 0.2)
IPV Emotional Common Confounders	0.11 (-0.33, 0.54)	0.05 (-0.25, 0.35)	0 (-0.29, 0.3)	-0.01 (-0.31, 0.29)	-0.04 (-0.34, 0.26)	-0.02 (-0.32, 0.28)

LEQ Common Confounders	-0.2 (-0.44, 0.04)	-0.11 (-0.27, 0.06)	-0.21 (-0.38, -0.04)	-0.15 (-0.32, 0.01)	-0.16 (-0.33, 0)	-0.16 (-0.32, 0.01)
SES Common Confounders	-0.23 (-0.74, 0.27)	-0.01 (-0.36, 0.34)	-0.01 (-0.36, 0.34)	-0.01 (-0.36, 0.34)	-0.01 (-0.36, 0.34)	-0.01 (-0.36, 0.34)
Food Insecurity Common Confounders	0 (-0.24, 0.23)	-0.05 (-0.22, 0.11)	-0.05 (-0.22, 0.12)	-0.07 (-0.24, 0.1)	-0.07 (-0.24, 0.1)	-0.04 (-0.21, 0.13)
			TNF-α			
PM10 Common Confounders	-0.08 (-0.16, 0)	-0.04 (-0.1, 0.01)	-0.03 (-0.08, 0.03)	-0.03 (-0.08, 0.03)	-0.03 (-0.09, 0.02)	-0.04 (-0.09, 0.01)
CO Common Confounders	0.02 (-0.02, 0.05)	0.01 (-0.01, 0.04)	0.02 (-0.01, 0.04)	0.01 (-0.02, 0.04)	0.02 (-0.01, 0.05)	0.01 (-0.01, 0.04)
Benzene Common Confounders	0.05 (-0.03, 0.12)	0.05 (-0.01, 0.11)	0.05 (-0.01, 0.1)	0.05 (-0.01, 0.1)	0.06 (0, 0.12)	0.04 (-0.01, 0.1)
Toluene Common Confounders	0.03 (-0.03, 0.1)	0.02 (-0.03, 0.07)	0.02 (-0.03, 0.07)	0.02 (-0.02, 0.07)	0.04 (-0.01, 0.09)	0.02 (-0.03, 0.07)
SO2 Common Confounders	-0.13 (-0.34, 0.08)	-0.1 (-0.24, 0.04)	-0.09 (-0.23, 0.06)	-0.1 (-0.25, 0.04)	-0.11 (-0.25, 0.04)	-0.1 (-0.25, 0.04)
NO2 Common Confounders	0.06 (-0.05, 0.17)	-0.03 (-0.11, 0.05)	-0.05 (-0.12, 0.03)	-0.02 (-0.1, 0.06)	-0.04 (-0.11, 0.04)	-0.04 (-0.12, 0.04)
Cotinine Common Confounders	0.02 (-0.06, 0.1)	-0.02 (-0.08, 0.03)	-0.02 (-0.07, 0.04)	-0.02 (-0.08, 0.04)	-0.02 (-0.08, 0.04)	-0.01 (-0.07, 0.05)
ASSIST Tobacco Common Confounders	0.04 (-0.05, 0.13)	0 (-0.07, 0.06)	0 (-0.07, 0.06)	-0.01 (-0.07, 0.06)	0 (-0.06, 0.07)	-0.01 (-0.08, 0.05)
ASSIST Alcohol Common Confounders	0.05 (-0.05, 0.15)	-0.01 (-0.08, 0.07)	0 (-0.07, 0.08)	0.01 (-0.06, 0.08)	0.01 (-0.06, 0.08)	-0.03 (-0.1, 0.04)
EPDS Common Confounders	0.16 (-0.02, 0.35)	0.08 (-0.04, 0.21)	0.12 (0, 0.25)	0.13 (0.01, 0.26)	0.09 (-0.04, 0.22)	0.09 (-0.04, 0.23)
SRQ Common Confounders	-0.07 (-0.2, 0.06)	-0.13 (-0.22, -0.04)	-0.14 (-0.23, -0.04)	-0.14 (-0.23, -0.04)	-0.16 (-0.25, -0.07)	-0.14 (-0.24, -0.05)
IPV Physical Common Confounders	0.11 (-0.22, 0.45)	-0.05 (-0.29, 0.19)	-0.05 (-0.29, 0.19)	-0.03 (-0.27, 0.21)	-0.06 (-0.29, 0.18)	-0.06 (-0.3, 0.18)
IPV Emotional Common Confounders	0.17 (-0.16, 0.49)	0.02 (-0.21, 0.25)	0 (-0.22, 0.23)	0.02 (-0.21, 0.25)	0 (-0.22, 0.23)	-0.01 (-0.24, 0.21)

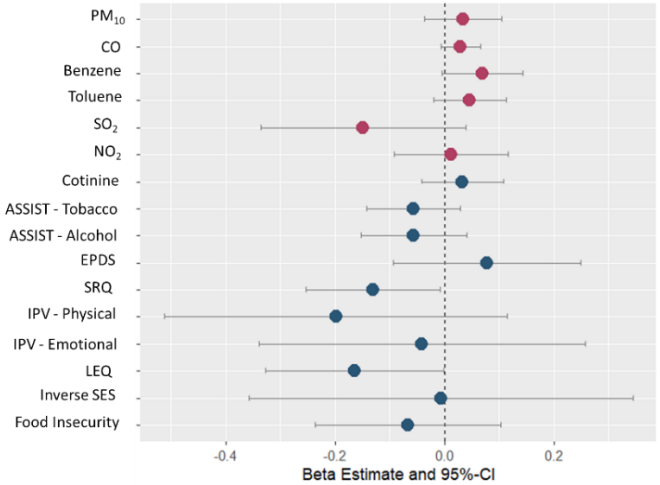
LEQ Common Confounders	0.12 (-0.06, 0.3)	0.02 (-0.11, 0.15)	-0.02 (-0.14, 0.11)	-0.01 (-0.14, 0.12)	0.02 (-0.1, 0.15)	0.03 (-0.1, 0.16)
SES Common Confounders	-0.12 (-0.5, 0.25)	0.02 (-0.24, 0.29)	0.02 (-0.24, 0.29)	0.02 (-0.24, 0.29)	0.02 (-0.24, 0.29)	0.02 (-0.24, 0.29)
Food Insecurity Common Confounders	-0.05 (-0.22, 0.13)	-0.04 (-0.17, 0.09)	-0.03 (-0.15, 0.1)	-0.03 (-0.15, 0.1)	-0.05 (-0.18, 0.07)	-0.04 (-0.17, 0.09)

Abbreviations: Matter (PM10); Carbon monoxide (CO); Nitrogen dioxide (NO2); Sulfur dioxide (SO2); Socioeconomic Status (SES); Self-Reporting Questionnaire (SRQ-20); Edinburgh Postnatal Depression Scale (EPDS); Life Experiences Questionnaire (LEQ); Intimate Partner Violence (IPV); Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST)

A. IL-1β



B. IL-6



C. TNF-α

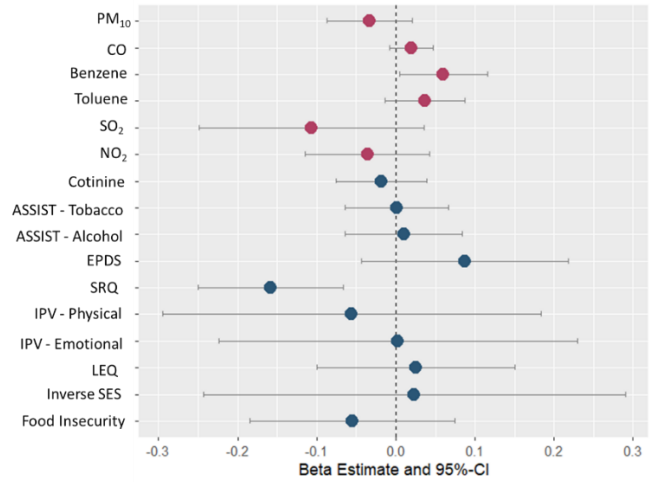


Figure 4-5: *Single-exposure linear regression models of the association between prenatal indoor air pollution and psychosocial factor exposures on inflammatory markers at 6 weeks postnatal. All linear regression models were adjusted for maternal age, maternal HIV status, ancestry and socioeconomic status (when not the exposure of interest).* ***A****. Models using Il-1β as the outcome.* ***B.*** *Models using Il-6 as the outcome.* ***C.*** *Models using TNF-α as the outcome.*

Table 4-6: *Beta estimates and 95% CIs for individual exposure adjusted linear regression models. The common confounder linear regression models were adjusted for maternal HIV status, maternal age, ancestry, and socioeconomic status. Extended confounder set models using indoor air pollutant exposures were additionally adjusted principal components of psychosocial factors, and vice versa.*

	IL-1β	IL-6	TNF-α
PM10 Common Confounders	0.03 (-0.01, 0.07)	0.03 (-0.04, 0.1)	-0.03 (-0.09, 0.02)
PM10 Extended Confounder Set	0.03 (-0.01, 0.07)	0.03 (-0.04, 0.11)	-0.03 (-0.09, 0.02)
CO Common Confounders	0.01 (-0.01, 0.03)	0.03 (-0.01, 0.07)	0.02 (-0.01, 0.05)
CO Extended Confounder Set	0.01 (-0.01, 0.03)	0.03 (-0.01, 0.06)	0.02 (-0.01, 0.05)
Benzene Common Confounders	0.03 (-0.01, 0.07)	0.07 (0, 0.14)	0.06 (0, 0.12)
Benzene Extended Confounder Set	0.03 (-0.02, 0.07)	0.07 (0, 0.14)	0.06 (0.01, 0.12)
Toluene Common Confounders	0 (-0.03, 0.04)	0.05 (-0.02, 0.11)	0.04 (-0.01, 0.09)
Toluene Extended Confounder Set	0 (-0.04, 0.04)	0.05 (-0.02, 0.12)	0.04 (-0.01, 0.09)
SO2 Common Confounders	-0.04 (-0.15, 0.07)	-0.15 (-0.34, 0.04)	-0.11 (-0.25, 0.04)
SO2 Extended Confounder Set	-0.05 (-0.16, 0.07)	-0.17 (-0.36, 0.02)	-0.13 (-0.27, 0.02)
NO2 Common Confounders	0.01 (-0.05, 0.07)	0.01 (-0.09, 0.12)	-0.04 (-0.11, 0.04)
NO2 Extended Confounder Set	0.01 (-0.05, 0.07)	0.03 (-0.08, 0.13)	-0.03 (-0.12, 0.05)
Cotinine Common Confounders	-0.01 (-0.05, 0.03)	0.03 (-0.04, 0.11)	-0.02 (-0.08, 0.04)
Cotinine Extended Confounder Set	-0.01 (-0.05, 0.04)	0.04 (-0.03, 0.12)	-0.02 (-0.07, 0.04)
ASSIST Tobacco Common Confounders	-0.04 (-0.09, 0.01)	-0.06 (-0.14, 0.03)	0 (-0.06, 0.07)
ASSIST Tobacco Extended Confounder Set	-0.03 (-0.08, 0.02)	-0.05 (-0.14, 0.03)	0 (-0.07, 0.06)
ASSIST Alcohol Common Confounders	-0.01 (-0.06, 0.05)	-0.06 (-0.15, 0.04)	0.01 (-0.06, 0.08)
ASSIST Alcohol Extended Confounder Set	-0.01 (-0.06, 0.05)	-0.06 (-0.16, 0.04)	0.01 (-0.07, 0.08)
EPDS Common Confounders	0.1 (0, 0.2)	0.08 (-0.09, 0.25)	0.09 (-0.04, 0.22)
EPDS Extended Confounder Set	0.08 (-0.02, 0.18)	0.04 (-0.13, 0.21)	0.07 (-0.06, 0.2)
SRQ Common Confounders	-0.06 (-0.13, 0.01)	-0.13 (-0.25, -0.01)	-0.16 (-0.25, -0.07)
SRQ Extended Confounder Set	-0.06 (-0.13, 0.02)	-0.13 (-0.26, -0.01)	-0.16 (-0.25, -0.07)
IPV Physical Common Confounders	-0.1 (-0.28, 0.08)	-0.2 (-0.51, 0.12)	-0.06 (-0.29, 0.18)
IPV Physical Extended Confounder Set	-0.1 (-0.28, 0.09)	-0.17 (-0.49, 0.14)	-0.02 (-0.26, 0.22)
IPV Emotional Common Confounders	-0.06 (-0.23, 0.11)	-0.04 (-0.34, 0.26)	0 (-0.22, 0.23)
IPV Emotional Extended Confounder Set	-0.06 (-0.23, 0.12)	-0.03 (-0.33, 0.26)	0.01 (-0.22, 0.24)
LEQ Common Confounders	-0.08 (-0.18, 0.01)	-0.16 (-0.33, 0)	0.02 (-0.1, 0.15)
LEQ Extended Confounder Set	-0.09 (-0.18, 0.01)	-0.18 (-0.34, -0.01)	0.02 (-0.1, 0.15)

SES Common Confounders	-0.03 (-0.23, 0.18)	-0.01 (-0.36, 0.34)	0.02 (-0.24, 0.29)
SES Extended Confounder Set	-0.08 (-0.29, 0.13)	-0.1 (-0.47, 0.27)	0.03 (-0.25, 0.31)
Food Insecurity Common Confounders	-0.03 (-0.13, 0.07)	-0.07 (-0.24, 0.1)	-0.05 (-0.18, 0.07)
Food Insecurity Extended Confounder Set	-0.03 (-0.13, 0.07)	-0.09 (-0.26, 0.08)	-0.07 (-0.2, 0.06)

Abbreviations: Matter (PM10); Carbon monoxide (CO); Nitrogen dioxide (NO2); Sulfur dioxide (SO2); Socioeconomic Status (SES); Self-Reporting Questionnaire (SRQ-20); Edinburgh Postnatal Depression Scale (EPDS); Life Experiences Questionnaire (LEQ); Intimate Partner Violence (IPV); Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST)

In effect modification analyses, the effect of psychological distress (SRQ) on inflammatory markers was stronger in Black African participants compared to mixed ancestry participants **(figure 4-6A, 4-6D**; effect modification statistically significant for IL-6). There was not significant effect modification by HIV status **(Figure 4-7)**.

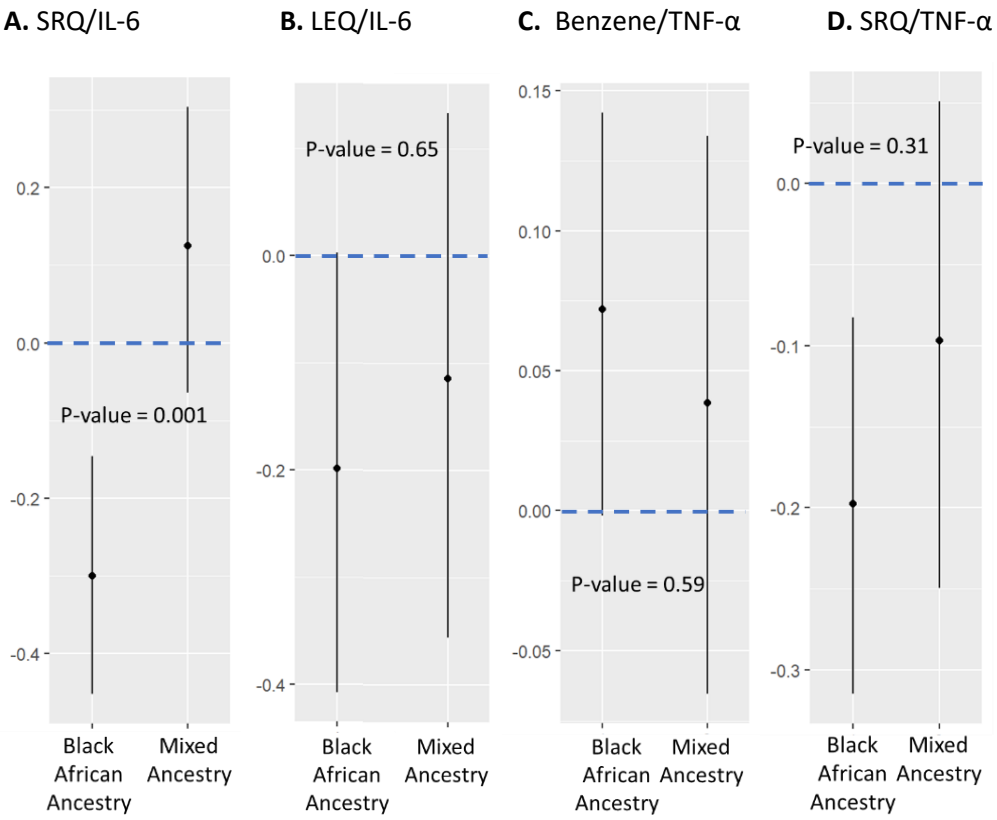


***Figure 4-6**: Interaction of selected exposures and participant ancestry. Effect estimates presented of select exposures among ancestry groups. All models adjusted for maternal age, maternal HIV, and socioeconomic status.*

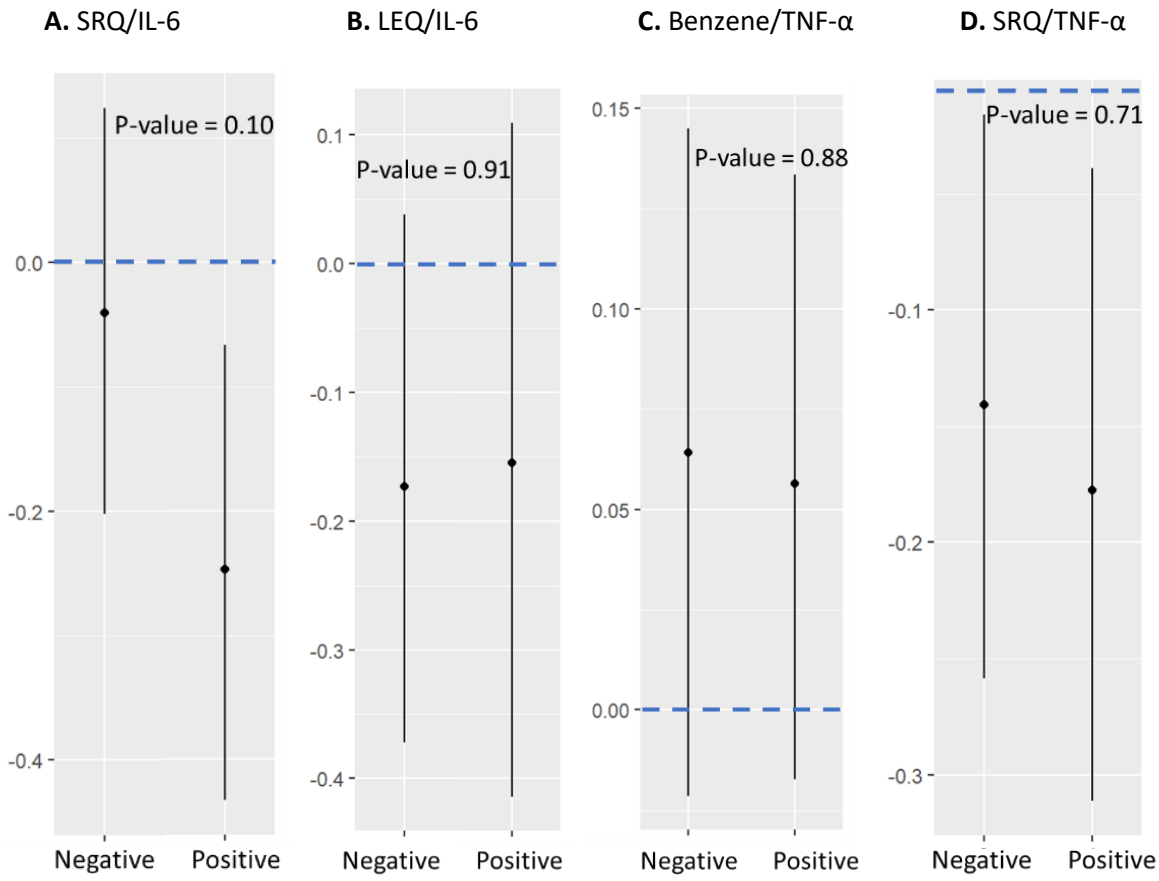


Figure 4-7: *Interaction of selected exposures and participant HIV status. Effect estimates presented of select exposures among HIV status groups. All models adjusted for maternal age, ancestry, and socioeconomic status.*

Joint Effects Analyses

SOM analysis grouped our study population into 4 exposure profiles, which characterize different distributions of the joint exposure to environmental and psychosocial factors. Cluster 1 was selected as the reference cluster in regression analyses because it had the lowest exposure to all psychosocial factors and indoor air pollutants, except for SO_2 **(Table 4-7, Figure 4-8A)**. Compared to cluster 1, cluster 2, a profile with high indoor air pollution, low SES, and high depression symptoms (EPDS) was associated with higher inflammation. Associations were strongest for IL-6 (beta: 0.35; 95% CI: 0.07, 0.62) and TNF-α (Beta: 0.22; 95% CI: 0.01, 0.43) and smaller for IL-1β (beta: 0.13; 95% CI: -0.03, 0.29) **(Table 4-8, Figure 4-8B-D)**. Cluster 3 (high cotinine and ASSIST tobacco and alcohol scores) and cluster 4 (high levels of

psychosocial factors and PM_{10}) were not associated with any inflammatory marker, compared to cluster 1 **(Table 4-8, Figure 4-8B-D)**.

Table 4-7: *Descriptive statistics (Median (IQR)) of indoor air pollutant and psychosocial factor exposures, demographic characteristics and inflammatory markers in Self-Organizing Map (SOM) exposure clusters.*

	SOM Cluster			
	1	**2**	**3**	**4**
N (%)	88 (40.11)	49 (21.78)	41 (18.22)	47 (20.89)
Maternal Age (mean (SD))	27.49 (5.80)	29.66 (5.05)	24.06 (4.94)	28.98 (6.73)
Male Child (%)	52 (59.1)	28 (57.1)	29 (70.7)	21 (44.7)
Mixed Ancestry (%)	20 (22.7)	8 (16.3)	36 (87.8)	26 (55.3)
Mother HIV Positive (%)	39 (44.3)	32 (65.3)	7 (17.1)	17 (36.2)
Indoor Air Pollutants				
PM10 µg/m3 (median [IQR])	31.99 [15.09, 69.16]	44.25 [17.03, 71.68]	48.04 [13.94, 66.42]	44.05 [15.32, 70.71]
CO mg/m3 (median [IQR])	0.00 [0.00, 0.00]	120.00 [0.00, 1060.00]	0.00 [0.00, 120.00]	0.00 [0.00, 0.00]
Benzene µg/m3 (median [IQR])	3.15 [1.27, 4.68]	47.01 [22.78, 100.57]	5.48 [2.77, 14.27]	2.73 [1.12, 5.49]
Toluene µg/m3 (median [IQR])	11.12 [4.90, 18.14]	53.72 [27.01, 403.17]	20.78 [10.63, 63.24]	9.42 [3.79, 20.94]
NO2 µg/m3 (median [IQR])	4.41 [1.54, 7.97]	10.57 [5.36, 19.82]	9.24 [3.97, 12.61]	5.70 [3.64, 9.90]
SO2 µg/m3 (median [IQR])	0.00 [0.00, 0.12]	0.00 [0.00, 0.00]	0.00 [0.00, 0.25]	0.00 [0.00, 0.08]
Psychosocial Factors				
Urine Cotinine ng/ml (median [IQR])	19.00 [10.00, 63.02]	30.00 [13.70, 61.00]	500.00 [500.00, 500.00]	500.00 [43.20, 500.00]
SES Asset Sum (median [IQR])	7.00 [5.75, 8.00]	5.00 [4.00, 7.00]	7.00 [6.00, 8.00]	7.00 [5.00, 8.00]
Food Insecurity Total Score (median [IQR])	0.00 [0.00, 1.00]	2.00 [0.00, 4.00]	0.00 [0.00, 0.00]	1.00 [0.00, 4.00]
SRQ-20 Total Score (median [IQR])	4.00 [1.00, 7.00]	2.00 [1.00, 5.00]	5.00 [3.00, 8.00]	8.00 [5.00, 12.00]
Emotional IPV Score (median [IQR])	4.00 [4.00, 5.00]	4.00 [4.00, 6.00]	5.00 [4.00, 7.00]	11.00 [8.50, 13.50]
Physical IPV Score (median [IQR])	5.00 [5.00, 6.00]	6.00 [5.00, 6.00]	6.00 [5.00, 7.00]	12.00 [9.00, 15.00]
LEQ Total Score (median [IQR])	1.00 [0.00, 2.25]	1.00 [0.00, 2.00]	2.00 [1.00, 4.00]	3.00 [1.00, 4.50]
EPDS Total Score (median [IQR])	9.00 [6.00, 12.00]	12.00 [9.00, 14.00]	10.00 [6.00, 16.00]	10.00 [8.00, 18.00]
ASSIST Tobacco Score (median [IQR])	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	21.00 [18.00, 24.00]	13.00 [0.00, 24.00]
ASSIST Alcohol Score (median [IQR])	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	3.00 [0.00, 12.00]	0.00 [0.00, 15.00]
Inflammatory Markers				
IL1b (median [IQR])	1.00 [0.42, 1.79]	1.08 [0.72, 1.78]	1.00 [0.45, 1.43]	1.11 [0.49, 1.68]

IL6 (median [IQR])	1.70 [0.58, 3.80]	3.10 [1.22, 7.12]	1.69 [0.68, 3.96]	1.69 [0.49, 3.16]
TNFa (median [IQR])	19.23 [14.61, 26.61]	23.38 [16.61, 32.08]	20.68 [13.43, 29.74]	17.55 [13.37, 22.62]

Table 4-8: *Results from linear regression models using SOM cluster as the exposure, adjusted for maternal age, maternal HIV status, and ancestry.*

IL-1β	
SOM Cluster	Beta (95% CI)
1 (Reference)	-
2	0.13 (-0.03, 0.29)
3	-0.02 (-0.22, 0.18)
4	0.02 (-0.15, 0.19)
IL6	
SOM Cluster	Beta (95% CI)
1 (Reference)	-
2	**0.35 (0.07, 0.62)**
3	0.15 (-0.18, 0.48)
4	-0.06 (-0.35, 0.23)
TNF-α	
SOM Cluster	Beta (95% CI)
1 (Reference)	-
2	**0.22 (0.01, 0.43)**
3	0.10 (-0.15, 0.36)
4	-0.01 (-0.23. 0.21)

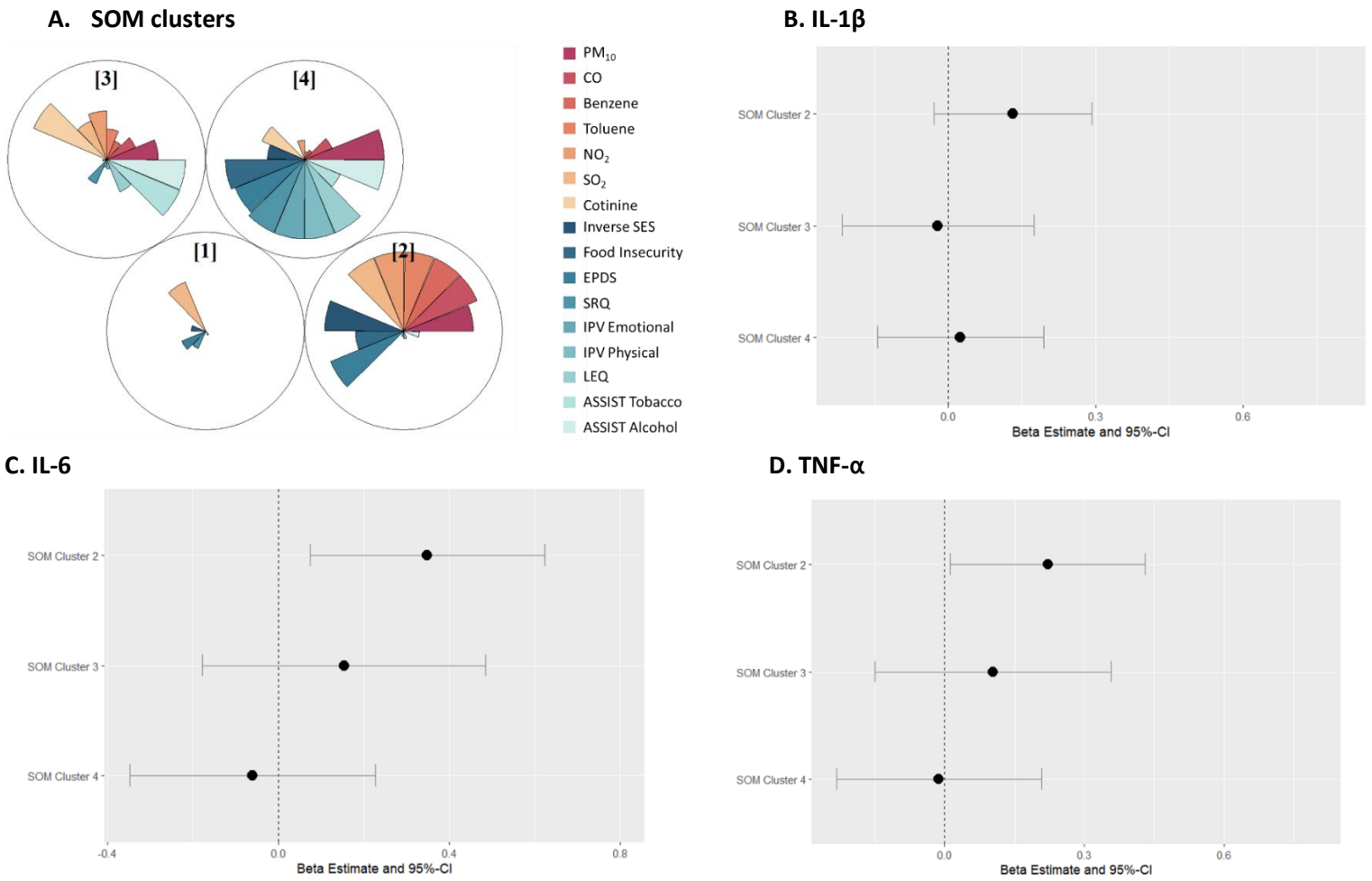


Figure 4-8: *Results from self-organizing map (SOM) analysis using prenatal indoor air pollutants and psychosocial factors. Regression models adjusted for maternal age, maternal HIV status, and ancestry, using SOM cluster 1 as the reference group.* ***A.*** *SOM clusters created using pre- natal indoor air pollutants and psychosocial factors.* ***B.*** *Associations between SOM clusters and IL-1β* ***C.*** *Associations between SOM clusters and IL-6* ***D.*** *Associations between SOM clusters and TNF-α.*

Discussion

In our study of prenatal exposure to indoor air pollutants and psychosocial factors on markers of neuroinflammation at 6 weeks old in the South African DCHS, indoor air pollutants were consistently associated with increased inflammatory markers, IL-1β, IL-6 and TNF-α. This positive association was seen across the three inflammatory markers measures, and in both individual and joint effects models. Specifically, benzene was positively associated with increased TNF-α in single-exposure models, and the SOM cluster associated with high indoor air pollution and depression symptoms was associated with IL-6 and TNF-α. The trend for psychosocial factors was less clear.

Both individual and joint effects models identified a positive trend between prenatal indoor air pollution and all inflammatory markers. This trend has also been seen in some other studies investigating prenatal exposure to air pollution and inflammation, however findings in the literatures are mixed. There is evidence of prenatal exposure to air pollution impacting inflammatory markers in cord blood, a proxy for infant inflammation. One study investigating traffic-related air pollution exposure during pregnancy in a Spanish cohort found NO_2 and PM_{10} were associated with increased odds of detecting IL-1β and IL-6 in cord blood [127]. Another study found PM_{10} exposure during the last 3 months of pregnancy was associated with increased IL-1β levels in cord blood[128]. Another study, investigating prenatal exposure to traffic-related air pollutants found $PM_{2.5}$ was associated with decreased IL-6, TNF-α, and IL-10 levels in cord blood[124]. A majority of the association between air pollutants and inflammation in pregnant individuals only measure inflammation in cord blood samples, rather than in infants, as was done in our study. Another study found comparing pre- and postnatal exposure to air pollution and inflammation found only postnatal exposure was associated with increased Il-4, IL-5, IL-6, and TNF-α, at 1-2 years old[129]. As previously mentioned, few studies have investigated

inflammation at the same time period as our study. This may be due to difficulty in obtaining enough blood for measurement in infants.

We found prenatal benzene exposure was significantly associated with increased TNF-α. To date, no previous study has investigated prenatal exposure to benzene and inflammation. A study investigating human cell responses to benzene found benzene stimulated the production of cytokines in human peripheral blood mononuclear cells[130]. However, another study found that adults occupationally exposed to a benzene-toluene-xylene mixture had decreased production of TNF-α[131]. More research needs to be done to determine the association between benzene and inflammation.

While many of the psychosocial factors investigated in our study were not associated with inflammation at 6-weeks old, prenatal depression had a suggestive positive association with IL-1β, and TNF-α. Few epidemiology studies have investigated prenatal depression in association with inflammation in the child, however, research has shown depressed pregnant women have elevated serum inflammatory cytokines[132,133]. Another study in the DCHS found prenatal depression, using the beck Depression Inventory as opposed to the EPDS, was associated with increased inflammatory cytokine levels at 6-10 weeks old[134]. Specifically, increased IL-1β levels were associated with prenatal depression, which is in line with our study[134].

Surprisingly, the SRQ-20, a measure of psychological distress, was associated with decreased IL-6, and TNF-α levels at 6 weeks, particularly among mothers of Black African ancestry Adverse life events were also associated with decreased IL-6 levels in our study, particularly among Black African Mothers. In the DCHS, HIV-infected mothers were primarily of Black African ancestry[57]. In this cohort, maternal HIV infection was associated with lower cytokine levels in the infant at 6 weeks[125]. Though in this study we did not see effect modification by HIV status. There were also significant differences in age at enrollment, employment, and partner support between Black African and mixed ancestry mothers in the DCHS[57]. These differences

could be driving the effect modification by ancestry that we found for the associations between psychological distress, adverse life events, and inflammatory cytokines. Another surprising aspect of these findings is that as discussed above, depression was associated with increased inflammation while psychological distress was associated with decreased inflammation. As seen in the SOM analysis, high psychological distress co-occurred with low air pollution exposure in this population. The protective effect of SRQ score may therefore be due to the low exposure to indoor air pollution.

In our joint effects SOM analysis, we found a prenatal exposure profile with high indoor air pollution, low SES, and depression exposure was associated with increased IL-6 and TNF-α. Indicating that indoor air pollution and psychosocial stressors may jointly increase inflammation. This is consistent with a prior study which investigated effect modification of traffic-related air pollutants and inflammation by depression, finding that infants of ever depressed mothers had lower cord blood cytokine concentrations compared to those with never depressed mothers[124].

There are several limitations of this study. First, inflammatory measures were only measured in a small subset of the DCHS population. Due to the small sample size, there were wide confidence intervals for many of the individual psychosocial factor associations. A larger sample size would increase power to detect associations among psychosocial factors. There may also be limitations surrounding selection bias with this subsample of the DCHS. The subsample of DCHS mother-child pairs selected for measurement of inflammatory markers was enriched with HIV-infected mothers. Second, exposures were only measured once during the prenatal period and represent the exposure during that entire period. This assumption may lead to exposure misclassification particularly for the indoor air pollutants. An additional limitation is the lack of fine ($PM_{2.5}$) and ultrafine PM measurements which have the largest direct effect on neuroinflammation. PM smaller than PM_{10} are hypothesized to increase neuroinflammation because their smaller size allows for particles to travel throughout the body and brain[27]. Fine

and ultrafine PM were not collected during pregnancy for this cohort because at the time it was not feasible for a cohort of this size.

This study also has several strengths that are worth highlighting. First, there are few epidemiology studies that investigate prenatal exposure to environmental and psychosocial factors on inflammation in the infant. This study adds valuable insight into the individual and joint effects of prenatal exposure to indoor air pollutants and psychosocial factors on inflammation in the infant. Infancy is an important time period of brain development and shaping of synapses, ad increased inflammation may contribute to CNS disease[27,68]. Additionally, the DCHS is a unique cohort that provided prospective data from an understudied population. The DCHS also measures a variety of indoor air pollutants and psychosocial factor exposures during pregnancy which allows for estimation of joint effects of these exposures.

This study identified indoor air pollution exposure during pregnancy as a possible source of increased inflammation in infancy. The association between psychosocial factors and inflammation remains unclear and should be studied in a larger population. Future studies should additionally investigate fine and ultrafine PM exposure. Additionally, future work is needed on the mechanisms underpinning how inflammation may mediate the association between prenatal environmental and psychosocial exposures and outcomes like child neurodevelopment and psychopathology.

Chapter 5 : Mediation of the prenatal indoor air pollution and psychosocial factor association with CBCL at 6.5 years by inflammation at 6 weeks old

This chapter addresses specific aim 3b, investigating inflammation as a potential mediator for the joint effects of air pollution and psychosocial factors on CBCL score at 6.5 years. Due to sample size limitations, unstable estimates, and possible effect modification by HIV status, this analysis was considered a pilot project and will not be submitted for peer-reviewed publication.

Introduction

In previous chapters of this dissertation, we have shown that exposure to indoor air pollutants and psychosocial stress during pregnancy is associated with psychopathology in the child. However, more evidence is needed to determine a causal relationship. One possible biological mechanism through which air pollutants and psychosocial factors may act on the brain is inflammation. Understanding the biological mechanisms can help elucidate causal risk factors.

It has been hypothesized that air pollution affects the central nervous system (CNS) through mechanisms involving inflammation[8,16,27,70,71]. Air pollutant particles create an inflammatory response in the brain during the immune system response. Microglia, the immune cells in the brain, respond to invading particles by releasing inflammatory cytokines like TNF-α, IL-1β, and IL-6, and reactive oxygen species (ROS)[27]. Prenatal stress can also affect microglial activity and inflammatory response[68,71,72]. During gestation and early life, an inflammatory response may affect brain development through microglial involvement in pruning and shaping of the neuronal synapses[68,71]. Disruption or changes in synaptic pruning may contribute to psychopathology[32,135,136].

Few epidemiology studies have examined inflammation as a mediator for the association between prenatal exposure to psychosocial factors and psychopathology. One study found the association between maternal depression during pregnancy and infant egative affect was mediated by maternal inflammation during pregnancy[137]. Another study found the association between maternal stress during pregnancy and child ADHD symptoms at 4-6 years old was mediated by maternal inflammation during the 3rd trimester[138].

For the relationship between prenatal air pollutants and psychopathology, very few studies have investigated mediation by inflammation. One study found possible mediation by maternal inflammation in the 3rd trimester of the effect of prenatal air pollution on development of Autism

Spectrum Disorder[139]. A majority of primary epidemiology studies on air pollution, inflammation, and cognition/psychopathology are conducted during adulthood.

Currently there are no epidemiology studies that have investigated how inflammation may mediate the joint effect of prenatal exposure to air pollutants and psychosocial factors on child psychopathology. As we have shown previously in Chapter 2 of this dissertation, indoor air pollution and psychosocial stress jointly affect child development trajectories and psychopathology measured at 6.5 years. We have also shown a joint effect of these exposures during pregnancy on inflammation in the infant at 6 weeks old. Next, we will investigate how inflammation at 6 weeks may mediate the observed relationship between our joint prenatal exposures and psychopathology.

Using data leveraged from the DCHS, this study aims to investigate inflammation as a potential mediator for the individual and joint effects of air pollution and psychosocial factors on CBCL score at 6.5 years using causal mediation analysis. We will investigate mediation by three inflammatory markers, interleukin-1β, interleukin-6, and tumor necrosis factor-α.

Methods

Study Population

This study is based on a subset of participants from the Drakenstein Child Health Study (DCHS) as discussed previously in chapter 4. Of the N = 1,141 mother-child pairs recruited, a subset of n = 185 were included in this analysis **(Figure 5-1, Table 5-1)**. To be included in this analysis participants had indoor air pollution measurements in the second trimester of pregnancy, infants were not HIV infected, had valid measurements of inflammation at 6 weeks old, and CBCL measurements at 6.5 years. The primary reason for the reduction in sample size is that only a small subset of infants were selected for measurement of inflammatory markers at 6 weeks old. The DCHS was approved by the Human Research Ethics Committee of the Faculty of Health

Sciences, University of Cape Town, by Stellenbosch University and the Western Cape Provincial Research committee. Written informed consent was provided by the mothers for herself and her child and is renewed annually.

The assessments of indoor air pollution and psychosocial factor exposure during pregnancy, and the assessment of inflammation at 6 weeks old are described in chapter 4.

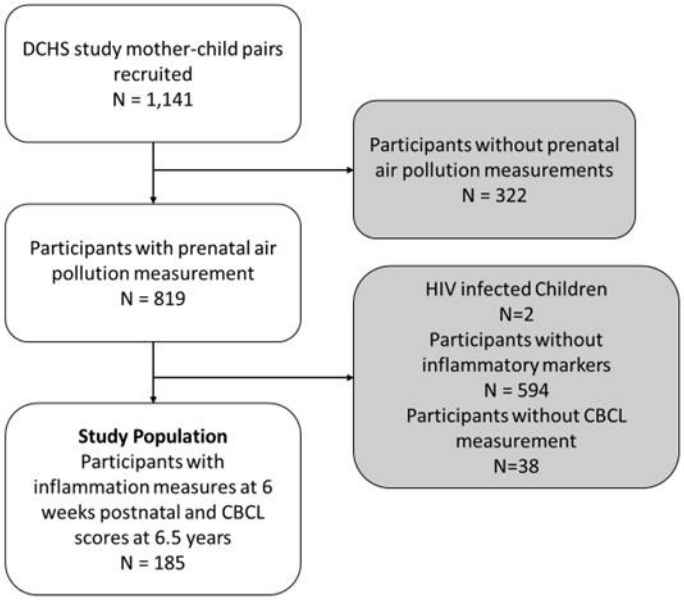


Figure 5-1: *Flow diagram of study participant inclusion.*

***Table 5-1**: Study characteristics of the DCHS and our study subsample.*

	Full DCHS Cohort	IAP Subsample	Inflammatory Maker Subsample	Analysis Sample
N	1143	819	225	185
Maternal Age (mean (SD))	26.60 (5.68)	26.60 (5.67)	27.65 (5.98)	27.36 (5.85)
Male Child (%)	586 (51.3)	422 (51.5)	130 (57.8)	111 (60.0)
Mixed Ancestry (%)	510 (44.7)	379 (46.3)	90 (40.0)	73 (39.5)
Mother HIV Positive (%)	248 (21.7)	171 (20.9)	95 (42.2)	77 (41.6)
Indoor air pollutants				
PM10 µg/m3 (median [IQR])	33.37 [12.49, 64.80]	33.45 [12.49, 65.43]	39.01 [14.97, 69.62]	38.63 [15.30, 69.76]
CO mg/m3 (median [IQR])	0.00 [0.00, 102.50]	0.00 [0.00, 120.00]	0.00 [0.00, 120.00]	0.00 [0.00, 70.00]
Benzene µg/m3 (median [IQR])	4.28 [1.75, 11.29]	4.34 [1.75, 11.50]	4.34 [1.91, 12.72]	4.68 [2.32, 15.07]
Toluene µg/m3 (median [IQR])	16.79 [7.04, 44.24]	16.94 [7.09, 44.79]	16.02 [6.61, 45.02]	17.63 [9.01, 50.10]
NO2 µg/m3 (median [IQR])	7.13 [3.33, 12.69]	7.19 [3.34, 12.70]	6.05 [3.10, 11.27]	6.42 [2.83, 11.99]
SO2 µg/m3 (median [IQR])	0.00 [0.00, 0.28]	0.00 [0.00, 0.28]	0.00 [0.00, 0.14]	0.00 [0.00, 0.20]
Psychosocial Factors				
Urine Cotinine ng/ml (median [IQR])	43.00 [10.70, 500.00]	43.35 [10.70, 500.00]	52.70 [14.60, 500.00]	48.30 [11.50, 500.00]
SES Asset Sum (median [IQR])	7.00 [5.00, 8.00]	7.00 [5.00, 8.00]	7.00 [5.00, 8.00]	7.00 [5.00, 8.00]
Food Insecurity Total Score (median [IQR])	0.00 [0.00, 2.00]	0.00 [0.00, 2.00]	0.00 [0.00, 3.00]	0.00 [0.00, 3.00]
SRQ-20 Total Score (median [IQR])	4.00 [1.00, 7.00]	4.00 [1.50, 7.00]	4.00 [2.00, 8.00]	4.00 [1.00, 8.00]
EPDS Total Score (median [IQR])	9.00 [6.00, 12.00]	9.00 [6.00, 13.00]	10.00 [7.00, 14.00]	10.00 [7.00, 15.00]
LEQ Total Score (median [IQR])	1.00 [0.00, 3.00]	1.00 [0.00, 3.00]	2.00 [1.00, 3.00]	2.00 [1.00, 3.00]
Emotional IPV Score (median [IQR])	4.00 [4.00, 7.00]	5.00 [4.00, 7.00]	5.00 [4.00, 7.00]	5.00 [4.00, 7.00]
Physical IPV Score (median [IQR])	5.00 [5.00, 7.00]	5.00 [5.00, 7.00]	6.00 [5.00, 8.00]	6.00 [5.00, 8.00]
ASSIST Tobacco Score (median [IQR])	0.00 [0.00, 13.00]	0.00 [0.00, 14.00]	0.00 [0.00, 15.00]	0.00 [0.00, 15.00]
ASSIST Alcohol Score (median [IQR])	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]
Inflammatory Markers				
IL-1β (median [IQR])	-	-	1.05 [0.48, 1.76]	1.11 [0.50, 1.78]
IL-6 (median [IQR])	-	-	1.93 [0.69, 4.08]	2.03 [0.67, 4.08]

TNF-α (median [IQR])	-	-	19.57 [14.48, 28.23]	20.22 [15.49, 28.25]
CBCL at 6.5 years				
Total Problems Score (median [IQR])	-	-	-	8.00 [3.00, 14.00]
Externalizing Problems Score (median [IQR])	-	-	-	3.00 [1.00, 7.00]
Internalizing Problems Score (median [IQR])	-	-	-	1.00 [0.00, 3.00]

Outcome Assessment

Parent-reported child psychopathology was assessed using the school version of the Child Behavior Checklist (CBCL) at 6.5 years of age[90]. The CBCL, consisting of 113 questions, assesses child behavior using a Likert scale (0 = absent; 1= occurs sometimes; 2 = occurs often) to create a score, defined as total problems score. These questions can be sub divided into internalizing and externalizing sub scales. The internalizing scale includes questions from the anxious/depressed, withdrawn/depressed, and somatic complaints syndromic scales. The externalizing scale includes the rule-breaking and aggressive behavior syndromic scales[90]. CBCL total problems, internalizing problems, and externalizing problems scores were right skewed and were therefore natural log-transformed to be used in modeling approaches described below.

Statistical Analysis

Multiple Imputation of Missing Values

While there were no missing values in the outcome or covariates, some participants were missing exposure data including certain indoor air pollutants and psychosocial factors. Based on inspections of missingness patterns, we assume these values are missing at random. Using the *hmisc* R package, multiple imputation was preformed to impute missing exposure variables. Exposure variables were imputed using predictive mean matching, models included pre- and postnatal (4 months) measurements of indoor air pollution, psychosocial factors, and household characteristics. Five seed numbers were created using a random number generator, each seed resulted in its own set (k=10) of variables with missing values imputed. One of the k sets was randomly selected to use for analyses as pooling of the k sets was not compatible with one method used in the statistical analysis. The seed with the highest R^2 values, a measure

available within *hmisc* used to explain how well missing values were predicted, was selected for use in primary analyses and results.

Exposure-Outcome Analyses

To investigate the total effect of our prenatal exposures on CBCL at 6.5 years, in this subsample, we first conducted single-exposure linear regression models. All exposures were right skewed and natural-log transformed for analysis. Each single-exposure model was adjusted for maternal HIV status, maternal age, ancestry, and socioeconomic status when not the exposure of interest. Confounding was assessed using directed acyclic graphs (DAG)**(Figure 5-2).**

The total effect of the exposure mixture on CBCL at 6.5 years was assessed using self-organizing maps (SOM). Self-organizing maps (SOM) is an unsupervised algorithm that creates profiles of exposure. SOM was used to create profiles of prenatal exposure to indoor air pollution and psychosocial factors. SOM identifies clusters of exposure, or profiles of exposure, that are homogeneous within cluster and heterogeneous between clusters[109,126]. To prepare for the SOM algorithm, exposures were natural log-transformed and scaled to have a mean of 0 and a standard deviation of 1. The number of clusters chosen for association analyses was based on statistical measures of group structure, including Akaike information criterion (AIC), and adjusted R^2. Additionally, visual inspection of the clusters for interpretability and appropriate distribution of participants among clusters was also used to select the number of clusters. To investigate the association between the SOM clusters and inflammation, SOM clusters were assigned to participants and added to linear regression models as a categorical exposure variable. The linear regression model using SOM clusters as the exposure was adjusted for maternal age, maternal HIV status, and ancestry. We used the SOM R package as implemented in https://github.com/johnlpearce/ECM.

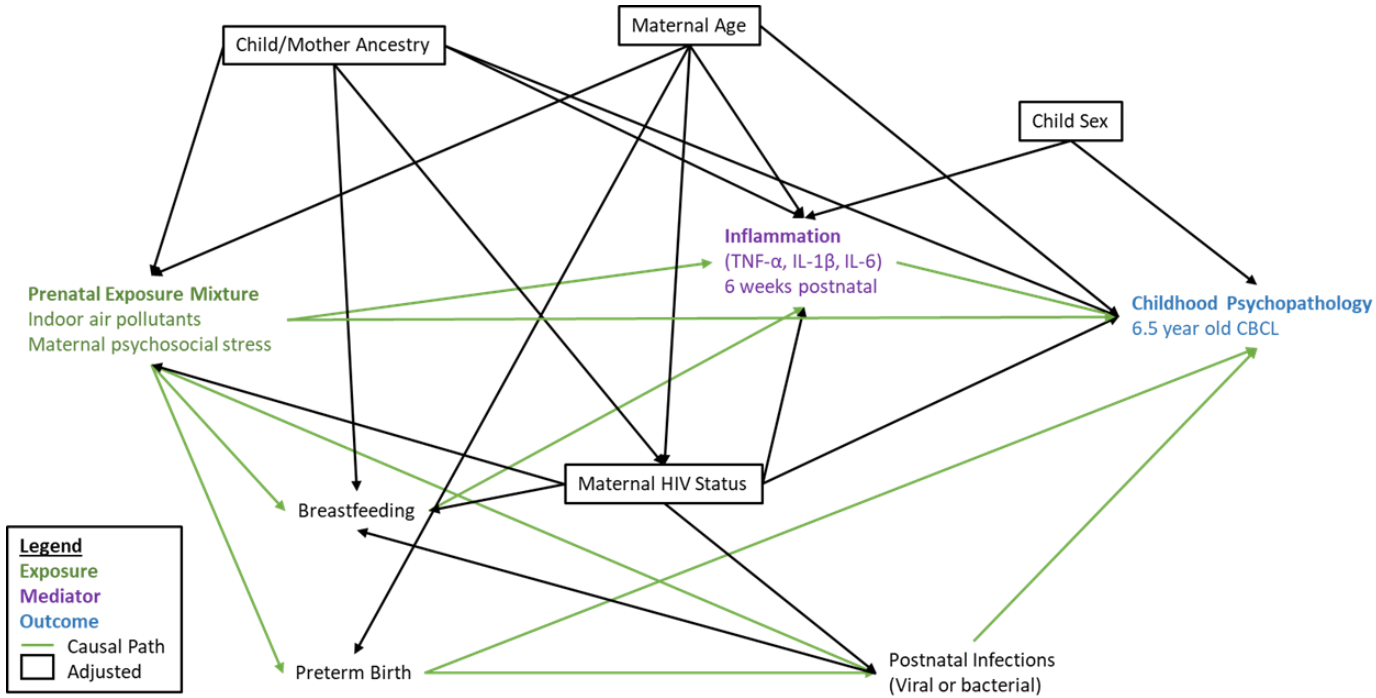


Figure 5-2: *Directed Acyclic Graph (DAG) for mediation analysis.*

Mediator-Outcome Analyses

Associations between inflammatory markers (mediators) and CBCL at 6.5 years (outcome) was also assessed using linear regression modeling. All inflammatory markers were right-skewed and natural log-transformed for analyses. Mediator-outcome models were adjusted for maternal age, maternal HIV status, ancestry, socioeconomic status, and child sex.

Mediation analyses

Mediation analyses rely on three assumptions. 1) No confounding of the exposure-mediator relationship, 2) no confounding of the mediator-outcome relationship, and 3) no confounding of the exposure-outcome relationship. As discussed above, confounding was assessed using DAGs **(Figure 5-2).**

Individual exposures with a statistically significant total effect in exposure-outcome analyses were investigated for mediation with inflammatory markers. Single-exposure mediation by inflammatory markers was assessed using the *mediation* R package. The *mediate* function was used to estimate the average cause mediation effects (indirect effect), the average direct effect, the total effect, and the proportion of the total effect mediated by the mediator. Mediation models were adjusted for confounders as described above.

We were unable to use the *mediation* R package to investigate the mediation of SOM cluster exposure on CBCL by inflammatory markers. The *mediation* package and other R packages available for causal mediation analysis are currently unable to accommodate multilevel categorical exposure variables like SOM clusters. Total effects were estimated using linear regression analysis for the association between SOM exposure clusters and CBCL scores adjusting for maternal age, maternal HIV status, and ancestry. The direct effects were derived by additionally adjusting these models for the potential mediators in individual linear regression models as well as the additional mediator-outcome confounder, child sex.

All analyses were performed using R version 4.1.2 (R Core Team, Vienna, Austria).

Results

In our subsample of 185 mother-child pairs from the DCHS, mothers were 27 years (SD: 5.85) old on average. This is similar to the overall DCHS cohort average age of 26 years. There were also a higher proportion of male children (60% vs. 51%), participants of Black African ancestry (61.5% vs. 55.3%), and HIV-infected mothers (41.6% vs. 21.7%) in our subsample compared to the full cohort **(Table 5-1)**. Indoor air pollutants were slightly higher on average in our analysis sample compared to the full cohort, particularly PM_{10} (38.63 vs 33.37 $\mu g/m^3$). Psychosocial factors were on average similar between our subsample and the full cohort.

Exposure-Outcome Analyses

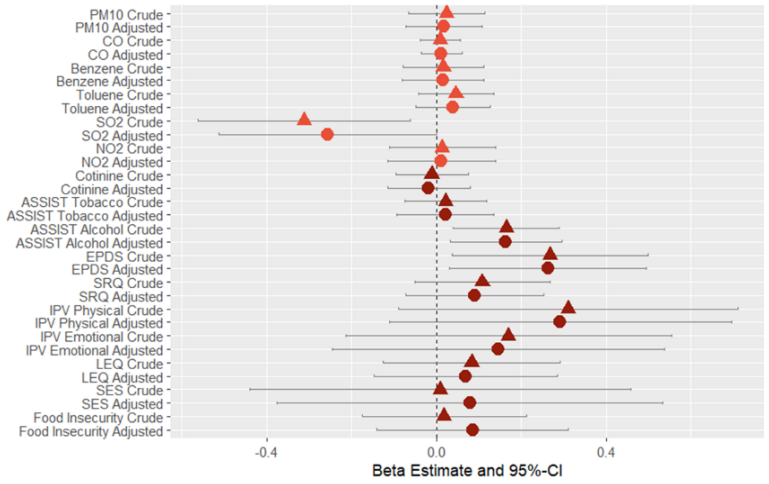
In single-exposure linear regression models estimating the total effect of our exposures on CBCL at 6.5 years, only ASSIST Alcohol (beta: 0.16; 95% CI: 0.03, 0.30) and EPDS (0.26; 0.03, 0.5) scores were significantly associated with CBCL total problems. Prenatal EPDS (0.26; 0.05, 0.48) score was also associated with CBCL externalizing problems, and ASSIST alcohol (0.14; 0.04, 0.24) was associated with CBCL internalizing problems **(Table 5-2, Figure 5-3)**.

For SOM analysis we used the same 4 clusters as described in chapter 4 **(Table 5-3, Figure 5-4A)**. Using cluster 1, a cluster with low indoor air pollutant and psychosocial stressor exposure, as the reference group, no SOM cluster was associated with either CBCL total, externalizing, or internalizing problems in total effect analyses **(Table 5-4, Figures 5-4;5-6)**.

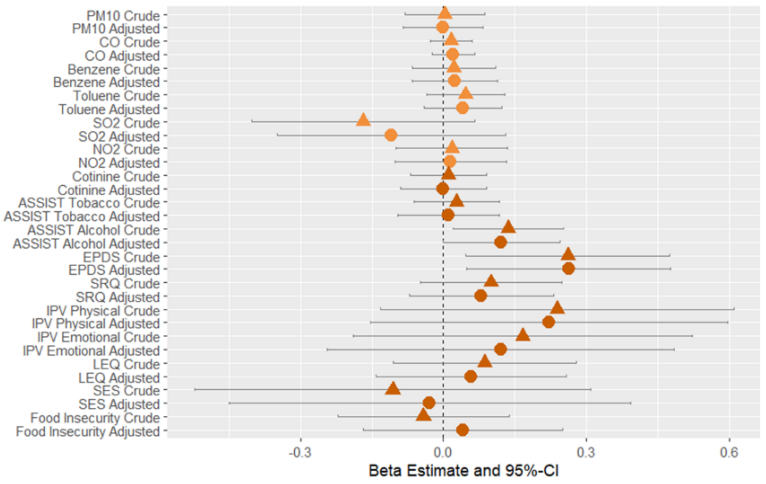
Table 5-2: *Results from total effect linear regression analyses. All adjusted models were adjusted for maternal age, maternal HIV status, ancestry, and socioeconomic status when not the exposure of interest. Bold indicates statistical significance.*

	Beta Estimate (95% CI)		
	Total Problems	Externalizing Problems	Internalizing Problems
PM10 Crude	0.02 (-0.07, 0.11)	0 (-0.08, 0.09)	0.06 (-0.01, 0.12)
PM10 Adjusted	0.02 (-0.07, 0.11)	0 (-0.08, 0.08)	0.04 (-0.02, 0.11)
CO Crude	0.01 (-0.04, 0.06)	0.02 (-0.03, 0.06)	0 (-0.04, 0.03)
CO Adjusted	0.01 (-0.04, 0.06)	0.02 (-0.02, 0.07)	0 (-0.04, 0.03)
Benzene Crude	0.02 (-0.08, 0.11)	0.02 (-0.07, 0.11)	0 (-0.07, 0.07)
Benzene Adjusted	0.02 (-0.08, 0.11)	0.02 (-0.07, 0.11)	0 (-0.08, 0.07)
Toluene Crude	0.05 (-0.04, 0.13)	0.05 (-0.03, 0.13)	0 (-0.06, 0.07)
Toluene Adjusted	0.04 (-0.05, 0.13)	0.04 (-0.04, 0.12)	0 (-0.07, 0.06)
SO2 Crude	**-0.31 (-0.56, -0.06)**	-0.17 (-0.4, 0.07)	**-0.21 (-0.4, -0.02)**
SO2 Adjusted	-0.26 (-0.51, 0)	-0.11 (-0.35, 0.13)	-0.16 (-0.35, 0.03)
NO2 Crude	0.01 (-0.11, 0.14)	0.02 (-0.1, 0.13)	0 (-0.09, 0.1)
NO2 Adjusted	0.01 (-0.11, 0.14)	0.02 (-0.1, 0.13)	0 (-0.09, 0.09)
Cotinine Crude	-0.01 (-0.1, 0.07)	0.01 (-0.07, 0.09)	-0.01 (-0.07, 0.06)
Cotinine Adjusted	-0.02 (-0.12, 0.08)	0 (-0.09, 0.09)	-0.02 (-0.1, 0.05)
ASSIST Tobacco Crude	0.02 (-0.08, 0.12)	0.03 (-0.06, 0.12)	-0.01 (-0.09, 0.06)
ASSIST Tobacco Adjusted	0.02 (-0.09, 0.14)	0.01 (-0.1, 0.12)	-0.02 (-0.1, 0.07)
ASSIST Alcohol Crude	**0.16 (0.04, 0.29)**	**0.14 (0.02, 0.25)**	**0.13 (0.04, 0.23)**
ASSIST Alcohol Adjusted	**0.16 (0.03, 0.3)**	0.12 (0, 0.24)	**0.14 (0.04, 0.24)**
EPDS Crude	**0.27 (0.04, 0.5)**	**0.26 (0.05, 0.48)**	0.08 (-0.09, 0.26)
EPDS Adjusted	**0.26 (0.03, 0.5)**	**0.26 (0.05, 0.48)**	0.05 (-0.12, 0.23)
SRQ Crude	0.11 (-0.05, 0.27)	0.1 (-0.05, 0.25)	0.1 (-0.03, 0.22)
SRQ Adjusted	0.09 (-0.07, 0.25)	0.08 (-0.07, 0.23)	0.07 (-0.05, 0.19)
IPV Physical Crude	0.31 (-0.09, 0.71)	0.24 (-0.13, 0.61)	0.16 (-0.14, 0.47)
IPV Physical Adjusted	0.29 (-0.11, 0.69)	0.22 (-0.15, 0.6)	0.12 (-0.18, 0.42)
IPV Emotional Crude	0.17 (-0.21, 0.55)	0.17 (-0.19, 0.52)	-0.14 (-0.43, 0.15)
IPV Emotional Adjusted	0.15 (-0.25, 0.54)	0.12 (-0.24, 0.48)	-0.13 (-0.42, 0.16)
LEQ Crude	0.08 (-0.13, 0.29)	0.09 (-0.11, 0.28)	0 (-0.16, 0.16)
LEQ Adjusted	0.07 (-0.15, 0.29)	0.06 (-0.14, 0.26)	-0.02 (-0.18, 0.14)
SES Crude	0.01 (-0.44, 0.46)	-0.11 (-0.52, 0.31)	0.26 (-0.08, 0.6)
SES Adjusted	0.08 (-0.37, 0.53)	-0.03 (-0.45, 0.39)	0.32 (-0.02, 0.66)
Food Insecurity Crude	0.02 (-0.18, 0.21)	-0.04 (-0.22, 0.14)	0.07 (-0.08, 0.22)
Food Insecurity Adjusted	0.09 (-0.14, 0.31)	0.04 (-0.17, 0.25)	0.11 (-0.06, 0.28)

A. CBCL Total Problems



B. CBCL Externalizing Problems



C. CBCL Internalizing Problems

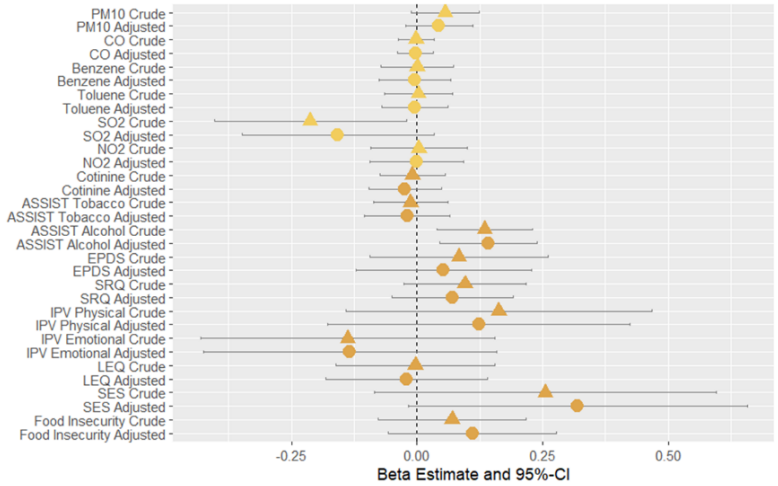


Figure 5-3: *Total effect single-exposure linear regression models. Adjusted models adjusted for maternal age, maternal HIV status, ancestry and socioeconomic stats when not the exposure of interest.*

Table 5-3: *SOM cluster participant and exposure characteristics.*

	SOM Cluster			
	1	**2**	**3**	**4**
N (%)	85 (	47	40	40
Maternal Age (mean (SD))	27.21 (5.84)	29.96 (5.26)	23.86 (4.72)	27.98 (5.97)
Male Child (%)	53 (62.4)	26 (55.3)	31 (77.5)	22 (55.0)
Mixed Ancestry (%)	19 (22.4)	9 (19.1)	36 (90.0)	20 (50.0)
Mother HIV Positive (%)	39 (45.9)	27 (57.4)	6 (15.0)	15 (37.5)
Indoor Air Pollutants				
PM10 µg/m3 (median [IQR])	30.01 [14.43, 68.08]	45.47 [17.65, 78.66]	48.09 [12.78, 70.22]	41.67 [15.54, 70.14]
CO mg/m3 (median [IQR])	0.00 [0.00, 0.00]	60.00 [0.00, 955.00]	0.00 [0.00, 132.50]	0.00 [0.00, 0.00]
Benzene µg/m3 (median [IQR])	3.14 [1.32, 4.50]	42.46 [11.01, 102.77]	5.64 [2.84, 14.34]	2.84 [1.30, 5.45]
Toluene µg/m3 (median [IQR])	11.50 [6.45, 19.02]	53.72 [24.76, 444.13]	18.78 [10.34, 48.80]	12.52 [3.53, 23.83]
NO2 µg/m3 (median [IQR])	4.50 [0.00, 7.95]	13.86 [5.95, 20.14]	9.54 [3.22, 12.70]	6.30 [4.19, 11.25]
SO2 µg/m3 (median [IQR])	0.00 [0.00, 0.23]	0.00 [0.00, 0.00]	0.00 [0.00, 0.18]	0.00 [0.00, 0.18]
Psychosocial Factors				
Urine Cotinine ng/ml (median [IQR])	16.20 [10.00, 50.80]	32.60 [14.30, 76.65]	500.00 [500.00, 500.00]	305.50 [31.65, 500.00]
SES Asset Sum (median [IQR])	7.00 [6.00, 8.00]	6.00 [4.50, 7.00]	7.00 [6.75, 8.00]	7.00 [5.00, 8.00]
Food Insecurity Total Score (median [IQR])	0.00 [0.00, 1.00]	3.00 [0.00, 4.00]	0.00 [0.00, 0.00]	1.00 [0.00, 4.00]
SRQ-20 Total Score (median [IQR])	4.00 [1.00, 7.00]	3.00 [1.00, 5.00]	5.00 [3.00, 8.25]	8.00 [5.00, 12.00]
Emotional IPV Score (median [IQR])	4.00 [4.00, 5.00]	4.00 [4.00, 6.00]	5.00 [4.00, 7.00]	10.50 [8.75, 13.00]
Physical IPV Score (median [IQR])	5.00 [5.00, 6.00]	6.00 [5.00, 6.00]	6.00 [5.00, 7.00]	13.00 [10.00, 15.25]
LEQ Total Score (median [IQR])	1.00 [1.00, 2.00]	1.00 [0.00, 2.50]	2.00 [1.00, 3.25]	3.00 [1.00, 4.00]
EPDS Total Score (median [IQR])	9.00 [6.00, 12.00]	11.00 [9.00, 13.00]	11.00 [6.00, 16.00]	10.00 [8.00, 17.25]
ASSIST Tobacco Score (median [IQR])	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	21.00 [17.75, 24.00]	0.00 [0.00, 24.00]
ASSIST Alcohol Score (median [IQR])	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	3.00 [0.00, 11.25]	0.00 [0.00, 14.25]
Inflammatory Markers				
IL-1β (median [IQR])	1.05 [0.47, 1.79]	1.11 [0.73, 1.98]	1.06 [0.53, 1.64]	1.16 [0.57, 1.76]

IL-6 (median [IQR])	1.70 [0.48, 3.89]	3.00 [1.05, 6.69]	1.86 [0.71, 3.96]	1.69 [0.49, 3.16]
TNF-α (median [IQR])	20.26 [15.52, 26.70]	22.68 [16.23, 29.83]	21.07 [14.15, 29.75]	17.88 [14.14, 23.55]
CBCL at 6.5 years				
Total Problems Score (median [IQR])	7.00 [2.00, 14.00]	8.00 [4.00, 12.00]	9.50 [5.00, 14.25]	8.00 [4.00, 17.50]
Externalizing Problems Score (median [IQR])	2.00 [1.00, 6.00]	3.00 [1.00, 5.50]	4.00 [1.75, 9.25]	4.00 [1.00, 7.00]
Internalizing Problems Score (median [IQR])	0.00 [0.00, 2.00]	1.00 [0.00, 2.00]	1.00 [0.00, 2.00]	1.00 [0.00, 3.00]

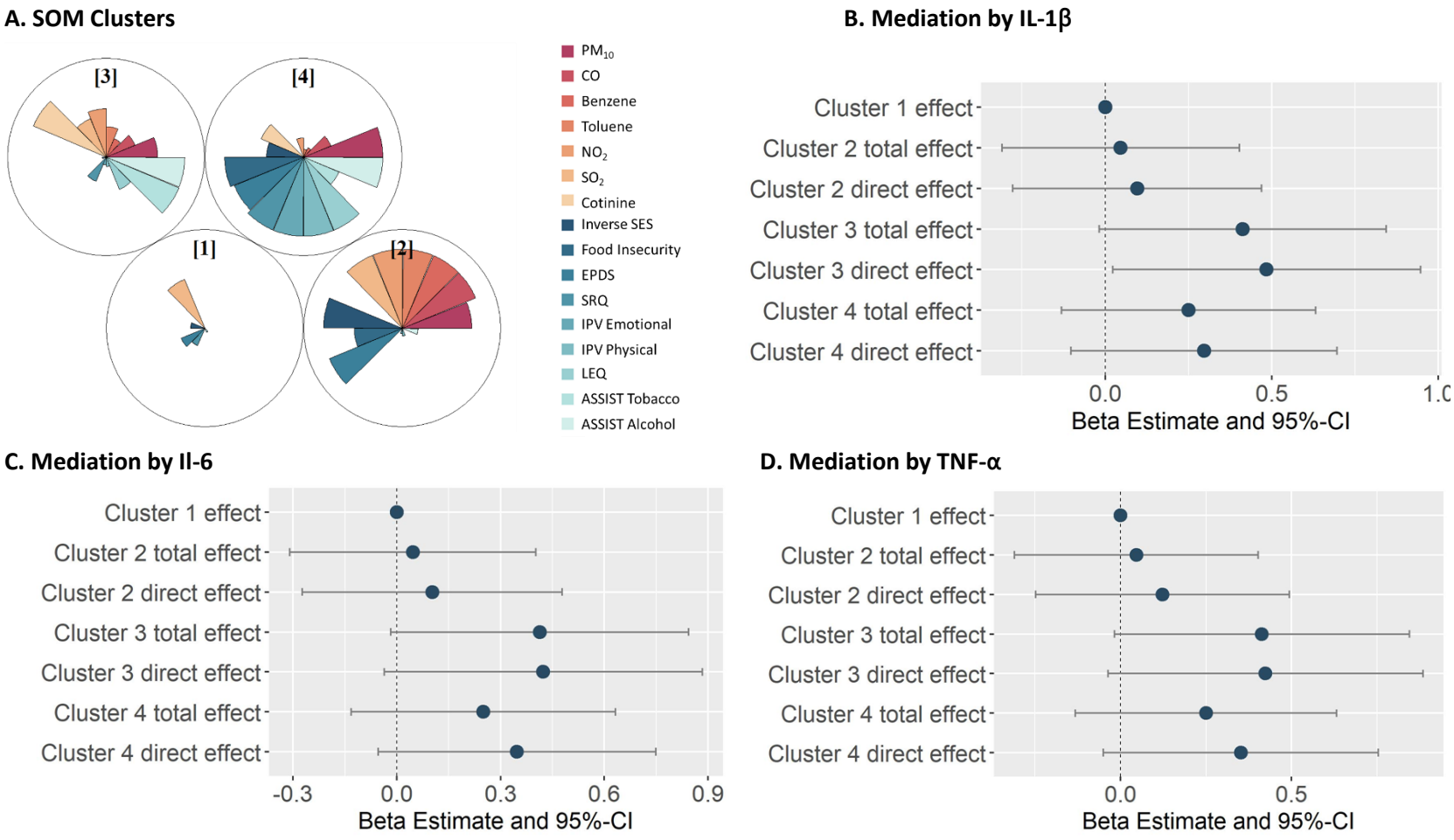


Figure 5-4: *Mediation analysis of SOM cluster association with CBCL Total problems. Total effect models adjusted for maternal age, maternal HIV status, and ancestry. Direct effect models adjusted for maternal age, maternal HIV status, ancestry, child sex, and the mediator of interest.* ***A.*** *SOM clusters created using pre- natal indoor air pollutants and psychosocial factors.* ***B.*** *Direct and total effect of SOM cluster on CBCL total problems mediated by IL-1β.* ***C.*** *Direct and total effect of SOM cluster on CBCL total problems mediated by IL-6.* ***D.*** *Direct and total effect of SOM cluster on CBCL total problems mediated by TNF-α.*

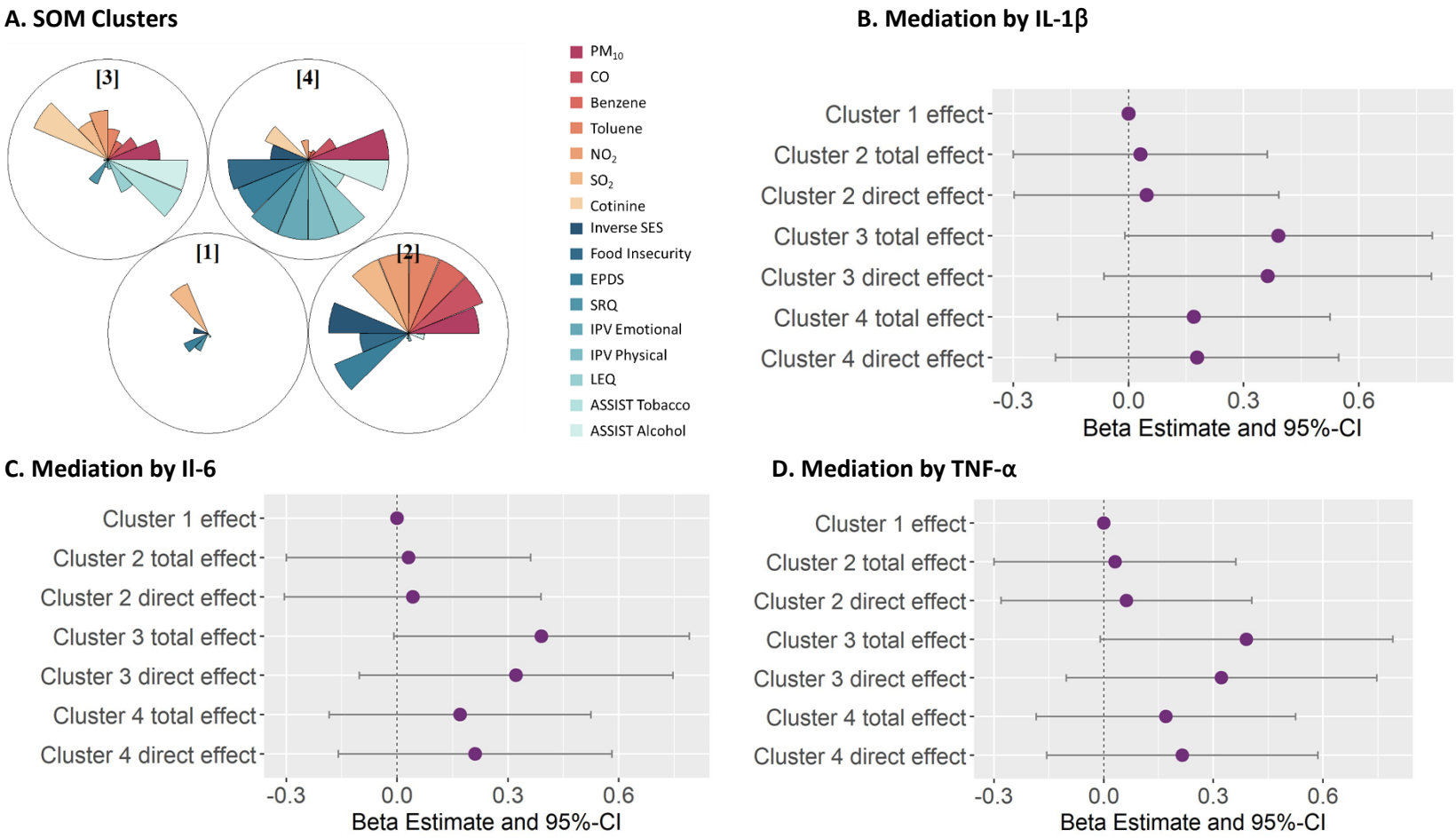


Figure 5-5: *Mediation analysis of SOM cluster association with CBCL Externalizing problems. Total effect models adjusted for maternal age, maternal HIV status, and ancestry. Direct effect models adjusted for maternal age, maternal HIV status, ancestry, child sex, and the mediator of interest.* ***A.*** *SOM clusters created using pre- natal indoor air pollutants and psychosocial factors.* ***B.*** *Direct and total effect of SOM cluster on CBCL externalizing problems mediated by IL-1β.* ***C.*** *Direct and total effect of SOM cluster on CBCL externalizing problems mediated by IL-6.* ***D.*** *Direct and total effect of SOM cluster on CBCL externalizing problems mediated by TNF-α.*

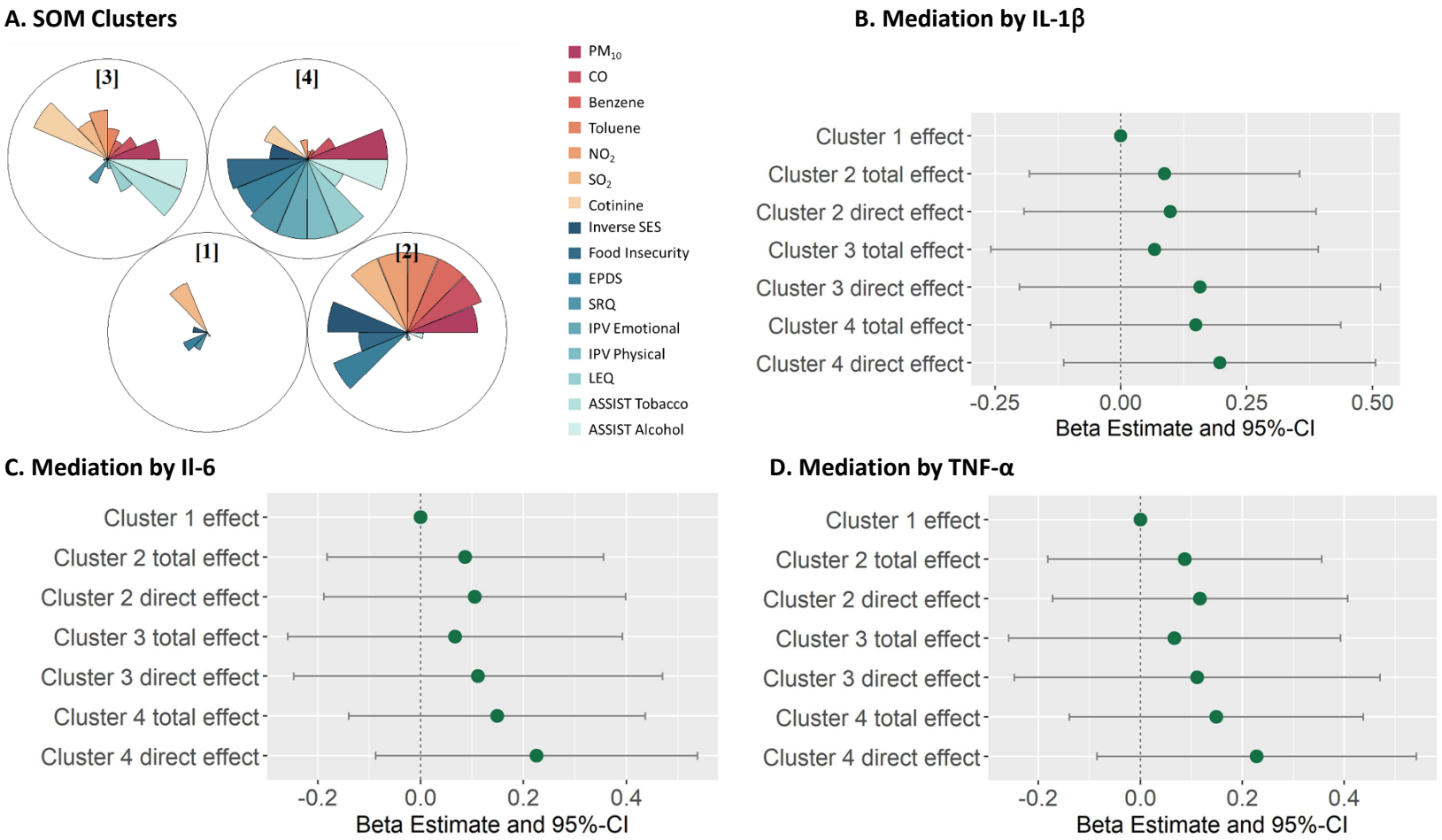


Figure 5-6: *Mediation analysis of SOM cluster association with CBCL internalizing problems. Total effect models adjusted for maternal age, maternal HIV status, and ancestry. Direct effect models adjusted for maternal age, maternal HIV status, ancestry, child sex, and the mediator of interest. A. SOM clusters created using pre- natal indoor air pollutants and psychosocial factors. B. Direct and total effect of SOM cluster on CBCL internalizing problems mediated by IL-1β. C. Direct and total effect of SOM cluster on CBCL internalizing problems mediated by IL-6. D. Direct and total effect of SOM cluster on CBCL internalizing problems mediated by TNF-α.*

Table 5-4: *Results from SOM cluster total effect and mediation analyses. Total effect models adjusted for maternal HIV status, maternal age, and ancestry. Direct effect models additionally adjusted for inflammatory markers and child sex.*

CBCL Total Problems							
		Adjusted for IL-1β		Adjusted for IL-6		Adjusted for TNF-α	
SOM Cluster	Total Effect (95% CI)	Direct Effect (95% CI)	Proportion Mediated	Direct Effect (95% CI)	Proportion Mediated	Direct Effect (95% CI)	Proportion Mediated
1 (Reference)	-	-	-	-	-	-	-
2	0.05 (-0.31, 0.40)	0.10 (-0.28, 0.47)	-106%	0.10 (-0.27, 0.48)	-120%	0.19 (-0.25, 0.49)	-164%
3	0.41 (-0.02, 0.84)	**0.48 (0.02, 0.95)**	-17%	0.42 (-0.04, 0.88)	-2%	0.42 (-0.04, 0.88)	-3%
4	0.25 (-0.13, 0.63)	0.30 (-0.10, 0.70)	-19%	0.35 (-0.05, 0.75)	-39%	0.35 (-0.05, 0.75)	-41%
CBCL Externalizing Problems							
		Adjusted for IL-1β		Adjusted for IL-6		Adjusted for TNF-α	
SOM Cluster	Total Effect (95% CI)	Direct Effect (95% CI)	Proportion Mediated	Direct Effect (95% CI)	Proportion Mediated	Direct Effect (95% CI)	Proportion Mediated
1 (Reference)	-	-	-	-	-	-	-
2	0.03 (-0.30, 0.36)	0.05 (-0.30, 0.39)	-51%	0.04 (-0.30, 0.39)	-37%	0.06 (-0.28, 0.40)	-100%
3	0.39 (-0.01, 0.79)	0.36 (-0.06, 0.79)	7%	0.32 (-0.10, 0.75)	17%	0.32 (-0.10, 0.75)	17%
4	0.17 (-0.18, 0.53)	0.18 (-0.19, 0.55)	-5%	0.21 (-0.16, 0.58)	-24%	0.22 (-0.06, 0.59)	-26%
CBCL Internalizing Problems							
		Adjusted for IL-1β		Adjusted for IL-6		Adjusted for TNF-α	
SOM Cluster	Total Effect (95% CI)	Direct Effect (95% CI)	Proportion Mediated	Direct Effect (95% CI)	Proportion Mediated	Direct Effect (95% CI)	Proportion Mediated
1 (Reference)	-	-	-	-	-	-	-
2	0.09 (-0.18, 0.36)	0.10 (-0.19, 0.39)	-13%	0.11 (-0.19, 0.40)	-21%	0.12 (-0.17, 0.41)	-35%
3	0.07 (-0.26, 0.39)	0.16 (-0.20, 0.52)	-134%	0.11 (-0.25, 0.47)	-66%	0.11 (-0.25, 0.47)	-65%
4	0.15 (-0.14, 0.44)	0.20 (-0.11, 0.51)	-32%	0.13 (-0.09, 0.54)	-51%	0.23 (-0.08, 0.54)	-53%

Mediator-Outcome Analyses

Adjusted linear regression models estimating the effect of potential inflammatory marker mediators on CBCL outcomes did not find any significant associations. Inflammatory markers IL-1β, IL-6, and TNF-α had suggestive positive associations with CBCL total, externalizing, and internalizing problems **(Table 5-5, figure 5-7).**

Table 5-5: *Results from linear regression models investigating the association between inflammatory markers and CBCL score at 6.5 years.*

	Beta (95% CI)		
	Total Problems	Externalizing Problems	Internalizing Problems
IL-1β	0.22 (-0.08, 0.52)	0.16 (-0.12, 0.43)	0.17 (-0.06, 0.4)
IL-6	0.09 (-0.08, 0.27)	0.09 (-0.07, 0.25)	0.06 (-0.08, 0.2)
TNF-α	0.12 (-0.12, 0.35)	0.11 (-0.1, 0.33)	0.08 (-0.11, 0.26)

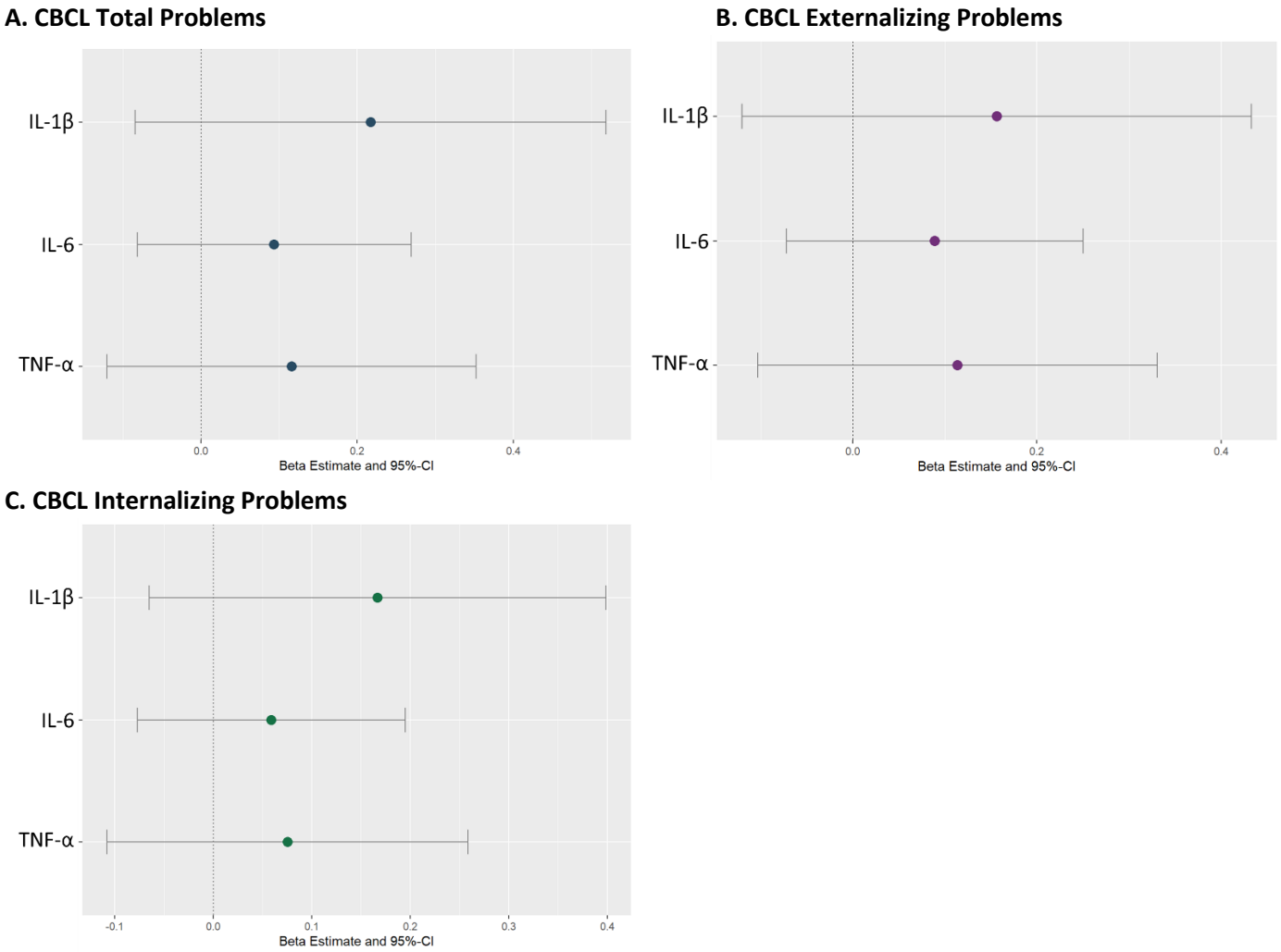


Figure 5-7: *Mediator-outcome linear regression models. Models adjusted for maternal age, maternal HIV status, ancestry, socioeconomic status, and child sex.*

Mediation Analyses

In single-exposure mediation models, there was no significant mediation by any inflammatory marker on the relationship between ASSIST Alcohol or EPDS score on CBCL total problems score **(Figure 5-8)**. In models estimating mediation of ASSIST Alcohol and CBCL total problems score the proportion mediated by inflammatory markers ranged from 0-3%. This was similar for EPDS and CBCL total problem models which had proportion mediated values between -5-1% **(Figure 5-8)**. A negative proportion mediated values would indicate that the direct effect was stronger than the total effect. In models investigating mediation of EPDS score and CBCL externalizing problems, there was no significant mediation by any inflammatory markers. Proportion mediated values ranged from 0-2% **(Figure 5-9)**. Models investigating ASSIST Alcohol and CBCL internalizing problems were also not significantly mediated by inflammatory markers, proportion mediated values ranged from -4-1% **(Figure 5-10)**.

The association between SOM cluster and CBCL total problems was also not mediated by inflammatory markers **(Figure 5-4, Table 5-4)**. In fact, the direct effect of the SOM cluster was strengthened after adjusting for IL-1β, IL-6, or TNF-α, leading to proportion mediated values between -2 and -164%. Similar results were seen for the CBCL externalizing and internalizing problem models **(Figure 5-5;5-6, Table 5-4).**

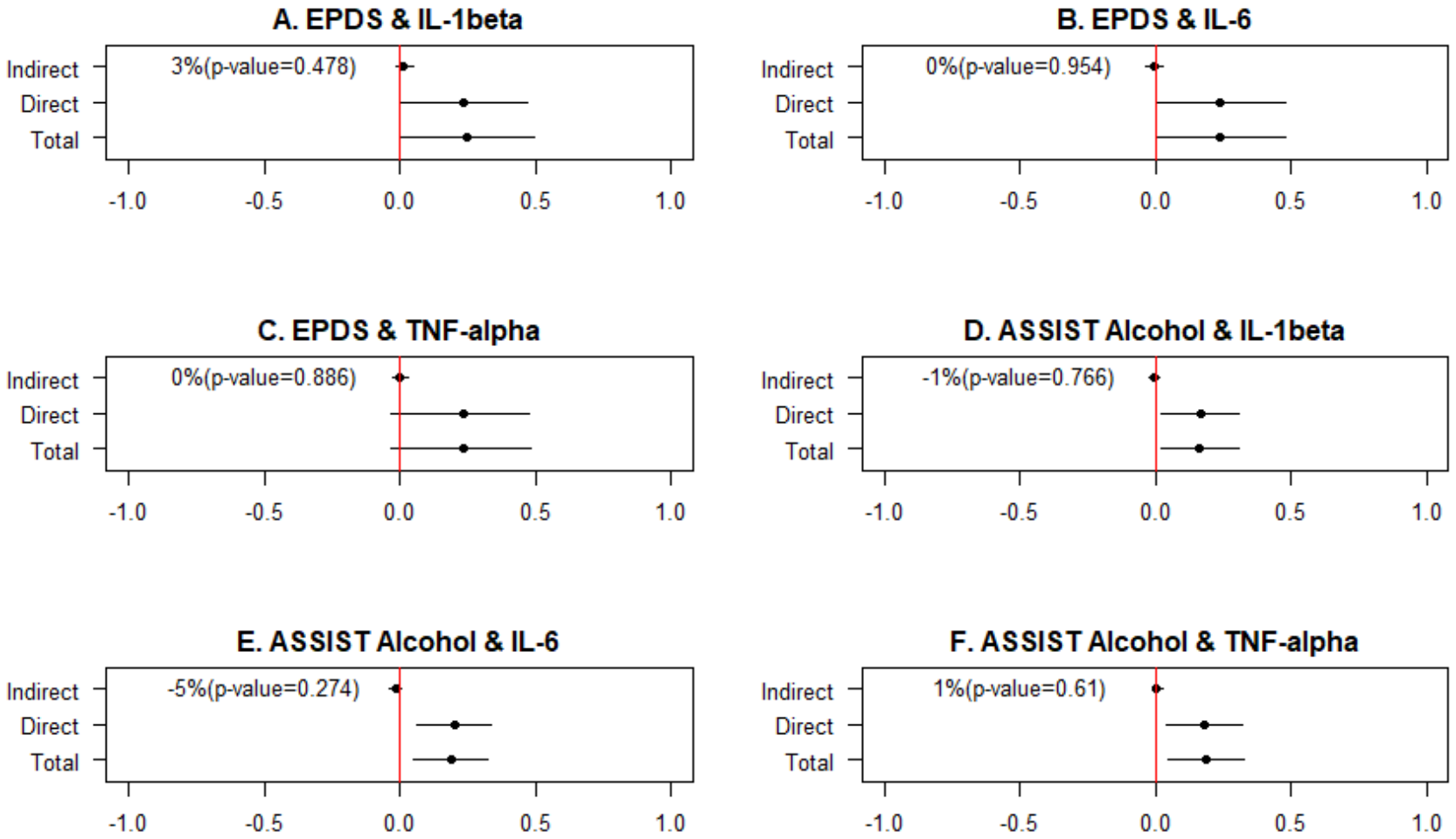


Figure 5-8: *Mediation of EPDS or ASSIST Alcohol sore and CBCL Total problems by inflammatory markers. Mediation models adjusted for confounders including child sex, maternal age, maternal HIV status, ancestry, and socioeconomic status.* ***A.*** *Association of EPDS score and CBCL total problems mediated by IL-1β.* ***B.*** *Association of EPDS score and CBCL total problems mediated by IL-6.* ***C.*** *Association of EPDS score and CBCL total problems mediated by TNF-α.* ***D.*** *Association of ASSIST Alcohol score and CBCL total problems mediated by IL-1β. E. Association of ASSIST Alcohol score and CBCL total problems mediated by IL-6. F. Association of ASSIST Alcohol score and CBCL total problems mediated by TNF-α.*

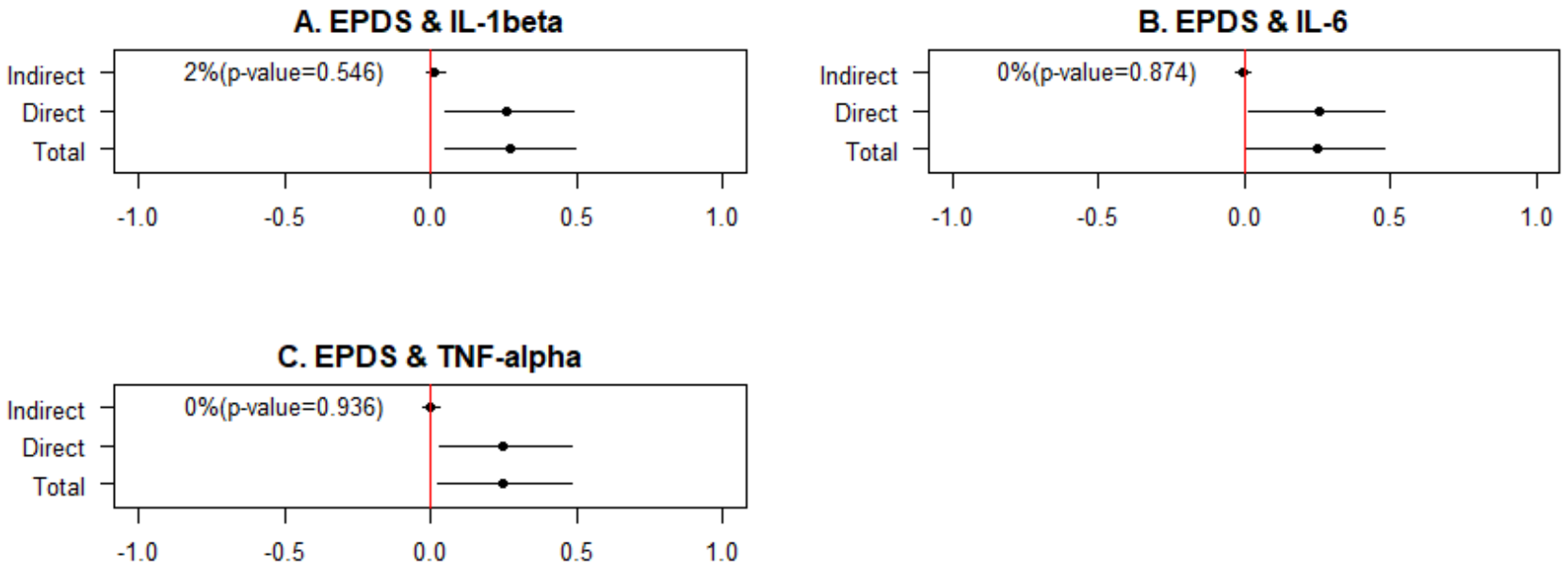


Figure 5-9: *Mediation of EPDS score and CBCL externalizing problems by inflammatory markers. Mediation models adjusted for confounders including child sex, maternal age, maternal HIV status, ancestry, and socioeconomic status.* ***A.*** *Association of EPDS score and CBCL externalizing problems mediated by IL-1β.* ***B.*** *Association of EPDS score and CBCL externalizing problems mediated by IL-6.* ***C.*** *Association of EPDS score and CBCL externalizing problems mediated by TNF-α.*

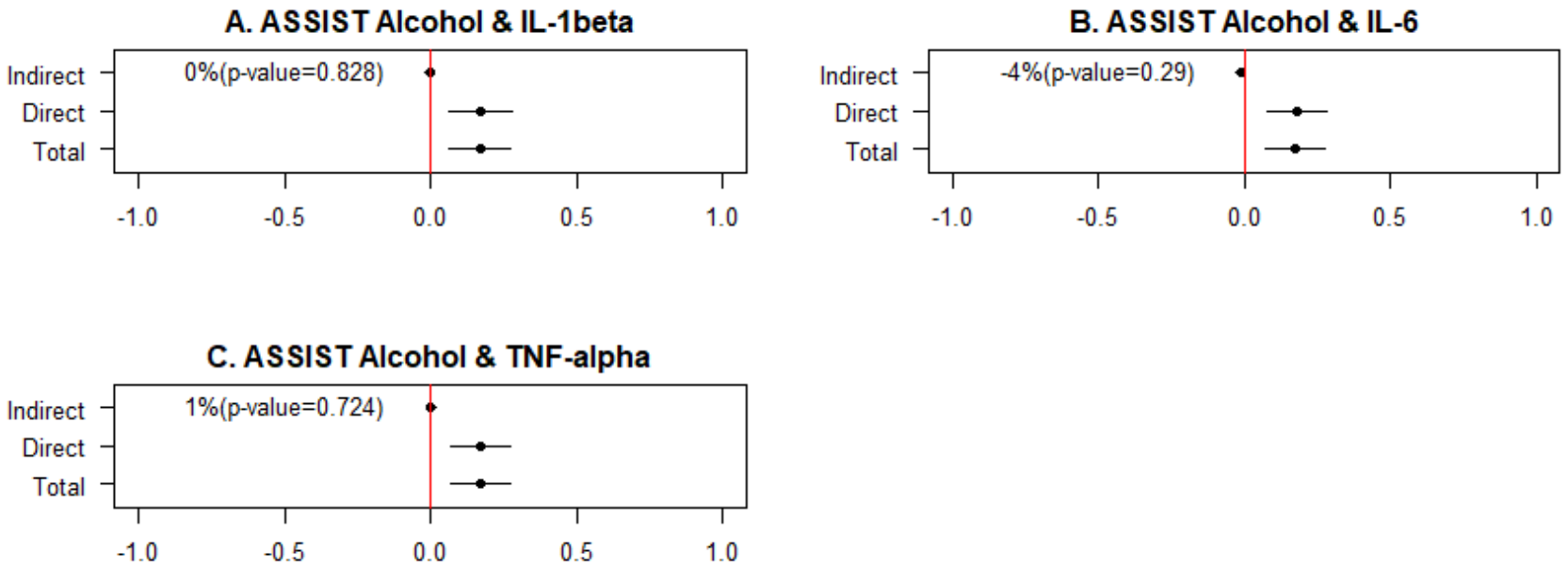


***Figure 5-10**: Mediation of ASSIST Alcohol score and CBCL internalizing problems by inflammatory markers. Mediation models adjusted for confounders including child sex, maternal age, maternal HIV status, ancestry, and socioeconomic status. **A**. Association of ASSIST Alcohol score and CBCL internalizing problems mediated by IL-1β. **B.** Association of ASSIST Alcohol score and CBCL internalizing problems mediated by IL-6. **C.** Association of ASSIST Alcohol score and CBCL internalizing problems mediated by TNF-α.*

Discussion

In this study of 185 mother-child pairs from the DCHS, we investigated mediation of the relationship between prenatal indoor air pollution and psychosocial factor exposure and psychopathology at 6.5 years by inflammation at 6 weeks old. We found prenatal maternal depression and alcohol use was associated with increased psychopathology at 6.5 years, but neither association was mediated by any inflammatory marker. There were suggestive positive associations between inflammatory markers at 6-weeks (IL-β, IL-6, and TNF-α) and psychopathology at 6.5 years. Additionally, in this smaller sub-sample, we did not find joint-effect associations of prenatal exposure to indoor air pollution and psychosocial stressors, and psychopathology at 6.5 years.

Single-exposure exposure-outcome analyses from this sub-sample of the DCHS only found associations between prenatal maternal depression and alcohol use and psychopathology at 6.5 years. In chapter 3, we examine the relationship between our prenatal exposures and CBCL at 6.5 years in the larger DCHS sample (n=599). In the larger sample we found PM_{10}, toluene, psychological distress (SRQ), physical IPV, depression, and alcohol use were associated with psychopathology **(Table 3-4, Figure 3-5)**. With our sample size reduced by over two thirds in the current analysis we lost power to detect associations between prenatal exposure to PM_{10}, toluene, psychological distress, and physical IPV, and psychopathology at 6.5 years. As previously discussed in chapter 3, associations between prenatal depression[65,66] and alcohol use[63] and psychopathology in the child have been shown in other studies. The power to detect joint exposure-outcome relationships was also reduced in the current sub-sample of DCHS participants used in this analysis. As previously discussed in chapter 3, we found joint effects of prenatal exposure to indoor air pollutants and psychosocial factors on psychopathology at 6.5 years using SOM **(Table 3-6, Figure 3-8)**.

While our study did not find significant associations between inflammatory markers and CBCL score in this subsample of DCHS participants, there was a suggestive positive association. Previous research has hypothesized inflammation may elicit functional and structural changes in the brain, leading to psychopathology[140,141]. Animal models have shown increased perinatal inflammation is associated with adult brain physiology and behavior[141]. Few epidemiologic studies in humans have also observed inflammation as a mediator of the associations between both environmental and social factors and psychopathology[134,142]. The sample size of our study may have been so small to detect these associations, and further research is needed.

The mediation analysis investigating the effect of prenatal alcohol use and dependency on child psychopathology did not find any mediation by inflammation. Alcohol is a known teratogen and has been shown to cross the placenta and disrupt the formation of the CNS of the fetus[69]. It is possible that alcohol impacts the CNS through biological pathways other than inflammation. One mechanism proposes alcohol consumption can generate free radicals as by-products of CYP2E1 metabolism. The free radicals target polyunsaturated fatty acids side chains in brain tissue membranes, causing fetal brain tissue damage during organogenesis which manifests as CNS dysfunction in the offspring after delivery[69].

In a previous analysis of DCHS cohort data, Naudé et al. found the association between prenatal material depression and neurodevelopment at 2 years old was mediated by inflammation, particularly IL-1β, at 6 weeks old[134]. In our study, we found prenatal maternal depression and psychopathology at 6.5 years old was not mediated by IL-1β, or any of the other inflammatory markers investigated. While neurodevelopment and psychopathology are different, we expected similar mediation by inflammation based on a theoretically similar biological mechanism of action. One explanation for the difference in findings is the timing of outcome measurements. Naudé et al. investigated neurodevelopment at 2 years old, while we investigated psychopathology at 6.5 years. It is possible that mediation by inflammation occurs

when the outcome is measured more proximally to the exposure and mediator. One other study investigating prenatal maternal depression and negative affect at 6 months old found 3rd trimester IL-6 and TNF-α levels mediated the association[137]. Future research should replicate this study with earlier CBCL measurements in the DCHS to investigate if timing of outcome measurement can explain the lack of mediation found in this study.

As discussed in chapter 4 and throughout this dissertation, this study is limited by several factors. First, this study used three markers of inflammation measure in serum. While these inflammatory markers are typically associated with neuroinflammation, these peripheral measures of inflammation may not directly correspond with neuroinflammation. Second, inflammatory markers were only available in a small subset of the cohort and the sub-sample was additionally subset by those who also had CBCL measurements. As previously discussed, a larger sample size (as seen in chapter 3) has more power to detect associations between prenatal exposures, infant inflammatory markers, and child psychopathology. As discussed previously in this dissertation, measuring exposure at only one time point during pregnancy and the lack of $PM_{2.5}$ measurements are also limitations.

This study is strengthened by using longitudinal data from a unique cohort from South Africa. Few studies have investigated mediation of prenatal air pollution and psychosocial factors exposure and childhood psychopathology. This study adds to limited epidemiology research on how inflammation impacts the developing brain and future psychopathology.

Chapter 6 : Summary of Findings, Future Directions

Summary of Findings

Overall Findings

There is very little research investigating the effects of indoor air pollution exposure and psychosocial factors on childhood psychopathology in LMICs. The majority of research into the effects of prenatal and early life exposure to air pollution on child psychopathology are conducted in high income countries and use outdoor air pollution measures[3,4,6,35,40]. Similarly, studies focusing on psychosocial factors are primarily conducted in high income countries[9–12]. LMICs typically have higher levels of indoor air pollution than high-income countries and there is evidence that indoor air pollution constitutes the majority of air pollutant exposure in LMICs[26,29]. Additionally, women and children typically spend more time in the home and cooking areas making them at higher risk for exposure to air pollutants[24]. LMICs also have higher prevalence of depression and exposure to violence than high income countries[57]. This study identified risk factors for child psychopathology that can lead to interventions to reduce disease burden and improve health.

Indoor air pollution and adverse psychosocial factors are common exposures that often co-occur, though there has been very little research on the joint effects of these exposures on child psychopathology. Additionally, both indoor air pollution and adverse psychosocial factors are potentially modifiable exposures through targeted interventions. Through investigating joint effects of exposure, we identified vulnerable subgroups to target for interventions to reduce exposure and risk of child psychopathology. Advancements in methodology allowed us to use statistical methods to evaluate joint effects of exposure mixtures, as well as identify ‘bad actors’ from correlated exposure mixtures in these analyses. We also were able to investigate timing of exposure to better target exposure reduction interventions.

This research has led to improved understanding of the individual and joint effects of prenatal and early life exposure to indoor air pollution and psychosocial factors. The findings in this dissertation lay the groundwork for identifying vulnerable subgroups to target for interventions to reduce exposure and burden of childhood psychopathology as described below.

Findings from AIM 1

Childhood psychopathology symptomology in early childhood, including emotional and behavioral problems, affect parents, teachers, and most importantly the child. In this aim we observed single-exposure and joint effects of prenatal exposure to indoor air pollutants and psychosocial factors on trajectories of childhood psychopathology in 24-60 months old children from South Africa. Trajectories of internalizing and externalizing child behavior at 24, 42, and 60 months were differentially associated with prenatal indoor air pollution and psychosocial exposures. Internalizing problems trajectory was individually associated with both exposures to indoor air pollution and adverse psychosocial factors, while the externalizing problems trajectory was mostly associated with smoking related exposures. This analysis indicates that different exposures might differently affect internalizing and externalizing problem trajectories. Previous research on prenatal exposure to pollutants and psychosocial factors has focused on one exposure and its association with psychopathology symptoms or a diagnosis of psychiatric disorder at one time period. Investigating both indoor air pollutants and psychosocial factors allowed us to show internalizing and externalizing behavior trajectories were associated with different kinds of exposures.

Previous single-exposure research investigating prenatal exposures and childhood psychopathology has also found PM_{10} and smoking exposure to be associated with externalizing behaviors[94–96]. Smoking during pregnancy has long been identified as a danger to the fetus and has been associated with a variety of outcomes in childhood, this study adds to that evidence[64]. To our knowledge, our study is the first to investigate the association between

prenatal volatile organic compounds exposure and childhood psychopathology. In joint effect analyses, high air pollution exposure coupled with low socioeconomic status was associated with internalizing behavior trajectories. This finding indicates that pregnant women with low SES could benefit from indoor air pollution interventions to reduce childhood psychopathology. In support of our findings, prior studies investigating neurodevelopmental or psychopathological outcomes at one time period found an interaction between air pollutants and adverse psychosocial factors. However, these studies did not use environmental mixture methods and instead used interaction terms between one air pollutant and one psychosocial factor[13,81,100,101].

Findings from AIM 2a

Gestation and the first few months of life are important periods for brain development. During these periods, exposure to environmental toxicants and psychosocial stressors are particularly harmful and may impact brain development. Specifically, exposure to indoor air pollutants and psychosocial factors during these sensitive periods has been shown to predict childhood psychopathology. The first part of this aim investigates the association between pre- and postnatal exposures on child psychopathology at 6.5 years separately. We found prenatal exposure to indoor air pollution, as opposed to postnatal exposure, was most strongly associated with childhood psychopathology at 6.5 years. This result was seen in both traditional single-exposure, single-period modeling, as well as join effects analyses using environmental mixture methods. We also found exposure to psychosocial factors including depression, alcohol use, and psychological distress in the prenatal period to be most strongly associated with child psychopathology.

These findings are in line with previous literature that investigate prenatal exposures to PM_{10}[37,38,115], smoking[34,64,103], alcohol[63,118], and depression[65,134] and childhood psychopathology outcomes. Our study adds evidence from a LMIC population to the literature. We also add to the

literature by using environmental mixture methodology to investigate the joint effects of these exposures in each period.

Findings from AIM 2b

Building on the first part of this aim, understanding the role of these exposures and their timing in developing psychopathology will allow for targeted interventions with the goal of reducing incidence and symptoms of childhood psychopathology. Models investigating sensitive periods of exposure indicated that the prenatal period is a sensitive period for indoor air pollution exposure on childhood psychopathology. Depression and alcohol were associated in both the pre- and postnatal period, while CO was associated with the postnatal period. These findings can be used to target the timing of interventions to reduce childhood psychopathology.

Most research on air pollution exposure focuses on one single time period, as shown in a recent review[116]. Additionally there are few epidemiological studies that investigate early life or childhood exposure to air pollution and childhood psychopathology[116]. Most studies explore exposure and psychopathology in adulthood, or only prenatal exposure on childhood psychopathology[116]. Few studies have compared how psychosocial factors experienced during pregnancy and early life of the child impact later childhood psychopathology. A systematic review on childhood maltreatment and psychopathology found no consensus on sensitive periods among available epidemiology studies[106]. To our knowledge, this is the first study investigating sensitive periods of the joint effects of indoor air pollution and psychosocial factors on child psychopathology. We additionally add a novel use of the SOM method, using SOM to identify profiles of pre- and postnatal exposure mixtures and their association with a health outcome.

Findings from AIM 3a

It is hypothesized that air pollution and stress impact the central nervous system through neuroinflammatory mechanisms. However, few studies have investigated the association between prenatal exposure to indoor air pollution and psychosocial factors on inflammatory markers during infancy. We found positive associations between most indoor air pollutants and inflammatory markers, and no consistent patterns for psychosocial factors. In joint effects models, an exposure profile with high air pollution, low SES, and high depressive symptoms were shown to increase inflammation.

In the current literature, few studies have investigated prenatal exposure to indoor air pollutants or psychosocial factors in association with infant inflammatory markers, and even fewer studies have investigated joint effects of these exposures. The literature presents mixed findings of prenatal exposure to indoor air pollutants[127–129], psychosocial factors[125,132,133] and infant inflammation. The only other study investigating joint effects of air pollutants and depression also found joint effects of this association on infant inflammation[124]. Our study adds to sparse literature investigating prenatal exposure and infant inflammatory response.

Findings from AIM 3b

To further investigate the role of inflammation in the association between indoor air pollution, psychosocial factors, and child psychopathology we conducted a mediation analysis. We found prenatal maternal depression and alcohol use was associated with increased psychopathology at 6.5 years in the subsample, but neither association was mediated by any inflammatory marker. We also found suggestive positive associations between inflammatory markers at 6-weeks and psychopathology at 6.5 years. Additionally, in this smaller subsample, we did not find joint-effect associations of prenatal exposure to indoor air pollution and psychosocial stressors, and psychopathology at 6.5 years.

As of this dissertation, few epidemiology studies have examined inflammation as a mediator for the association between prenatal exposure to air pollution, psychosocial factors and psychopathology[15,134]. Comparison between our study and previous literature is limited by differences in measurements of inflammation. Our study is the first to investigate mediation of the joint effects of these exposure and child psychopathology.

Strengths and Limitations

Strengths

The DCHS is a unique cohort of mothers and children of Black African and mixed ancestry from a LMIC, a group historically underrepresented in research studies. This study has many strengths including indoor air pollution and psychosocial factor measurements at multiple time points, a variety of immune markers, and multiple time point measurements of child psychopathology. These exposure and outcome measurements at multiple time points allowed for advanced analyses including CBCL trajectory analysis, sensitive exposure period analysis, and mediation analysis.

Another strength of this study is the variety of statistical analysis techniques used to investigate multiple dimensions of the joint effect of indoor air pollution and psychosocial factors on child psychopathology. We used SOM to identify exposure profiles observed in this population and investigate the effect of that exposure profile on child psychopathology outcomes. We also used PCA to investigate the effect of our exposure mixture on child psychopathology trajectories. In addition to SOM and PCA, we used quantile g-computation to identify the effect of the total exposure mixture on psychopathology outcomes. Quantile g-computation also identified which exposures were driving the overall mixture association. Using all of these techniques provides a more holistic picture of how these exposures jointly influence childhood psychopathology.

We also expanded the use of exposure mixture method SOM to novel applications. First, we used SOM to explore exposure profiles of pre- and postnatal exposure to indoor air pollutants

and psychosocial factors. By adding exposures from both time periods, we were able to identify profiles of joint pre- and postnatal exposure and investigate their association with childhood psychopathology. Second, we used SOM to investigate if inflammation mediated the joint effect of our exposures and child psychopathology. As of this dissertation, there are few methods to investigate mediation of exposure mixtures.

Limitations

One limitation of this project is sample size. While the total cohort has over 1000 participants, only a subsample had indoor air pollution and CBCL measurements. Of this subsample, some participants were missing selected exposure measurements at the prenatal or postnatal time period. To increase sample size, we used multiple imputation techniques to impute the missing values. We were also limited by the sub-sample of participants who were measured for inflammatory markers at 6 week old. While this study had a relatively small sample size, few studies have such detailed exposure information and repeated outcomes, especially in a LMIC.

Another limitation of this dissertation is the lack of fine ($PM_{2.5}$) and ultrafine PM measurements. $PM_{2.5}$ measurement was not collected because, at the time, personal $PM_{2.5}$ monitoring was not easily available for this large of a study. Additionally, this study uses indoor air pollution measurements from one point (24 hours or two-week average, depending on pollutant) in the 2nd trimester and in early life to characterize exposure for the whole period. This could create some misclassification of the exposure.

Other limitations include biases from residual confounding, and selection bias. By using DAGs to control for the minimum sufficient set of confounders we adjusted for confounding in these analyses to the best of our ability. However, there may be additional bias from residual confounding or unknown confounders. Selection bias in this cohort is unlikely as this cohort was selected to be population based and representative of peri-urban populations in South Africa

and other LMICs. While there is not likely selection bias, this study's results may not be generalizable to non-LMIC populations.

Future research

As demonstrated in this dissertation, environmental and psychosocial exposures jointly affect childhood psychopathology. Future research on maternal exposures and childhood psychopathology should investigate these joint effects and expand on the exposures used in this dissertation. Particularly by incorporating other environmental pollutants such as persistent organic pollutants, endocrine disrupting chemicals, etc. Future research should also expand on the methods used in this dissertation to investigate synergy and interaction between exposures.

In AIM 1, we investigated trajectories of childhood psychopathology behaviors at 3 time periods. As the DCHS cohort ages, future research will be able to investigate trajectories spanning through childhood and adolescence.

In AIM 2, we investigated sensitive periods of exposure to indoor air pollutants and psychosocial factors and the effect on childhood psychopathology. Future research should investigate timing of exposure during pregnancy (e.g., 1st trimester) to further pinpoint sensitive periods of exposure. Additionally, as we were only able to investigate two periods of exposure, future studies should expand this. Investigating more exposure periods will allow for testing of additional life course hypotheses.

In AIM 3, we investigated how prenatal exposure to indoor air pollutants and psychosocial factors affect inflammatory markers in infancy. We also investigated how inflammation mediates the association between our exposure mixture and childhood psychopathology. We found evidence of effect modification by ancestry and HIV status of the relationship between exposure and mediator. Future research should investigate the effect modification by HIV status of the mother, as HIV infection has important consequences for immune system functioning and inflammation. Future research should also investigate other potential mediators of the

association between environmental and psychosocial factors and childhood psychopathology, like epigenetics.

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