Is neurodevelopment influenced by atopy in the mother or infant? **Exploring the role of infant and maternal atopic status, infant gut microbiome, and metabolites in early child neurodevelopment**

by

Nicole Anne Marie Rodriguez

A thesis submitted in partial fulfillment of the requirements for the degree of

Master of Science

Medical Sciences - Paediatrics

University of Alberta

Abstract

Background: Allergic diseases affect about 30% to 35% of all children, and the frequency of these diseases has been increasing in recent years. Growing epidemiological data suggests interactions exist between infant neurodevelopment and inflammatory immune diseases, including food sensitization and allergies. In this study, we aim to characterize and determine how atopic disease in both the infant and the mother shape infant neurodevelopment, as well as explore factors that play a role in this relationship.

Research Aims:

Research Aim I - I will investigate the association of allergic sensitization in 1-year old infants, especially food sensitization, in relation to the Bayley's scale of neurodevelopment.

Research Aim II - I will test the association between maternal prenatal atopy status and infant neurodevelopment.

Research Aim III - I will determine the mediating role of the gut microbiome and metabolome (short-chain fatty acids and amino acids metabolites) in the pathway between maternal atopic disease and infant neurodevelopmental scores.

Methods:

As assessed by the Bayley's neurodevelopmental scale at 1 year and 2 years of age, statistical analysis will be performed to determine the association between Infant and maternal allergic sensitization and infant neurodevelopment. Using 16S rDNA sequencing and NMR methods to profile gut microbe and metabolite abundance at 1 year, mediating tests on infant gut microbial and metabolite abundance will be conducted to determine whether certain metabolites or infant

gut microbiome is in the pathway between prenatal maternal atopic status and infant neurodevelopment.

Results:

Result for Research Aim I - In the current study, AS was present among 16.4% of infants, while 13.4% had FS. Both atopic and food sensitization at 1 year of age were associated with statistically significantly lower social-emotional scores at that age, independent of the infant's ethnicity. These findings were sex-specific and only observed among boys, among whom social-emotional scores were lowered by 5 points if AS was present (-5.22 [95%CI: -9.96, -0.47] p = 0.03) or if FS was present (-4.85 [95%CI: -9.82, 0.11], p=0.06).

Result for Research Aim II & III – Combined atopic conditions is present among 66.57% of mothers and 22.39% live with maternal asthma. Combined maternal atopy is associated with decrease in cognitive and motor scores at 2 years of age among male infants; and with increased cognitive scores at 2 years of age among female infants. In particular, cognitive scores are lowered by 3.87 points (-3.87 [95%CI: -8.28, 0.54], p = 0.09) and motor scores are lowered by 3 points (-3.00 [95%CI: -6.28,0.27], p = 0.072). Female infants whose mothers have combined maternal atopy experience an increase of 4.12 points in cognitive scores (4.12 [95%CI: -0.85, 9.08), p = 0.10). Infants born from Moms of Asian ethnicity experience the greatest decrease in infant neurodevelopmental scores (Table 3.5). On the other hand, maternal asthma decreases socio-emotional scores at 2 years among all infants (-3.70 [95%CI: -8.05, 0.64], p = 0.094). Sex-stratification demonstrate an increase in male infant language scores at 1 year (6.56, [95%CI: 1.76, 11.37], p = 0.008) and a decrease in male socio-emotional scores at 2 years (-6.60 [95%CI: -14.07, 0.88], p = 0.08). In the mediation analysis, creatinine mediates the association between maternal asthma and infant cognitive scores at 2 years, specifically of female infants with White

Caucasian mothers. Furthermore, when sequential mediation was performed with prenatal depression as mediator 1 and infant gut microbiome as mediator 2 in the pathway between maternal atopic status and child neurodevelopment, this resulted in no statistically significant mediating effect.

Conclusion:

Allergic symptomatology may adversely affect neurodevelopment because of the related clinical manifestations and necessary treatments. Creating a pathway from food sensitization to infant neurodevelopment through the gut microbiome will fill the existing knowledge gap in understanding the interaction between neurological and immunological development. Interventions in preventing atopic disease associated with impaired neurodevelopment are valuable to clinicians, mothers, and their families, as they help increase positive maternal and neonatal health outcomes and overall quality of life.

Preface

This thesis is an original work by Nicole Anne Marie Rodriguez. The thesis was written in accordance with the guidelines set by the Faculty of Graduate Studies and Research at the University of Alberta. This thesis is subdivided into 3 separate sections:

Chapter 1: consists of a literature review that is followed by an outline of the overall purpose, objectives, hypotheses, and sample size calculation for the studies.

Chapter 2: presents the first research study on the association between infant atopic and food sensitization and neurodevelopment. This chapter has been accepted for publication in Frontiers in Pediatrics, Pediatric Neurology, under the topic of Allergic Diseases and Neurodevelopment.

Chapter 3: presents the second research study on maternal atopic status and infant neurodevelopment. The potential mediating role of infant gut metabolites and infant gut microbiome on this pathway will be explored.

Chapter 4: presents final discussion and concluding remarks on the two studies, as well as outlines the bias assessment and summary of significance and future research directions.

Dedication

Dedicated to all single parents, immigrant families, neurodivergent students, and the Filipino community – you are all where I come from and why I find the strength in every day. Padayon kita - budlay budlay pero kuha! (Onwards we go!).

Acknowledgements

My most heartfelt gratitude to the SyMBIOTA (Synergy in Microbiota Research) team members for their inspiration, mentorship, and support during my time at the lab. A million thanks to my wonderful and brilliant supervisor, Dr. Anita Kozyrskyj who demonstrated that scientific excellence is not only about scholarly achievements but also the community, friendship, and laughter we share with our dear colleagues. I also would like to thank my committee members, Dr. Jacqueline Pei and Dr. Piushkumar Mandhane, whose dedication to improving countless lives through scientific research is something that I hope to emulate in my career journey.

Additionally, it has been a pleasure and an honor to work alongside incredibly talented fellow scientists in the SyMBIOTA Lab in Edmonton – thank you so much Carmen, Yuanyao, David, Sabrin, Maryam, and Sarah. Thank you for your friendship, advice, and encouragements.

I also would like to acknowledge the amazing efforts of my friends and family in supporting me throughout this journey – my sister and number one cheer leader, Therese; my super mom, Rhoda; and my bestfriends Klaudine, Quentin, Kleinberg, Andrea, and Zaineb – thank you for helping me brave life's toughest storms. I also dedicate this to my Uncle Mike and Papa Rudy in heaven, my guardian angels – I know you were with me all along. This is for you.

To my partner, Venugopal Hegde, who stood with me and who never got tired of reminding me of my strength – I love you! Here's to more adventures and chasing our dreams – together.

To my fellow mental health advocates and friends in the student entrepreneurship community – Sahand, Paulami, and Aylar – I am forever grateful to all of you!

To Mark Angelo Tarvina, my best friend, I would not be here without you. Thank you for being my compass. You deserve all the love in the world. This is most especially for you.

Table of Contents

List of Tables

Chapter 3

List of Figures

<u>**Supplementary**</u>

List of Abbreviations

AS	Atopic Sensitization
ASD	Autism Spectrum Disorders
ADHD	Attention Deficit Hyperactivity Disorder
BBB	Blood Brain Barrier
BSID – III	Bayley Scales of Infant Development – Third Edition
FS	Food Sensitization
CESD	Center for Epidemiological Studies-Depression
CHILD	Canadian Healthy Infant Longitudinal Development Study
CIs	Confidence Intervals
CNS	Central Nervous System
DAG	Directed Acyclic Graph
IgE	Immunoglobulin E
IgE-FA	immunoglobulin E–mediated food allergy
M	mediator
MIA	Maternal Immune Inflammation
ND	Neurodevelopment
NDD	Neurodevelopmental Disorders
SCFAs	Short Chain Fatty Acids
SEM	Structural Equation Modeling
sIgA	Secretory Immunoglobulin A
SPT	Skin Prick Test
X	Independent or exposure variable
Y	Dependent or outcome variable

CHAPTER 1: Introduction

Chapter 1 provides a literature review on the association between (i) infant atopic and food sensitization and neurodevelopment and between (ii) maternal combined atopy and infant neurodevelopment. First, the chapter explores established research on factors that influence infant atopy and food sensitization, including sex-specific patterns in sensitization risk. Second, the chapter covers factors that shape infant neurodevelopment, with a focus on the connection between infant and maternal atopic disease. Third, the chapter describes the potential mediating role of the infant gut microbiome with sensitization, immunity, and neurodevelopment. The final section of this chapter outlines the research question, hypothesis, and sample size calculation.

1.1 Infant Atopy and Food Sensitization

1.1.1 Defining atopy and food sensitization

Food and atopic sensitizations are known to be multifactorial diseases that are shaped by complex interactions of a child's geographic, genetic, ethnic, and dietary exposures (1,2). Food sensitization is a first and strong indicator of immune deviation and is defined as the presence of IgE antibodies against certain foods (3–5). This immune- mediated process is more specifically referred to as a classic Type 1 hypersensitivity response which develops over time when repeated exposure to a food antigen activates allergen-specific T cells in susceptible infants. When T helper (TH2) activity is enhanced, it leads to the recruitment of eosinophils, basophils, and allergen-specific IgE (sIgE). T cells provide 'help' to B cells to secret allergen-specific IgE (immunoglobulin E), which then primes mast cells to degranulate on subsequent exposure to the allergen, releasing histamine and other inflammatory mediators (6). Furthermore, the induction and maintenance of FS and atopy is due in part by secretion of certain cytokines (e.g. IL-4, IL-

13, IL-5) that comes with the upregulation of Th2 responses (7).

Additionally, FS, determined by skin prick testing or serum IgE levels to the allergen, affects up to 28% of preschool children in the U.S. (4). The resultant IgE- mediated immune response to the allergen initiates the inflammatory process resulting in food hypersensitivity or sensitization (6). If the food allergen is blocked by serum or intestinal immunoglobulins (such as IgA), the immune response will be diminished and tolerance to the allergen will occur.

1.1.2 Rising atopic and food sensitization rates

The prevalence of allergic diseases has reached approximately 20% globally and has been particularly widespread amongst children(8). Recent analysis report that about 30 percent to 35 percent of all children suffer from allergic diseases, and the frequency of these illnesses has been rising in recent years (9).The U.S. in particular has seen a 50% increase in food allergy from 1997 to 2011, resulting in an overall 8% prevalence of food allergy among U.S. children (10).

1.1.3 Factors that lead to infant atopic and food sensitization

Research points to a common temporal order of allergic diseases among children also known as the "atopic march" which follows the following order: atopic dermatitis (AD), and food allergy in infancy to later on allergic asthma (AA) and allergic rhinitis (AR) in childhood (11,12). Globally, the topmost common food items that trigger sensitization are cow's milk and eggs, while peanuts are more common triggers in the North America (1).While cow's milk, eggs, and wheat related food allergies usually subside by age 2 to 10 years old, infant sensitization to peanut is the most likely to persist into later childhood and/or to proceed to food allergy (13–15).

It is important to note that sensitization does not always lead to clinically-significant and symptomatic allergic response. However, when sensitization does develop to allergy, it can be life threatening and could lead to stress and low quality of life among children and their caregivers.

1.1.4 Infant sex differences in sensitization risks

Currently, there is no definite consensus in the scientific community regarding the influence of an infant's biological sex on the development of food and/or atopic sensitization (16). However, several observations have been documented including a pattern of higher frequency of food sensitization and allergy among male infants (higher IgE levels were reported) than females (16). These associations appear to be reversed later in adult years — with females having higher FS than males). For example, a Norwegian study reported that sex differences in severe allergic reactions to food were only observable during the adolescence and adulthood periods but not at 2 years of age (17). Starting adolescence, females experienced 20% more allergic reactions compared to males. Other researchers argue that the difference might not be so much attributable to biological sex but to gender, which appears to be a better predictor of differential coping or management strategies for dealing with allergic diseases among males and (17–19). The exact mechanism of why these differences is observed is not clear. However, some studies suggest the potential impact of factors including differential immune system processing, influence of sex hormones on antigen receptors, variations in microbiome composition, and other mediators (19–21).

Although the findings regarding the association of sex with allergic outcomes is not clear, there still is an agreement that future prospective studies need to investigate and clarify the influences of sex and gender difference. Making this distinction is critical to provide personalized diagnosis, management and treatment of food allergy (16,19).

1.1.5. Impact of food sensitization on infant development

The harmful impact of childhood food allergy on quality of life of children and their families has been well researched (22–24). Food sensitization poses a significant economic and quality of life burden to children and their families (25). For example, a U.S. prospective study examined parent-reported health-related quality of life (HRQoL) scores of children 0-12 years. Results of the study revealed that reduced HROQoL scores are associated with older children, especially those with multiple and severe food allergies (25). These findings are consistent with a Swedish study that assessed overall health related quality of life of children 6-12 years and revealed that multiple food allergies, severe symptoms, and older children have worse HRQoL outcomes (23).

Additionally, the financial burden brought by food allergies to children and their families is becoming more pronounced. For example, a Canadian cross-sectional study of families examined the impact of childhood food allergy on household costs (22).Compared to families with no food-allergic children, families with food-allergic children incur a 20% increase in total annual direct costs which is largely influenced by food costs (22).

Therefore, since food allergy contributes substantial financial stress and impaired quality of life, research efforts to better understand how to meet the needs of vulnerable and high-risk children and their families must be taken into account.

1.2 Infant Neurodevelopment

1.2.1 The "window of opportunity" of the early infant brain development

The infant's first year of life is known as the "window of opportunity" because it is a period of development when the brain is most vulnerable to all kinds of pre and post-natal factors (26). It is well known that an infant's brain has a high degree of plasticity and is easily influenced early disruptions (26). Prenatal factors including antibiotic use, infections, environment, dietary habits, and mode of delivery are strong predictors of maternal health status, fetal development, and can shape the infant microbiome and cognitive development from birth up to 3 years (27,28).

Findings from other systemic reviews also point to the effectiveness of certain interventions for infants born high-risk for cognitive impairments. One systematic review points to the overall effectiveness of multisensory stimulation (e.g. soft lullabies, gentle rocking and massage) in improving infant neuromuscular and neurological development (29).

On the other hand, because most data on infant neurodevelopment are gathered from parental self-reports, studies still recommend additional measures that will verify the reliability of parent-reported data (30, 31). However, several studies have supported the reliability of parent- reported evaluations of their child's cognitive development. For example, parent subjective assessments of their infant's attention and regulatory abilities match expected objective measures of cortical rhythms of their child (32). Therefore, it is possible that patterns of brain activity may match parent observations of their child's development, suggesting that data from parent evaluations provide useful supplementary information regarding brain-behavior relations among infants.

Thus, understanding how easily malleable the infant brain is to early interventions and pre and postnatal elements is critical to studying which alterations to a child's normal cognitive trajectories need to be addressed early on to prevent both mental and behavioral disorders in the future.

1.2.2 Infant neurodevelopment risk factors

Neurodevelopmental disorders affect intellectual and psychosocial abilities of the child and harmful consequences may persist till later years in life. Risk factors that lead to neurodevelopmental disabilities are complex, multifaceted, and are often themselves associated with each other (1). Therefore, identifying biological and environmental factors that put infants at high risk is a critical priority in health research as early timing of interventions are known to improve outcomes of children affected by NDs (1). Risk factors associated with maternal milieu, including maternal diet, infection, stress, and maternal history of immune and psychiatric disorders are proposed to have influences with infant brain development, starting in utero.

Infant in utero environment – maternal immune conditions, maternal diet, and maternal stress

The blood brain barrier (BBB), a dynamic and semipermeable structure, restricts components from the circulating blood from crossing over to the extracellular space of the central nervous system (CNS) (2). However, since the BBB is still in its early developing stages in the fetus, it is more permeable and thus, certain antibodies are able to breach this protective barrier. Specifically, maternal-derived brain-reactive antibodies are hypothesized to cross-react with CNS antigens after breaching the fetal BBB. Research supports that women with impaired B-cell tolerance due to autoimmune disease tend to produce these antibodies and their infants are more likely to have ASD and be positive for brain-reactive antibodies ((3)Animal studies demonstrate that when the brain-reactive antibodies of mothers whose offspring live with autism were injected into pregnant mice, neurodevelopmental impairments were observed including decreased motor skills, reduced exploration, and altered cerebellar metabolites (4). A population-based case-control study from the U.S. produced results consistent with the animal study, wherein mid-gestation antibodies of mothers whose children with ASD had higher reactivity to human fetal brain proteins compared to the general population control group (5).

Another maternal factor suggested to have programming effects on the developing fetal brain is maternal diet and early nutrition. For example, maternal low-protein diet was not only associated with impaired offspring growth and malnutrition, it also disrupted expression of dopamine systems in the brain and a several dopamine-dependent pathways responsible for reward-related behaviors (5,6).

Other maternal elements that contribute to fetal programming include maternal psychological stress and psychiatric disorders during the pregnancy period. When a mother engages in smoking and/or substance abuse during pregnancy, it results to altered gene expression of certain fetal brain regulatory genes important for brain growth, myelination, and neuronal migration — all leading to altered brain structure and function. Moreover, maternal anxiety during the pregnancy period increases exposure of the infant to maternal stress hormones such as cortisol, which can compromise brain regions involved in decision making, emotional regulation, and social behavior (7).

These findings lend support that adverse maternal factors have the potential to alter brain development of their infants *in utero*, that may heighten the risk of the child developing neurodevelopmental disorders.

Insecure Attachment Styles and Low Income Households

The World Health Organization (WHO) warns that more than 200 million children under the age of five are not fulfilling their developmental potential due to exposure to adverse risk factors including poverty, malnutrition, and unsafe home environments (8). There are five critical components of nurturing care that may offset harmful effects of social disadvantage on neurodevelopment: good health, adequate nutrition, safety and security, responsive caregiving, and opportunities for learning (9). Healthy formation of parental and/or care-giver bonds and secure attachments improve an infant's capacity of emotional connectivity, the ability to build safe and secure relationships, and the development of positive self-esteem in later life. Children who experience neglect and lack of consistent parental figures (for example, children placed in numerous foster care homes) are more likely to experience self-regulation difficulties and thus are at greater risk of developing addiction and other mental health illness.

Low financial resources may also affect children by limiting their access to adequate health and nutrition as well as increase their exposure to familial interpersonal stresses (10). Disruptions in household relationships stemming from arguments on financial challenges are linked to negative parenting behaviors including greater hostility, irritability, rejection, and explosive disciplinary actions. As a result, children in these households face greater socioemotional difficulties, impairing healthy neurodevelopment.

Infant Preterm Birth

There is sufficient research evidence that present the dangers of preterm birth to infant neurological outcomes through complex causal pathways including hypoxia/ischemia, infection, and inflammation of fetal membrane structures (11). Among the consequences of early birth include risk of brain injury, including white matter damage, intraventricular hemorrhage, and cortical and deep gray matter damage (12). Furthermore, pre-term birth affects the timing of neurobiological processes including synapse formation, dendrite formation, and neuronal migration and differentiation (13). One of the consequences of premature birth is also low birth weight and a meta-analysis revealed that low birth weight infants exhibit the strongest associations with inattention, hyperactivity, internalizing problems in childhood and adolescence and higher risks of mental health problems in adult years. Since a significant portion of brain development occurs around the last 6 weeks of gestation, missing this critical period can have significant consequences for the preterm infant (14).

Atopic and food sensitization as risk factors on early brain development

Atopy and impaired neurodevelopment have immune dysregulation and inflammation in common, and share many risk factors, for example, maternal history of atopic disease (33). Accumulating epidemiologic evidence further supports a connection between the infant's immune system and neurodevelopmental disorders. A recent study of school-children revealed that peanut sensitivity or allergic rhinitis in 6-year olds predicted symptoms of attention-deficit hyperactivity disorder (ADHD) at 12 years of age(34). A temporal association between atopic disease and neurodevelopment has also been demonstrated in very young children with a family history of atopy whereby infants with any atopic disease (eczema or food allergy) at 12 months exhibited lower motor scores on the Bayley Scales of Infant Toddler Development at 18 months (35). Among infants with diagnosed food allergy at 12 months, lower social-emotional scores were reported at 18 months (35).

Parental atopic sensitization status as a risk factor for infant atopy and neurodevelopment

Parental histories of food sensitization and other allergic diseases are known to influence the allergic outcomes of their children (36–39). Some studies suggest that infant sensitization may even begin as early as prenatal and or initial postnatal periods (37, 40–43). Research has demonstrated that high levels of maternal and cord blood inflammatory markers are linked to increased offspring risk of eczema, wheezing, and lower respiratory tract infections (37, 44, 45).

Among the various maternal and paternal influences, maternal allergy/asthma emerged as having the most associations with the development of allergies in offspring (37). Additionally, it is the mother's history of asthma and not the father's history that is a stronger predictor of childhood asthma (2,46–48). Thus, this association implies that apart from genetics, other in utero mother-child system interactions may explain why maternal allergen exposure is a large contributor to the child's allergic outcomes (49). For example, in human and mouse studies, allergic moms tend to transfer immune responses to their offspring via placenta and breastmilk which then shapes the infant immune response to certain allergens (50). A combination of genetic and environmental maternal factors regulate the induction of tolerance and allergy responses in infants, mainly through immune T cell responses (50). However, the exact mechanisms that occur in the maternal-child interface including allergen exposure during breastfeeding and how they shape future disease susceptibility of the infant is still largely unknown. Further investigations are needed to better understand the role of maternal factors on offspring food allergy (50).

Recently, maternal immune activation (MIA) or excessive maternal immune response during pregnancy is suspected to be attenuated by microglia which are immune cells in the central nervous system that influence neurodevelopment and brain disorders (51,52). Findings of an Australian study revealed that children ages 5, 8, 10, 14, and 17, who are born from mothers with asthma, allergy, atopy and eczema scored higher in having behavioral/emotional problems (52). Increased behavioral and emotional problems occurred especially in children with more than one allergy exposure and/or those whose mothers have an infection condition (52). Interestingly, they found that females scored higher in internalizing scales from maternal infection, whereas males showed equal increase in scores in both internalizing and externalizing problems (52).

Infant gut microbiome and immune system interactions shape neural development

Previous studies support that the microbiome's role in the immune system development and regulation is a hypothesized mechanism for its association with neurodevelopmental disorders — a well-documented one being autism spectrum disorders (ASDs), which is linked with immune dysfunction (80,81). Further support on the influence of the gut microbiome in infant brain development presented an association between differential microbiome composition and cognition scores of typically developing infants up to 2 years of age (82). Consistent with these findings infant gut microbiome composition was also related to neurodevelopmental outcomes in communication, personal and social, and fine motor skills was found in children at age 3 years (83). Furthermore, recent research strengthened the support for the association of infant gut microbiome and early brain development by revealing strong, sex-specific findings on the positive association between Bacteroideted abundance in late infancy and change in cognitive and language performance from 1 to 2 years (84).

In addition to the well-documented associations of the infant gut microbiome to atopy and food sensitization, infant bacterial composition was also determined as a key factor in infant neurodevelopment. Specifically, previous studies support that the microbiome's role in the immune system development and regulation is a hypothesized mechanism for its association with neurodevelopmental disorders — a well-documented one being autism spectrum disorders

(ASDs), which is linked with immune dysfunction (80,81).

1.3 Infant Gut Microbiota

1.3.1 Infant gut microbiome's role in infant atopic and food sensitization

Association between infant gut microbial diversity and composition with atopic and food sensitization

The expanding rates of immunoglobulin E–mediated food allergy (IgE-FA) has made it a global public health concern (53). Perturbations to the infant gut microbiome also known as "dysbiosis" and IgE-FA both have immune dysregulation as a common denominator (53).

Findings of a study regarding the association between infant gut bacterial composition and food- related atopy at age 3–5 revealed less diverse gut microbiome composition in children with IgE- FA compared with children without IgE-FA (53).In particular, children with IgE-FA in milk and peanuts showed the least diverse microbiome and specifically in the orders Lactobacillales, Bacteroidales, and Clostridiales (53).

Increasing evidence implicates the infant gastrointestinal microbiota as a critical player in the development of diseases in children, including atopic conditions such as asthma and allergies. Previous literature support that interactions between infant diet and commensal microbiota may shape food allergy and consequently determine the infant's mucosal immune tolerance (54,55). Additionally, different compositions of the neonatal human gut microbiota were shown to predict varying risks of childhood atopy (50). Literature also suggests that distinct types of food sensitization may exhibit differential infant gut microbial profiles (55). For example, infants allergic to peanuts have higher levels of Bacteroides, and those with cow's milk allergy (CMA) have higher levels of anaerobic bacteria Ruminococcaceae and Lachnospiraceae (56–58). Furthermore, a recent study demonstrated that temporal changes in the ecologic composition of gut microbiota during infancy is associated with food sensitization (59). In particular, persistently low gut Bacteroidetes abundance throughout the infancy period was associated with a 3-fold risk of sensitization to food allergens, specifically to peanuts (59).

Infant gut microbiome's mediating role in the association between immunity and IgE-FA

Research suggests that gut microbes modify a child's risk of IgE-FA through its role in the immune pathways (53). For example, breastfeeding supplies the child with secretory immunoglobulian A (sigA) which can then bind to harmful microbial antigens (60–62). Other breastmilk components including oligosaccharides promote the growth of beneficial bacteria including Bifidobacterium and Lactobacillus which induce the production of cytokines that are key to preventing immune dysregulation. Furthermore, gut bacteria produce essential short chain fatty acids (SCFA) which contribute to strengthen the intestinal barrier and B-cell functions and thus minimizes potential inflammation. Therefore, since the gut microbiota plays a critical role in regulating the immune response and thus prevent IgE-FA, its role as a mediator in preventing IgE- FA via the immune control merits further research.

Differential gut bacterial composition as a key factor to infant neurodevelopment

Further support on the influence of the gut microbiome in infant brain development were presented by Carlson et. al (2018), wherein differential microbiome composition was related to cognition scores of typically developing infants up to 2 years of age. Consistent with these findings, an association was found between infant gut microbiome composition and neurodevelopmental outcomes in communication, personal and social, and fine motor skills was found in children at age 3 years (83). Furthermore, sex-specific findings were linked to the positive association between Bacteroidetes abundance in late infancy and change in cognitive and language performance from 1 to 2 years (84).

1.3.2 Potential mediating effect of the infant GM in the pathway of infant atopic and food sensitization and the infant brain development

Atopy and impaired neurodevelopment have immune dysregulation and inflammation in common, and share many risk factors, for example, maternal history of atopic disease (33).

Accumulating epidemiologic evidence further supports a connection between the infant's immune system and neurodevelopmental disorders. A recent study of school-children revealed that peanut sensitivity or allergic rhinitis in 6-year olds predicted symptoms of attention-deficit hyperactivity disorder (ADHD) at 12 years of age (34). A temporal association between atopic disease and neurodevelopment has also been demonstrated in very young children with a family history of atopy whereby infants with any atopic disease (eczema or food allergy) at 12 months exhibited lower motor scores on the Bayley Scales of Infant Toddler Development at 18 months (35). Among infants with diagnosed food allergy at 12 months, lower social-emotional scores were reported at 18 months.

While the influence of infant atopy and food sensitization on their corresponding neurodevelopment is well recognised, it is still not well understood. Furthermore infant gut microbial colonization and exposure has been known to play a critical role in both infant atopy and food sensitization and infant brain development, however gaps in research exist in determining whether and in what ways the infant microbiome plays a mediating role in the pathway between infant sensitization and neurodevelopment.

1.4 Potential covariates affecting infant sensitization status, infant neurodevelopment, and the infant gut microbiota

1.4.1 Maternal characteristics

Prenatal diet (fruit intake)

There is strong support for the influence of maternal prenatal diet on the sensitization risk of their offspring (85–87). However no clear consensus currently exists specifically for the exact effect of prenatal fruit intake. For example, a study suggested that higher maternal consumption of green and yellow vegetables, citrus fruit, and β-carotene during pregnancy was associated with lower occurrence of eczema in the offspring (88). Additionally, higher maternal vitamin E intake during pregnancy was inversely associated with risk of infantile wheeze (88). However, contrary to these findings, other researchers argue that food items high in advanced glycosylated end products including fruit juice are associated with increased risk of allergic disease(89). Lastly, contrary to both of these findings which found a significant effect, other studies did not find other dietary exposures including prebiotic supplements, maternal allergenic food avoidance, and vitamin, mineral, fruit, and vegetable intake to strongly influence risk of allergic or autoimmune disease (90,91). One particular study however, found that probiotic and fish oil supplementation during later pregnancy and lactation is associated with lower risk of eczema or allergic sensitisation to food during childhood (91).

Overall, prenatal diet is still a factor of interest for our study because although research appears to be conflicting, all of the studies still support that components of prenatal diet play a role in sensitization of the infant.

Prenatal smoking

Maternal smoking is known to harm a child's development both in-utero and during the postnatal period (92–94). An early study states that exposure to prenatal smoking significantly increases allergen-specific immunoglobulins IgE and IgD in newborn infants even if they were born to parents without any allergic histories (95). In particular, infants of non-allergic parents who were exposed to prenatal smoking had three times higher levels of cord IgE and four times higher risk of developing atopy before 18 months of age compared to infants born to moms who did not smoke (95). In support to these findings, second hand smoke exposure during infancy increases food sensitization and eczema risk up to 16 years of age (96).

Prenatal depression

Prenatal psychosocial stress is a contributing factor that increases a child's risk of having developmental delays, dysregulated immune responses, and psychopathology in later life (97– 100). For example, prenatal stress is associated with higher levels of inflammatory biomarkers including C-reative protein and IL-6 that appears to persist in adulthood (98,101–103). In support of these findings, researchers presented the first human study to show an independent association between prenatal depression and lower infant gut immunity (104,105). Specifically, mothers experiencing depression during pregnancy tend to have lower sigA concentrations, a protective component of the body's immune system (104). Since the an infant's early source of sigA comes from their mother's breastmilk, low sigA concentrations and thus a compromised immune system are subsequently observed among infants born from mothers living with depression. It is also important to note that low sigA harms gut immunity as it makes the infant's gut more susceptible to harmful C-difficile infection and development of atopic disease (104,105).

Breastfeeding duration

The push for longer breastfeeding duration by the clinicians and the scientific community is grounded in well-established data regarding the abundant nutrients and protective benefits it confers to the child (106). From obesity prevention, immune protection, allergy protection, and promotion of a healthy gut microbiome, it is well established that breastfeeding, especially prolonged breastfeeding duration has lasting beneficial effects for both mother and child (93,107).

1.4.2 Infant characteristics

Infant introduction to solid food

The infant's period of complementary feeding (6–24 months of age) is a demanding period of infant nutrition due to high requirements for metabolic processes, rapid developmental processes, and limited gastric capacity (108). In addition, high caloric intake is necessary during this period to facilitate healthy brain development which includes wiring of neurons for communication, maintenance of synapses, and myelination to name a few.

Aside from its important role in infant brain development, the introduction to diverse kinds of solid food, most especially those known to be "allergenic" reduces the risk of allergic sensitization (109). Several randomized controlled trials (RCTs) of introduction to allergenic solid foods found that early introduction, usually from age 4 to 6 months, reduced the risk of food sensitization and allergic disease. A recent comprehensive systematic review and meta- analysis of randomized controlled trials (RCTs) presented that early introduction of egg at 4 to 6 months of infant age reduced egg allergy by 46% (110). Additionally, introduction of peanut reduced peanut allergy by 71% (110).

Siblings

Previous research supports that the presence of older siblings may contribute to a decreased risk of food allergy - a phenomenon also termed the "sibling effect". First coined by Golding and Peters in their British Birth survey, the "sibling effect" was observed when the risk for eczema and hay fever decreased in infants with higher sibling count (111). Moreover older siblings were associated with a lower risk of developing food allergy (112,113). Researchers suggest that the protective effect of siblingship might be due to exposure to microbial stimulation from close contact with siblings during the early life years (111). Others speculate that exposure to infections through sibling interaction may prevent allergies (111,114).

A possible explanation for the protective association of the presence of older siblings is because of increased exposure to microbial stimulation in early childhood resulting from close contact with siblings. In addition, several studies have proposed that exposure to certain infections may protect against allergies (115,116). On the other hand, other findings support this by showing that having older sibling/s improves social communication in children with autism spectrum disorders (ASD) which may be due to increase opportunities of having social interactions with their siblings (117).

Birth mode

Birth mode is known to be a critical player in the development of atopic sensitization (118). For instance, research from a Finnish child population report that cumulative incidences of atopic sensitization were highest among those born by assisted vaginal delivery or c-section (118). However, neonates born via elective c-section have the highest incidence of food allergy among infants of mothers without atopic diseases. This finding is further supported by research that demonstrated an increased risk of asthma medication in infants born by emergency C- section (119).

Furthermore, birth mode has also been distinguished as an important determinant in shaping the infant gut microbiota during infancy (7). Delivery via c-section strongly influences the infant gut by decreasing colonization rates of Bacteroides and increasing the prevalence of clostridia until seven months postpartum. Consistent with these findings, infants born via c- section delivery also showed impaired Bacteroidetes colonization, lower microbial diversity, and a compromised immune response (120).

With regards to neurodevelopment, birthmode is associated with differences in neurodevelopmental effects but only in early infant life (121,122). Further research is needed to determine the extent of birth mode's consequences on infant brain development in the adult years.

Infant sex

Infant sex and neurodevelopmental disorders

There is currently an observed pattern of males having a higher risk for neurodevelopmental disorders compared to females (123,124). In particular, males appear to be up to four times at higher susceptibility to impaired brain development which includes intellectual disability, autism spectrum disorder (autism) and attention deficit hyperactivity disorder (ADHD) (123). The exact causes of these discrepancies are currently being investigated but previous research points to variations in genetics, hormones and their interaction with other risk factors including stress and lead exposure (123,124). For example, a study demonstrated that a certain protein transferase crucial in brain functioning and metabolism is higher in females than males due to the extra X chromosome found in females. Other studies report lead exposure measured via maternal blood samples is associated with ADHD risk for male children but not in females (125). However, this association is later reversed during early adolescence, where females appear to have higher diagnosis of ADHD (126).

Infant sex and atopic and food sensitization

Researchers have argued for further investigation regarding the roles of sex and gender differences in allergy studies to provide personalized diagnosis, management and treatment of food allergy (19). Differences in food and allergic prevalence between males and females are well documented with a higher number of male children suffering from general atopic symptoms, including asthma, food allergies, and skin reactions against multiple allergens (127). However, a reversal of this trend occurs in adulthood with more females experiencing food intolerance and food hypersensitivities compared to men (19). Several causal pathways have been suggested to explain the gender gap in food allergy including hormonal influences on immune cells, gender-specific influence of the gut microbiome on food allergy, effect of prebiotics, and potential gender effects on approaching food allergy (19).

1.5 Research Question and Hypothesis

1.5.1 The Canadian Healthy Infant Longitudinal Development (CHILD) Cohort Study

Datasets for both research study one and research study two were derived from the Canadian Healthy Infant Longitudinal Development (CHILD) Study which is a national, prospective longitudinal birth cohort that recruited pregnant women from the general population from 4 cities across Canada (15). The cohort was developed to address research priorities in uncovering gene-environment interactions during pregnancy and early childhood and to provide a platform to study factors that alter risk of subsequent allergy and asthma development in children. The cohort consists of healthy, full-term infants and the mother-child pairs are followed which allows us to explore infant neurodevelopmental outcomes through time. Both parental and infant assessments were collected from pregnancy up to five years of infant age. Questionnaires include environmental, psychosocial, nutrition, and health assessments. Additionally, biological samples include blood, urine, nasal, stool, and breastmilk samples. This comprehensive data collection of child and parental health health information allows CHILD researchers to test hypothesis related to fetal and early infant origins of complex diseases such as atopic and food sensitization, providing insight into the role of these critical windows of exposure on immune, physiological, and microbiome trajectories.

1.5.2 Objectives

For children who are a subsample of the CHILD birth cohort (www.childstudy.ca) from the Edmonton site, we aim to determine a) the association between food or any allergen sensitization in the first year of life and children's neurodevelopment at toddler age in a general (not high atopy-risk) population and b) to assess any weather any of the resulting associations are sex-specific. My secondary objective is to investigate the potential mediating role of the infant gut microbiome in the pathway between atopic and food sensitization and neurodevelopmental outcomes.

1.5.3 Research Questions

Primary Research Question - How does positive food and atopic sensitization (ie. a wheal size ≥ 2mm) at 1 and 2 years of infant age influence neurodevelopmental scores (Bayley Scale of Infant Development Third Edition or BSID-III) on the cognitive, language, social-emotional, and motor domains?

Secondary Research Question - What is the sequential mediating role of infant gut microbiota composition at 4 months, on the association from maternal atopic status and child neurodevelopment scores?

1.5.4 Sample Size Calculation

Differences have been found in neurodevelopmental scores as measured by Bayley Scales of Infant Toddler Development III Edition (BSID-III) between infants with atopic

$$n = 2\left[\left(\frac{Z\alpha}{2} + Z\beta\right) * \frac{SD}{Mean1 - Mean2}\right]^2$$

$$n = 2\left[(1.96 + 0.84) * \frac{20.9}{111.9 - 103.54}\right]^2$$

$$n = 98$$

sensitization and those without atopic sensitization at 18 months of infant age. An Australian study found a statistically significant difference between the socioemotional BSID-III scores of infants with IgE-mediated food allergy (Mean: 103.54, SD: 20.9) and those with no food allergies (Mean: 111.9, SD: 19.3) (35). Thus, this sample size calculation was done comparing infants with food sensitization and those without food sensitization, using mean BSID-III socioemotional scores. Assuming 80% power and a two-sided alpha or 0.05, a sample size of 98 infants in each group is required to detect a difference of 15.46 in the BSID-III socioemotional scores among infants. Therefore, with our sample numbers n = 537, we will have sufficient power to detect meaningful differences in the BSID-III neurodevelopmental scores between infants with or without sensitization status.

1.6 Summary

The rise of infant immune diseases including food and atopic sensitization is becoming a noticeable trend in children's health. This trend indicates the vulnerability of the developing immune system to early environmental changes and stressors (1). Parallel to the rise in allergic diseases is the link to subsequent infant neurodevelopmental challenges and metabolic diseases, conditions which are even more common to infants born from mothers with history of allergic conditions (2,3). To date, there is scarce literature that further explains more to the story – what is the link between allergic and infant neurodevelopmental outcomes, which factors play a key role, and what is its connection to the infant gut microbiome, if any?

The next two Chapters – Chapters 2 and 3 will be two papers that bring results that may act as promising clues to help uncover parts of this story.

CHAPTER 2: Sex-specific associations among infant food and atopic sensitizations and infant neurodevelopment

2.1 Abstract

Introduction:

Food sensitization is a first and strong indicator of immune deviation in the progression to other allergic conditions. Sensitization to food or other allergens and related inflammation during critical windows of infant development may adversely affect neurodevelopmental milestones. However, additional research is needed to test this association further.

Methods:

Associations between atopic (any food or aeroallergen) or food sensitization (specific to egg, soybean, peanut, and milk) at age 1 year and neurodevelopment up to 2 years of age were evaluated in the national CHILD Cohort Study, with a secondary aim examining whether these associations were sex-specific. Food and atopic sensitization were assessed by skin prick tests (SPT) in one-year-old infants, with neurodevelopment assessed using the cognitive, language, motor, and social-emotional subscales of the Bayley Scales of Infant Development (BSID-III) administered at 1 and 2 years of age.

Results:

Atopic sensitization was present among 16.4% of infants, while 13.4% had food sensitizations. Only socioemotional scores reached statistical significance among the four BSID-III domains. Both atopic and food sensitization at one year of age was associated with lower social-emotional scores, independent of the infant's ethnicity. These findings were sex-specific and only observed among boys, among whom social-emotional scores were lowered by 5 points if atopic

sensitization was present (-5.22 [95%CI: -9.96, -0.47], p=0.03) or if food sensitization was present (-4.85 [95%CI: -9.82, 0.11], p=0.06). Similar results were observed using the standard SPT cut-off of ≥ 3mm — for atopic sensitization (-5.17 [95%CI: -11.14, -0.80], p=0.09) and for food sensitization (-4.61 [95%CI: -10.96, 1.74], p=0.15).

Conclusion:

In our study of term infants, we found an inverse, cross-sectional association between atopic and food sensitization status and social-emotional development scores in males but not females.

2.2 Introduction

Food allergy in high-income countries is on the rise, with an allergy to common foods reported in more than 10% of 1-year-old infants (1). Food allergy is a classic Type 1 hypersensitivity response that develops over time when repeated exposure to a food antigen activates allergen-specific T cells. These T cells provide “help” to B cells to secrete allergenspecific IgE (immunoglobulin E), which then primes mast cells to degranulate on subsequent exposure to the allergen, releasing histamine and other inflammatory mediators (2). Mast cells can cause neuroinflammation, and children with high levels of mast cells have a greater risk of developing autism spectrum disorder (ASD) (3).

The phenomenon of the “atopic march,” wherein allergic diseases happen in progression, begins in childhood (4). Food sensitization, determined by skin prick testing or serum IgE levels to the allergen, affects up to 28% of preschool children in the United States (5). While it may not develop into clinically significant food allergy, food sensitization is a first and strong indicator of immune deviation in the atopic march (5, 6). The resultant IgE-mediated immune response to the allergen initiates the inflammatory process resulting in food sensitization (2). Conversely, if the food allergen is blocked by serum or intestinal immunoglobulins (such as IgA), the immune response will be diminished, and tolerance to the allergen will occur. Disease severity is related to the amount of circulating IgE. Among the various food allergens, infant sensitization to peanuts is the most likely to persist into later childhood and/or proceed to food allergy (7, 8). The infant’s 1st year of life is the “window of opportunity,” wherein nutrition and other exposures can significantly impact an infant’s developing immune and nervous systems (9).

Atopy and impaired neurodevelopment have immune dysregulation and inflammation in common and share many risk factors (10). Accumulating epidemiologic evidence further supports a connection between the infant's immune system and neurodevelopmental disorders. In the comprehensive review by Jyonouchi et al. (11), it was pointed out that allergic symptoms commonly worsen behavioral symptoms of ASD. A newer study of school children revealed that peanut sensitivity or allergic rhinitis in 6-year-olds predicted symptoms of attention-deficit hyperactivity disorder (ADHD) at 12 years of age (12). Temporal associations between atopic disease and neurodevelopment have been also found in very young children with a family history of atopy, whereby 12-month-old infants with any atopic disease (eczema or food allergy) exhibited lower motor scores on the Bayley Scales of Infant Toddler Development at 18 months (13). Among infants with diagnosed food allergy at 12 months, lower social-emotional scores were reported at 18 months (13). Recent findings from the Boston Birth Cohort have demonstrated a higher incidence of neurodevelopmental disabilities among children with atopic disease compared to children without atopy (14). In this study, we determined the association between food or any allergen sensitization as a marker of IgE dysregulation in the 1st year of life and children's neurodevelopment at the toddler age in a general (not high atopy risk) population. Sex-specific associations were tested. We hypothesized that atopic sensitization adversely affects the neurodevelopment of the growing infant and thus will lead to lower neurodevelopmental scores.

2.2 Methods and Study Design

Our present study accessed data from a subsample of the CHILD birth cohort (www.childstudy.ca) consisting of 537 infants from the Edmonton site. The CHILD birth cohort recruited pregnant women aged ≥18 years who delivered singleton infants at ≥35 weeks of gestational age and a birth weight of ≥2500 g. Multiple gestations, in vitro fertilized births, and preterm births were excluded, as were children born with congenital abnormalities or respiratory distress syndrome. Mothers were followed throughout pregnancy, atopic and food sensitization were both assessed at one year of infant age, and infant neurodevelopmental scores at ages one and two years. Study covariates were collected from study questionnaires during pregnancy and three months post-partum and/or hospital birth records. They consisted of the following maternal factors: maternal ethnicity (White Caucasian, Asian, Other), maternal age (18 to 29, 30 to 39, over 40), maternal education (some/finished high school, some university/college, university degree), asthma treatment during pregnancy (yes or no), prenatal smoking (yes or no), and maternal depression (never, prenatal, postnatal, persistent). Maternal diet was also included and was based on the prenatal fruit intake ("5-a-day" method), which measures the sum of "servings of fruit, not including juices, "plus servings of juice" per day (15).

In the CHILD Cohort Study, fruit intake was associated with infant cognition and was based on the 5- day method from a modified 174-item, self-reported Food Frequency Questionnaire (15, 16). Studied infant factors included child sex (male or female), gestational age (in weeks), presence of older siblings (yes or no), birth mode (Vaginal-no IAP [intrapartum antibiotic prophylaxis], Vaginal-IAP, CS-elective, CS- emergency), breastfeeding at three months (exclusive breastfeeding, partial breastfeeding, zero, and unknown) and introduction of solid foods at three months of infant age (yes or no).

A Direct Acyclic Graph (DAG) approach was pursued to select a minimal adjustment set of potential confounding factors to test further associations between infant sensitization and child Neurodevelopment (Figure 1; (17)). A DAG gold-standard change-in-estimate procedure was used where covariates were selected by backward elimination from the initial DAG adjusted model (18). The Human Research Ethics Boards at the University of Alberta approved this study (Ethics number Pro00103296).

2.2.1 Food and Atopic Sensitization Assessments

Measures for sensitization were outlined in a previous CHILD Cohort Study paper (19). In our sample, food sensitization was defined as any positive skin prick test to peanut, milk, egg, or soybean allergens. On the other hand, atopic sensitization was defined as any positive skin prick test to test food or aeroallergens. Data from food and atopic sensitization were obtained at 1 year of infant age through a skin prick test (SPT) performed by trained staff with one point of a plastic, bifurcated needle (a Duotip II device by Lincoln Diagnostics), held at a 45◦ angle with the skin plane after complete submersion into an allergen solution. Ten standardized and common food allergens (peanut, soybean, egg white, and cow's milk) and aeroallergens (Alternaria tenuis, cat hair, dog epithelium, *Dermatophagoides pteronyssinus, Dermatophagoides farinae*, German cockroach), a positive control (histamine), and a negative control (glycerin) were tested. As implemented in large-scale infant studies, a wheal size of ≥2 mm in diameter in response to any allergen was considered to indicate positive sensitization for that particular allergen (20). The standard skin prick test procedure that uses a cut-off wheal size ≥3 mm in diameter (21) was also tested in sensitivity analyses.

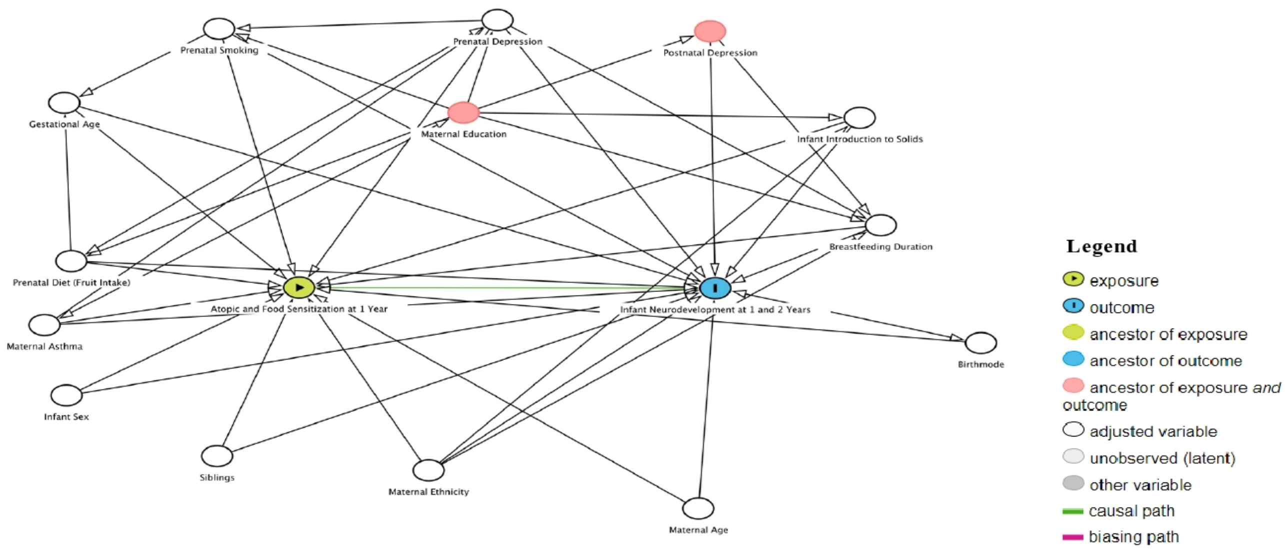
2.2.2 Neurodevelopmental assessments

Infant neurodevelopmental scores were obtained from the Bayley Scale of Infant Development Third Edition (BSIDIII) at 1 year and 2 years of age. Since BSID-III score assessments are unique to the CHILD Cohort Study's Edmonton site, only infants from this location are included in this study. These scores are a validated and objective measure of a child's neurodevelopment, including cognitive, language, motor development, and social-emotional domains (22, 23). Primary caregivers completed BSID-III questionnaires before the child's bedtime. The Cognitive scale (91 items) assesses visual preference, attention, memory, exploration, manipulation, and concept formation. The Language scale assesses receptive communication (49 items) and expressive communication (48 items). The Motor scale assesses gross motor (72 items) and fine motor (66 items) skills. The Cognitive (0.91), Language (0.93), and Motor (0.92) subscales have high-reliability coefficients, and good test-retest stability with coefficients around 0.80 (22, 23). The Social-Emotional scale (35 items) measures six functional and emotional development milestones that are subdivided into different age groups (24). A registered psychologist trained research staff to administer the SID-III instrument and conducted semi-annual assessments. All scores were obtained based on the child's chronological age at testing. Raw scores were converted to scaled scores, and then to composite scores. The standardized population means for the composite score is 100 (standard deviation of 15). A higher score on the BSID-III scales indicates better abilities.

2.3 Statistical analysis

The distribution of one-year atopic and food sensitization status and BSID-III scores across study covariates was determined. Comparisons of categorical variables were made using the Chi-square or Fisher's exact tests. Continuous variables were compared with the t-test if binary and one-way analysis of variance (ANOVA) if more than two categories. ANOVA was also used to compare the means of neurodevelopmental scores from BSID-III subscales by atopic and food sensitization status. Univariable and multivariable linear regressions were conducted to quantify (via beta-coefficients) the association between atopic or food sensitization status and neurodevelopmental scores. Potential confounding factors selected by the DAG approach were retained in multivariable regression models if they met the criterion of 15% change in estimate for atopic or food sensitization. From the minimum DAG set of maternal ethnicity, age, asthma, prenatal depression, prenatal smoking and prenatal diet, infant sex, gestational age, older siblingship, birth mode, breastfeeding duration, and introduction of solid foods (Figure 2.1). Each multivariable model had a unique minimal set of adjustments based on the DAG and 15% backwards selection model building approach (Table S1). Additionally, we have assessed the normality of all BSID-III scores (see attached supplementary FigureS1 and Figure S2).

Figure 2.1. Direct Acyclic Graph (DAG) representing exposure, covariate, and outcome direct associations to select potential confounding factors.



2.4 Results

2.4.1 Participant characteristics

In our study of 537 infants, 52.0% were male, and 56.5% had an older sibling (Table S2). The mean gestational age was 39 weeks (mean = 39.1, SD = 1.4). The majority of their mothers were of Caucasian ethnicity (78.8%), between the ages of 30 to 39 years (68.2%), did not smoke (96.3%), and completed university (55.5%). Most infants were born vaginally, in the absence (52.1%) or presence (23.9%) of intrapartum antibiotic prophylaxis (IAP). At 3 months of age, 58.1% were exclusively breastfed, 27.2% were partially breastfed (breastmilk and formula), and 14.3% were not breastfed; almost all infants (97.6%) were not yet introduced to solid foods. At 1 year of age, atopic sensitization (to food or aeroallergens) was present in 16.4% of infants; the prevalence of food sensitization was 13.4%, making food the predominant allergen for sensitization at this age.

Atopic or food sensitization was more likely among infants of mothers with a university education ($p<0.05$) or Asian ethnicity ($p<0.001$, Table S4). At age one year, language and motor scores increased by 1 point for each week of gestational age; infants of Asian ethnicity had the lowest scores on the cognition, language, and social-emotional domains, and boys had the lowest language scores (Table S5). In addition to gestational age and Asian ethnicity, several more covariates were associated with lower BSID scores at age two years, including male sex (all domains), pre/postnatal maternal depression (social-emotional), lack of breastfeeding (cognitive/language), and absence of siblings (motor, Table S6).

2.4.2 Assessing the association of infant atopic and food sensitization at 1 year with neurodevelopment at one year and two years of age

Mean scores from four neurodevelopmental domains at 1 and 2 years were compared between atopy status. We found no statistically significant differences between atopic or food sensitization at age one year and BSID-III cognitive, language, or motor scores at age one year (Table 1). However, the crude linear regression comparison indicated an inverse association between one-year social-emotional scores and atopic sensitization (4.6 points lower, $p = 0.01$) or food sensitization (4.5 points lower, $p = 0.01$). In male infants (Table 1), these crude differences were of a greater magnitude for atopic sensitization (98.0 versus 104.1, $p = 0.005$) and for food sensitization (98.1 versus 104.0, $p =0.01$). No sensitization differences in BSID-III mean scores were seen among female infants at one year of age. There were no statistically significant crude differences in mean scores between any of the 2-year BSID subscale domains and atopic or food sensitization in 1-year old infants in total or in sex-specific strata (Tables 1, 2). Although lower two-year social-emotional scores were observed for food sensitization in female infants (mean, 105.89 versus 110.75, $p = 0.1$, Table 2.1), this was not statistically significant.

Multivariable regression models revealed that the inverse association between one-year social-emotional scores and food or atopic sensitization remained after adjusting for maternal ethnicity. Specifically, there was a reduction in social-emotional scores among infants who developed atopic (adjusted beta-coefficient: -4.13; 95%CI: -7.41, -0.86) or food sensitization (adjusted beta-coefficient: -4.01; 95%CI: -7.55, -0.47) compared to their infants who did not develop atopic or food sensitization (Figure 2.2, Table 2.2). For sensitization to a food or aeroallergen, this association was limited to male infants (adjusted beta-coefficient: -5.22; 95%CI: -9.96, -0.47) and not found among female infants (adjusted beta-coefficient: -2.92; 95%CI: -7.50, 1.66, Figure 2, Table 2.2). For sensitization to food, the association was also more evident in male infants (adjusted beta-coefficient: -4.85; 95%CI: -9.82, 0.11, p = 0.06) than female infants (adjusted beta-coefficient: -2.82; 95%CI: -8.07, 2.43), although it did not reach statistical significance in either sex (Figure 2, Table 2.2).

In order to strengthen the validity of our results, we conducted a sensitivity analysis for the associations between sensitization and infant neurodevelopment using the standard ≥ 3mm SPT cut-off (Heinzerling et al., 2013). Results from the fully-adjusted model using the conventional ≥ 3mm wheal size also revealed decreased socio-emotional scores for atopic (adjusted beta-coefficient: -4.99; 95%CI: -8.93, -1.04) and food sensitization (adjusted beta-coefficient: -5.22; 95%CI: -9.50, -0.94). Male infants with atopic sensitization remained more affected than their female counterparts (-5.17 [95%CI: -11.14, -0.80], p=0.09 versus adjusted beta-coefficient: -4.21; 95%CI: -9.72, 1.31, respectively). When the standard ≥ 3 mm cut-off for sensitization was used, results were consistent with our findings that used the ≥ 2 mm wheal size — male infants with food sensitization at 1 year had lower, albeit non- significant socio-emotional scores (adjusted beta-coefficient: -4.61; 95%CI: -10.96, 1.74, p = 0.154) than female infants (adjusted beta-coefficient: -4.88 %CI: -11.08, 1.32).

Since non-normal distributions were noted in all four BSID-III subscales for atopy and food sensitization at one year of infant age, we conducted a log transformation of these scores. Our analysis revealed no changes to the significance of the β-coefficients of the transformed variables. For example, the crude socio-emotional scores at 2 years among all infants was not statistically significant (-2.36 [95%CI: -5.98, 1.27], p=0.2) and the same is observed when it was log-transformed (-0.131 [95%CI: -0.347, -0.085], p=0.2). Again, running the same crude analysis with the ≥ 3 mm SPT cut-off also led to a non-significant association between atopy at 1 year and socio-emotional scores at 2 years (- 2.79 [95%CI: -8.29, 2.70], p=0.3) and in a log-transformed model (-0.022 [95%CI: -0.07, -0.03], p=0.4). Using an SPT cut-off of ≥ 3 mm did not produce a statistically significant outcome with any of the other Bayley's III neurodevelopmental subscales.

Consequently, this resulted in no changes to our main findings.

Covariate adjustment did not uncover statistically significant associations between infant atopic or food sensitization, and neurodevelopmental outcomes, with one exception: cognitive and language scores at age 2 were higher in male infants with food sensitization (Table 2.2).

Table 2.1 Comparison of mean scores for neurodevelopmental domains at age 1 and 2 years across atopic and food sensitization status at 1 year, all infants and stratified by infant sex.

All infants

	Atopic sensitization 1YR - **YES** **N=88** **(16.39% overall)** Mean (SD)	Atopic sensitization at 1YR - **NO** **N=449** **(83.61% overall)** Mean (SD)	p-value	Food sensitization 1YR- **YES** **N=72** **(13.41% overall)** Mean (SD)	Food sensitization at 1YR- **NO** **N=465** **(86.59% overall)** Mean (SD)	p-value
Infant neurodevelopment 1YR						
BSID-III cognitive 1 year	109.32 (10.89)	110.18 (10.19)	0.472	108.89 (10.98)	110.22 (10.19)	0.308
BSID-III language 1 year	107.37 (9.89)	107.95 (12.34)	0.679	107.75 (9.48)	107.87 (12.32)	0.935
BSID-III motor 1 year	101.58 (12.28)	102.80 (15.08)	0.474	101.36 (12.42)	102.80 (14.97)	0.440
BSID-III social-emotional 1 year	98.76 (10.94)	103.36 (14.23)	**0.005**	98.71 (11.15)	103.21 (14.13)	**0.011**
Infant neurodevelopment 2YR						
BSID-III cognitive 2 year	105.51 (14.24)	105.80 (14.37)	0.865	105.76 (14.72)	105.74 (14.29)	0.992
BSID-III language 2 year	99.80 (12.40)	100.24 (11.97)	0.752	99.89 (12.26)	100.21 (12.01)	0.834
BSID-III motor 2 year	98.74 (9.33)	98.94 (9.53)	0.856	99.01 (9.73)	98.89 (9.46)	0.918
BSID-III social-emotional 2 year	106.72 (14.74)	109.08 (15.90)	0.202	106.69 (14.97)	109.00 (15.84)	0.250

Sex stratified

	Female infants				**Male infants**			
	Atopic sensitization 1YR - **YES** **N=40 (7.45% among all infants)** Mean (SD)	Atopic sensitization at 1YR - **NO** **N=218 (40.60% among all infants)** Mean (SD)	Food sensitization 1YR - **YES** **N=28 (5.21% among all infants)** Mean (SD)	Food sensitization at 1YR - **NO** **N=230 (42.83% among all infants)** Mean (SD)	Atopic sensitization 1YR - **YES** **N=48 (8.94% among all infants)** Mean (SD)	Atopic sensitization at 1YR - **NO** **N=231 (43.02% among all infants)** Mean (SD)	Food sensitization 1YR - **YES** **N=235 (43.76 % among all infants)** Mean (SD)	Food sensitization at 1YR - **NO** **N=44 (8.19% among all infants)** Mean (SD)
Infant neurodevelopment 1YR								
BSID-III cognitive 1 year	109.88 (7.72)	110.75 (10.14)	109.64 (7.06)	110.73 (10.9)	98.04 (11.38)	104.12 (14.62)	108.41 (12.93)	109.72 (10.29)
BSID-III language 1 year	107.78 (9.05)	110.13 (12.01)	108.82 (7.07)	109.88 (12.06)	107.02 (10.63)	105.89 (12.32)	107.05 (10.78)	105.91 (12.27)
BSID-III motor 1 year	100.15 (11.39)	103.66 (15.63)	99.29 (11.54)	103.58 (15.42)	102.77 (12.97)	12.00 (14.53)	102.68 (12.90)	102.03 (14.52)
BSID-III social-emotional 1 year	99.62 (10.47)	102.54 (13.78)	99.64 (10.09)	102.39 (13.69)	98.04 (11.38)	**104.12** (14.62)	98.10 (11.89)	**104.00** (14.52)
Infant neurodevelopment 2YR								
BSID-III cognitive 2 year	107.88 (12.90)	108.42 (15.24)	108.57 (12.83)	108.30 (15.13)	103.54 (15.12)	103.32 (13.06)	103.98 (15.69)	103.24 (12.97)
BSID-III language 2 year	101.50 (10.71)	103.76 (11.49)	101.18 (9.21)	103.69 (11.61)	98.38 (13.58)	96.93 (11.48)	99.07 (13.90)	96.82 (11.43)
BSID-III motor 2 year	99.45 (9.12)	99.9 (9.53)	99.79 (9.62)	99.88 (9.46)	98.15 (9.55)	97.99 (9.45)	98.52 (9.88)	97.92 (9.39)
BSID-III social-emotional 2 year	107.38 (11.71)	110.74 (15.69)	105.89 (11.14)	110.75 (15.53)	106.17 (17.01)	107.49 (15.98)	107.21 (17.12)	107.27 (15.99)

Note: SD= standard deviation; Statistical comparison of means completed by ANOVA. [a]Bold values are statistically significant

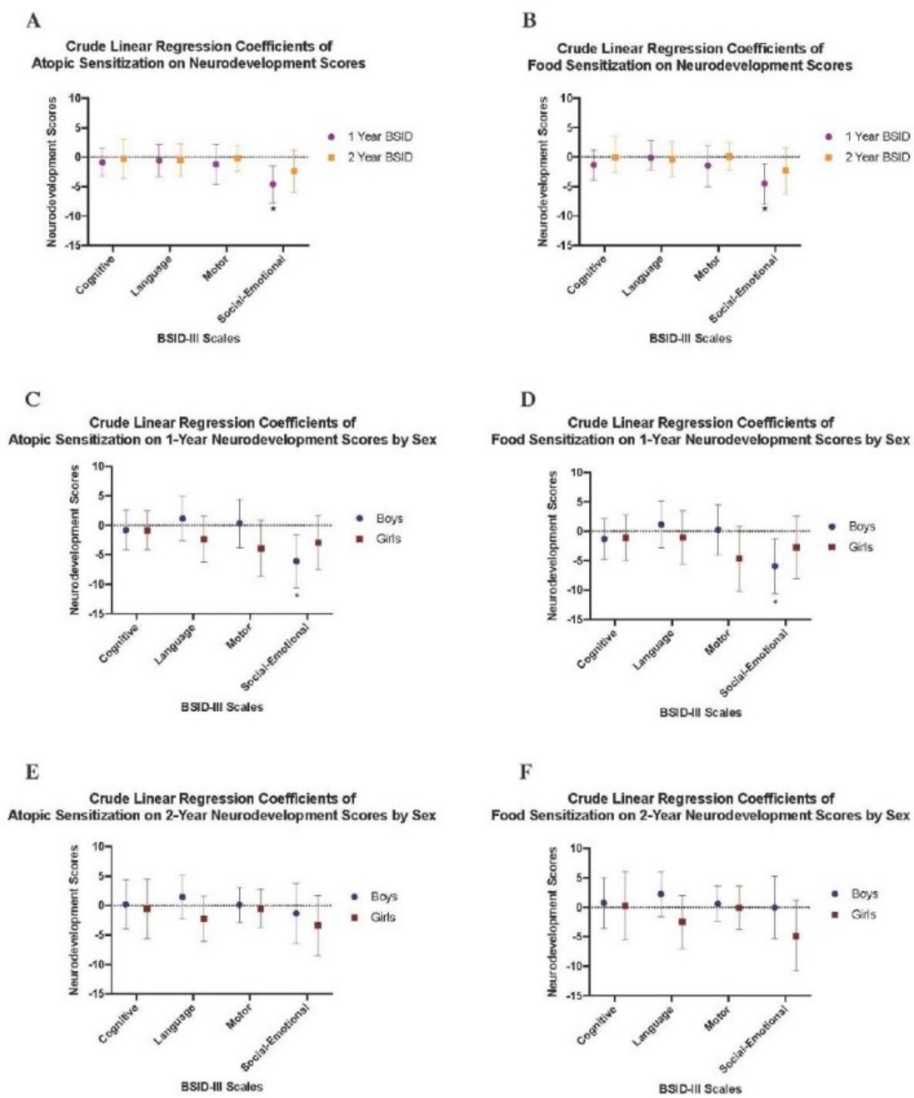
Table 2.2 Univariate and multivariate linear regression for sensitization at 1 year versus social-emotional scores at 1 and 2 years, all infants and stratified by infant sex (N=537).

		Atopic Sensitization Multivariate Model Adjustments - All Infants		
BSID - III Scores at 1YR	**Crude Estimate (95% CI)**	**p-value**	**Fully-Adjusted Model Estimate (95% CI)**	**p-value**
Cognitive 1-Year	-0.86 (-3.22, 1.50)	0.47	0.441 (-2.17, 3.05)	0.74
Language 1-Year	-0.58 (-3.34, 2.18)	0.68	0.64 (- 2.25, 3.54)	0.66
Motor 1-Year	-1.22 (-4.58, 2.13)	0.47	-1.93 (-5.06, 1.20)	0.23
Social-Emotional 1-Year	-4.59 (-7.80, -1.39)	**0.01**	-4.13 (-7.41, -0.86)	**0.01**
BSID - III Scores at 2YR	**Crude Estimate (95% CI)**	**p-value**	**Fully-Adjusted Model Estimate (95% CI)**	**p-value**
Cognitive 2-Year	-0.28 (-3.57, 3.00)	0.87	1.99 (-1.74, 5.72)	0.30
Language 2-Year	-0.44 (-3.20, 2.31)	0.75	2.17 (-0.78, 5.11)	0.15
Motor 2-Year	-0.20 (-2.38, 1.97)	0.86	0.89 (-1.49, 3.27)	0.24
Social-Emotional 2-Year	-2.36 (-5.98, 1.27)	0.20	-0.61 (-4.43, 3.21)	0.76
		Food Sensitization Multivariate Model Adjustments - All Infants		
BSID - III Scores at 1YR	**Crude Estimate (95% CI)**	**p-value**	**Fully-Adjusted Model Estimate (95% CI)**	**p-value**
Cognitive 1-Year	-1.33 (-3.89, 1.23)	0.31	-0.27 (-2.90, 2.36)	0.84
Language 1-Year	-0.12 (-3.12, 2.87)	0.94	0.76 (-2.36, 3.89)	0.63
Motor 1-Year	-1.43 (-5.08, 2.21)	0.44	-2.37 (-5.77, 1.03)	0.17
Social-Emotional 1-Year	-4.50 (-7.97, -1.02)	**0.01**	-4.01 (-7.55, -0.48)	**0.03**
BSID - III Scores at 2YR	**Crude Estimate (95% CI)**	**p-value**	**Fully-Adjusted Model Estimate (95% CI)**	**p-value**
Cognitive 2-Year	0.02 (-3.55, 3.59)	0.99	2.28 (-1.74, 6.30)	0.27
Language 2-Year	-0.32 (-3.32, 2.68)	0.83	2.19 (-1.00, 5.38)	0.18
Motor 2-Year	0.12 (-2.24, 1.49)	0.92	1.25 (- 1.33, 3.83)	0.34
Social-Emotional 2-Year	-2.31 (-6.25, 1.63)	0.25	-0.59 (-4.72, 3.54)	0.78
		Atopic Sensitization Multivariate Model Adjustments - Male Infants		
BSID - III Scores at 1YR	**Crude Estimate (95% CI)**	**p-value**	**Fully-Adjusted Model Estimate (95% CI)**	**p-value**
Cognitive 1-Year	-0.80 (-4.15, 2.56)	0.64	0.80 (-3.06, 4.66)	0.68
Language 1-Year	1.13 (-2.67, 4.93)	0.56	2.49 (-1.68, 6.65)	0.24
Motor 1-Year	0.37 (-3.73, 4.48)	0.73	-0.02 (-4.17, 4.13)	0.99
Social-Emotional 1-Year	-6.08 (-10.58, -1.58)	**0.01**	-5.22 (-9.96, -0.47)	**0.03**
BSID - III Scores at 2YR	**Crude Estimate (95% CI)**	**p-value**	**Fully-Adjusted Model Estimate (95% CI)**	**p-value**
Cognitive 2-Year	0.22 (-3.97, 4.42)	0.92	4.53 (-0.49, 9.54)	0.08
Language 2-Year	1.45 (-2.26, 5.15)	0.44	5.40 (1.22, 9.58)	**0.01**
Motor 2-Year	0.15 (-2.80, 3.11)	0.92	1.61 (-1.83, 5.04)	0.36

Social-Emotional 2-Year	-1.32 (-6.42, 3.78)	0.61	1.79 (-3.95, 7.52)	0.54
Food Sensitization Multivariate Model Adjustments - Male Infants				
BSID - III Scores at 1YR	**Crude Estimate (95% CI)**	**p-value**	**Fully-Adjusted Model Estimate (95% CI)**	**p-value**
Cognitive 1-Year	-1.31 (-4.78, 2.16)	0.46	1.15 (-2.59, 4.89)	0.55
Language 1-Year	1.14 (-2.80, 5.08)	0.57	2.30 (-2.08, 6.68)	0.30
Motor 1-Year	0.26 (-4.00, 4.51)	0.78	-0.19 (-4.48, 4.11)	0.93
Social-Emotional 1-Year	-5.91 (-10.59, - 1.23)	**0.01**	-4.85 (-9.82, -0.11)	0.06
BSID - III Scores at 2YR	**Crude Estimate (95% CI)**	**p-value**	**Fully-Adjusted Model Estimate (95% CI)**	**p-value**
Cognitive 2-Year	0.73 (-3.61, 5.08)	0.74	5.53 (0.34, 10.72)	**0.04**
Language 2-Year	2.25 (-1.58, 6.08)	0.25	6.54 (2.23, 10.85)	**0.00**
Motor 2-Year	0.60 (-2.46, 3.66)	0.70	2.25 (-1.32, 5.82)	0.22
Social-Emotional 2-Year	-0.06 (-5.35, 5.23)	0.98	3.57 (-2.39, 9.53)	0.24
Atopic Sensitization Multivariate Model Adjustments- Female Infants				
BSID - III Scores at 1YR	**Crude Estimate (95% CI)**	**p-value**	**Fully-Adjusted Model Estimate (95% CI)**	**p-value**
Cognitive 1-Year	-0.87 (-4.20, 2.45)	0.61	-0.15 (-3.78, 3.48)	0.94
Language 1-Year	-2.35 (-6.29, 1.58)	0.24	-1.40 (-5.43, 2.62)	0.49
Motor 1-Year	-3.92 (-8.67, 0.83)	0.18	-4.36 (-9.22, 0.50)	0.08
Social-Emotional 1-Year	-2.92 (-7.50, 1.66)	0.21	-2.99 (-7.57, 1.58)	0.20
BSID - III Scores at 2YR	**Crude Estimate (95% CI)**	**p-value**	**Fully-Adjusted Model Estimate (95% CI)**	**p-value**
Cognitive 2-Year	-0.54 (-5.59, 4.51)	0.83	-0.82 (-6.34, 4.71)	0.77
Language 2-Year	-2.26 (-6.12, 1.59)	0.25	-1.17 (-5.09, 2.75)	0.56
Motor 2-Year	-0.49 (-3.70, 2.71)	0.76	0.09 (-3.34, 3.51)	0.96
Social-Emotional 2-Year	-3.37 (-8.51, 1.77)	0.20	-1.96 (-7.28, 3.37)	0.47
Food Sensitization Multivariate Model Adjustments - Female Infants				
BSID - III Scores at 1YR	**Crude Estimate (95% CI)**	**p-value**	**Fully-Adjusted Model Estimate (95% CI)**	**p-value**
Cognitive 1-Year	-1.09 (-4.95, 2.78)	0.58	-1.36 (-5.29, 2.57)	0.50
Language 1-Year	-1.06 (-5.64, 3.53)	0.65	-0.70 (-5.32, 3.92)	0.77
Motor 1-Year	-4.68 (-10.21, 0.85)	0.16	-5.54 (-11.15, 0.07)	0.05
Social-Emotional 1-Year	-2.74 (-8.02, 2.53)	0.31	-2.82 (-8.07, 2.43)	0.29
BSID - III Scores at 2YR	**Crude Estimate (95% CI)**	**p-value**	**Fully-Adjusted Model Estimate (95% CI)**	**p-value**
Cognitive 2-Year	0.27 (-5.61, 6.40)	0.93	-1.06 (-7.43, 5.31)	0.74
Language 2-Year	-2.51 (-6.99, 1.98)	0.27	-1.91 (-6.46, 2.63)	0.41
Motor 2-Year	-0.09 (-3.83, 3.64)	0.96	0.52 (-3.44, 4.49)	0.80
Social-Emotional 2-Year	-4.86 (-10.82, 1.11)	0.11	-3.71 (-9.80, 2.38)	0.23

Note: Bolded p-values are statistically significant

Figure 2.2 Crude linear regression models demonstrating (A) Crude models of atopic sensitization at 1 year on neurodevelopment scores at 1 and 2 years; (B) Food sensitization at 1 year on neurodevelopment scores at land 2 years; (C) Atopic sensitization at 1 year on neurodevelopment scores at 1 year stratified by child sex; (D) Food sensitization at 1 year on neurodevelopment scores at 1 year stratified by child sex; (E) Atopic sensitization at 1 year on neurodevelopment scores at 2 years stratified by child sex; and (F) Food sensitization at 1 year on neurodevelopment scores at 2 year stratified by child sex. Crude regression coefficient estimates are shown by closed circles and whiskers represent the 95% confidence interval.



3.0 Discussion

In a general population of 537 Canadian infants, there was no convincing evidence of temporal associations between IgE-mediated atopy or food sensitization status at 1 year and neurodevelopmental outcomes at 2 years of age. These findings concur with the reported absence of association between 12-month atopic or food sensitization and BSID-III neurodevelopment milestones at 18 months in a high-allergyrisk Australian cohort (13), as well as between infant serum IgE levels during the 1st years of life and attention deficit disorders at school age in a general population US cohort (25). Also, we did not find correlational associations between atopy status and neurodevelopment in 1-year-old children, with one exception. Independent of maternal ethnicity, infants with atopic sensitization had reduced scores by 4.13 points ($p = 0.01$) on the social-emotional domain of Bayley's scales compared to their infant counterparts who were not atopic. Similarly, the infants experiencing food sensitization also exhibited 4- point lower social-emotional scores than the infants who did not have food sensitization ($p = 0.03$). However, all of these associations were limited to male infants, such that socialemotional scores were lowered by 5 points if atopic sensitization was present (−5.22 (95% CI: −9.96, −0.47)] and, similarly, if food sensitization was present [−4.85 (95% CI: −9.82, 0.11), $p = 0.06$]. No cross-sectional associations were found in the female infants, and their social-emotional scores were equivalent to that of the male infants. The social-emotional subscale evaluates an infant's interaction, emotionality, self-regulation, and reactivity (26). It is a strong predictor of future behavioral or emotional disorders in childhood and academic achievement in later life (26, 27). We will consider possible bi-directional explanations for our findings in the following paragraphs.

Indeed, the cross-sectional nature of the atopy-socioemotional development association would not support a causal hypothesis put forward by Chua et al. (10), which points to evidence on temporal associations and common risk factors between atopic conditions and neurodevelopment disorders. The association was not affected by study covariates and possibly acted through factors we did not measure. Mikkelsen et al. (28) reported that food sensitization in infants, for example, to milk, presents challenges and induces stress for new parents as they attempt to feed their infant. Such stressful environments may impact negatively on infant social-emotional development scores. Indeed, this has been reported in preterm and term infants, where studies document the influence of parental postnatal stress or a lack of positive affect on the socio-emotional development of offspring (29, 30). Finally, we observed lower but not statistically significant socialemotional scores at age 2 years in female infants with food sensitization, which appears to be a similar trend to that reported among 1-year-old infants with food allergy in the Australian cohort (13).

An alternate speculation involves reverse causation in which socio-emotional impairment, secondary to a stressful environment, is in the pathway to atopic or food sensitization. Stressors for infants, such as low maternal sensitivity or psychological distress, have been linked to atopic dermatitis (31) and functional gastrointestinal disorders (32). A mother's distress while breastfeeding can alter milk microbiota (33) or lower milk secretory immunoglobulin A (34), both of which affect infant gut immunity (35). Hence, impaired mother-infant feeding or social interactions may lower socioemotional responses in the infant (36) and, via the gutbrain axis, lead to food intolerance (37). Since parentchild interactions, namely strategies for infant soothing, were not assessed in our study, we are unable to offer explanations for the unexpected findings on food sensitization and improved cognition or language in boys. Parent use of strategies, such as cuddling to soothe fussy infants, may change electrocortical rhythms in the infant's brain toward improved neurodevelopmental outcomes (38). A detailed assessment of infant stress responses in studies of atopic disease and neurodevelopmental outcomes is needed to unpack these associations.

Furthermore, we believe that gender bias may also influence our male-specific findings that are worthy of further investigation. Globally, research reporting parental gender bias is becoming well established. For example, a study in Germany revealed that male children of parents who believe girls are better at reading exhibited lower readingrelated competence beliefs and were discouraged from reading (39). Consistent with this research, a study in Bangladesh demonstrates that more parents invest in their male children's education and health expenses than their female offsprings (40). Research from Balkan and Scandinavian countries confirms these findings that biased parents allocate greater resources to children of their preferred gender (41). Overall, these studies demonstrate the need to address gender bias in pediatric research as it appears to impair critical areas of child development.

There are several strengths of our study: (i) objective and standard assessment of atopic sensitization in infants with skin prick testing, (ii) objective assessment of neurodevelopment by experts using a well-validated and widely-used standardized measure, (iii) neurodevelopmental assessment at two-time points to enable testing of cross-sectional and temporal associations, and (iv) large sample size in a general population of children that enabled adjustment for early life covariates that were determined from the construction of a direct acyclic graph (DAG). On the other hand, we had no information on whether the study infants with food sensitization had clinically significant signs and symptoms of food allergy, a critical element for proposed hypotheses for our findings. However, their parents would likely have seen the skin wheal reactions to the skin prick testing. We were also unable to examine the infants at high risk for neurodevelopmental morbidity as the CHILD Cohort Study excluded preterm birth below 34 weeks of gestation. Other high-risk groups under-represented in our study were families of low socioeconomic status. Further studies are required to investigate the generalizability of our findings to other populations.

4.0 Conclusion

In our study, atopic and food sensitization at one year did not predict neurodevelopmental outcomes at 2 years of age. However, atopic and food sensitization status at one year was cross-sectionally associated with reduced social- emotional scores among male infants. We speculated on bidirectional associations that may explain this inverse association. Since mother-infant interactions play a critical role in the socio-emotional development of infants, our study supports the need for additional research on maternal and infant risk factors between atopic and food sensitization and neurodevelopmental disorders. Possible biologic pathways that explain associations between atopic and food sensitization on infant neurodevelopment also merit further evaluation. Click or tap here to enter text.

5.0 Acknowledgement

We thank the CHILD Cohort Study (CHILD) participant families for their dedication and commitment to advancing health research. CHILD was initially funded by CIHR and AllerGen NCE. Visit CHILD at childcohort.ca. (16)

6.0 Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

7.0 Funding

The Canadian Institutes of Health Research and the Allergy, Genes, and Environment (AllerGen) Network of Centres of Excellence provided initial funding for the CHILD Cohort

Study. This research was part of the Edmonton-site Sleep and Neurodevelopment substudy, supported by grant number #211722 from The Canadian Institutes of Health Research and by the Women and Children's Health Research Institute. These entities had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

CHAPTER 3. Sex-dependent patterns in the association of maternal atopy and infant neurodevelopmental scores

3.1 Introduction

Neurodevelopmental disorders (NDD) in children including autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) account for 7% to 14% of all children in developed countries and pose a significant burden in the health system and the quality of life of many families ((17,18). Factors that give rise to developmental impairments include genetic, biological, and environmental influences – among which, maternal immune factors during pregnancy are proposed to play a strong role in shaping infant neurodevelopmental outcomes ((19).

In particular, the role of inflammatory disorders, including maternal asthma and allergic status in mothers during NDD pathogenesis is an emerging area of research. Maternal atopic status indicates an underlying immune dysregulation, effects of which may be transduced to the fetus through inflammatory cell signaling pathways and epigenetic mechanisms (19). Since key neuronal networks are being rapidly established during this critical window of early infant development, maternal stress and adverse immune reactions can impair typical developmental trajectory and lead to long-term negative effects (20–25). In animal models, maternal inflammatory response during pregnancy alters offspring brain function independent of pathogens and other risk factors (23). For example, rodent models showed that offspring exposed to maternal infection during pregnancy had abnormalities in brain morphology and possess behavioral characteristics like those with ASD (26). Another study in primates described significant volume decrease in the frontal lobe and defects in cognitive functioning in those whose mothers are immune compromised (27).

In humans studies, parental history of allergies remains to be one of the strongest and well-established predictors of subsequent allergic disease in the offspring (28). A meta-analysis revealed that maternal asthma predisposes their child to asthma and greater risks of wheezing (29,30). Another systematic review indicated that parental history of atopic disease increases the risk of atopic dermatitis and allergic rhinitis in children, with the risk being higher in those whose parents have multiple atopic conditions (28,31)

On the other hand, studies specifically examining the association between maternal atopic conditions and alterations in infant neurodevelopment remains limited. A comprehensive systematic review and meta-analysis highlight that those with atopic diseases have 30-50% greater risk of developing ADHD (32). Other research studies provided evidence for maternal asthma increasing the risk of ADHD and comorbid maternal asthma and allergies increasing the risk of ASD in the offspring (33,34). Researchers even argue that the effects of maternal allergy on child neurodevelopment follow sex-specific patterns. For example, ADHD risk of infants born to mothers with atopic disease was found to be higher in female than male infants (35).

Despite growing research efforts on exploring the associations between maternal atopic status and infant neurodevelopment, research investigating possible mechanisms that explain these relationships remain scarce. We extend this research by assessing: (i) the associations between combined maternal atopic conditions and subsequent infant neurodevelopmental scores, (ii) the association between maternal asthma and infant neurodevelopmental scores, and (iii) exploring mediators in these associations.

3.2 Methods

3.2.1 Study Design

Similar to the first study assessing the effect of infant atopic status on child neurodevelopment, our second study also accessed data from the CHILD birth cohort (www.childstudy.ca) consisting of 335 infants from the Edmonton site. Neurodevelopmental scores as measured by Bayley Scale of Infant Development Third Edition (BSID-III) are specific only to the Edmonton site. The CHILD birth cohort recruited pregnant women aged ≥18 years who delivered singleton infants at ≥35 weeks of gestational age and a birthweight of ≥2500 g. Multiple gestation, in vitro fertilized births, and preterm births were excluded, as were children born with major congenital abnormalities or respiratory distress syndrome. Mothers were followed throughout pregnancy, atopic and food sensitization were both assessed at one year of infant age, and infant neurodevelopmental scores at ages one and two years. Study covariates were collected from study questionnaires during pregnancy and at 3 months postpartum and/or hospital birth records. They consisted of the following maternal factors: maternal ethnicity (White Caucasian, Asian, Other), maternal age (18 to 29, 30 to 39, over 40), maternal education (some/finished high school, some university/college, university degree), asthma treatment during pregnancy (yes or no), prenatal smoking (yes or no), and maternal depression (never, prenatal, postnatal, persistent). Maternal diet was also included and was based on the prenatal fruit intake ("5-a-day" method), which measures the sum of "servings of fruit, not including juices, "plus servings of juice" per day (Kristal et al., 2000). In the CHILD Cohort Study, fruit intake was found to be associated with infant cognition and was based on the 5-day method from a modified

174-item, self-reported Food Frequency Questionnaire (Bolduc et al., 2016; Kristal et al., 2000). Studied infant factors included child sex (male or female), gestational age (in weeks), presence of older siblings (yes or no), birth mode (Vaginal-no IAP [intrapartum antibiotic prophylaxis], Vaginal-IAP, CS-elective CS-emergency), breastfeeding at 3 months (exclusive breastfeeding, partial breastfeeding, zero, and unknown) and introduction of solid foods at 3 months of infant age (yes or no).

3.2.2 Using DAG to identify covariates

A Direct Acyclic Graph (DAG) approach was pursued to select a minimal adjustment set of potential confounding factors to further test associations between infant sensitization and child Neurodevelopment (Figure 1) (128). A DAG gold-standard change-in-estimate procedure was used where covariates were selected by backward elimination from the initial DAG adjusted model (129). The Human Research Ethics Boards at the University of Alberta approved this study (Ethics number Pro00103296).

3.2.3 Maternal Atopic Status Assessments

Detailed questionnaires on key maternal covariates, including maternal asthma and other diagnoses of atopic conditions were administered at recruitment and is again completed at 1 year of infant age (36). Combined maternal atopy is defined as the presence of any allergic condition in addition to maternal asthma; while maternal asthma indicates a diagnosis of asthma without any comorbid allergic conditions.

3.3.4 Neurodevelopmental Assessments

Infant neurodevelopmental scores were obtained from the Bayley Scale of Infant Development Third Edition (BSID-III) at one year and two years of age. BSID III is a validated and objective measure of a child's neurodevelopment, including cognitive, language, motor development, and social-emotional domains (131,132). Primary caregivers completed BSID-III questionnaires before the child's bedtime. The Cognitive scale (91 items) assesses visual preference, attention, memory, exploration, manipulation, and concept formation. The Language scale assesses receptive communication (49-items) and expressive communication (48-items).

The Motor scale assesses gross motor (72-items) and fine motor (66-items) skills. The Cognitive (0.91), Language (0.93), and Motor (0.92) subscales have high-reliability coefficients, and good test-retest stability with coefficients around 0.80 (132). The Social-Emotional scale (35 items) measures six functional emotional development milestones that are subdivided into different age groups (Tede et al., 2016). A registered psychologist trained research staff to administer the BSID-III instrument and conducted semi-annual assessments. All scores were obtained based on the child's chronological age at the time of testing. Raw scores were converted to scaled scores, then to composite scores. The standardized population mean for the composite score is 100 (standard deviation of 15). A higher score on the BSID-III scales indicates better abilities.

3.3 Statistical Analysis

3.3.1 Evaluating the association between maternal atopy and infant neurodevelopmental scores

The distribution of one-year atopic and food sensitization status, and BSID-III scores across study covariates was determined. Comparisons of categorical variables were made with use of the Chi-square or Fisher's exact tests. Continuous variables were compared with the t-test if binary and one-way analysis of variance (ANOVA) if more than 2 categories. ANOVA was also used to compare the means of neurodevelopmental scores from BSID-III subscales by maternal atopy status (Table 3.4). Univariable and multivariable linear regressions were conducted to quantify (via beta-coefficients) the association between atopic or food sensitization status and neurodevelopmental scores. Potential confounding factors selected by the DAG approach were retained in multivariable regression models if they met the criterion of 15% change in estimate for atopic or food sensitization. From the minimum DAG set of maternal ethnicity, age, asthma, prenatal depression, prenatal smoking and prenatal diet, infant sex, gestational age, older siblingship, birth mode, breastfeeding duration, and introduction of solid foods (Figure 1). Each multivariable model had a unique minimal set of adjustments based on the DAG and 15% backwards selection model building approach.

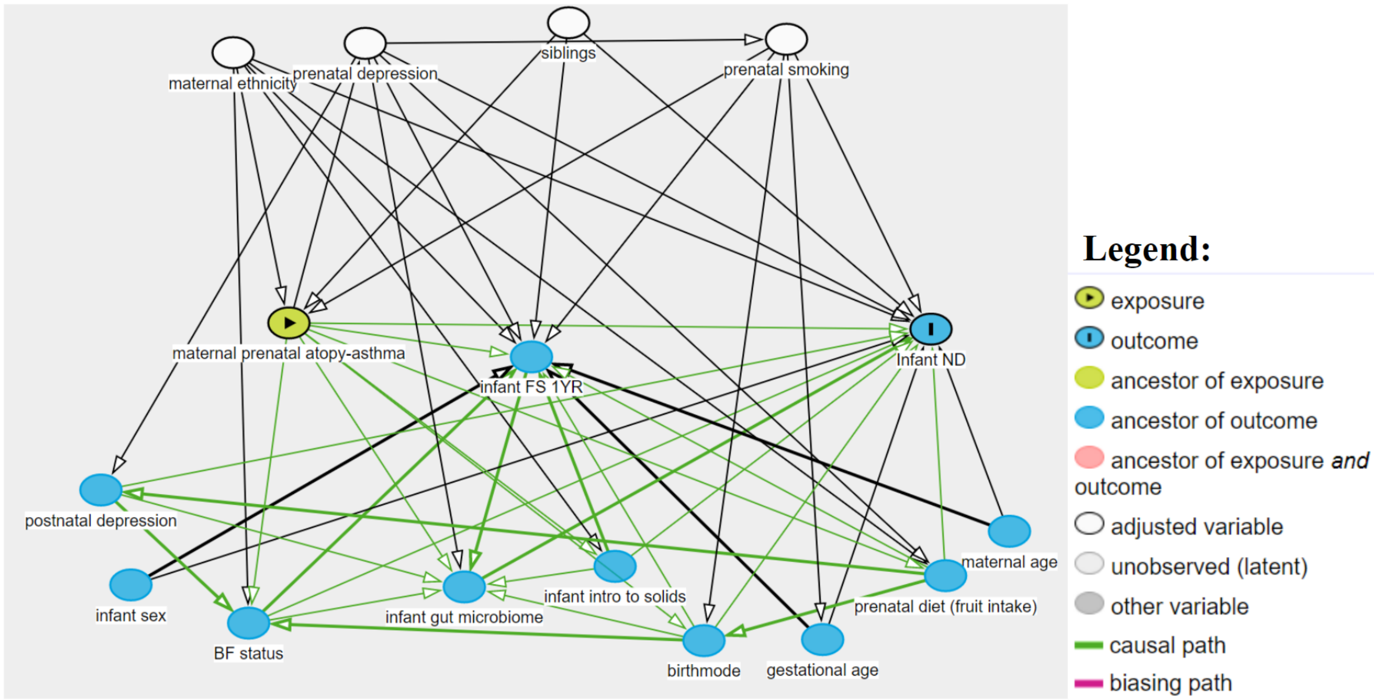
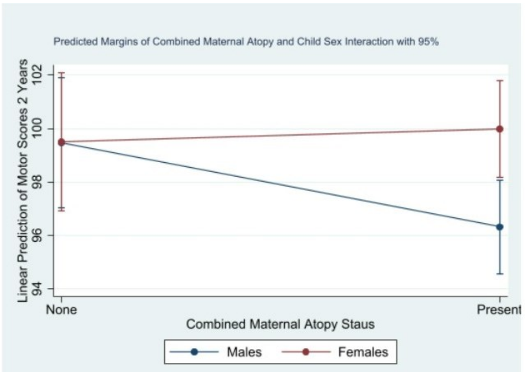


Figure 3.1 DAG exploring the association between maternal atopy status and infant neurodevelopment

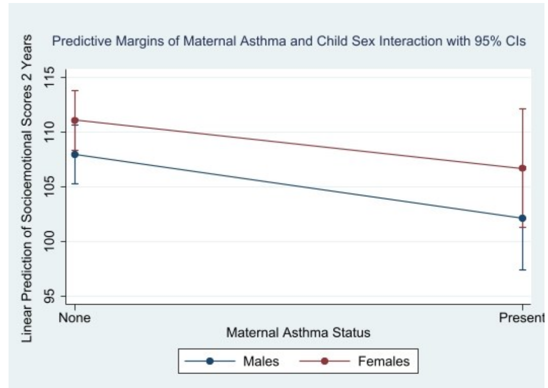
3.3.2 Assessing the interaction effect of infant sex in the association between maternal atopy and infant neurodevelopmental scores

Since several research studies observe a sex-dependent patterns on the effect of prenatal immune disorders (37–40), including maternal on infant gut and psychiatric health, we tested interaction effects of infant sex in our model where maternal atopy is the exposure and neurodevelopmental scores is the outcome (Figure 3.2).

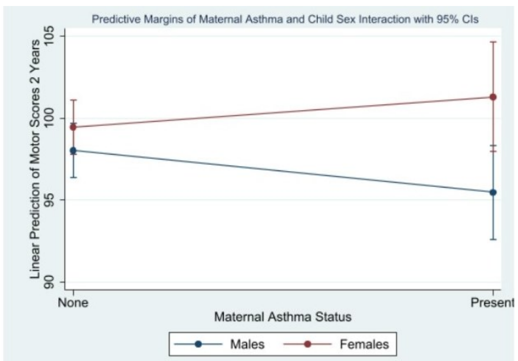
A.



C.



B.



D.

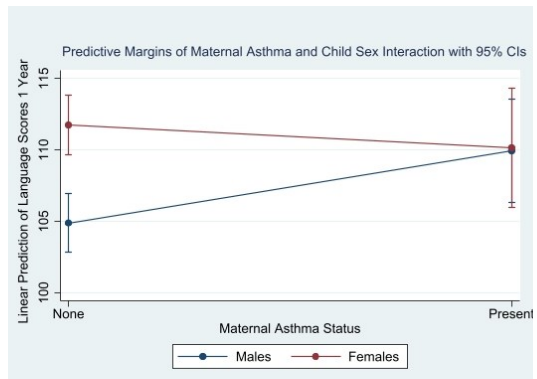


Figure 3.2 Evaluating the interaction effect of infant sex in the association between maternal atopy and infant neurodevelopmental scores. Note that the above only displays results for infant scores that showed a statistically significant interaction between the exposure and outcome.

3.3.3 Testing the potential mediating role of the infant gut microbiome

Mediation tests whether the association between the exposure and outcome (ie. known as the direct effect) can be explained via intermediates or mediators within the temporal pathway (133). The causal steps strategy developed by Baron and Kenny in 1986 and the product of coefficients approach will be applied to assess mediation results. To perform structural equation models in STATA, mediators and outcomes in the model must be in their linear form (41).

In particular, the exposures for the analysis are maternal atopic status and the outcome is the infant neurodevelopmental scores (cognitive, language, socio-emotional, and motor scores) at 1 and 2 years of age. Potential infant gut microbiome mediators from fecal samples taken from home assessments at 1 year of infant age include the gut microbiome in the phylum and order level and the relative abundance of short-chain fatty acids (SCFAs). Regression models will be performed to identify microbial mediators that have significant crude associations with maternal atopy and infant neurodevelopmental scores. If an infant gut microbial passes the Baron and Kenney mediation criteria – that is, it produces a significant association with maternal atopy and neurodevelopmental scores, then their effect will be further analyzed using sequential mediation models.

In our study, a multiple mediator path model was used to examine indirect associations of prenatal depression at 36 weeks (mediator 1) and α diversity or relative abundance of microbiota of the infant gut at the phylum and order level (mediator 2). To generate 95% Cis in mediation models, bootstrapping, which is a nonparametric resampling technique (1000 bootstrap resamples) was applied.

3.4 Results

3.4.1 Participant characteristics

In our study of 337 infants, 51.6% were male, and 48.4% were female (Table 3.3). The mean gestational age was 39 weeks (mean = 39.1, SD = 1.4). Most of the mothers were of Caucasian ethnicity (81.8%), between the ages of 30 to 39 years (67.5%), did not smoke (95.5%), and completed university (53.0%). Most infants were delivered vaginally, in the absence (54.7%) or presence (21.8%) of intrapartum antibiotic prophylaxis (IAP). At 3 months of age, 58.0% were exclusively breastfed, 31.0% were partially breastfed (breastmilk and formula), and 17.9% were not breastfed. Additionally, almost all infants (97.3%) were not yet introduced to solid foods. At 1 year of age, 66.6% of infants were born to mothers with combined atopic status (any diagnosed allergy or asthma); and the prevalence of maternal asthma alone was 22.4%.

Combined maternal atopy is more likely among mothers with White Caucasian ethnic backgrounds ($p<0.10$, Table 3.4). Additionally, mothers with combined atopic status are more likely to give birth vaginally without IAP ($p<0.10$, Table 3.4).

3.4.2 Assessing the crude linear regression associations of maternal atopy status and maternal asthma with neurodevelopment at one year and two years of infant age

In the crude linear regression models of maternal atopy, there were no statistically significant associations between combined maternal atopic status and infant neurodevelopment scores at 1 or 2 years (Table 3.1, Table 3.2). However, when stratified into male and female infant sex, crude models showed that cognitive and motor scores at 2 years are associated with combined maternal atopic status in male infants; and combined maternal atopy is associated with female cognitive scores at 2 years for female infants. Specifically, a marginal, inverse association is observed between male cognitive scores at 2 years and combined maternal atopy (3.8 points lower, $p = 0.07$; Table 3.2); while a significant association is observed in male infant motor scores at 2 years (3.17 points lower, $p = 0.04$; Table 3.2). In contrast, female infants experience a marginal increase in 2-year cognitive scores if their mothers have combined atopic disease (4.21 points higher, $p = 0.07$; Table 3.2).

Table 3.1 Comparison of mean scores for neurodevelopmental domains at age 1 and 2 years across combined maternal atopy and maternal asthma status at 1 year, all infants and stratified by infant sex.

All infants

	Combined Maternal Atopy 1YR - **YES**	Combined Maternal Atopy at 1YR - **NO**	p-value	Maternal Asthma 1YR- **YES**	Maternal Asthma at 1YR- **NO**	p-value
	N=223 (66.57% overall) Mean (SD)	**N=112 (33.43% overall)** Mean (SD)		**N=75 (22.39% overall)** Mean (SD)	**N=260 (77.61% overall)** Mean (SD)	
Infant neurodevelopment 1YR						
BSID-III cognitive 1 year	110.4395 (10.12777)	110.8482 (11.2684)	0.738	110.954 (10.758)	109.267 (9.54)	0.221
BSID-III language 1 year	109.4279 (12.32889)	107.2857 (12.21241)	0.134	108.328 (12.263)	110.027 (12.477)	0.294
BSID-III motor 1 year	103.6188 (17.17984)	101.8393 (13.24445)	0.337	102.408 (16.325)	105.16 (14.594)	0.189
BSID-III social-emotional 1 year	102.2897 (12.69506)	102.0909 (14.50058)	0.899	101.833 (13.343)	103.562 (13.215)	0.33
Infant neurodevelopment 2YR						
BSID-III cognitive 2 year	105.3453 (14.45596)	105.2232 (12.45512)	0.939	105.135 (13.841)	105.893 (13.735)	0.676
BSID-III language 2 year	100.3767 (12.20367)	99.81982 (10.70361)	0.683	100.158 (11.811)	100.307 (11.445)	0.539
BSID-III motor 2 year	98.10314 (9.620883)	99.48214 (9.690696)	0.218	98.738 (9.647)	97.96 (9.709)	0.923
BSID-III social-emotional 2 year	108.6136 (16.21096)	107.7477 (15.07163)	0.639	109.533 (15.662)	**104.122 (15.754)**	**0.009****

Sex stratified

	Female infants				**Male infants**			
	Combined Atopy 1YR - **YES** **N=40 (7.45% among all infants)**	Combined Atopy at 1YR - **NO** **N=218 (40.60% among all infants)**	Maternal Asthma 1YR - **YES** **N=28 (5.21% among all infants)**	Maternal Asthma at 1YR - **NO** **N=230 (42.83% among all infants)**	Combined Atopy 1YR - **YES** **N=40 (7.45% among all infants)**	Combined Atopy at 1YR - **NO** **N=218 (40.60% among all infants)**	Maternal Asthma 1YR - **YES** **N=28 (5.21% among all infants)**	Maternal Asthma at 1YR - **NO** **N=230 (42.83% among all infants)**
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Infant neurodevelopment 1YR								
BSID-III cognitive 1 year	110.99083 (9.3823074)	112.64151 (11.033331)	110.313 (8.322)	111.831 (10.316)	109.91228 (10.807701)	109.23729 (11.326409)	108.488 (10.382)	110.077 (11.154)
BSID-III language 1 year	111.87156 (11.118137)	110.50943 (12.83718)	110.156 (13.026)	111.738 (11.365)	107.0708 (13.012162)	104.38983 (10.938727)	**109.93 (12.207)****	**104.891 (12.217)****

BSID-III motor 1 year	103.73394	103.86792	105.875	103.262	103.50877	100.01695	104.628	101.554
	(17.231884)	(14.04257)	(13.54)	(16.813)	(17.205291)	(12.319723)	(15.467)	(15.842)
BSID-III social-emotional 1 year	101.05769	104.80392	104.677	101.694	103.45455	99.745763	**102.738**	**101.969**
	(11.817238)	(15.873273)	(12.037)	(13.643)	(13.422312)	(12.879539)	**(14.108)****	**(13.095)****
Infant neurodevelopment 2YR								
BSID-III cognitive 2 year	109.40367	105.18868	110.156		101.46491	105.25424	102.721	102.769
	(14.809356)*	(11.967997)*	(13.409)	107.5 (14.2)	(13.033096)*	(12.979551)*	(13.247)	(13.105)
BSID-III language 2 year	104.44954	102.03846	106.219	103.039	96.482456	97.864407	95.907	
	(10.986091)	(10.493624)	(9.527)	(11.104)	(12.080286)	(10.590265)	(10.834)	97.3 (11.838)
BSID-III motor 2 year	99.981651	99.490566	101.313	99.454	**96.307018**	**99.474576**	95.465	98.023
	(9.7941608)	(8.8331165)	(9.586)	(9.437)	**(9.1381987)****	**(10.477161)****	(9.127)	(9.837)
BSID-III social-emotional 2 year	110.04587	110.57692	106.719	111.085 (14.999)	107.20721	105.25424	**102.143**	**107.969**
	(14.8526)	(15.199776)	(14.29)		(17.39494)	(14.634151)	**(16.68)****	**(16.21)****

Note: SD= standard deviation; Statistical comparison of means completed by ANOVA. *p<0.10 **p<0.05

On the other hand, crude results in the association between maternal asthma and infant BSID-III scores demonstrated that in non-sex-stratified model that looks at all infants, maternal asthma leads to a decrease of 5.41 points in the socio-emotional scores at 2 years ($p = 0.009$; Table 3.2). Male infants exhibit a 5.04-point increase in language scores at 1 year ($p = 0.02$, Table 3.2). Moreover, while male infant socio-emotional scores do not seem to have significant links with combined maternal atopy, the opposite is true when maternal asthma was assessed on its own. In particular, male infants experience a significant decrease in their socio-emotional scores at 2 years (5.83 points lower, $p = 0.04$). No significant associations between maternal asthma and neurodevelopmental scores were observed in female infants at 1 or 2 years of age.

3.4.3 Multivariable regression model results examining the association between maternal combined atopy status with neurodevelopment at one year and two years of infant age

In the fully adjusted models, only the inverse relationship between male infant motor scores at 2 years and maternal atopy had a statistically significant association at 2 years (adjusted beta-coefficient: -4.04; 95% CI: -7.6, -0.47; Table 3.2; Table 3.6).

The inverse association between combined maternal atopy and male infant cognitive scores at 2 years remained after adjusting for key covariates that include maternal ethnicity and prenatal depression at 36 weeks (adjusted beta-coefficient: -3.87; 95% CI: -8.28, 0.54). However, this association is not significant ($p = 0.085$). Infants belonging to Asian ethnicities experience the most decrease in cognitive scores (adjusted beta-coefficient: -9.86; 95% CI: -18.74, -0.98, $p = 0.03$) (Table 3.5). Using prenatal depression in the second semester or at 18 weeks as a covariate in the fully-adjusted model did not produce similar significant associations with male infant cognitive scores (Table 3.2; Table 3.6).

Additionally, male infant motor scores at 2 years also retained its inverse, albeit non-significant association with combined maternal atopy (adjusted beta-coefficient: -3.003; 95% CI: -6.28, 0.27, $p = 0.072$). However, when the prenatal depression covariate is changed from 36 weeks to 18 weeks, results reveal that prenatal depression in 18 weeks retains the significant association between male infant motor scores at 2 years and maternal atopy atopy (adjusted beta-coefficient: -4.04; 95% CI: -7.6, 0.47, $p = 0.027$; Table 3.6). At both prenatal depression timepoints (ie. at 18 weeks and at 36 weeks), mothers of Asian background experience the highest reduction in motor scores (Table 3.5, Table 3.6). Finally, the increase in cognitive scores among female infants whose moms have combined maternal atopy was not retained in the fully-adjusted models.

A summary of statistically significant associations ($p < 0.05$) between maternal atopy and infant neurodevelopmental scores is shown in the figure below (Figure 3.3).

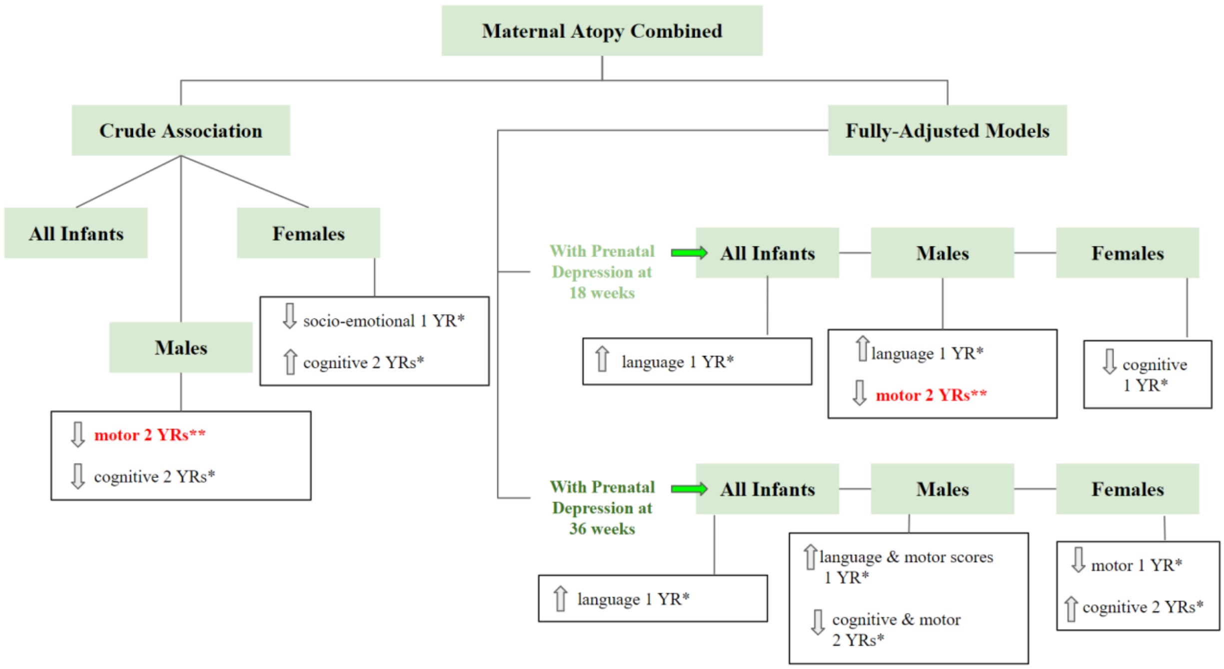


Figure 3.3. Flow diagram presenting a summary overview of statistically significant (p<0.05)** and marginal associations (p<0.10)* between maternal atopy and infant neurodevelopmental scores. The left-hand side of the diagram shows the associations in the crude or univariate linear regression analyses and the right hand side shows the results from fully-adjusted or multivariate linear regression analyses. Both crude and fully-adjusted models include stratified analyses of all infants, male, and female groups. Under fully-adjusted models, 2 separate models are shown - the first model uses prenatal depression at 18 weeks as a covariate and the second model uses prenatal depression at 36 weeks as a covariate. Any associations between maternal atopy and infant neurodevelopmental scores are listed under their respective groups and to the left of the scores are arrows representing either an increase (upward direction) or decrease (downward direction) of scores. Significant associations (p<0.05) are also emphasized in red text.

3.4.4 Multivariable regression model results examining the association between maternal asthma and neurodevelopment at one year and two years of infant age

Furthermore, fully-adjusted models for the association between maternal asthm***a*** and infant BSID-III scores present prenatal depression as a covariate. The statistically significant decrease in socioemotional scores at 2 years in all infants was retained in the multivariate model with prenatal depression at the second trimester or 18 weeks (adjusted beta-coefficient: -6.14; 95% CI: -11.04, -1.24, p = 0.014) rather than at 36 weeks (adjusted beta-coefficient: -3.70; 95% CI: -8.05, 0.64, p = 0.094, Table 3.2; Table 3.7, Table 3.8). The increase in male infant language scores at 2 years linked with maternal asthma also remained in all fully-adjusted models . Higher language scores were observed during prenatal depression at 36 weeks compared to 18 weeks (adjusted beta-coefficient: 6.56; 95% CI: 1.76, 11.37, p = 0.008 versus adjusted beta-coefficient: 5.39; 95% CI: 0.48, 10.29, p = 0.032, Table 3.7, Table 3.8).

Lastly, there was no significant relationship between maternal asthma and male infant socio-emotional scores at 2 years in the fully-adjusted models (Table 3.7, 3.8). A summary of statistically significant associations ($p < 0.05$) between maternal asthma and infant neurodevelopmental scores is shown in the figure below (Figure 3.4).

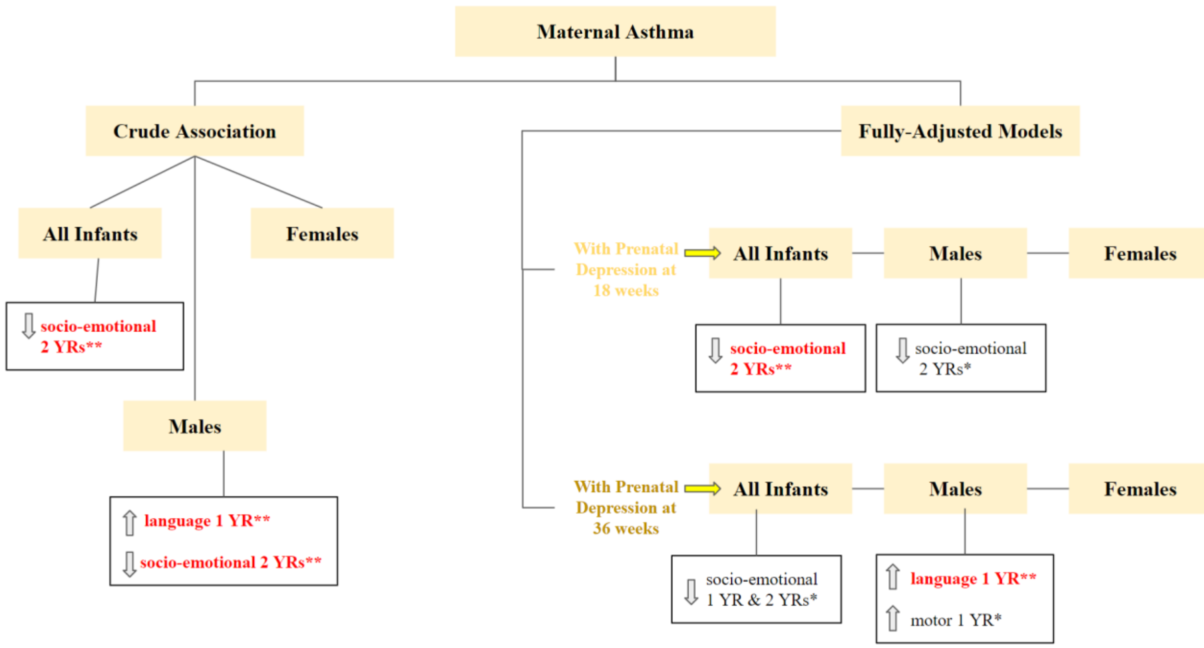


Figure 3.4. Flow diagram presenting a summary overview of statistically significant (p<0.05)** and marginal associations (p<0.10)* between maternal asthma and infant neurodevelopmental scores. The left-hand side of the diagram shows the associations in the crude or univariate linear regression analyses and the right hand side shows the results from fully-adjusted or multivariate linear regression analyses. Both crude and fully-adjusted models include stratified analyses of all infants, male, and female groups. Under fully-adjusted models, 2 separate models are shown - the first model uses prenatal depression at 18 weeks as a covariate and the second model uses prenatal depression at 36 weeks as a covariate. Any associations between maternal asthma and infant neurodevelopmental scores are listed under their respective groups and to the left of the scores are arrows representing either an increase (upward direction) or decrease (downward direction) of scores. Significant associations (p<0.05) are also emphasized in red text.

3.4.5 Determining gut microbiome and metabolites that may be in the pathway between combined maternal atopy and maternal asthma and neurodevelopmental scores

Regression analysis was used to evaluate the hypothesis that certain bacterial metabolites in the infant gut mediate the effect of combined maternal atopy or maternal asthma on infant neurodevelopmental scores (Table 3.10, Table 3.11). The first mediation analysis uses combined maternal atopy as the independent (*X*) variable, while maternal asthma on its own, without the presence of other maternal atopic conditions was used as the X variable for the second mediation test (Table 3.13 and Table 3.14). As previously mentioned, mediators were identified using the Baron and Kenny 1986 mediation criteria – that is, a variable is considered a mediator if there is a significant exposure (*X*) to mediator (*M*) association and a mediator (*M*) to outcome (*Y*) association, in addition to a significant association between exposure (*X*) and outcome (*Y*).

The initial mediation analysis aims to identify which of the infant gut metabolites at 4 months of age are mediators in the path between combined maternal atopy and neurodevelopmental scores. From the previous analysis, I already have data regarding the ***X* -> *Y*** associations – that is, which specific neurodevelopmental scores (*Y*) have significant associations with maternal atopy or maternal asthma (*X*) and in which group of infants (Figure 3.3 and Figure 3.4). Thus, knowing which X and Y variables and from which groups have marginal ($p<0.10$) and significant ($p<0.05$) associations, I then proceeded to test each of the infant gut metabolites for associations with maternal atopy and asthma (***X* -> *M***) and neurodevelopmental scores (***M* -> *Y***). Results from testing which metabolites mediate the association between maternal atopy and infant Bayley-III scores are found in Table 3.9 to Table 3.12; while metabolites for maternal asthma and Bayley-III scores are in Table 3.13 to Table 3.15.

Results from the analysis show that the metabolites dimethylamine and phenylalanine are candidate mediators for the pathway between maternal asthma and the increase in male infant language scores at 1 year (Figure 3.5).

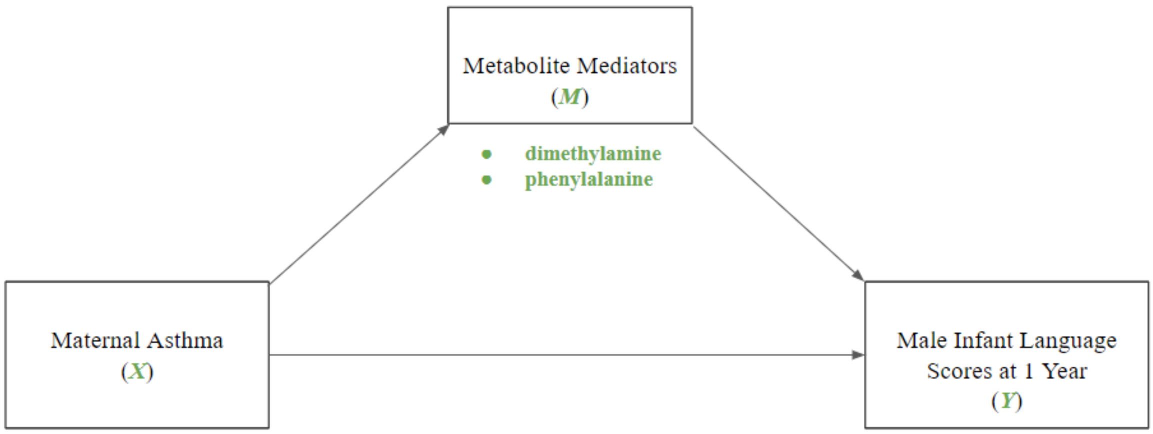
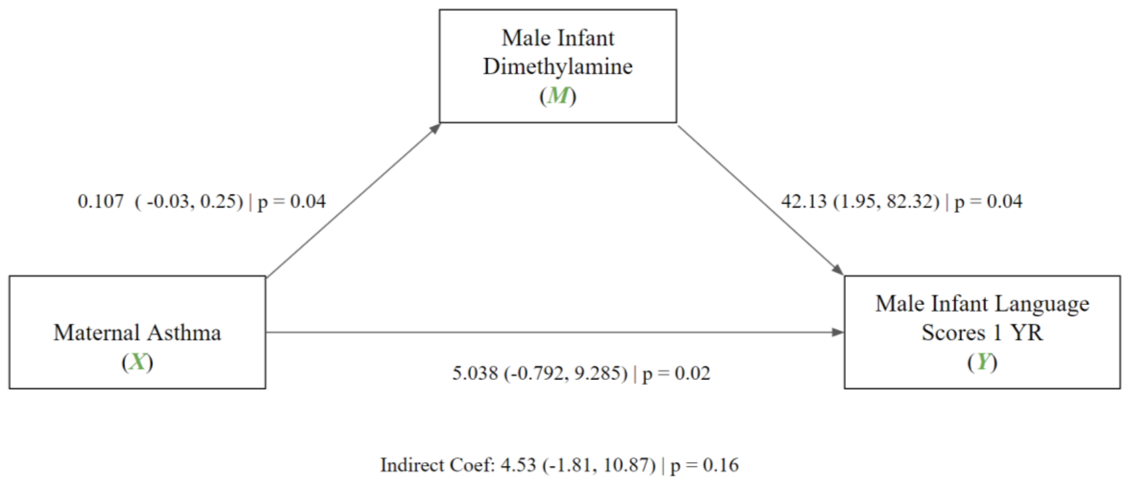


Figure 3.5. Metabolites identified as mediators in the association between maternal asthma and male infant language scores at 1 year of infant age.

After these potential metabolite mediators were identified, structural equation modelling (SEM) was conducted to see if these mediators have a significant mediating effect in the pathway. Examining each of the pathways reveal two separate trends. First, looking at the infant gut metabolite dimethylamine, maternal asthma is linked to an increase in dimethylamine (beta-coefficient: 0.107; 95%CI: -0.03, 0.25; p-value = 0.04; Figure 3.6A), which is then linked to a subsequent increase in male infant language scores at 1 year (beta-coefficient: 42.13; 95%CI: 1.95, 82.32; p-value = 0.04; Figure 3.6A). Second, looking at the infant gut metabolite phenylalanine reveals an opposite M -> Y association in which maternal asthma is marginally associated with an increase in phenylalanine (beta-coefficient: 1.19; 95%CI: -0.09, 2.46; p-value = 0.07; Figure 3.6B), which is then related to a subsequent decrease in male infant language scores at 1 year (beta-coefficient: -2.17; 95%CI: -3.69, -0.65; p-value = 0.005; Figure 3.6B). However, results reveal that none of these mediating effects are statistically significant (Figure 3.6A and Figure 3.6B).

A.



B.

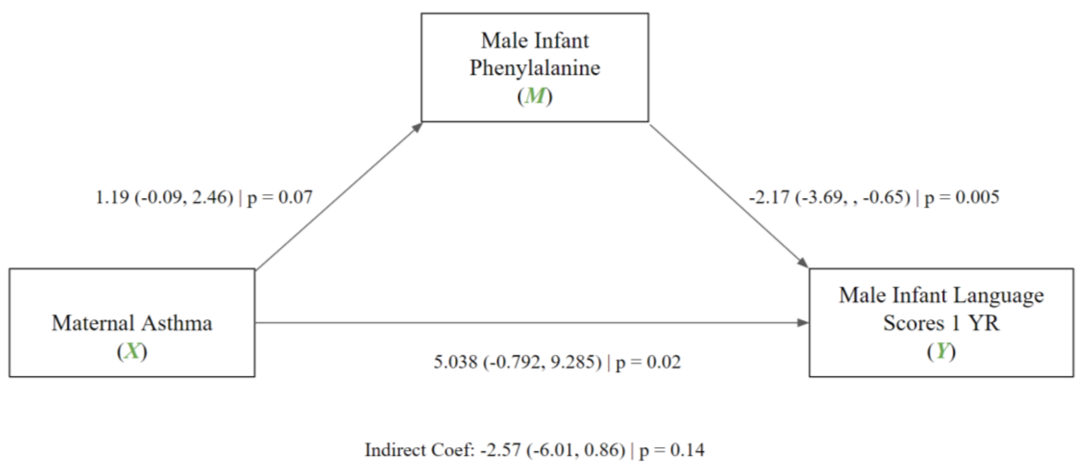


Figure 3.6. Structural equation model (SEM) diagrams showing the associations between metabolites, maternal asthma, and 1-year male infant language scores. Pathways are labeled in the form of coefficient (confidence intervals) | p-value.

Furthermore, similar identification of potential mediators was used for infant gut microbiome at 4 months. According to the DAG (Figure 3.1), there is not a direct path from maternal atopy to infant gut microbiome (direct paths are indicated by bold lines), but a direct path exists through infant atopy and food sensitization. However, the analysis in Chapter 2 that investigated the relationship between infant food sensitization and neurodevelopment scores already revealed the lack of significant association between infant sensitization and neurodevelopmental scores. This lack of association is also summarized in Table 3.16 below. Therefore, structural mediation cannot be pursued with infant atopic sensitization or food sensitization as the exposure (X).

Table 3.16. Logistic regression presenting the association between infant sensitization status and maternal atopic status.

ALL INFANTS					
Maternal Atopy (Combined)	**Coef.**	**p-value**	**[95% Conf**	**Interval]**	**Sig**
Food sensitization	.005	.989	-.703	.713	
Atopic sensitization	.116	.729	-.541	.774	
Maternal Asthma	**Coef.**	**p-value**	**[95% Conf**	**Interval]**	**Sig**
Food sensitization	-.31	.481	-1.171	.552	
Atopic sensitization	.17	0.64	-.541	.881	
MALE INFANTS					
Maternal Atopy (Combined)	**Coef.**	**p-value**	**[95% Conf**	**Interval]**	**Sig**
Food sensitization	-.045	0.928	-1.023	.933	
Atopic sensitization	-1.852	0.941	-.957	.887	
Maternal Asthma	**Coef.**	**p-value**	**[95% Conf**	**Interval]**	**Sig**
Food sensitization	-.314	.594	-1.468	.841	
Atopic sensitization	0.075	0.883	-.927	1.077	
FEMALE INFANTS					
Maternal Atopy (Combined)	**Coef.**	**p-value**	**[95% Conf**	**Interval]**	**Sig**
Food sensitization	.059	0.910	-.969	1.087	
Atopic sensitization	.262	0.585	-.680	1.205	
Maternal Asthma	**Coef.**	**p-value**	**[95% Conf**	**Interval]**	**Sig**
Food sensitization	-.305	0.645	-1.604	.994	
Atopic sensitization	.299	0.563	-.714	1.311	

Note: Each row represents a separate model. Infant groups (all infants, males, and females) are in dark blue row headings, while lighter blue headings represent the exposure or (X) variable.

On the other hand, mediation analysis (Stata 17) was used to examine the indirect effects of maternal atopy and maternal asthma (***X***) on infant neurodevelopmental scores (***Y***) mediated through prenatal depression at 18 and 36 weeks and infant gut microbiome (Figure 3.7). For the potential mediators, depression was considered as mediator 1 (*M1*) and infant gut microbiome as mediator 2 (*M2*).

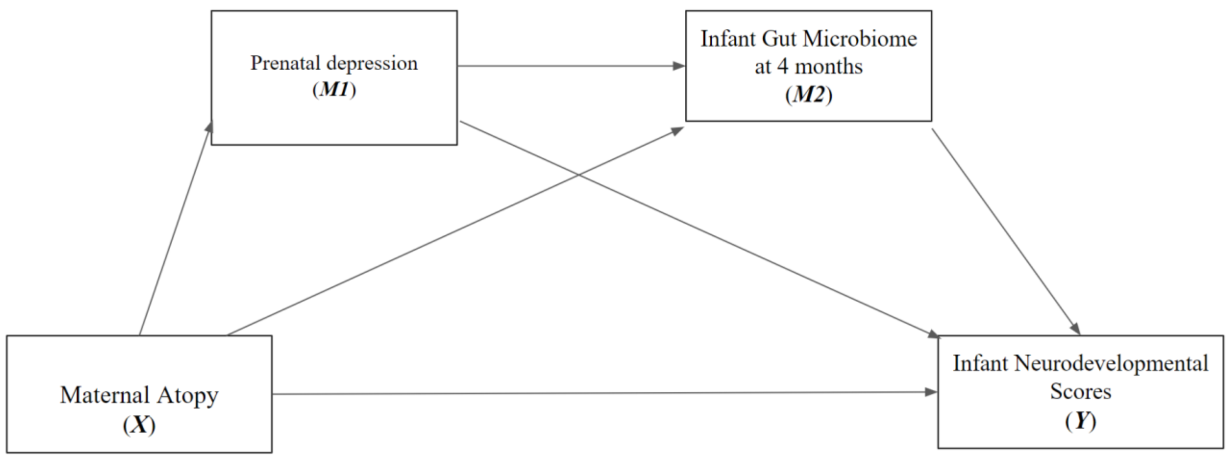


Figure 3.7 Proposed sequential mediation model to test the associations between maternal atopy (combined maternal atopy and maternal asthma), prenatal depression, and infant neurodevelopment.

As previously mentioned, before proceeding to run sequential mediation assessments, there needs to be a significant exposure (X) to mediator (M) association ($p<0.05$). To test this, I ran linear regression tests between: (i) maternal atopy and prenatal depression scores at 18 weeks, (ii) maternal atopy and prenatal depression scores at 36 weeks, (iii) maternal asthma and prenatal depression scores at 18 weeks, and (iv) maternal asthma and prenatal depression scores at 36 weeks

(Table 3.18). These analyses were run for each of the three groups: all infants, male infants, and female infants (Table 3.17).

Table 3.17. Linear regression that tests the exposure to mediator (*X* -> *M*) association between maternal asthma and prenatal depression and between maternal atopy and prenatal depression.

ALL INFANTS					
Maternal Atopy (Combined)	**Coef.**	**p-value**	**[95% Conf**	**Interval]**	**Sig**
Prenatal depression 18 weeks	1.331	.133	-.41	3.072	
Prenatal depression 36 weeks	1.76	.029	.178	3.342	
Maternal Asthma	**Coef.**	**p-value**	**[95% Conf**	**Interval]**	**Sig**
Prenatal depression 18 weeks	.127	.902	-1.9	2.155	
Prenatal depression 36 weeks	.829	.374	-1.003	2.661	
MALE INFANTS					
Maternal Atopy (Combined)	**Coef.**	**p-value**	**[95% Conf**	**Interval]**	**Sig**
Prenatal depression 18 weeks	1.198	.288	-1.025	3.421	
Prenatal depression 36 weeks	1.29	.171	-.561	3.142	
Maternal Asthma	**Coef.**	**p-value**	**[95% Conf**	**Interval]**	**Sig**
Prenatal depression 18 weeks	.909	.467	-1.555	3.372	
Prenatal depression 36 weeks	-.093	.931	-2.229	2.043	
FEMALE INFANTS					
Maternal Atopy (Combined)	**Coef.**	**p-value**	**[95% Conf**	**Interval]**	**Sig**
Prenatal depression 18 weeks	1.474	.28	-1.217	4.166	
Prenatal depression 36 weeks	2.229	.096	-.398	4.856	
Maternal Asthma	**Coef.**	**p-value**	**[95% Conf**	**Interval]**	**Sig**
Prenatal depression 18 weeks	-.641	.702	-3.95	2.669	
Prenatal depression 36 weeks	1.907	.218	-1.14	4.954	

*Note: Each row is a separate model. *** p<.01, ** p<.05, * p<.1*

Based on the above Table 3.17 results that tests the mediation criterion for an exposure to mediator association (*X* -> *M*), none of the associations between prenatal depression scores either at 18 or 36 weeks were significantly related to maternal atopy or maternal asthma, with the exception of two models: (i) maternal atopy and prenatal depression at 36 weeks in the all infants group and (ii) maternal atopy and prenatal depression at 36 weeks in the females group. Since an *X* -> *M* association exists for these two models, the next step will be to test the *M* -> *Y* association – that is, between prenatal depression at 36 weeks and infant neurodevelopmental scores (Table 3.18). Since none of the models show a significant *M* -> *Y* association, my results do not fulfill this criterion and thus, sequential mediation cannot be performed.

Table 3.18 Linear regressions that tests the mediator to outcome (*M* -> *Y*) association between prenatal depression at 36 weeks and infant neurodevelopmental scores at 1 and 2 years of infant age.

All Infants at 1 Year					
Cognitive 1 Year	**Coef.**	**p-value**	**[95% Conf**	**Interval]**	**Sig**
Prenatal depression 36 weeks	.026	.78	-.157	.209	
Language 1 Year	**Coef.**	**p-value**	**[95% Conf**	**Interval]**	**Sig**
Prenatal depression 36 weeks	.007	.95	-.209	.223	
Motor 1 Year	**Coef.**	**p-value**	**[95% Conf**	**Interval]**	**Sig**
Prenatal depression 36 weeks	-.037	.798	-.317	.244	
Socioemotional 1 Year	**Coef.**	**p-value**	**[95% Conf**	**Interval]**	**Sig**
Prenatal depression 36 weeks	-.066	.574	-.298	.166	
All Infants at 2 Years					
Cognitive 2 Years	**Coef.**	**p-value**	**[95% Conf**	**Interval]**	**Sig**
Prenatal depression 36 weeks	-.062	.61	-.304	.18	
Language 2 Years	**Coef.**	**p-value**	**[95% Conf**	**Interval]**	**Sig**
Prenatal depression 36 weeks	-.066	.52	-.268	.136	
Motor 2 Years	**Coef.**	**p-value**	**[95% Conf**	**Interval]**	**Sig**
Prenatal depression 36 weeks	-.053	.54	-.221	.116	
Socioemotional 2 Years	**Coef.**	**p-value**	**[95% Conf**	**Interval]**	**Sig**
Prenatal depression 36 weeks	-.107	.44	-.376	.162	

*Note: Each row is a separate model; *** p<.01, ** p<.05, * p<.1*

On the other hand, even if results do not support proceeding to sequential mediation analysis, crude significant mediation (M) to outcome (Y) associations between the infant gut microbiota Firmicutes, Clostridia, and *Clostridium difficile* with decreased male infant motor scores at two years were observed (Table 3.19, Table 3.20).

3.5 Discussion

3.5.1 The relationship between maternal atopy and asthma and infant neurodevelopment

In our study, maternal atopy in general (wherein the mother may have a combination of atopic conditions), significantly lowers male infant motor scores at 2 years in the presence of prenatal depression at 18 weeks. Similarly, maternal asthma on its own is linked to an increase in male infant language scores at 1 year and a decrease in male socioemotional scores in 2 years.

The former finding regarding maternal atopy is consistent with results from an Australian Cohort wherein reduced motor scores were also observed in infants with any allergic sensitization (42). Several studies support the link between maternal immune conditions including maternal asthma and allergies and subsequent developmental delays in their offspring, with most highlighting the impact of immune dysregulation in allergic disease (1–3). In particular, the underlying maternal immune activation (MIA) in asthma and allergies which result from genetic or environmental factors became a key topic of interest in increasing the risk of impaired child neurobehavior (4–7). Some studies offer explanations wherein underlying MIA in maternal asthma and allergies compromises the placenta's ability to regulate the maternal-fetal immune interface, which may lead to increased inflammatory cells and signaling that disturb the developing immune system and brain functions (11–13). A large population-based case-control study found consistent associations between a history of maternal immune disorders and childhood developmental disorders, specifically child autism spectrum disorders (ASD) and developmental delays without autism (DD) (8). In human infants, one particular study concluded that maternal prenatal total IgE was positively and significantly correlated with infant ADHD (3). This is further supported by another research study demonstrating that a positive immune history of maternal allergies or asthma was associated with increased severity of social symptoms, including cognition and mannerisms in the child (9). Even animal models have similar results wherein allergen-induced models of maternal inflammation in rodents present increased abnormal motor, cognitive, and social behaviors in offspring (10).

On the other hand, the latter finding of our study presents that maternal asthma increases in male infant language scores at 1 year and reduces male socioemotional scores at 2 years, even after controlling for prenatal depression. Consistent with our findings on socioemotional development, a positive maternal immune history of asthma and allergies increase the severity of social symptoms of ASD (43). On the other hand, the increase it is noteworthy that the increase in language scores does not support our original hypothesis that maternal allergy impairs all neurodevelopmental scores in the offspring. Interestingly, several research findings agree that on inconclusive findings regarding the exact impact of maternal asthma on the cognitive domains of child neurodevelopment (44). For example, a comprehensive systematic review looking specifically at maternal asthma and infant neurodevelopment concluded that the relationship between maternal asthma during pregnancy and neurobehavioral outcomes in the offspring is weak (44). A cross-sectional study published after this systematic review also produced consistent results – that is, infants up to 1 year of age whose mothers had asthma during pregnancy displayed no difference in sensory and temperament features when compared to infants whose mothers did not have asthma (45).

It is important to note however, that findings of the systematic review states that the neurodevelopmental trajectory of infants whose mothers have well-managed asthma during pregnancy did not differ when compared to infants whose moms did not have asthma (44). We speculate that since the majority of the participating mothers of our current study do not smoke, have mid to above average income, and obtained university education – all of which are positive social determinants of health (46)– it is likely that they have had adequate access to health resources and asthma treatment and medications, leading to better management of their asthma symptoms.

3.5.2 Determining potential metabolite mediators in the pathway between maternal atopy and infant neurodevelopment

Our results show that dimethylamine and phenylalanine are metabolites that mediate the effect between maternal asthma and female infant cognitive scores at 2 years (Figure 3.5, Table 3.14). However, structural mediation analysis reveals that the mediating effect of these two metabolites are not significant (Figure 3.5). In our study, the observed association of maternal asthma with increased levels of phenylalanine and the subsequent decrease in male infant language scores is consistent with research evidence that state the harmful effects of prenatal phenylalanine exposure on infant neurodevelopment, specifically on infant cognition (47–49). For instance, a study presented that prenatal phenylalanine exposure is not only related to cognitive impairment at 1 year of infant age, but these detrimental effects on offspring intelligence persist till early childhood, up to 7 years of age (47).

Meanwhile, previous research suggest that dimethylamine has been implicated as one of the volatile nitrogenous amino acids linked to hypergastrinemia in infants, a condition that suggests compromised digestive health (50). Additionally, dimethylamine is also one of the urinary metabolites determined as a potential objective biomarker for post-natal depression (51). This is contrary to our research finding which observed an increase in dimethylamine associated with increased male infant language scores at 1 year. It is worth noting however, that this observed mediating effect is not significant ($p = 0.16$).

Although our study presents that the mediating effect of these metabolites are non-significant, research is starting to uncover supporting evidence that point the potential role of metabolites in modulating an infant's early-life immune system. The degree to which metabolites impact infant health and immune or metabolic programming remains to be fully understood. Consistent with existing literature, we recommend future studies to examine human milk and microbiome-associated metabolites that may play a role in programming immune and metabolic functions in an infant's early life.

3.5.3 Sex-dependent patterns in the relationship between maternal atopy and infant neurodevelopment

In our study, the impact of maternal atopy and maternal asthma on infant neurodevelopmental scores exhibit a sex-dependent pattern, specific to male infants. These male sex-specific associations have also been observed in other literature investigating factors that shape infant neurodevelopment. A recent study presented that maternal immune conditions differentially have more adverse behavioral and emotional impact on male infants than females (52). Furthermore, the same study found a higher prevalence of maternal immune conditions in male than female infants, suggesting that maternal immune conditions may also be influenced by offspring sex. Overall, our studies support existing research that male infants appear to be more vulnerable to maternal inflammation-mediated neurodevelopmental disorders. However, the biological pathways that describe this association remains unclear.

3.5.4 Determining the mediating effect of infant gut microbiome via prenatal depression in the association between maternal atopy status and infant neurodevelopment

In our study, the significant association between maternal atopy status and infant cognitive or motor scores were not sequentially mediated by infant atopy (Table 3.17) or prenatal depression (Table 3.18). However, there were crude significant mediation (M) to outcome (Y) associations between the infant gut microbiota potential mediators Firmicutes, Clostridia, and *Clostridium difficile* with decreased male infant motor scores at two years (Table 3.17, Table 3.18).

In the early infant gut development, the early bacterial colonizers are dominated by Bifidobacteria and Lactobacillus and later the infant gut eventually becomes enriched with Bacteroides and Firmicutes (38). In Firmicutes, the Clostridium genera represent 95% of the

Firmicutes phyla (39,40). Meanwhile, *C. difficile* remains a harmless commensal in neonates and infants (41,42). In terms of a normal gut microbiome trajectory, *C. difficile* is expected to peak around the first month of life and then gradually decrease – *C. difficile* is found to be present in about 37% of healthy infants less than 1 month of age, with its levels gradually decreasing to about 30% between 1 and 6 months of infant age (43). At 3 years of age, the infant gut microbiota composition and diversity resembles that of the adult (44).

Noting the normal infant gut trajectories is important because deviation from the expected colonization patterns is often indicative of perturbations that threaten infant immunity and overall health (45). In our study, a unit increase in Firmicutes at 3 months of infant age is associated with a crude decrease in motor scores, a finding that is consistent with a study that showed significant relationship between Firmicutes levels and reduced gross motor behavior scores in infants 2-3 years of age (46). However, contrary to our findings, higher proportions of Firmicutes at the phylum level was proposed to be beneficial or protective for the development of the neural system (46). This is further supported by another study from the CHILD cohort that presented Firmicutes microbiota clusters in late infancy to be associated with enhanced neurodevelopmental outcomes, specifically with cognitive scores (47). Since the association between motor scores and Firmicutes were not influenced by any of the covariates we measured, the difference in our results with other previous research highlights the need to further assess more pathways in which Firmicutes abundance and composition play a role in shaping infant motor function.

The role of *C. difficile* in the infant gut microbiota is mostly explored in certain hypervirulent strains that colonizes the gastrointestinal tract leading to *C. difficile* infection (CDI) which is influenced by several factors including antibiotics (48). Current study in mice has linked CDI in altering specific brain regions that lead to the dysregulation in the metabolism of brain dopamine, an important area of the brain that is known to play a role in the onset of neurodevelopmental disorders (49). However, this leaves an important gap for gut microbiome research: that is, in exploring how *C. difficile* impacts infant brain development of human infants.

While much is yet to be uncovered about the pathways through which the infant gut microbiome influences brain development, research suggest that the gut-brain interactions begin in utero and is shaped by maternal factors that include maternal stress, chemical exposures, diet, immune conditions, and delivery mode among many others (50,51). Research evidence supports that the gut-brain axis intersects with microbe-immune activities wherein neuroimmune cells communicate with gut microbes and metabolites during early brain development (51,52). While studies have explored the gut and brain connection in adults and animal models, still, there is paucity in research regarding the microbiome-brain connection during the critical window of early infant development (53,54). Therefore, we recommend additional prospective longitudinal studies that will further add pieces to the puzzle that will reveal a clearer picture of the connection between atopic diseases, neurodevelopment, and the role of the brain-gut connection.

3.6 Conclusion

Our study supports that maternal atopy status plays a critical role in shaping the gut microbiome composition. Male infants whose mothers have atopic conditions are at a higher risk of neurodevelopmental impairment. We show that this association is mediated by metabolites creatinine. Although no mediation has been found by the gut microbiota, we found significant associations between gut microbiota Firmicutes, Clostridia, and *C. difficile,* and infant motor scores. Our research supports that since maternal inflammation-mediated expression of neurodevelopmental challenges is becoming more prevalent, the need to explore biological mechanistic evidence that demonstrates clear pathways between the gut bacteria, gut metabolites, and neuronal dysregulation should be a research priority. Information from these studies is important to identify potential interventions, early detection, and alternative therapeutic recommendations that improve overall health of infants.

3.7 Chapter 3: Tables

Table 3.1 Comparison of mean scores for neurodevelopmental domains at age 1 and 2 years across combined maternal atopy and maternal asthma status at 1 year, all infants and stratified by infant sex.

All infants

	Combined Maternal Atopy 1YR - **YES** **N=223 (66.57% overall)** Mean (SD)	Combined Maternal Atopy at 1YR - **NO** **N=112 (33.43% overall)** Mean (SD)	p-value	Maternal Asthma 1YR- **YES** **N=75 (22.39% overall)** Mean (SD)	Maternal Asthma at 1YR- **NO** **N=260 (77.61% overall)** Mean (SD)	p-value
Infant neurodevelopment 1YR						
BSID-III cognitive 1 year	110.4395 (10.12777)	110.8482 (11.2684)	0.738	110.954 (10.758)	109.267 (9.54)	0.221
BSID-III language 1 year	109.4279 (12.32889)	107.2857 (12.21241)	0.134	108.328 (12.263)	110.027 (12.477)	0.294
BSID-III motor 1 year	103.6188 (17.17984)	101.8393 (13.24445)	0.337	102.408 (16.325)	105.16 (14.594)	0.189
BSID-III social-emotional 1 year	102.2897 (12.69506)	102.0909 (14.50058)	0.899	101.833 (13.343)	103.562 (13.215)	0.33
Infant neurodevelopment 2YR						
BSID-III cognitive 2 year	105.3453 (14.45596)	105.2232 (12.45512)	0.939	105.135 (13.841)	105.893 (13.735)	0.676
BSID-III language 2 year	100.3767 (12.20367)	99.81982 (10.70361)	0.683	100.158 (11.811)	100.307 (11.445)	0.539
BSID-III motor 2 year	98.10314 (9.620883)	99.48214 (9.690696)	0.218	98.738 (9.647)	97.96 (9.709)	0.923
BSID-III social-emotional 2 year	108.6136 (16.21096)	107.7477 (15.07163)	0.639	109.533 (15.662)	**104.122 (15.754)**	**0.009****

Sex stratified

	Female infants				**Male infants**			
	Combined Atopy 1YR - **YES** **N=40 (7.45% among all infants)**	Combined Atopy at 1YR - **NO** **N=218 (40.60% among all infants)**	Maternal Asthma 1YR - **YES** **N=28 (5.21% among all infants)**	Maternal Asthma at 1YR - **NO** **N=230 (42.83% among all infants)**	Combined Atopy 1YR - **YES** **N=40 (7.45% among all infants)**	Combined Atopy at 1YR - **NO** **N=218 (40.60% among all infants)**	Maternal Asthma 1YR - **YES** **N=28 (5.21% among all infants)**	Maternal Asthma at 1YR - **NO** **N=230 (42.83% among all infants)**
Infant neurodevelopment 1YR	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
BSID-III cognitive 1 year	110.99083 (9.3823074)	112.64151 (11.033331)	110.313 (8.322)	111.831 (10.316)	109.91228 (10.807701)	109.23729 (11.326409)	108.488 (10.382)	110.077 (11.154)
BSID-III language 1 year	111.87156 (11.118137)	110.50943 (12.83718)	110.156 (13.026)	111.738 (11.365)	107.0708 (13.012162)	104.38983 (10.938727)	**109.93 (12.207)****	**104.891 (12.217)****

BSID-III motor 1 year	103.73394 (17.231884)	103.86792 (14.04257)	105.875 (13.54)	103.262 (16.813)	103.50877 (17.205291)	100.01695 (12.319723)	104.628 (15.467)	101.554 (15.842)
BSID-III social-emotional 1 year	101.05769 (11.817238)	104.80392 (15.873273)	104.677 (12.037)	101.694 (13.643)	103.45455 (13.422312)	99.745763 (12.879539)	102.738 (14.108)**	101.969 (13.095)**
Infant neurodevelopment 2YR								
BSID-III cognitive 2 year	109.40367 (14.809356)	105.18868 (11.967997)	110.156 (13.409)	107.5 (14.2)	101.46491 (13.033096)	105.25424 (12.979551)	102.721 (13.247)	102.769 (13.105)
BSID-III language 2 year	104.44954 (10.986091)	102.03846 (10.493624)	106.219 (9.527)	103.039 (11.104)	96.482456 (12.080286)	97.864407 (10.590265)	95.907 (10.834)	97.3 (11.838)
BSID-III motor 2 year	99.981651 (9.7941608)	99.490566 (8.8331165)	101.313 (9.586)	99.454 (9.437)	96.307018 (9.1381987)**	99.474576 (10.477161)**	95.465 (9.127)	98.023 (9.837)
BSID-III social-emotional 2 year	110.04587 (14.8526)	110.57692 (15.199776)	106.719 (14.29)	111.085 (14.999)	107.20721 (17.39494)	105.25424 (14.634151)	102.143 (16.68)**	107.969 (16.21)**

Note: SD= standard deviation; Statistical comparison of means completed by ANOVA. **p<0.05

Table 3.2. Univariate and multivariate linear regression for maternal atopic status and maternal asthma at 1 year versus neurodevelopmental scores at 1 and 2 years, all infants and stratified by infant sex (N=335).

Combined Maternal Atopy Multivariate Model Adjustments - All Infants						
BSID - III Scores at 1YR	**Crude Estimate (95% CI)**	**p-value**	**Fully-Adjusted Model Estimate (95% CI)[a]**	**p-value[a]**	**Fully-Adjusted Model Estimate (95% CI)[b]**	**p-value[b]**
Cognitive 1-Year	-0.409 (-2.806, 1.988)	0.74	-1.343(-3.875, 1.189)	0.30	0.139 (-2.439, 2.716)	0.92
Language 1-Year	2.14 (-0.670, 4.944)	0.13	2.664 (-0.490, 5.819)	0.10*	2.509 (-0.497, 5.516)	0.10*
Motor 1-Year	1.78 (-1.860, 5.419)	0.34	1.840 (-2.230, 5.909)	0.37	2.541 (-1.414, 6.496)	0.21
Social-Emotional 1-Year	0.199 (-2.879, 3.276)	0.90	-1.132 (-4.569, 2.305)	0.52	0.422 (-2.863, 3.706)	0.80
BSID - III Scores at 2YR	**Crude Estimate (95% CI)**	**p-value**	**Fully-Adjusted Model Estimate (95% CI)[a]**	**p-value[a]**	**Fully-Adjusted Model Estimate (95% CI)[b]**	**p-value[b]**
Cognitive 2-Year	0.122 (-3.027, 3.271)	0.94	-0.565 (-3.980, 2.850)	0.75	-0.114 (-3.471, 3.243)	0.95
Language 2-Year	0.557 (-2.123, 3.238)	0.68	-0.420 (-3.466, 2.625)	0.79	1.139 (-1.565, 3.843)	0.41
Motor 2-Year	-1.379 (-3.576, 0.818)	0.22	-1.783 (-4.265, 0.698)	0.16	-1.200 (-3.569, 1.168)	0.32
Social-Emotional 2-Year	0.866 (-2.762, 4.494)	0.64	0.270 (-4.076, 4.616)	0.90	1.519 (-2.289, 5.327)	0.43

Maternal Asthma Multivariate Model Adjustments - All Infants						
BSID - III Scores at 1YR	**Crude Estimate (95% CI)**	**p-value**	**Fully-Adjusted Model Estimate (95% CI)[a]**	**p-value[a]**	**Fully-Adjusted Model Estimate (95% CI)[b]**	**p-value[b]**
Cognitive 1-Year	-1.687 (-4.394, 1.02)	0.22	-1.655 (-4.553, 1.243)	0.26	-1.130 (-4.082, 1.821)	0.45
Language 1-Year	1.698 (-1.477, 4.874)	0.29	1.953 (-1.660, 5.567)	0.29	2.718 (-0.741, 6.176)	0.12
Motor 1-Year	2.752 (-1.362, 6.866)	0.19	2.832 (-1.800, 7.465)	0.23	4.841 (0.348, 9.335)	0.87
Social-Emotional 1-Year	1.730 (-1.754, 5.212)	0.33	0.398 (-3.521, 4.318)	0.84	-3.703 (-8.046, 0.64)	0.09*
BSID - III Scores at 2YR	**Crude Estimate (95% CI)**	**p-value**	**Fully-Adjusted Model Estimate (95% CI)[a]**	**p-value[a]**	**Fully-Adjusted Model Estimate (95% CI)[b]**	**p-value[b]**
Cognitive 2-Year	0.759 (-2.804, 4.321)	0.68	-1.048 (-4.966, 2.870)	0.60	1.821 (-2.069, 5.712)	0.36
Language 2-Year	0.148 (-2.878, 3.174)	0.92	-1.743 (-5.262, 1.776)	0.33	1.231 (-2.014, 4.475)	0.46
Motor 2-Year	-0.778 (-3.269, 1.712)	0.54	-2.178 (-4.994, 0.637)	0.13	-0.542 (-3.257, 2.174)	0.70

Social-Emotional 2-Year	-5.41 (-9.48, -1.34)	0.009**	-6.141 (-11.043, -1.239)	0.014**	-3.703 (-8.046, 0.640)	0.10*
Combined Maternal Atopy Multivariate Model Adjustments – Male Infants						
BSID – III Scores at 1YR	**Crude Estimate (95% CI)**	**p-value**	**Fully-Adjusted Model Estimate (95% CI)[a]**	**p-value[a]**	**Fully-Adjusted Model Estimate (95% CI)[b]**	**p-value[b]**
Cognitive 1-Year	0.675 (-2.803, 4.153)	0.70	0.322 (-3.387, 4.03)	0.86	1.989 (-1.698, 5.676)	0.29
Language 1-Year	2.681 (-1.233, 6.595)	0.18	4.113 (-0.429, 8.656)	0.08*	3.712 (-0.608, 8.03)	0.09*
Motor 1-Year	3.492 (-1.485, 8.468)	0.17	-5.503 (-0.324, 10.681)	0.39	5.283 (-0.156, 10.724)	0.06*
Social-Emotional 1-Year	3.709 (-0.508, 7.926)	0.29	1.948 (-2.976, 6.873)	0.44	4.607 (0.131, 9.084)	0.34
BSID - III Scores at 2YR	**Crude Estimate (95% CI)**	**p-value**	**Fully-Adjusted Model Estimate (95% CI)[a]**	**p-value[a]**	**Fully-Adjusted Model Estimate (95% CI)[b]**	**p-value[b]**
Cognitive 2-Year	-3.79 (-7.91, 0.33)	0.07*	-3.636 (-8.447, 1.175)	0.14	-3.87 (-8.278, 0.536)	0.09*
Language 2-Year	-1.382 (-5.053, 2.289)	0.46	1.568 (-2.451, 5.587)	0.441	2.715 (-0.894, 6.323)	0.14
Motor 2-Year	-3.17 (-6.21, -0.124)	0.04**	-4.035 (-7.600, -0.470)	0.03**	-3.003 (-6.276, 0.270)	0.07*
Social-Emotional 2-Year	1.953 (-3.293, 7.199)	0.46	-1.306 (-6.721, 4.11)	0.63	0.515 (-4.87, 5.901)	0.85
Maternal Asthma Multivariate Model Adjustments - Male Infants						
BSID - III Scores at 1YR	**Crude Estimate (95% CI)**	**p-value**	**Fully-Adjusted Model Estimate (95% CI)[a]**	**p-value [a]**	**Fully-Adjusted Model Estimate (95% CI) [b]**	**p-value [b]**
Cognitive 1-Year	-1.589 (-5.398, 2.221)	0.41	-1.966 (-5.976, 2.045)	0.33	-0.674 (-4.887, 3.539)	0.75
Language 1-Year	5.038 (-0.792, 9.285)	0.02**	-5.385 (-0.482, 10.287)	0.76	6.56 (1.76, 11.37)	0.008**
Motor 1-Year	3.074 (-2.395, 8.543)	0.27	3.159 (-2.579, 8.897)	0.28	5.707 (-0.458, 11.871)	0.07*
Social-Emotional 1-Year	0.770 (-3.92, 5.76)	0.75	-0.653 (-6.069, 4.763)	0.81	1.55 (-3.58, 6.69)	0.55
BSID - III Scores at 2YR	**Crude Estimate (95% CI)**	**p-value**	**Fully-Adjusted Model Estimate (95% CI) [a]**	**p-value [a]**	**Fully-Adjusted Model Estimate (95% CI) [b]**	**p-value [b]**
Cognitive 2-Year	-0.048 (-4.611, 4.515)	0.98	-1.430 (-6.727, 3.867)	0.59	1.411 (-3.674, 6.496)	0.58
Language 2-Year	-1.393 (-5.421, 2.635)	0.50	-5.314 (-10.086, -0.543)	0.74	0.258 (-4.167, 4.683)	0.91
Motor 2-Year	-2.558 (-5.915, 0.799)	0.13	-4.290 (-8.176, -0.404)	0.65	-1.914 (-5.664, 1.837)	0.32

Social-Emotional 2-Year	-5.826 (-11.56, -0.094)	0.04**	-6.595 (-14.065, 0.876)	0.08*	-3.68 (-9.80, 2.44)	0.24
Combined Maternal Atopy Multivariate Model Adjustments - Female Infants						
BSID - III Scores at 1YR	**Crude Estimate (95% CI)**	**p-value**	**Fully-Adjusted Model Estimate (95% CI)** [a]	**p-value** [a]	**Fully-Adjusted Model Estimate (95% CI)** [b]	**p-value** [a]
Cognitive 1-Year	-1.651 (-4.941, 1.640)	0.32	-3.093 (-6.619, 0.432)	0.09*	-1.433 (-5.056, 2.189)	0.44
Language 1-Year	1.362 (-2.509, 5.233)	0.49	1.169 (-3.155, 5.493)	0.17	1.468 (-2.603, 5.538)	0.48
Motor 1-Year	-0.0001 (-0.005, 0.004)	0.96	-1.487 (-7.739, 4.764)	0.86	-0.013 (-5.855, 5.829)	0.10*
Social-Emotional 1-Year	-0.005 (-0.01, 0.0009)	0.10*	-3.879 (-8.678, 0.920)	0.11	-3.752 (-8.599, 1.095)	0.13
BSID - III Scores at 2YR	**Crude Estimate (95% CI)**	**p-value**	**Fully-Adjusted Model Estimate (95% CI)** [a]	**p-value** [a]	**Fully-Adjusted Model Estimate (95% CI)** [b]	**p-value** [a]
Cognitive 2-Year	4.21 (-0.398, 8.82)	0.07*	2.603 (-2.217, 7.424)	0.29	4.115 (-0.852, 9.083)	0.10*
Language 2-Year	0.005 (-0.002, 0.011)	0.19	1.568 (-2.451, 5.587)	0.44	2.715 (-0.894, 6.323)	0.14
Motor 2-Year	-0.134 (-5.513, 5.245)	0.96	0.641 (-2.788, 4.071)	0.71	0.646 (-2.791, 4.083)	0.71
Social-Emotional 2-Year	-3.746 (-8.231, 0.739)	0.15	-1.306 (-6.721, 4.110)	0.63	0.515 (-4.870, 5.901)	0.85
Maternal Asthma Multivariate Model Adjustments - Female Infants						
BSID - III Scores at 1YR	**Crude Estimate (95% CI)**	**p-value**	**Fully-Adjusted Model Estimate (95% CI)** [a]	**p-value** [a]	**Fully-Adjusted Model Estimate (95% CI)** [b]	**p-value** [b]
Cognitive 1-Year	-1.518 (-5.400, 2.364)	0.44	-1.033 (-5.341, 3.276)	0.64	-1.562 (-5.745, 2.621)	0.46
Language 1-Year	-1.582 (-6.144, 2.980)	0.50	-1.285 (-6.506, 3.936)	0.63	-1.546 (-6.327, 3.234)	0.52
Motor 1-Year	2.614 (-3.712, 8.940)	0.42	3.198 (-4.211, 10.607)	0.71	3.525 (-3.116, 10.167)	0.30
Social-Emotional 1-Year	2.984 (-2.310, 8.277)	0.27	1.585 (-4.213, 7.382)	0.59	2.195 (-3.458, 7.847)	0.44
BSID - III Scores at 2YR	**Crude Estimate (95% CI)**	**p-value**	**Fully-Adjusted Model Estimate (95% CI)** [a]	**p-value** [a]	**Fully-Adjusted Model Estimate (95% CI)** [b]	**p-value** [b]
Cognitive 2-Year	2.656 (-2.820, 8.132)	0.34	0.367 (-5.438, 6.173)	0.90	2.446 (-3.377, 8.268)	0.41
Language 2-Year	3.180 (-1.038, 7.398)	0.14	3.638 (-1.249, 8.526)	0.14	2.352 (-2.037, 6.742)	0.29
Motor 2-Year	1.857 (-1.831, 5.548)	0.32	0.938 (-3.112, 4.988)	0.65	1.080 (-2.869, 5.030)	0.59

Social-Emotional 2-Year	-4.37 (-10.16, 1.43)	0.14	-3.944 (-10.127, 2.239)	0.209	-3.94 (-10.13, 2.24)	0.21

Note: [a]Prenatal depression at 18 weeks was a covariate; [b]Prenatal depression at 36 weeks was used as a covariate; *p<0.10 **p<0.05

Table 3.3. Frequency characteristics for categorical variables in the study sample of maternal atopy status at 1 year and neurodevelopmental data at 1 and 2 years of age (n=335)

Maternal characteristics	Total N	n (%)	Infant characteristics	Total N	n (%)
Family Income	331		**Child Sex**	335	
Less than 39,999		13 (4.14)	Boys		173 (51.64)
40,000 to 79,999		77 (24.52)	Girls		162 (48.36)
80,000 to 99,999		53 (16.88)	**Breastfeeding 3 Months**	335	
Exceeds 100,000		171 (54.46)	None		60 (17.91)
Maternal Education	332		Partial		104 (31.04)
Some/finished high school		23 (6.93)	Exclusive		60 (17.91)
Some university/college		130 (39.16)	**Birthmode**	331	
University degree		179 (53.92)	Vaginal no IAP		181 (54.68)
Maternal Asthma	335		Vaginal IAP		72 (21.75)
Yes		260 (77.61)	CS-Elective		35 (10.57)
No		75 (22.39)	CS-Emergency		43 (12.99)
Combined Maternal Atopy	335	223 (66.57)			
Yes		112 (33.43)			
No					
Prenatal Smoking	335		**Gestational Age**	333	
Yes		15 (4.48)	37 weeks+		314 (94.29)
No		320 (95.52)	34-36 weeks		19 (5.71)
Maternal Depression	335		**Siblings**	334	
Yes		41 (12.24)	Yes		186 (55.69)

No		294 (87.76)	No	148 (44.31)
Maternal Age	335			
18-29		93 (27.76)		
30-39		226 (67.46)		
40+	16 (4.78)			
Maternal Ethnicity	335			
White Caucasian		274 (81.79)		
Asian	26 (7.76)			
Other		35 (10.45)		

Table 3.4. Percentage distribution of combined maternal atopy and maternal asthma status at 1 year across candidate covariates (n=335)

Categorical variables	Combined Maternal Atopy 1YR (**YES**) (66.57% overall) N[c] (%)	Combined Maternal Atopy on 1YR (**NO**) (33.43% overall) N[c] (%)	p-value	Maternal Asthma (**YES**) (22.39% overall) N[c] (%)	Maternal Asthma 1YR (**NO**) (77.61%) N[c] (%)	p-value
Maternal Characteristics						
Maternal age			0.914[a]			**0.029[a]**
18 to 29	63 (67.74)	30 (32.26)		29 (31.18)	64 (68.82)	
30 to 39	150 (66.37)	76 (33.63)		45 (19.91)	181 (80.09)	
Over 40	10 (62.5)	6 (37.5)		1 (6.25)	15 (93.75)	
Maternal education			0.561			**0.029**
Some/finished high school	16 (69.57)	7 (30.43)		9 (39.13)	14 (60.87)	
Some university/ college	90 (69.23)	40 (30.80)		33 (25.38)	97 (74.62)	
University degree	114 (63.69)	65 (36.31)		31 (17.32)	148 (82.68)	
Prenatal smoking			0.266[a]			0.751
Yes	8 (53.33)	7 (46.67)		4 (26.67)	11 (73.33)	
No	215 (67.19)	105 (32.81)		71 (22.19)	249 (77.81)	
Maternal ethnicity			**0.099**			**0.026**
White Caucasian	189 (68.98)	85 (31.02)		68 (24.82)	206 (75.18)	
Asian	16 (61.54)	10 (38.46)		1 (3.85)	25 (96.15)	

Other	18 (51.43)	17 (48.57)		6 (17.14)	29 (82.86)	
Infant characteristics						
Child sex			0.788			0.263
Boys	114 (65.90)	59 (34.10)		43 (24.86)	130 (75.14)	
Girls	109 (67.28)	53 (32.72)		32 (19.75)	130 (80.25)	
Older siblings			0.749			0.167
Yes	125 (67.20)	61 (32.80)		47 (25.27)	139 (74.73)	
No	97 (65.54)	51 (34.46)		28 (18.92)	120 (81.08)	
Birth mode			**0.084**			0.164
Vaginal-noIAP	112 (61.88)	69 (38.12)		34 (18.78)	147 (81.22)	
Vaginal-IAP	49 (68.06)	23 (31.94)		23 (31.94)	49 (68.06)	
CS-elective	29 (82.86)	6 (17.14)		8 (22.86)	27 (77.14)	
CS-emergency	31 (72.09)	12 (27.91)		10 (23.26)	33 (76.74)	
Infant introduction to solids at 3 months			0.169			0.690[a]
Yes	4 (44.44)	5 (55.56)		1 (11.11)	8 (88.89)	
No	218 (67.08)	107 (32.92)		74 (22.77)	251 (77.23)	
Infant breastfeeding duration (months) | Mean (Standard Deviation)			0.141			0.187
	9.17 (6.63)	10.34 (7.05)		8.61 (6.43)	9.82 (6.87)	
Prenatal Depression | Mean (Standard Deviation)			0.133			0.902
18 weeks	10.27 (7.23)	8.93 (5.47)		9.91 (6.99)	9.78 (6.63)	
Prenatal Depression | Mean (Standard Deviation)			**0.029**			0.374
36 weeks	10.64 (7.10)	8.88 (5.32)		10.70 (7.41)	9.87 (6.37)	
Maternal prenatal fruit intake | Mean (Standard Deviation)			0.493			0.651
	3.15 (1.99)	3.32 (2.43)		3.31 (2.42)	3.18 (2.06)	
Gestational age (in weeks)| Mean (Standard Deviation)						0.912
	39.07 (1.42)	39.34 (1.26)	0.093	39.15 (1.41)	39.17 (1.36)	

[a]Fisher's exact test [b]Bold values are statistically significant [c]Total number of observations (N) is based per column per atopy/food sensitization yes/no

Table 3.5. Fully adjusted model results for the association between combined maternal atopy and neurodevelopmental scores including maternal ethnicity and prenatal depression at 36 weeks as covariates.

Fully-Adjusted Models for Combined Maternal Atopy – All Infants					
Cognitive Scores at 2 Years	Coef.	[95% Conf	Interval]	p-value	Significance
Combined Maternal Atopy	-.114	-3.471	3.243	.947	
White Moms[a]	0	.	.	.	
Asian Moms	-9.59	-15.686	-3.495	.002	***
Other Ethnicities	-5.756	-11.172	-.339	.037	**
Prenatal depression 36 weeks	-.109	-.352	.134	.378	
Language Scores at 2 Years	Coef.	[95% Conf	Interval]	p-value	Significance
Combined Maternal Atopy	1.139	-1.565	3.843	.408	
White Moms[a]	0	.	.	.	
Asian Moms	-14.506	-19.499	-9.514	0	***
Other Ethnicities	-4.57	-8.921	-.218	.04	**
Prenatal depression 36 weeks	-.146	-.341	.049	.143	
Motor Scores at 2 Years	Coef.	[95% Conf	Interval]	p-value	Significance
Combined Maternal Atopy	-1.2	-3.569	1.168	.319	
White Moms[a]	0	.	.	.	
Asian Moms	-4.526	-8.827	-.225	.039	**
Other Ethnicities	-1.765	-5.587	2.057	.364	
Prenatal depression 36 weeks	-.066	-.237	.105	.449	
Socio-emotional Scores at 2 Years	Coef.	[95% Conf	Interval]	p-value	Significance
Combined Maternal Atopy	1.519	-2.289	5.327	.433	
White Moms[a]	0	.	.	.	
Asian Moms	-3.923	-10.818	2.972	.264	
Other Ethnicities	-3.534	-9.767	2.699	.265	
Prenatal depression 36 weeks	-.138	-.413	.137	.325	
Fully-Adjusted Models for Combined Maternal Atopy – Male Infants					
Cognitive Scores at 2 Years	Coef.	[95% Conf	Interval]	p-value	Significance
Combined Maternal Atopy	-3.872	-8.28	.536	.085	*
White Moms[a]	0	.	.	.	
Asian Moms	-9.862	-18.742	-.983	.03	**
Other Ethnicities	-4.718	-10.867	1.431	.132	
Prenatal depression 36 weeks	-.171	-.551	.21	.377	
Language Scores at 2 Years	Coef.	[95% Conf	Interval]	p-value	Significance
Combined Maternal Atopy	2.715	-.894	6.323	.139	
White Moms[a]	0	.	.	.	
Asian Moms	-13.341	-19.487	-7.194	0	***
Other Ethnicities	2.281	-5.5	10.063	.563	

Prenatal depression 36 weeks	-.088	-.318	.141	.448	
Motor Scores at 2 Years	Coef.	[95% Conf	Interval]	p-value	Significance
Combined Maternal Atopy	-3.003	-6.276	.27	.072	*
White Moms[a]	0	.	.	.	
Asian Moms	-6.029	-12.623	.564	.073	*
Other Ethnicities	-3.377	-7.944	1.189	.146	
Prenatal depression 36 weeks	-.065	-.347	.218	.651	
Socioemotional Scores at 2 Years	Coef.	[95% Conf	Interval]	p-value	Significance
Combined Maternal Atopy	.515	-4.87	5.901	.85	
White Moms[a]	0	.	.	.	
Asian Moms	-5.863	-14.803	3.078	.197	
Other Ethnicities	-9.398	-21.063	2.267	.113	
Prenatal depression 36 weeks	-.062	-.405	.282	.723	
Fully-Adjusted Models for Combined Maternal Atopy – Female Infants					
Cognitive Scores at 2 Years	Coef.	[95% Conf	Interval]	p-value	Significance
Combined Maternal Atopy	4.115	-.852	9.083	.104	
White Moms[a]	0	.	.	.	
Asian Moms	-9.787	-18.033	-1.541	.02	**
Other Ethnicities	-4.698	-15.456	6.061	.389	
Prenatal depression 36 weeks	-.165	-.482	.152	.305	
Language Scores at 2 Years	Coef.	[95% Conf	Interval]	p-value	Significance
Combined Maternal Atopy	2.715	-.894	6.323	.139	
White Moms[a]	0	.	.	.	
Asian Moms	-13.341	-19.487	-7.194	0	***
Other Ethnicities	2.281	-5.5	10.063	.563	
Prenatal depression 36 weeks	-.088	-.318	.141	.448	
Motor Scores at 2 Years	Coef.	[95% Conf	Interval]	p-value	Significance
Combined Maternal Atopy	.646	-2.791	4.083	.711	
White Moms[a]	0	.	.	.	
Asian Moms	-3.413	-9.119	2.293	.239	
Other Ethnicities	3.846	-3.598	11.291	.309	
Prenatal depression 36 weeks	-.078	-.298	.141	.481	
Socioemotional Scores at 2 Years	Coef.	[95% Conf	Interval]	p-value	Significance
Combined Maternal Atopy	.515	-4.87	5.901	.85	
White Moms[a]	0	.	.	.	
Asian Moms	-5.863	-14.803	3.078	.197	
Other Ethnicities	-9.398	-21.063	2.267	.113	
Prenatal depression 36 weeks	-.062	-.405	.282	.723	

[a]Reference group; *** *p<.01,* ** *p<.05,* * *p<.1*

Table 3.6. Fully adjusted model results for the association between combined maternal atopy and neurodevelopmental scores including maternal ethnicity and prenatal depression at 18 weeks as covariates.

Fully-Adjusted Models for Combined Maternal Atopy – All Infants					
Cognitive Scores at 2 Years	Coef.	[95% Conf	Interval]	p-value	Significance
Combined Maternal Atopy	-.565	-3.98	2.851	.745	
White Moms[a]	0	.	.	.	
Asian Moms	-4.189	-11.035	2.657	.229	
Other Ethnicities	-5.835	-11.216	-.454	.034	**
Prenatal depression 18 weeks	-.152	-.392	.088	.214	
Language Scores at 2 Years	Coef.	[95% Conf	Interval]	p-value	Significance
Combined Maternal Atopy	-.42	-3.466	2.625	.786	
White Moms[a]	0	.	.	.	
Asian Moms	-9.939	-16.223	-3.654	.002	***
Other Ethnicities	-2.518	-7.31	2.275	.302	
Prenatal depression 36 weeks	-.128	-.342	.086	.24	
Motor Scores at 2 Years	Coef.	[95% Conf	Interval]	p-value	Significance
Combined Maternal Atopy	-1.783	-4.265	.698	.158	
White Moms[a]	0	.	.	.	
Asian Moms	-.443	-5.417	4.531	.861	
Other Ethnicities	.014	-3.896	3.924	.994	
Prenatal depression 18 weeks	-.158	-.332	.016	.075	*
Socio-emotional Scores at 2 Years	Coef.	[95% Conf	Interval]	p-value	Significance
Combined Maternal Atopy	.27	-4.076	4.616	.903	
White Moms[a]	0	.	.	.	
Asian Moms	-3.907	-12.841	5.027	.39	
Other Ethnicities	-1.207	-8.154	5.74	.733	
Prenatal depression 36 weeks	-.309	-.615	-.003	.047	**
Fully-Adjusted Models for Combined Maternal Atopy – Male Infants					
Cognitive Scores at 2 Years	Coef.	[95% Conf	Interval]	p-value	Significance
Combined Maternal Atopy	-3.636	-8.447	1.175	.137	
White Moms[a]	0	.	.	.	
Asian Moms	-5.107	-19.79	9.576	.492	
Other Ethnicities	-4.246	-10.875	2.382	.207	
Prenatal depression 18 weeks	-.306	-.692	.08	.119	
Language Scores at 2 Years	Coef.	[95% Conf	Interval]	p-value	Significance
Combined Maternal Atopy	1.568	-2.451	5.587	.441	
White Moms[a]	0	.	.	.	
Asian Moms	-9.709	-16.518	-2.901	.006	***

	Coef.	[95% Conf	Interval]	p-value	Significance
Other Ethnicities	-1.352	-9.099	6.394	.73	
Prenatal depression 36 weeks	-.057	-.313	.199	.661	
Motor Scores at 2 Years	Coef.	[95% Conf	Interval]	p-value	Significance
Combined Maternal Atopy	-4.035	-7.6	-.47	.027	**
White Moms[a]	0	.	.	.	
Asian Moms	-3.545	-14.426	7.335	.52	
Other Ethnicities	.82	-4.092	5.731	.742	
Prenatal depression 18 weeks	-.373	-.658	-.087	.011	**
Socioemotional Scores at 2 Years	Coef.	[95% Conf	Interval]	p-value	Significance
Combined Maternal Atopy	-1.306	-6.721	4.11	.634	
White Moms[a]	0	.	.	.	
Asian Moms	-10.54	-19.696	-1.383	.024	**
Other Ethnicities	-7.943	-18.369	2.483	.134	
Prenatal depression 36 weeks	-.268	-.612	.076	.126	
Fully-Adjusted Models for Combined Maternal Atopy – Female Infants					
Cognitive Scores at 2 Years	Coef.	[95% Conf	Interval]	p-value	Significance
Combined Maternal Atopy	2.603	-2.217	7.424	.287	
White Moms[a]	0	.	.	.	
Asian Moms	-4.461	-12.36	3.439	.266	
Other Ethnicities	-6.837	-16.142	2.469	.148	
Prenatal depression 18 weeks	-.096	-.402	.21	.536	
Language Scores at 2 Years	Coef.	[95% Conf	Interval]	p-value	Significance
Combined Maternal Atopy	1.568	-2.451	5.587	.441	
White Moms[a]	0	.	.	.	
Asian Moms	-9.709	-16.518	-2.901	.006	***
Other Ethnicities	-1.352	-9.099	6.394	.73	
Prenatal depression 36 weeks	-.057	-.313	.199	.661	
Motor Scores at 2 Years	Coef.	[95% Conf	Interval]	p-value	Significance
Combined Maternal Atopy	.641	-2.788	4.071	.712	
White Moms[a]	0	.	.	.	
Asian Moms	.309	-5.311	5.929	.914	
Other Ethnicities	-.084	-6.705	6.537	.98	
Prenatal depression 36 weeks	-.049	-.267	.169	.656	
Socioemotional Scores at 2 Years	Coef.	[95% Conf	Interval]	p-value	Significance
Combined Maternal Atopy	-1.306	-6.721	4.11	.634	
White Moms[a]	0	.	.	.	
Asian Moms	-10.54	-19.696	-1.383	.024	**
Other Ethnicities	-7.943	-18.369	2.483	.134	
Prenatal depression 36 weeks	-.268	-.612	.076	.126	

[a]Reference group; *** *p<.01*, ** *p<.05*, * *p<.1*

Table 3.7. Fully adjusted model results for the association between maternal asthma and neurodevelopmental scores including maternal ethnicity and prenatal depression at 36 weeks as covariates.

Fully-Adjusted Models for Maternal Asthma – All Infants at 1 Year					
Language Scores at 1 Year	Coef.	[95% Conf	Interval]	p-value	Significance
Maternal Asthma	2.718	-.741	6.176	.123	
Prenatal depression 36 weeks	-.002	-.217	.214	.988	
Socioemotional Scores at 2 Years	Coef.	[95% Conf	Interval]	p-value	Significance
Maternal Asthma	-3.703	-8.046	.64	.094	*
Prenatal depression 36 weeks	-.096	-.365	.173	.482	
Fully-Adjusted Models for Maternal Asthma – Male Infants					
Language Scores at 1 Year	Coef.	[95% Conf	Interval]	p-value	Significance
Maternal Asthma	6.561	1.758	11.365	.008	***
Prenatal depression 36 weeks	-.177	-.537	.183	.332	
Socioemotional Scores at 2 Years	Coef.	[95% Conf	Interval]	p-value	Significance
Maternal Asthma	-3.681	-9.799	2.438	.236	
Prenatal depression 36 weeks	-.373	-.826	.08	.106	
Fully-Adjusted Models for Maternal Asthma – Female Infants					
Language Scores at 1 Year	Coef.	[95% Conf	Interval]	p-value	Significance
Maternal Asthma	-1.546	-6.327	3.234	.523	
Prenatal depression 36 weeks	.069	-.19	.327	.602	
Socioemotional Scores at 2 Years	Coef.	[95% Conf	Interval]	p-value	Significance
Maternal Asthma	-3.944	-10.127	2.239	.209	
Prenatal depression 36 weeks	.026	-.309	.361	.88	

Note: Only models that resulted in significant associations in the crude, univariate analysis are included in the above multivariate table. [a]Reference group; *** *p<.01*, ** *p<.05*, * *p<.1*

Table 3.8. Fully adjusted model results for the association between maternal asthma and neurodevelopmental scores including maternal ethnicity and prenatal depression at 18 weeks as covariates.

Fully-Adjusted Models for Maternal Asthma – All Infants					
Language Scores at 1 Year	Coef.	[95% Conf	Interval]	p-value	Significance
Maternal Asthma	1.953	-1.66	5.567	.288	
Prenatal depression 36 weeks	-.071	-.292	.151	.531	
Socioemotional Scores at 2 Years	Coef.	[95% Conf	Interval]	p-value	Significance
Maternal Asthma	-6.141	-11.043	-1.239	.014	**
Prenatal depression 18 weeks	-.301	-.601	-.001	.049	**
Fully-Adjusted Models for Maternal Asthma – Male Infants					
Language Scores at 1 Year	Coef.	[95% Conf	Interval]	p-value	Significance
Maternal Asthma	5.385	.482	10.287	.032	**
Prenatal depression 18 weeks	-.043	-.399	.313	.81	
Socioemotional Scores at 2 Years	Coef.	[95% Conf	Interval]	p-value	Significance
Maternal Asthma	-6.595	-14.065	.876	.083	*
Prenatal depression 18 weeks	-.388	-.93	.154	.159	
Fully-Adjusted Models for Maternal Asthma – Female Infants					
Language Scores at 1 Year	Coef.	[95% Conf	Interval]	p-value	Significance
Maternal Asthma	-1.285	-6.506	3.936	.627	
Prenatal depression 36 weeks	-.136	-.413	.141	.333	
Socioemotional Scores at 2 Years	Coef.	[95% Conf	Interval]	p-value	Significance
Maternal Asthma	-5.091	-11.59	1.409	.124	
Prenatal depression 36 weeks	-.264	-.61	.081	.132	

Note: Only models that resulted in significant associations in the crude, univariate analysis are included in the above multivariate table. [a]Reference group; *** *p<.01, ** p<.05, * p<.10*

Table 3.9 Linear regression results assessing *X to M* and *M to Y* associations with maternal atopy as the exposure (X), individual male infant gut metabolites as potential mediators (M), and male infant cognitive scores at 2 years as the outcome (Y).

	Linear Regression Results of the Association between Combined Maternal Atopy (*X*) and each Metabolite (*M*) *X -> M*						Linear Regression Results of the Association between each Metabolite (*M*) and Male Infant Cognitive Scores at 2 Years *M -> Y*					
Metabolites	**β-coefficient**	**[95% C.I.]**		**p-value**	**R^2**	**N**	**β-coefficient**	**[95% C.I.]**		**p-value**	**R^2**	**N**
formate	-2.035e-01	-1.534e+00	1.127e+00	0.761	0.002	58	9.426e-02	-6.112e-02	2.496e-01	0.229	0.030	50
acetate	1.140e+01	-1.511e+01	3.790e+01	0.394	0.010	73	1.372e+00	1.490e-01	2.595e+00	0.029	0.080	60
butyrate	-1.284e+00	-5.473e+00	2.905e+00	0.543	0.005	73	-1.022e-01	-2.591e-01	5.467e-02	0.197	0.028	60
propionate	3.137e+00	-4.460e+00	1.073e+01	0.413	0.009	73	-5.413e-02	-3.410e-01	2.328e-01	0.707	0.002	60
valerate	2.118e-01	-6.809e-01	1.104e+00	0.638	0.003	73	-1.214e-02	-5.319e-02	2.891e-02	0.556	0.006	60
isobutyrate	2.002e-01	-3.283e-01	7.286e-01	0.453	0.008	73	-5.316e-03	-2.482e-02	1.419e-02	0.587	0.005	60
isovalerate	2.158e-01	-4.660e-01	8.976e-01	0.530	0.006	73	-1.508e-02	-4.592e-02	1.575e-02	0.332	0.016	60
lactate	-4.110e+00	-9.293e+00	1.074e+00	0.118	0.038	66	3.843e-01	2.274e-02	7.459e-01	0.038	0.078	56
succinate	-2.760e-01	-1.060e+01	1.005e+01	0.958	0.000	73	6.167e-01	2.201e-02	1.211e+00	0.042	0.069	60
hydroxyglutarate	3.417e+00	1.026e+00	5.808e+00	0.012	0.000	8	-1.974e-01	-1.464e+00	1.069e+00	0.298	0.797	3
aminobutyrate	2.132e-01	-6.934e-01	1.120e+00	0.628	0.013	21	1.122e-01	3.295e-03	2.210e-01	0.044	0.137	30
hydroxyphenylacetate	1.717e-02	-3.988e-01	4.331e-01	0.933	0.000	29	-8.658e-03	-2.361e-02	6.295e-03	0.247	0.042	34
aminopentanoate	3.819e-01	-3.033e+00	3.797e+00	0.820	0.002	27	-5.567e-02	-1.937e-01	8.233e-02	0.415	0.026	28
acetoin	3.674e-01	-7.958e-01	1.531e+00	0.515	0.024	20	2.612e-02	-5.334e-02	1.056e-01	0.504	0.019	26
alanine	3.258e+00	-1.235e+00	7.751e+00	0.152	0.036	58	1.046e-01	-2.598e-02	2.351e-01	0.114	0.051	50
aspartate	1.125e+00	-6.898e-01	2.940e+00	0.219	0.027	57	1.788e-02	-4.754e-02	8.330e-02	0.585	0.006	49
betaalanine	5.686e-01	-2.894e-01	1.427e+00	0.165	0.226	10	-1.779e-02	-9.292e-02	5.734e-02	0.583	0.053	8
cadaverine	-2.614e-01	-3.499e+00	2.976e+00	0.870	0.001	33	-1.198e-01	-2.793e-01	3.971e-02	0.136	0.068	34
choline	1.105e-02	-2.750e-01	2.971e-01	0.939	0.000	56	2.627e-02	1.581e-02	3.674e-02	0.000	0.362	47
creatine	1.165e-01	-2.008e-01	4.338e-01	0.465	0.010	56	1.324e-02	-8.576e-04	2.733e-02	0.065	0.075	46
creatinine	-9.876e-02	-3.987e-01	2.012e-01	0.512	0.008	57	1.376e-02	3.238e-03	2.428e-02	0.011	0.128	49
dimethylamine	3.230e-02	-5.124e-02	1.158e-01	0.436	0.020	32	-2.561e-03	-5.832e-03	7.091e-04	0.120	0.076	33
ethanol	-2.611e+00	-5.779e+00	5.576e-01	0.104	0.052	52	1.329e-01	3.860e-02	2.273e-01	0.007	0.158	45
fucose	-7.763e-01	-4.430e+00	2.877e+00	0.667	0.007	30	2.239e-01	-3.782e-01	8.261e-01	0.454	0.018	34
fumarate	1.168e-01	-2.575e-01	4.912e-01	0.534	0.007	57	3.049e-03	-7.677e-03	1.377e-02	0.570	0.007	49
galactose	7.896e-01	-2.700e+00	4.279e+00	0.648	0.007	34	2.066e-01	-1.887e-02	4.321e-01	0.071	0.090	37
glucose	1.398e+00	-1.662e+00	4.458e+00	0.364	0.015	58	2.917e-01	1.270e-01	4.565e-01	0.001	0.209	50
glutamate	2.982e+00	-4.924e+00	1.089e+01	0.453	0.010	57	1.223e-01	-2.764e-01	5.210e-01	0.540	0.008	47
glycerol	-2.559e-01	-2.423e+00	1.911e+00	0.811	0.002	34	2.269e-02	-1.937e-02	6.474e-02	0.281	0.033	37
glycine	4.370e-01	-2.027e+00	2.902e+00	0.724	0.002	57	1.069e-02	-8.755e-02	1.089e-01	0.828	0.001	49

histidine	3.732e-01	-3.721e-01	1.119e+00	0.317	0.028	38	-1.541e-02	-4.626e-02	1.545e-02	0.311	0.049	23
hypoxanthine	-1.475e-02	-1.117e+00	1.087e+00	0.978	0.000	23	-2.258e-02	-9.001e-02	4.484e-02	0.476	0.047	13
isoleucine	4.718e-01	-5.854e-01	1.529e+00	0.375	0.014	58	5.910e-03	-4.269e-02	5.451e-02	0.808	0.001	50
leucine	1.195e+00	-3.658e-01	2.755e+00	0.131	0.040	58	-1.957e-02	-9.581e-02	5.666e-02	0.608	0.006	50
lysine	2.634e-01	-5.345e+00	5.871e+00	0.925	0.000	46	-1.454e-02	-2.610e-01	2.319e-01	0.905	0.001	30
malonate	6.403e-02	-1.874e+00	2.002e+00	0.947	0.000	58	4.950e-02	-8.140e-03	1.071e-01	0.091	0.058	50
methanol	3.735e-01	-5.368e-01	1.284e+00	0.415	0.012	58	-2.108e-02	-4.899e-02	6.827e-03	0.135	0.046	50
methionine	3.967e-01	-2.795e-01	1.073e+00	0.245	0.024	58	3.033e-03	-2.460e-02	3.066e-02	0.826	0.001	50
methylamine	1.360e-02	-1.365e-01	1.637e-01	0.855	0.001	33	-3.907e-03	-8.240e-03	4.258e-04	0.075	0.098	33
methylhistidine	2.787e-01	-2.695e-01	8.270e-01	0.309	0.029	38	-2.183e-03	-2.292e-02	1.856e-02	0.829	0.002	23
myoinositol	3.678e+00	-1.397e+00	8.754e+00	0.137	0.207	12	1.912e-01	2.585e-02	3.566e-01	0.027	0.324	15
pcresol	-6.843e-02	-1.865e-01	4.968e-02	0.222	0.160	11	-2.183e-03	-1.326e-02	8.892e-03	0.575	0.116	5
phenylacetate	2.234e-01	-5.807e-01	1.027e+00	0.570	0.016	23	-3.089e-02	-5.505e-02	-6.723e-03	0.017	0.418	13
phenylalanine	8.285e-01	-2.363e-01	1.893e+00	0.125	0.042	58	8.874e-03	-2.496e-02	4.271e-02	0.600	0.006	49
proline	-6.258e+00	-1.120e+01	-1.312e+00	0.019	0.516	10	5.317e-02	-6.900e-02	1.753e-01	0.345	0.112	10
propyleneglycol	-7.793e-01	-2.473e+00	9.140e-01	0.360	0.016	56	1.528e-01	1.799e-02	2.876e-01	0.027	0.104	47
putrescine	-3.272e-01	-9.277e-01	2.732e-01	0.271	0.052	25	-6.876e-03	-4.318e-02	2.943e-02	0.698	0.007	24
pyroglutamate	1.646e+00	-1.827e+00	5.118e+00	0.312	0.113	11	2.831e-04	-7.601e-02	7.658e-02	0.994	0.000	16
pyruvate	5.186e-01	-8.584e-01	1.896e+00	0.454	0.010	58	8.664e-02	8.372e-03	1.649e-01	0.031	0.095	49
serine	7.821e-01	-1.723e+00	3.287e+00	0.531	0.011	38	6.074e-02	-2.291e-02	1.444e-01	0.147	0.089	25
taurine	-4.608e-01	-1.299e+00	3.769e-01	0.269	0.043	30	7.228e-03	-3.272e-02	4.717e-02	0.713	0.005	29
threonine	6.243e-01	-8.660e-01	2.115e+00	0.404	0.014	51	-6.672e-03	-7.381e-02	6.047e-02	0.842	0.001	48
trimethylamine	8.081e-02	-7.851e-02	2.401e-01	0.313	0.022	49	9.351e-04	-4.524e-03	6.394e-03	0.732	0.003	47
tryptophan	3.690e-02	-5.711e-02	1.309e-01	0.436	0.009	70	-3.308e-03	-7.007e-03	3.916e-04	0.079	0.053	59
tyrosine	6.215e-01	-3.456e-01	1.589e+00	0.203	0.029	58	1.050e-02	-2.833e-02	4.933e-02	0.589	0.006	49
uracil	2.606e-01	-4.967e-01	1.018e+00	0.493	0.009	57	7.402e-03	-1.745e-02	3.225e-02	0.552	0.008	47
valine	1.044e+00	-5.421e-01	2.629e+00	0.193	0.030	58	1.397e-02	-5.605e-02	8.399e-02	0.690	0.003	50
xanthine	4.437e-02	-1.868e-01	2.755e-01	0.698	0.005	32	-5.608e-05	-1.030e-02	1.019e-02	0.991	0.000	36
lactate	-4.110e+00	-9.293e+00	1.074e+00	0.118	0.038	66	3.843e-01	2.274e-02	7.459e-01	0.038	0.078	56

Note: Bolded rows in red text are metabolites that passed the X to M and M to Y criteria for mediation. In each cell, the letter "e" denotes powers of 10 (for example, 1.23e-01 means 1.23 multipled by 10^{-1} or 1.23 X 10^{-1}).

Table 3.10 Linear regression results assessing *X to M* and *M to Y* associations with maternal atopy as the exposure (X), individual male infant gut metabolites as potential mediators (M), and male infant motor scores at 2 years as the outcome (Y).

	Linear Regression Results of the Association between Combined Maternal Atopy (*X*) and each Metabolite (*M*) *X -> M*						Linear Regression Results of the Association between each Metabolite (*M*) and Male Infant Motor Scores at 2 Years *M -> Y*					
Metabolites	**β-coefficient**	**[95% C.I.]**		**p-value**	**R^2**	**N**	**β-coefficient**	**[95% C.I.]**		**p-value**	**R^2**	**N**
formate	-2.035e-01	-1.534e+00	1.127e+00	0.761	0.002	58	2.960e-02	-7.291e-02	1.321e-01	0.568	0.003	108
acetate	1.140e+01	-1.511e+01	3.790e+01	0.394	0.010	73	6.085e-01	-4.351e-01	1.652e+00	0.251	0.010	133
butyrate	-1.284e+00	-5.473e+00	2.905e+00	0.543	0.005	73	-6.835e-02	-2.162e-01	7.951e-02	0.362	0.006	133
propionate	3.137e+00	-4.460e+00	1.073e+01	0.413	0.009	73	1.022e-01	-1.636e-01	3.680e-01	0.448	0.004	133
valerate	2.118e-01	-6.809e-01	1.104e+00	0.638	0.003	73	1.402e-02	-2.033e-02	4.838e-02	0.421	0.005	133
isobutyrate	2.002e-01	-3.283e-01	7.286e-01	0.453	0.008	73	-4.337e-03	-2.273e-02	1.406e-02	0.642	0.002	133
isovalerate	2.158e-01	-4.660e-01	8.976e-01	0.530	0.006	73	-1.926e-03	-2.814e-02	2.429e-02	0.885	0.000	133
lactate	-4.110e+00	-9.293e+00	1.074e+00	0.118	0.038	66	1.239e-01	-1.485e-01	3.964e-01	0.370	0.007	122
succinate	-2.760e-01	-1.060e+01	1.005e+01	0.958	0.000	73	4.294e-01	-3.484e-02	8.936e-01	0.070	0.025	133
hydroxyglutarate	3.417e+00	1.026e+00	5.808e+00	0.012	0.000	8	3.896e-02	-2.382e-01	3.161e-01	0.758	0.011	11
aminobutyrate	2.132e-01	-6.934e-01	1.120e+00	0.628	0.013	21	7.999e-02	-7.979e-03	1.680e-01	0.074	0.064	51
hydroxyphenylacetate	1.717e-02	-3.988e-01	4.331e-01	0.933	0.000	29	-8.379e-03	-2.113e-02	4.367e-03	0.194	0.028	63
aminopentanoate	3.819e-01	-3.033e+00	3.797e+00	0.820	0.002	27	-6.887e-02	-1.816e-01	4.384e-02	0.226	0.028	55
acetoin	3.674e-01	-7.958e-01	1.531e+00	0.515	0.024	20	2.605e-02	-3.385e-02	8.596e-02	0.386	0.017	46
alanine	3.258e+00	-1.235e+00	7.751e+00	0.152	0.036	58	8.093e-02	-5.511e-02	2.170e-01	0.241	0.013	108
aspartate	1.125e+00	-6.898e-01	2.940e+00	0.219	0.027	57	1.862e-02	-4.165e-02	7.888e-02	0.541	0.004	106
betaalanine	5.686e-01	-2.894e-01	1.427e+00	0.165	0.226	10	-2.567e-02	-7.087e-02	1.952e-02	0.246	0.083	18
cadaverine	-2.614e-01	-3.499e+00	2.976e+00	0.870	0.001	33	-3.225e-02	-1.575e-01	9.304e-02	0.609	0.004	67
choline	1.105e-02	-2.750e-01	2.971e-01	0.939	0.000	56	7.965e-03	-2.099e-03	1.803e-02	0.120	0.024	103
creatine	1.165e-01	-2.008e-01	4.338e-01	0.465	0.010	56	7.822e-03	-3.702e-03	1.935e-02	0.181	0.018	102
creatinine	-9.876e-02	-3.987e-01	2.012e-01	0.512	0.008	57	2.882e-03	-7.241e-03	1.300e-02	0.574	0.003	106
dimethylamine	3.230e-02	-5.124e-02	1.158e-01	0.436	0.020	32	-1.154e-03	-3.985e-03	1.677e-03	0.418	0.010	65
ethanol	-2.611e+00	-5.779e+00	5.576e-01	0.104	0.052	52	1.095e-01	6.601e-03	2.125e-01	0.037	0.045	97
fucose	-7.763e-01	-4.430e+00	2.877e+00	0.667	0.007	30	2.327e-01	-1.546e-01	6.200e-01	0.234	0.023	64
fumarate	1.168e-01	-2.575e-01	4.912e-01	0.534	0.007	57	-5.038e-04	-1.166e-02	1.065e-02	0.929	0.000	106
galactose	7.896e-01	-2.700e+00	4.279e+00	0.648	0.007	34	1.435e-01	-2.033e-02	3.073e-01	0.085	0.042	71
glucose	1.398e+00	-1.662e+00	4.458e+00	0.364	0.015	58	6.279e-02	-7.167e-02	1.973e-01	0.357	0.008	108
glutamate	2.982e+00	-4.924e+00	1.089e+01	0.453	0.010	57	1.897e-01	-1.223e-01	5.018e-01	0.231	0.014	104
glycerol	-2.559e-01	-2.423e+00	1.911e+00	0.811	0.002	34	4.818e-02	-7.369e-03	1.037e-01	0.088	0.042	71
glycine	4.370e-01	-2.027e+00	2.902e+00	0.724	0.002	57	-3.208e-03	-8.782e-02	8.141e-02	0.940	0.000	106

histidine	3.732e-01	-3.721e-01	1.119e+00	0.317	0.028	38	2.801e-02	1.657e-03	5.436e-02	0.038	0.071	61
hypoxanthine	-1.475e-02	-1.117e+00	1.087e+00	0.978	0.000	23	2.266e-02	-1.589e-02	6.120e-02	0.241	0.040	36
isoleucine	4.718e-01	-5.854e-01	1.529e+00	0.375	0.014	58	-3.780e-03	-4.285e-02	3.529e-02	0.848	0.000	108
leucine	1.195e+00	-3.658e-01	2.755e+00	0.131	0.040	58	-6.688e-03	-6.685e-02	5.348e-02	0.826	0.000	108
lysine	2.634e-01	-5.345e+00	5.871e+00	0.925	0.000	46	-7.145e-02	-2.925e-01	1.496e-01	0.522	0.006	76
malonate	6.403e-02	-1.874e+00	2.002e+00	0.947	0.000	58	-1.302e-03	-6.035e-02	5.774e-02	0.965	0.000	108
methanol	3.735e-01	-5.368e-01	1.284e+00	0.415	0.012	58	-2.691e-02	-5.445e-02	6.324e-04	0.055	0.034	108
methionine	3.967e-01	-2.795e-01	1.073e+00	0.245	0.024	58	-3.037e-03	-2.659e-02	2.052e-02	0.799	0.001	108
methylamine	1.360e-02	-1.365e-01	1.637e-01	0.855	0.001	33	-6.268e-03	-1.048e-02	-2.060e-03	0.004	0.122	66
methylhistidine	2.787e-01	-2.695e-01	8.270e-01	0.309	0.029	38	-9.409e-03	-2.858e-02	9.762e-03	0.330	0.016	61
myoinositol	3.678e+00	-1.397e+00	8.754e+00	0.137	0.207	12	8.926e-02	-4.544e-02	2.240e-01	0.184	0.069	27
pcresol	-6.843e-02	-1.865e-01	4.968e-02	0.222	0.160	11	-7.982e-04	-6.064e-03	4.468e-03	0.750	0.007	16
phenylacetate	2.234e-01	-5.807e-01	1.027e+00	0.570	0.016	23	-2.125e-07	-2.353e-02	2.353e-02	1.000	0.000	36
phenylalanine	8.285e-01	-2.363e-01	1.893e+00	0.125	0.042	58	-4.288e-03	-3.826e-02	2.969e-02	0.803	0.001	107
proline	-6.258e+00	-1.120e+01	-1.312e+00	0.019	0.516	10	3.407e-02	-1.190e-01	1.872e-01	0.646	0.012	20
propyleneglycol	-7.793e-01	-2.473e+00	9.140e-01	0.360	0.016	56	9.541e-02	-3.087e-03	1.939e-01	0.057	0.035	103
putrescine	-3.272e-01	-9.277e-01	2.732e-01	0.271	0.052	25	1.001e-02	-1.623e-02	3.625e-02	0.447	0.012	49
pyroglutamate	1.646e+00	-1.827e+00	5.118e+00	0.312	0.113	11	-6.157e-02	-1.368e-01	1.362e-02	0.104	0.102	27
pyruvate	5.186e-01	-8.584e-01	1.896e+00	0.454	0.010	58	3.360e-02	-2.623e-02	9.343e-02	0.268	0.012	107
serine	7.821e-01	-1.723e+00	3.287e+00	0.531	0.011	38	2.261e-02	-5.606e-02	1.013e-01	0.568	0.005	63
taurine	-4.608e-01	-1.299e+00	3.769e-01	0.269	0.043	30	-1.027e-02	-4.633e-02	2.578e-02	0.571	0.006	59
threonine	6.243e-01	-8.660e-01	2.115e+00	0.404	0.014	51	-1.658e-02	-7.256e-02	3.941e-02	0.558	0.004	99
trimethylamine	8.081e-02	-7.851e-02	2.401e-01	0.313	0.022	49	2.988e-03	-2.283e-03	8.260e-03	0.263	0.013	96
tryptophan	3.690e-02	-5.711e-02	1.309e-01	0.436	0.009	70	-4.276e-03	-7.567e-03	-9.854e-04	0.011	0.049	129
tyrosine	6.215e-01	-3.456e-01	1.589e+00	0.203	0.029	58	-4.532e-03	-3.846e-02	2.939e-02	0.792	0.001	107
uracil	2.606e-01	-4.967e-01	1.018e+00	0.493	0.009	57	1.865e-03	-2.179e-02	2.552e-02	0.876	0.000	104
valine	1.044e+00	-5.421e-01	2.629e+00	0.193	0.030	58	1.480e-02	-4.268e-02	7.228e-02	0.611	0.002	108
xanthine	4.437e-02	-1.868e-01	2.755e-01	0.698	0.005	32	-2.496e-03	-1.075e-02	5.755e-03	0.548	0.005	68
lactate	-4.110e+00	-9.293e+00	1.074e+00	0.118	0.038	66	1.239e-01	-1.485e-01	3.964e-01	0.370	0.007	122

Note: Bolded rows in red text are metabolites that passed the X to M and M to Y criteria for mediation. In each cell, the letter "e" denotes powers of 10 (for example, 1.23e-01 means 1.23 multipled by 10^{-1} or 1.23 X 10^{-1}).

Table 3.11 Linear regression results assessing *X to M* and *M to Y* associations with maternal atopy as the exposure (X), individual female infant gut metabolites as potential mediators (M), and female infant socio-emotional scores at 1 year as the outcome (Y).

	Linear Regression Results of the Association between Combined Maternal Atopy (*X*) and each Metabolite (*M*) *X -> M*						Linear Regression Results of the Association between each Metabolite (*M*) and Female Infant Socio-emotional Scores at 1 Year *M -> Y*					
Metabolites	**β-coefficient**	**[95% C.I.]**		**p-value**	**R^2**	**N**	**β-coefficient**	**[95% C.I.]**		**p-value**	**R^2**	**N**
formate	-3.506e+00	-8.009e+00	9.962e-01	0.124	0.049	50	4.392e-02	-3.804e-02	1.259e-01	0.290	0.011	102
acetate	3.724e+01	1.439e+00	7.304e+01	0.042	0.070	60	3.958e-01	-4.113e-01	1.203e+00	0.334	0.007	127
butyrate	3.303e+00	-1.248e+00	7.854e+00	0.152	0.035	60	3.146e-02	-8.106e-02	1.440e-01	0.581	0.002	127
propionate	6.147e+00	-2.057e+00	1.435e+01	0.139	0.037	60	7.087e-02	-1.337e-01	2.754e-01	0.494	0.004	127
valerate	6.875e-01	-4.973e-01	1.872e+00	0.250	0.023	60	-1.501e-02	-4.151e-02	1.149e-02	0.264	0.010	127
isobutyrate	4.202e-01	-1.381e-01	9.785e-01	0.137	0.038	60	1.205e-03	-1.305e-02	1.546e-02	0.867	0.000	127
isovalerate	7.670e-01	-1.151e-01	1.649e+00	0.087	0.050	60	-5.594e-03	-2.584e-02	1.465e-02	0.585	0.002	127
lactate	-5.986e-01	-1.139e+01	1.019e+01	0.912	0.000	56	1.987e-01	-4.408e-03	4.018e-01	0.055	0.032	117
succinate	-4.268e+00	-2.217e+01	1.364e+01	0.635	0.004	60	-9.254e-02	-4.361e-01	2.511e-01	0.595	0.002	127
hydroxyglutarate	4.009e+00	-3.535e+01	4.337e+01	0.419	0.626	3	-2.743e-02	-2.728e-01	2.180e-01	0.803	0.008	10
aminobutyrate	9.195e-01	-2.062e+00	3.901e+00	0.533	0.014	30	3.295e-02	-3.643e-02	1.023e-01	0.344	0.019	48
hydroxyphenylacetate	7.132e-02	-2.742e-01	4.168e-01	0.677	0.005	34	-7.428e-03	-1.843e-02	3.573e-03	0.182	0.031	59
aminopentanoate	6.610e-01	-2.870e+00	4.192e+00	0.704	0.006	28	4.657e-02	-3.795e-02	1.311e-01	0.274	0.024	51
acetoin	1.101e+00	-8.387e-01	3.041e+00	0.253	0.054	26	2.615e-02	-1.941e-02	7.171e-02	0.253	0.030	45
alanine	1.567e+00	-2.328e+00	5.462e+00	0.423	0.013	50	6.334e-02	-4.544e-02	1.721e-01	0.251	0.013	102
aspartate	1.551e+00	-3.199e-01	3.422e+00	0.102	0.056	49	1.222e-02	-3.543e-02	5.988e-02	0.612	0.003	100
betaalanine	2.634e-01	-2.124e+00	2.651e+00	0.796	0.012	8	-1.857e-02	-6.440e-02	2.726e-02	0.401	0.047	17
cadaverine	-2.279e+00	-5.943e+00	1.385e+00	0.214	0.048	34	6.409e-02	-2.797e-02	1.562e-01	0.169	0.031	63
choline	-1.756e-01	-5.535e-01	2.022e-01	0.354	0.019	47	1.034e-02	2.191e-03	1.848e-02	0.013	0.063	97
creatine	1.224e-01	-2.936e-01	5.384e-01	0.556	0.008	46	6.530e-04	-8.457e-03	9.763e-03	0.887	0.000	96
creatinine	6.272e-02	-2.552e-01	3.807e-01	0.693	0.003	49	4.741e-03	-2.821e-03	1.230e-02	0.216	0.016	100
dimethylamine	6.412e-03	-8.253e-02	9.535e-02	0.884	0.001	33	1.758e-03	-4.523e-04	3.969e-03	0.117	0.040	62
ethanol	5.814e-01	-2.446e+00	3.608e+00	0.700	0.003	45	4.805e-02	-2.954e-02	1.256e-01	0.222	0.017	91
fucose	3.084e+00	-1.300e+01	1.916e+01	0.699	0.005	34	1.051e-02	-3.080e-01	3.290e-01	0.948	0.000	60
fumarate	2.112e-01	-9.929e-02	5.217e-01	0.178	0.038	49	-7.221e-04	-9.583e-03	8.139e-03	0.872	0.000	100
galactose	2.586e+00	-3.293e+00	8.466e+00	0.378	0.022	37	-2.793e-02	-1.629e-01	1.070e-01	0.681	0.003	67
glucose	3.741e+00	-1.568e+00	9.050e+00	0.163	0.040	50	8.060e-02	-2.605e-02	1.873e-01	0.137	0.022	102
glutamate	-3.551e+00	-1.539e+01	8.290e+00	0.549	0.008	47	-1.882e-01	-4.354e-01	5.891e-02	0.134	0.023	98
glycerol	-1.009e+00	-2.028e+00	9.487e-03	0.052	0.104	37	-1.615e-02	-6.196e-02	2.967e-02	0.484	0.008	67
glycine	-1.073e+00	-3.939e+00	1.794e+00	0.455	0.012	49	3.150e-02	-3.442e-02	9.742e-02	0.345	0.009	100

histidine	3.354e-01	-6.944e-01	1.365e+00	0.506	0.021	23	-1.737e-02	-3.697e-02	2.224e-03	0.081	0.052	59
hypoxanthine	1.781e+00	-2.021e-01	3.763e+00	0.074	0.262	13	1.394e-03	-2.952e-02	3.231e-02	0.927	0.000	34
isoleucine	1.183e+00	-1.975e-01	2.564e+00	0.091	0.058	50	2.607e-04	-3.046e-02	3.098e-02	0.987	0.000	102
leucine	1.722e+00	-4.579e-01	3.902e+00	0.119	0.050	50	-7.810e-03	-5.593e-02	4.031e-02	0.748	0.001	102
lysine	4.207e+00	-3.400e+00	1.181e+01	0.267	0.044	30	-5.860e-02	-2.081e-01	9.091e-02	0.437	0.009	71
malonate	1.642e+00	-2.980e-02	3.313e+00	0.054	0.075	50	1.308e-02	-3.382e-02	5.998e-02	0.581	0.003	102
methanol	-3.447e-01	-1.175e+00	4.853e-01	0.408	0.014	50	-1.377e-02	-3.595e-02	8.418e-03	0.221	0.015	102
methionine	8.509e-01	8.070e-02	1.621e+00	0.031	0.093	50	7.843e-03	-1.031e-02	2.600e-02	0.394	0.007	102
methylamine	9.349e-02	-3.637e-03	1.906e-01	0.059	0.111	33	-1.998e-04	-3.728e-03	3.328e-03	0.910	0.000	62
methylhistidine	-5.165e-01	-1.158e+00	1.252e-01	0.109	0.118	23	-3.149e-03	-1.734e-02	1.104e-02	0.659	0.003	59
myoinositol	6.275e-01	-3.827e+00	5.082e+00	0.766	0.007	15	-2.240e-02	-1.236e-01	7.883e-02	0.652	0.009	26
pcresol	8.620e-02	1.528e-02	1.571e-01	0.028	-0.000	5	1.487e-03	-2.832e-03	5.806e-03	0.470	0.041	15
phenylacetate	3.252e-01	-7.114e-01	1.362e+00	0.504	0.042	13	-1.462e-02	-3.244e-02	3.191e-03	0.104	0.080	34
phenylalanine	6.326e-01	-3.611e-01	1.626e+00	0.207	0.034	49	1.544e-02	-1.150e-02	4.239e-02	0.258	0.013	101
proline	-1.945e+00	-5.997e+00	2.106e+00	0.300	0.133	10	6.304e-02	-5.797e-02	1.841e-01	0.288	0.062	20
propyleneglycol	-1.519e+00	-5.751e+00	2.713e+00	0.474	0.011	47	1.614e-02	-6.123e-02	9.351e-02	0.680	0.002	99
putrescine	-3.414e-01	-1.293e+00	6.102e-01	0.465	0.025	24	1.016e-02	-1.118e-02	3.150e-02	0.342	0.021	45
pyroglutamate	9.414e-02	-1.399e+00	1.588e+00	0.894	0.001	16	1.116e-02	-5.852e-02	8.084e-02	0.742	0.005	23
pyruvate	-1.385e+00	-3.803e+00	1.033e+00	0.255	0.027	49	5.063e-03	-4.303e-02	5.315e-02	0.835	0.000	101
serine	1.956e-01	-2.714e+00	3.105e+00	0.891	0.001	25	-4.462e-02	-1.078e-01	1.851e-02	0.163	0.033	61
taurine	4.460e-01	-6.107e-01	1.503e+00	0.394	0.027	29	3.975e-04	-2.648e-02	2.727e-02	0.976	0.000	55
threonine	-5.166e-01	-2.502e+00	1.469e+00	0.603	0.006	48	3.171e-03	-4.314e-02	4.948e-02	0.892	0.000	93
trimethylamine	6.871e-02	-9.693e-02	2.343e-01	0.408	0.015	47	-1.202e-03	-5.325e-03	2.920e-03	0.564	0.004	90
tryptophan	4.047e-02	-7.020e-02	1.512e-01	0.467	0.009	59	-6.666e-05	-2.699e-03	2.566e-03	0.960	0.000	123
tyrosine	9.168e-01	-2.121e-01	2.046e+00	0.109	0.054	49	9.459e-03	-1.760e-02	3.652e-02	0.490	0.005	101
uracil	3.504e-01	-3.760e-01	1.077e+00	0.336	0.021	47	5.816e-03	-1.327e-02	2.490e-02	0.547	0.004	98
valine	1.667e+00	-3.273e-01	3.661e+00	0.099	0.056	50	4.666e-04	-4.529e-02	4.622e-02	0.984	0.000	102
xanthine	1.231e-01	-1.333e-01	3.795e-01	0.336	0.027	36	4.818e-03	-1.636e-03	1.127e-02	0.141	0.035	64
lactate	-5.986e-01	-1.139e+01	1.019e+01	0.912	0.000	56	1.987e-01	-4.408e-03	4.018e-01	0.055	0.032	117

Note: Bolded rows in red text are metabolites that passed the X to M and M to Y criteria for mediation. In each cell, the letter "e" denotes powers of 10 (for example, 1.23e-01 means 1.23 multipled by 10^{-1} or 1.23 X 10^{-1}).

Table 3.12 Linear regression results assessing *X to M* and *M to Y* associations with maternal atopy as the exposure (X), individual female infant gut metabolites as potential mediators (M), and female infant socio-emotional scores at 2 years as the outcome (Y).

	Linear Regression Results of the Association between Combined Maternal Atopy (*X*) and each Metabolite (*M*) *X -> M*						Linear Regression Results of the Association between each Metabolite (*M*) and Female Infant Socio-emotional Scores at 2 Years *M -> Y*					
Metabolites	**β-coefficient**	**[95% C.I.]**		**p-value**	**R^2**	**N**	**β-coefficient**	**[95% C.I.]**		**p-value**	**R^2**	**N**
formate	-3.506e+00	-8.009e+00	9.962e-01	0.124	0.049	50	5.827e-02	-9.795e-03	1.263e-01	0.093	0.027	106
acetate	3.724e+01	1.439e+00	7.304e+01	0.042	0.070	60	2.098e-01	-4.563e-01	8.760e-01	0.534	0.003	130
butyrate	3.303e+00	-1.248e+00	7.854e+00	0.152	0.035	60	-3.333e-03	-9.894e-02	9.227e-02	0.945	0.000	130
propionate	6.147e+00	-2.057e+00	1.435e+01	0.139	0.037	60	-2.573e-02	-1.978e-01	1.463e-01	0.768	0.001	130
valerate	6.875e-01	-4.973e-01	1.872e+00	0.250	0.023	60	4.746e-03	-1.747e-02	2.697e-02	0.673	0.001	130
isobutyrate	4.202e-01	-1.381e-01	9.785e-01	0.137	0.038	60	-5.899e-03	-1.773e-02	5.927e-03	0.326	0.008	130
isovalerate	7.670e-01	-1.151e-01	1.649e+00	0.087	0.050	60	-7.719e-03	-2.453e-02	9.088e-03	0.365	0.006	130
lactate	-5.986e-01	-1.139e+01	1.019e+01	0.912	0.000	56	1.801e-01	4.419e-03	3.559e-01	0.045	0.034	119
succinate	-4.268e+00	-2.217e+01	1.364e+01	0.635	0.004	60	1.266e-01	-1.758e-01	4.290e-01	0.409	0.005	130
hydroxyglutarate	4.009e+00	-3.535e+01	4.337e+01	0.419	0.626	3	6.575e-03	-1.801e-01	1.933e-01	0.937	0.001	10
aminobutyrate	9.195e-01	-2.062e+00	3.901e+00	0.533	0.014	30	3.262e-02	-2.409e-02	8.932e-02	0.253	0.027	50
hydroxyphenylacetate	7.132e-02	-2.742e-01	4.168e-01	0.677	0.005	34	-1.467e-03	-9.879e-03	6.944e-03	0.728	0.002	62
aminopentanoate	6.610e-01	-2.870e+00	4.192e+00	0.704	0.006	28	1.040e-02	-6.018e-02	8.097e-02	0.769	0.002	54
acetoin	1.101e+00	-8.387e-01	3.041e+00	0.253	0.054	26	3.867e-02	1.077e-03	7.627e-02	0.044	0.091	45
alanine	1.567e+00	-2.328e+00	5.462e+00	0.423	0.013	50	8.113e-02	-8.144e-03	1.704e-01	0.074	0.030	106
aspartate	1.551e+00	-3.199e-01	3.422e+00	0.102	0.056	49	1.838e-02	-2.168e-02	5.845e-02	0.365	0.008	104
betaalanine	2.634e-01	-2.124e+00	2.651e+00	0.796	0.012	8	2.990e-04	-2.795e-02	2.855e-02	0.982	0.000	17
cadaverine	-2.279e+00	-5.943e+00	1.385e+00	0.214	0.048	34	3.888e-02	-3.245e-02	1.102e-01	0.280	0.018	66
choline	-1.756e-01	-5.535e-01	2.022e-01	0.354	0.019	47	3.919e-03	-2.941e-03	1.078e-02	0.260	0.013	101
creatine	1.224e-01	-2.936e-01	5.384e-01	0.556	0.008	46	5.583e-03	-1.994e-03	1.316e-02	0.147	0.021	100
creatinine	6.272e-02	-2.552e-01	3.807e-01	0.693	0.003	49	5.362e-03	-1.229e-03	1.195e-02	0.110	0.025	104
dimethylamine	6.412e-03	-8.253e-02	9.535e-02	0.884	0.001	33	9.555e-04	-8.315e-04	2.742e-03	0.289	0.018	64
ethanol	5.814e-01	-2.446e+00	3.608e+00	0.700	0.003	45	5.758e-02	-7.611e-03	1.228e-01	0.083	0.032	95
fucose	3.084e+00	-1.300e+01	1.916e+01	0.699	0.005	34	3.079e-01	6.836e-02	5.475e-01	0.013	0.098	63
fumarate	2.112e-01	-9.929e-02	5.217e-01	0.178	0.038	49	1.052e-03	-6.459e-03	8.562e-03	0.782	0.001	104
galactose	2.586e+00	-3.293e+00	8.466e+00	0.378	0.022	37	1.092e-01	4.231e-03	2.143e-01	0.042	0.060	70
glucose	3.741e+00	-1.568e+00	9.050e+00	0.163	0.040	50	6.563e-02	-2.411e-02	1.554e-01	0.150	0.020	106
glutamate	-3.551e+00	-1.539e+01	8.290e+00	0.549	0.008	47	6.823e-02	-1.451e-01	2.816e-01	0.527	0.004	102
glycerol	-1.009e+00	-2.028e+00	9.487e-03	0.052	0.104	37	-2.276e-02	-5.880e-02	1.328e-02	0.212	0.023	70
glycine	-1.073e+00	-3.939e+00	1.794e+00	0.455	0.012	49	3.488e-02	-2.062e-02	9.038e-02	0.215	0.015	104

histidine	3.354e-01	-6.944e-01	1.365e+00	0.506	0.021	23	-1.036e-02	-2.667e-02	5.950e-03	0.209	0.028	59
hypoxanthine	1.781e+00	-2.021e-01	3.763e+00	0.074	0.262	13	9.666e-03	-1.848e-02	3.782e-02	0.490	0.015	35
isoleucine	1.183e+00	-1.975e-01	2.564e+00	0.091	0.058	50	4.022e-03	-2.063e-02	2.867e-02	0.747	0.001	106
leucine	1.722e+00	-4.579e-01	3.902e+00	0.119	0.050	50	-7.568e-03	-4.610e-02	3.096e-02	0.698	0.001	106
lysine	4.207e+00	-3.400e+00	1.181e+01	0.267	0.044	30	-1.967e-02	-1.631e-01	1.238e-01	0.785	0.001	74
malonate	1.642e+00	-2.980e-02	3.313e+00	0.054	0.075	50	1.684e-02	-2.273e-02	5.640e-02	0.401	0.007	106
methanol	-3.447e-01	-1.175e+00	4.853e-01	0.408	0.014	50	4.443e-03	-1.434e-02	2.322e-02	0.640	0.002	106
methionine	8.509e-01	8.070e-02	1.621e+00	0.031	0.093	50	5.447e-03	-1.020e-02	2.110e-02	0.492	0.005	106
methylamine	9.349e-02	-3.637e-03	1.906e-01	0.059	0.111	33	-2.003e-03	-4.782e-03	7.753e-04	0.155	0.032	65
methylhistidine	-5.165e-01	-1.158e+00	1.252e-01	0.109	0.118	23	-3.885e-03	-1.612e-02	8.354e-03	0.528	0.007	59
myoinositol	6.275e-01	-3.827e+00	5.082e+00	0.766	0.007	15	-1.783e-02	-9.813e-02	6.248e-02	0.651	0.009	26
pcresol	8.620e-02	1.528e-02	1.571e-01	0.028	-0.000	5	3.201e-04	-2.737e-03	3.377e-03	0.826	0.004	16
phenylacetate	3.252e-01	-7.114e-01	1.362e+00	0.504	0.042	13	-1.577e-02	-3.191e-02	3.757e-04	0.055	0.107	35
phenylalanine	6.326e-01	-3.611e-01	1.626e+00	0.207	0.034	49	1.118e-02	-1.067e-02	3.304e-02	0.313	0.010	105
proline	-1.945e+00	-5.997e+00	2.106e+00	0.300	0.133	10	7.059e-02	-4.692e-02	1.881e-01	0.223	0.081	20
propyleneglycol	-1.519e+00	-5.751e+00	2.713e+00	0.474	0.011	47	2.811e-02	-3.835e-02	9.458e-02	0.403	0.007	100
putrescine	-3.414e-01	-1.293e+00	6.102e-01	0.465	0.025	24	3.045e-03	-1.428e-02	2.037e-02	0.725	0.003	48
pyroglutamate	9.414e-02	-1.399e+00	1.588e+00	0.894	0.001	16	-1.124e-02	-5.952e-02	3.703e-02	0.635	0.010	26
pyruvate	-1.385e+00	-3.803e+00	1.033e+00	0.255	0.027	49	1.096e-02	-2.935e-02	5.128e-02	0.591	0.003	105
serine	1.956e-01	-2.714e+00	3.105e+00	0.891	0.001	25	-2.400e-02	-8.097e-02	3.297e-02	0.403	0.012	62
taurine	4.460e-01	-6.107e-01	1.503e+00	0.394	0.027	29	1.229e-02	-8.142e-03	3.272e-02	0.233	0.025	58
threonine	-5.166e-01	-2.502e+00	1.469e+00	0.603	0.006	48	9.455e-03	-2.931e-02	4.822e-02	0.629	0.002	97
trimethylamine	6.871e-02	-9.693e-02	2.343e-01	0.408	0.015	47	-2.564e-03	-6.178e-03	1.050e-03	0.162	0.021	94
tryptophan	4.047e-02	-7.020e-02	1.512e-01	0.467	0.009	59	-1.122e-03	-3.319e-03	1.074e-03	0.314	0.008	126
tyrosine	9.168e-01	-2.121e-01	2.046e+00	0.109	0.054	49	3.266e-03	-1.931e-02	2.585e-02	0.775	0.001	105
uracil	3.504e-01	-3.760e-01	1.077e+00	0.336	0.021	47	7.567e-03	-8.635e-03	2.377e-02	0.356	0.009	102
valine	1.667e+00	-3.273e-01	3.661e+00	0.099	0.056	50	1.094e-02	-2.477e-02	4.666e-02	0.545	0.004	106
xanthine	1.231e-01	-1.333e-01	3.795e-01	0.336	0.027	36	1.516e-03	-3.814e-03	6.846e-03	0.572	0.005	67
lactate	-5.986e-01	-1.139e+01	1.019e+01	0.912	0.000	56	1.801e-01	4.419e-03	3.559e-01	0.045	0.034	119

Note: Bolded rows in red text are metabolites that passed the X to M and M to Y criteria for mediation. In each cell, the letter "e" denotes powers of 10 (for example, 1.23e-01 means 1.23 multipled by 10^{-1} or 1.23 X 10^{-1}).

Table 3.13 Linear regression results assessing *X to M* and *M to Y* associations with maternal asthma as the exposure (X), infant gut metabolites as potential mediators (M), and infant socio-emotional scores at 2 years as the outcome (Y).

	Linear Regression Results of the Association between Maternal Asthma (*X*) and each Metabolite (*M*) *X -> M*						Linear Regression Results of the Association between each Metabolite (*M*) and Infant Socio-emotional Scores at 2 Years *M -> Y*					
Metabolites	**β-coefficient**	**[95% C.I.]**		**p-value**	**R^2**	**N**	**β-coefficient**	**[95% C.I.]**		**p-value**	**R^2**	**N**
formate	-1.074e+00	-3.570e+00	1.423e+00	0.396	0.007	108	5.827e-02	-9.795e-03	1.263e-01	0.093	0.027	106
acetate	6.473e+00	-1.861e+01	3.156e+01	0.611	0.002	133	2.098e-01	-4.563e-01	8.760e-01	0.534	0.003	130
butyrate	1.518e+00	-2.023e+00	5.060e+00	0.398	0.005	133	-3.333e-03	-9.894e-02	9.227e-02	0.945	0.000	130
propionate	2.308e+00	-4.057e+00	8.673e+00	0.475	0.004	133	-2.573e-02	-1.978e-01	1.463e-01	0.768	0.001	130
valerate	-3.264e-01	-1.149e+00	4.962e-01	0.434	0.005	133	4.746e-03	-1.747e-02	2.697e-02	0.673	0.001	130
isobutyrate	3.251e-02	-4.082e-01	4.732e-01	0.884	0.000	133	-5.899e-03	-1.773e-02	5.927e-03	0.326	0.008	130
isovalerate	-2.163e-02	-6.493e-01	6.061e-01	0.946	0.000	133	-7.719e-03	-2.453e-02	9.088e-03	0.365	0.006	130
lactate	-2.041e+00	-8.388e+00	4.305e+00	0.525	0.003	122	1.801e-01	4.419e-03	3.559e-01	0.045	0.034	119
succinate	-8.779e-01	-1.213e+01	1.038e+01	0.878	0.000	133	1.266e-01	-1.758e-01	4.290e-01	0.409	0.005	130
hydroxyglutarate	-1.538e+00	-8.863e+00	5.788e+00	0.646	0.024	11	6.575e-03	-1.801e-01	1.933e-01	0.937	0.001	10
aminobutyrate	2.575e+00	6.165e-01	4.534e+00	0.011	0.125	51	3.262e-02	-2.409e-02	8.932e-02	0.253	0.027	50
hydroxyphenylacetate	2.289e-02	-2.650e-01	3.107e-01	0.874	0.000	63	-1.467e-03	-9.879e-03	6.944e-03	0.728	0.002	62
aminopentanoate	6.157e-01	-1.923e+00	3.155e+00	0.629	0.004	55	1.040e-02	-6.018e-02	8.097e-02	0.769	0.002	54
acetoin	4.142e-02	-1.248e+00	1.331e+00	0.949	0.000	46	3.867e-02	1.077e-03	7.627e-02	0.044	0.091	45
alanine	3.113e-01	-3.030e+00	3.653e+00	0.854	0.000	108	8.113e-02	-8.144e-03	1.704e-01	0.074	0.030	106
aspartate	1.396e-01	-1.326e+00	1.606e+00	0.851	0.000	106	1.838e-02	-2.168e-02	5.845e-02	0.365	0.008	104
betaalanine	-3.645e-01	-1.177e+00	4.485e-01	0.356	0.053	18	2.990e-04	-2.795e-02	2.855e-02	0.982	0.000	17
cadaverine	-2.036e+00	-4.732e+00	6.605e-01	0.136	0.034	67	3.888e-02	-3.245e-02	1.102e-01	0.280	0.018	66
choline	-2.011e-01	-4.499e-01	4.773e-02	0.112	0.025	103	3.919e-03	-2.941e-03	1.078e-02	0.260	0.013	101
creatine	-1.062e-01	-3.830e-01	1.705e-01	0.448	0.006	102	5.583e-03	-1.994e-03	1.316e-02	0.147	0.021	100
creatinine	-1.082e-01	-3.490e-01	1.327e-01	0.375	0.008	106	5.362e-03	-1.229e-03	1.195e-02	0.110	0.025	104
dimethylamine	6.531e-02	1.042e-03	1.296e-01	0.047	0.061	65	9.555e-04	-8.315e-04	2.742e-03	0.289	0.018	64
ethanol	-6.448e-01	-3.064e+00	1.774e+00	0.598	0.003	97	5.758e-02	-7.611e-03	1.228e-01	0.083	0.032	95
fucose	-2.620e+00	-1.206e+01	6.822e+00	0.581	0.005	64	3.079e-01	6.836e-02	5.475e-01	0.013	0.098	63
fumarate	2.934e-02	-2.436e-01	3.023e-01	0.832	0.000	106	1.052e-03	-6.459e-03	8.562e-03	0.782	0.001	104
galactose	-8.113e-01	-4.696e+00	3.074e+00	0.678	0.003	71	1.092e-01	4.231e-03	2.143e-01	0.042	0.060	70
glucose	-2.736e-01	-3.568e+00	3.021e+00	0.870	0.000	108	6.563e-02	-2.411e-02	1.554e-01	0.150	0.020	106
glutamate	1.850e+00	-5.996e+00	9.696e+00	0.641	0.002	104	6.823e-02	-1.451e-01	2.816e-01	0.527	0.004	102
glycerol	2.429e-01	-1.077e+00	1.563e+00	0.715	0.002	71	-2.276e-02	-5.880e-02	1.328e-02	0.212	0.023	70
glycine	2.024e-01	-1.864e+00	2.268e+00	0.846	0.000	106	3.488e-02	-2.062e-02	9.038e-02	0.215	0.015	104

histidine	1.917e-01	-4.809e-01	8.644e-01	0.571	0.005	61	-1.036e-02	-2.667e-02	5.950e-03	0.209	0.028	59
hypoxanthine	1.650e-01	-8.724e-01	1.202e+00	0.748	0.003	36	9.666e-03	-1.848e-02	3.782e-02	0.490	0.015	35
isoleucine	-2.180e-01	-1.171e+00	7.347e-01	0.651	0.002	108	4.022e-03	-2.063e-02	2.867e-02	0.747	0.001	106
leucine	-4.329e-01	-1.899e+00	1.033e+00	0.560	0.003	108	-7.568e-03	-4.610e-02	3.096e-02	0.698	0.001	106
lysine	1.666e+00	-3.161e+00	6.494e+00	0.494	0.006	76	-1.967e-02	-1.631e-01	1.238e-01	0.785	0.001	74
malonate	4.796e-01	-9.584e-01	1.918e+00	0.510	0.004	108	1.684e-02	-2.273e-02	5.640e-02	0.401	0.007	106
methanol	5.979e-01	-7.617e-02	1.272e+00	0.082	0.028	108	4.443e-03	-1.434e-02	2.322e-02	0.640	0.002	106
methionine	-4.883e-02	-6.237e-01	5.261e-01	0.867	0.000	108	5.447e-03	-1.020e-02	2.110e-02	0.492	0.005	106
methylamine	2.134e-02	-7.882e-02	1.215e-01	0.672	0.003	66	-2.003e-03	-4.782e-03	7.753e-04	0.155	0.032	65
methylhistidine	1.613e-01	-3.135e-01	6.362e-01	0.499	0.008	61	-3.885e-03	-1.612e-02	8.354e-03	0.528	0.007	59
myoinositol	1.305e+00	-2.247e+00	4.858e+00	0.456	0.022	27	-1.783e-02	-9.813e-02	6.248e-02	0.651	0.009	26
pcresol	-6.723e-02	-1.989e-01	6.447e-02	0.292	0.079	16	3.201e-04	-2.737e-03	3.377e-03	0.826	0.004	16
phenylacetate	2.889e-01	-3.243e-01	9.021e-01	0.345	0.026	36	-1.577e-02	-3.191e-02	3.757e-04	0.055	0.107	35
phenylalanine	3.910e-01	-4.262e-01	1.208e+00	0.345	0.008	107	1.118e-02	-1.067e-02	3.304e-02	0.313	0.010	105
proline	-1.052e+00	-4.679e+00	2.575e+00	0.550	0.020	20	7.059e-02	-4.692e-02	1.881e-01	0.223	0.081	20
propyleneglycol	1.677e-01	-2.287e+00	2.623e+00	0.892	0.000	103	2.811e-02	-3.835e-02	9.458e-02	0.403	0.007	100
putrescine	-2.474e-01	-8.409e-01	3.461e-01	0.406	0.015	49	3.045e-03	-1.428e-02	2.037e-02	0.725	0.003	48
pyroglutamate	-4.428e-01	-2.588e+00	1.703e+00	0.674	0.007	27	-1.124e-02	-5.952e-02	3.703e-02	0.635	0.010	26
pyruvate	-3.862e-01	-1.854e+00	1.082e+00	0.603	0.003	107	1.096e-02	-2.935e-02	5.128e-02	0.591	0.003	105
serine	1.041e-01	-1.956e+00	2.165e+00	0.920	0.000	63	-2.400e-02	-8.097e-02	3.297e-02	0.403	0.012	62
taurine	-6.365e-01	-1.393e+00	1.198e-01	0.097	0.047	59	1.229e-02	-8.142e-03	3.272e-02	0.233	0.025	58
threonine	4.737e-01	-8.979e-01	1.845e+00	0.495	0.005	99	9.455e-03	-2.931e-02	4.822e-02	0.629	0.002	97
trimethylamine	1.954e-02	-1.055e-01	1.445e-01	0.757	0.001	96	-2.564e-03	-6.178e-03	1.050e-03	0.162	0.021	94
tryptophan	-4.370e-03	-8.754e-02	7.880e-02	0.917	0.000	129	-1.122e-03	-3.319e-03	1.074e-03	0.314	0.008	126
tyrosine	2.793e-01	-5.384e-01	1.097e+00	0.500	0.004	107	3.266e-03	-1.931e-02	2.585e-02	0.775	0.001	105
uracil	2.515e-01	-3.266e-01	8.296e-01	0.390	0.007	104	7.567e-03	-8.635e-03	2.377e-02	0.356	0.009	102
valine	-2.556e-02	-1.430e+00	1.379e+00	0.971	0.000	108	1.094e-02	-2.477e-02	4.666e-02	0.545	0.004	106
xanthine	1.092e-01	-8.443e-02	3.029e-01	0.264	0.019	68	1.516e-03	-3.814e-03	6.846e-03	0.572	0.005	67
lactate	-2.041e+00	-8.388e+00	4.305e+00	0.525	0.003	122	1.801e-01	4.419e-03	3.559e-01	0.045	0.034	119

Note: Bolded rows in red text are metabolites that passed the X to M and M to Y criteria for mediation. In each cell, the letter "e" denotes powers of 10 (for example, 1.23e-01 means 1.23 multipled by 10^{-1} or 1.23 X 10^{-1}).

Table 3.14 Linear regression results assessing *X to M* and *M to Y* associations with maternal asthma as the exposure (X), individual male infant gut metabolites as potential mediators (M), and male infant language scores at 1 year as the outcome (Y).

	Linear Regression Results of the Association between Maternal Asthma (*X*) and each Metabolite (*M*)						Linear Regression Results of the Association between each Metabolite (*M*) and Male Infant Language Scores at 1 Year					
	X -> M						*M -> Y*					
Metabolites	**β-coefficient**	**[95% C.I.]**		**p-value**	**R^2**	**N**	**β-coefficient**	**[95% C.I.]**		**p-value**	**R^2**	**N**
formate	-6.654e-01	-2.045e+00	7.138e-01	0.338	0.016	58	-7.057e-04	-9.139e-02	8.998e-02	0.988	0.000	108
acetate	2.059e+01	-8.071e+00	4.926e+01	0.156	0.028	73	7.563e-01	-8.836e-02	1.601e+00	0.079	0.023	133
butyrate	1.652e+00	-2.915e+00	6.219e+00	0.473	0.007	73	8.193e-03	-1.127e-01	1.291e-01	0.894	0.000	133
propionate	7.212e+00	-9.415e-01	1.537e+01	0.082	0.042	73	5.708e-02	-1.598e-01	2.739e-01	0.603	0.002	133
valerate	-5.974e-02	-1.035e+00	9.159e-01	0.903	0.000	73	1.308e-02	-1.489e-02	4.105e-02	0.357	0.006	133
isobutyrate	2.146e-01	-3.622e-01	7.914e-01	0.461	0.008	73	-5.313e-03	-2.029e-02	9.659e-03	0.484	0.004	133
isovalerate	4.663e-01	-2.717e-01	1.204e+00	0.212	0.022	73	5.331e-03	-1.601e-02	2.668e-02	0.622	0.002	133
lactate	-1.918e+00	-7.399e+00	3.562e+00	0.487	0.008	66	9.732e-02	-1.252e-01	3.199e-01	0.388	0.006	122
succinate	6.317e+00	-4.850e+00	1.748e+01	0.263	0.018	73	2.486e-01	-1.320e-01	6.293e-01	0.199	0.013	133
hydroxyglutarate	-2.079e+00	-1.257e+01	8.407e+00	0.645	0.038	8	4.823e-02	-2.521e-01	3.485e-01	0.725	0.014	11
aminobutyrate	5.647e-01	-4.396e-01	1.569e+00	0.254	0.068	21	2.570e-04	-7.289e-02	7.341e-02	0.994	0.000	51
hydroxyphenylacetate	2.323e-01	-2.376e-01	7.023e-01	0.319	0.037	29	1.097e-02	4.148e-04	2.153e-02	0.042	0.066	63
aminopentanoate	-1.948e+00	-5.385e+00	1.489e+00	0.254	0.052	27	7.908e-02	-1.038e-02	1.685e-01	0.082	0.056	55
acetoin	-1.446e-01	-1.585e+00	1.296e+00	0.835	0.002	20	-5.704e-03	-6.274e-02	5.133e-02	0.841	0.001	46
alanine	2.208e+00	-2.534e+00	6.951e+00	0.355	0.015	58	-1.002e-01	-2.196e-01	1.919e-02	0.099	0.025	108
aspartate	1.077e+00	-8.210e-01	2.974e+00	0.260	0.023	57	-4.086e-03	-5.753e-02	4.936e-02	0.880	0.000	106
betaalanine	1.096e-01	-1.106e+00	1.325e+00	0.840	0.005	10	5.805e-03	-2.603e-02	3.764e-02	0.704	0.009	18
cadaverine	-1.995e+00	-5.658e+00	1.669e+00	0.275	0.038	33	7.846e-02	-1.766e-02	1.746e-01	0.108	0.039	67
choline	-1.633e-01	-4.598e-01	1.331e-01	0.274	0.022	56	-1.442e-03	-1.041e-02	7.526e-03	0.750	0.001	103
creatine	8.509e-02	-2.380e-01	4.081e-01	0.600	0.005	56	4.234e-03	-5.752e-03	1.422e-02	0.402	0.007	102
creatinine	3.661e-02	-2.773e-01	3.506e-01	0.816	0.001	57	-3.027e-03	-1.178e-02	5.726e-03	0.494	0.005	106
dimethylamine	**1.074e-01**	**1.941e-02**	**1.954e-01**	**0.018**	**0.172**	**32**	**4.216e-01**	**1.958e-03**	**6.474e-03**	**0.000**	**0.181**	**65**
ethanol	-8.530e-01	-4.151e+00	2.445e+00	0.606	0.005	52	5.906e-03	-8.154e-02	9.336e-02	0.894	0.000	97
fucose	-1.378e-01	-4.627e+00	4.352e+00	0.950	0.000	30	-8.484e-02	-4.300e-01	2.603e-01	0.625	0.004	64
fumarate	1.498e-01	-2.400e-01	5.396e-01	0.444	0.011	57	2.215e-03	-7.727e-03	1.216e-02	0.660	0.002	106
galactose	-1.847e+00	-5.803e+00	2.109e+00	0.349	0.027	34	-1.019e-01	-2.417e-01	3.792e-02	0.151	0.030	71
glucose	1.004e+00	-2.204e+00	4.211e+00	0.533	0.007	58	1.327e-02	-1.059e-01	1.325e-01	0.826	0.000	108
glutamate	6.313e+00	-1.799e+00	1.443e+01	0.125	0.042	57	-2.421e-02	-3.000e-01	2.515e-01	0.862	0.000	104
glycerol	9.812e-01	-1.478e+00	3.441e+00	0.422	0.020	34	-1.470e-02	-6.286e-02	3.346e-02	0.545	0.005	71

glycine	1.781e+00	-7.948e-01	4.357e+00	0.171	0.034	57	4.007e-03	-7.069e-02	7.871e-02	0.915	0.000	106
histidine	3.262e-01	-4.407e-01	1.093e+00	0.394	0.020	38	5.547e-03	-1.583e-02	2.693e-02	0.606	0.005	61
hypoxanthine	3.218e-01	-6.590e-01	1.303e+00	0.502	0.022	23	2.355e-02	-1.293e-02	6.002e-02	0.198	0.048	36
isoleucine	6.318e-01	-4.670e-01	1.731e+00	0.254	0.023	58	-1.511e-02	-4.951e-02	1.928e-02	0.386	0.007	108
leucine	6.563e-01	-9.977e-01	2.310e+00	0.430	0.011	58	-1.490e-02	-6.798e-02	3.818e-02	0.579	0.003	108
lysine	2.989e+00	-2.456e+00	8.434e+00	0.275	0.027	46	4.234e-02	-1.226e-01	2.073e-01	0.611	0.004	76
malonate	7.649e-01	-1.249e+00	2.779e+00	0.450	0.010	58	7.233e-03	-4.490e-02	5.937e-02	0.784	0.001	108
methanol	7.296e-01	-2.066e-01	1.666e+00	0.124	0.042	58	1.157e-02	-1.308e-02	3.623e-02	0.354	0.008	108
methionine	4.302e-01	-2.752e-01	1.136e+00	0.227	0.026	58	-5.941e-03	-2.672e-02	1.484e-02	0.572	0.003	108
methylamine	2.672e-02	-1.462e-01	1.996e-01	0.755	0.003	33	1.624e-03	-2.097e-03	5.346e-03	0.386	0.012	66
methylhistidine	2.125e-01	-3.532e-01	7.781e-01	0.451	0.016	38	-3.551e-03	-1.867e-02	1.157e-02	0.640	0.004	61
myoinositol	-2.760e+00	-9.089e+00	3.569e+00	0.354	0.086	12	-1.067e-01	-2.295e-01	1.603e-02	0.085	0.114	27
pcresol	3.660e-02	-1.849e-01	2.581e-01	0.717	0.015	11	-6.260e-04	-6.076e-03	4.824e-03	0.809	0.004	16
phenylacetate	4.617e-01	-2.367e-01	1.160e+00	0.184	0.083	23	-2.281e-03	-2.463e-02	2.006e-02	0.837	0.001	36
phenylalanine	**1.187e+00**	**9.617e-02**	**2.277e+00**	**0.033**	**0.078**	**58**	**-2.717e-02**	**-2.170e-00**	**2.029e-03**	**0.068**	**0.031**	**107**
proline	-2.602e+00	-9.383e+00	4.178e+00	0.402	0.089	10	-1.050e-01	-2.554e-01	4.547e-02	0.160	0.107	20
propyleneglycol	-1.143e+00	-2.916e+00	6.294e-01	0.202	0.030	56	2.918e-02	-5.222e-02	1.106e-01	0.479	0.005	103
putrescine	1.076e-01	-5.638e-01	7.790e-01	0.743	0.005	25	9.885e-03	-1.216e-02	3.193e-02	0.372	0.017	49
pyroglutamate	-5.158e-01	-5.099e+00	4.067e+00	0.805	0.007	11	-3.884e-02	-9.737e-02	1.970e-02	0.184	0.070	27
pyruvate	-4.224e-01	-1.863e+00	1.018e+00	0.559	0.006	58	-1.391e-02	-6.702e-02	3.920e-02	0.605	0.003	107
serine	6.685e-01	-1.936e+00	3.273e+00	0.606	0.007	38	-1.549e-02	-8.921e-02	5.823e-02	0.676	0.003	63
taurine	-7.069e-01	-1.660e+00	2.467e-01	0.140	0.076	30	1.301e-03	-2.558e-02	2.819e-02	0.923	0.000	59
threonine	1.465e+00	-5.236e-02	2.982e+00	0.058	0.071	51	-3.274e-03	-5.230e-02	4.575e-02	0.895	0.000	99
trimethylamine	6.935e-02	-9.790e-02	2.366e-01	0.408	0.015	49	6.286e-05	-4.504e-03	4.629e-03	0.978	0.000	96
tryptophan	4.098e-02	-6.294e-02	1.449e-01	0.434	0.009	70	8.963e-04	-1.861e-03	3.654e-03	0.521	0.003	129
tyrosine	1.101e+00	1.201e-01	2.083e+00	0.029	0.083	58	-3.192e-03	-3.281e-02	2.643e-02	0.831	0.000	107
uracil	7.340e-01	-3.426e-02	1.502e+00	0.061	0.062	57	2.231e-03	-1.910e-02	2.357e-02	0.836	0.000	104
valine	1.258e+00	-3.894e-01	2.905e+00	0.132	0.040	58	-3.345e-02	-8.388e-02	1.697e-02	0.191	0.016	108
xanthine	6.871e-02	-1.929e-01	3.303e-01	0.596	0.009	32	7.882e-04	-6.188e-03	7.765e-03	0.822	0.001	68
lactate	-1.918e+00	-7.399e+00	3.562e+00	0.487	0.008	66	9.732e-02	-1.252e-01	3.199e-01	0.388	0.006	122

Note: Bolded rows in red text are metabolites that passed the X to M and M to Y criteria for mediation. In each cell, the letter "e" denotes powers of 10 (for example, 1.23e-01 means 1.23 multipled by 10^{-1} or 1.23 X 10^{-1}).

Table 3.15 Linear regression results assessing *X to M* and *M to Y* associations with maternal asthma as the exposure (X), individual male infant gut metabolites as potential mediators (M), and male infant socio-emotional scores at 2 years as the outcome (Y).

	Linear Regression Results of the Association between Maternal Asthma (*X*) and each Metabolite (*M*)						Linear Regression Results of the Association between each Metabolite (*M*) and Male Infant Socio-emotional Scores at 2 Years					
	X -> M						*M -> Y*					
Metabolites	**β-coefficient**	**[95% C.I.]**		**p-value**	**R^2**	**N**	**β-coefficient**	**[95% C.I.]**		**p-value**	**R^2**	**N**
formate	-6.654e-01	-2.045e+00	7.138e-01	0.338	0.016	58	5.827e-02	-9.795e-03	1.263e-01	0.093	0.027	106
acetate	2.059e+01	-8.071e+00	4.926e+01	0.156	0.028	73	2.098e-01	-4.563e-01	8.760e-01	0.534	0.003	130
butyrate	1.652e+00	-2.915e+00	6.219e+00	0.473	0.007	73	-3.333e-03	-9.894e-02	9.227e-02	0.945	0.000	130
propionate	7.212e+00	-9.415e-01	1.537e+01	0.082	0.042	73	-2.573e-02	-1.978e-01	1.463e-01	0.768	0.001	130
valerate	-5.974e-02	-1.035e+00	9.159e-01	0.903	0.000	73	4.746e-03	-1.747e-02	2.697e-02	0.673	0.001	130
isobutyrate	2.146e-01	-3.622e-01	7.914e-01	0.461	0.008	73	-5.899e-03	-1.773e-02	5.927e-03	0.326	0.008	130
isovalerate	4.663e-01	-2.717e-01	1.204e+00	0.212	0.022	73	-7.719e-03	-2.453e-02	9.088e-03	0.365	0.006	130
lactate	-1.918e+00	-7.399e+00	3.562e+00	0.487	0.008	66	1.801e-01	4.419e-03	3.559e-01	0.045	0.034	119
succinate	6.317e+00	-4.850e+00	1.748e+01	0.263	0.018	73	1.266e-01	-1.758e-01	4.290e-01	0.409	0.005	130
hydroxyglutarate	-2.079e+00	-1.257e+01	8.407e+00	0.645	0.038	8	6.575e-03	-1.801e-01	1.933e-01	0.937	0.001	10
aminobutyrate	5.647e-01	-4.396e-01	1.569e+00	0.254	0.068	21	3.262e-02	-2.409e-02	8.932e-02	0.253	0.027	50
hydroxyphenylacetate	2.323e-01	-2.376e-01	7.023e-01	0.319	0.037	29	-1.467e-03	-9.879e-03	6.944e-03	0.728	0.002	62
aminopentanoate	-1.948e+00	-5.385e+00	1.489e+00	0.254	0.052	27	1.040e-02	-6.018e-02	8.097e-02	0.769	0.002	54
acetoin	-1.446e-01	-1.585e+00	1.296e+00	0.835	0.002	20	3.867e-02	1.077e-03	7.627e-02	0.044	0.091	45
alanine	2.208e+00	-2.534e+00	6.951e+00	0.355	0.015	58	8.113e-02	-8.144e-03	1.704e-01	0.074	0.030	106
aspartate	1.077e+00	-8.210e-01	2.974e+00	0.260	0.023	57	1.838e-02	-2.168e-02	5.845e-02	0.365	0.008	104
betaalanine	1.096e-01	-1.106e+00	1.325e+00	0.840	0.005	10	2.990e-04	-2.795e-02	2.855e-02	0.982	0.000	17
cadaverine	-1.995e+00	-5.658e+00	1.669e+00	0.275	0.038	33	3.888e-02	-3.245e-02	1.102e-01	0.280	0.018	66
choline	-1.633e-01	-4.598e-01	1.331e-01	0.274	0.022	56	3.919e-03	-2.941e-03	1.078e-02	0.260	0.013	101
creatine	8.509e-02	-2.380e-01	4.081e-01	0.600	0.005	56	5.583e-03	-1.994e-03	1.316e-02	0.147	0.021	100
creatinine	3.661e-02	-2.773e-01	3.506e-01	0.816	0.001	57	5.362e-03	-1.229e-03	1.195e-02	0.110	0.025	104
dimethylamine	1.074e-01	1.941e-02	1.954e-01	0.018	0.172	32	9.555e-04	-8.315e-04	2.742e-03	0.289	0.018	64
ethanol	-8.530e-01	-4.151e+00	2.445e+00	0.606	0.005	52	5.758e-02	-7.611e-03	1.228e-01	0.083	0.032	95
fucose	-1.378e-01	-4.627e+00	4.352e+00	0.950	0.000	30	3.079e-01	6.836e-02	5.475e-01	0.013	0.098	63
fumarate	1.498e-01	-2.400e-01	5.396e-01	0.444	0.011	57	1.052e-03	-6.459e-03	8.562e-03	0.782	0.001	104
galactose	-1.847e+00	-5.803e+00	2.109e+00	0.349	0.027	34	1.092e-01	4.231e-03	2.143e-01	0.042	0.060	70
glucose	1.004e+00	-2.204e+00	4.211e+00	0.533	0.007	58	6.563e-02	-2.411e-02	1.554e-01	0.150	0.020	106
glutamate	6.313e+00	-1.799e+00	1.443e+01	0.125	0.042	57	6.823e-02	-1.451e-01	2.816e-01	0.527	0.004	102
glycerol	9.812e-01	-1.478e+00	3.441e+00	0.422	0.020	34	-2.276e-02	-5.880e-02	1.328e-02	0.212	0.023	70
glycine	1.781e+00	-7.948e-01	4.357e+00	0.171	0.034	57	3.488e-02	-2.062e-02	9.038e-02	0.215	0.015	104

histidine	3.262e-01	-4.407e-01	1.093e+00	0.394	0.020	38	-1.036e-02	-2.667e-02	5.950e-03	0.209	0.028	59
hypoxanthine	3.218e-01	-6.590e-01	1.303e+00	0.502	0.022	23	9.666e-03	-1.848e-02	3.782e-02	0.490	0.015	35
isoleucine	6.318e-01	-4.670e-01	1.731e+00	0.254	0.023	58	4.022e-03	-2.063e-02	2.867e-02	0.747	0.001	106
leucine	6.563e-01	-9.977e-01	2.310e+00	0.430	0.011	58	-7.568e-03	-4.610e-02	3.096e-02	0.698	0.001	106
lysine	2.989e+00	-2.456e+00	8.434e+00	0.275	0.027	46	-1.967e-02	-1.631e-01	1.238e-01	0.785	0.001	74
malonate	7.649e-01	-1.249e+00	2.779e+00	0.450	0.010	58	1.684e-02	-2.273e-02	5.640e-02	0.401	0.007	106
methanol	7.296e-01	-2.066e-01	1.666e+00	0.124	0.042	58	4.443e-03	-1.434e-02	2.322e-02	0.640	0.002	106
methionine	4.302e-01	-2.752e-01	1.136e+00	0.227	0.026	58	5.447e-03	-1.020e-02	2.110e-02	0.492	0.005	106
methylamine	2.672e-02	-1.462e-01	1.996e-01	0.755	0.003	33	-2.003e-03	-4.782e-03	7.753e-04	0.155	0.032	65
methylhistidine	2.125e-01	-3.532e-01	7.781e-01	0.451	0.016	38	-3.885e-03	-1.612e-02	8.354e-03	0.528	0.007	59
myoinositol	-2.760e+00	-9.089e+00	3.569e+00	0.354	0.086	12	-1.783e-02	-9.813e-02	6.248e-02	0.651	0.009	26
pcresol	3.660e-02	-1.849e-01	2.581e-01	0.717	0.015	11	3.201e-04	-2.737e-03	3.377e-03	0.826	0.004	16
phenylacetate	4.617e-01	-2.367e-01	1.160e+00	0.184	0.083	23	-1.577e-02	-3.191e-02	3.757e-04	0.055	0.107	35
phenylalanine	1.187e+00	9.617e-02	2.277e+00	0.033	0.078	58	1.118e-02	-1.067e-02	3.304e-02	0.313	0.010	105
proline	-2.602e+00	-9.383e+00	4.178e+00	0.402	0.089	10	7.059e-02	-4.692e-02	1.881e-01	0.223	0.081	20
propyleneglycol	-1.143e+00	-2.916e+00	6.294e-01	0.202	0.030	56	2.811e-02	-3.835e-02	9.458e-02	0.403	0.007	100
putrescine	1.076e-01	-5.638e-01	7.790e-01	0.743	0.005	25	3.045e-03	-1.428e-02	2.037e-02	0.725	0.003	48
pyroglutamate	-5.158e-01	-5.099e+00	4.067e+00	0.805	0.007	11	-1.124e-02	-5.952e-02	3.703e-02	0.635	0.010	26
pyruvate	-4.224e-01	-1.863e+00	1.018e+00	0.559	0.006	58	1.096e-02	-2.935e-02	5.128e-02	0.591	0.003	105
serine	6.685e-01	-1.936e+00	3.273e+00	0.606	0.007	38	-2.400e-02	-8.097e-02	3.297e-02	0.403	0.012	62
taurine	-7.069e-01	-1.660e+00	2.467e-01	0.140	0.076	30	1.229e-02	-8.142e-03	3.272e-02	0.233	0.025	58
threonine	1.465e+00	-5.236e-02	2.982e+00	0.058	0.071	51	9.455e-03	-2.931e-02	4.822e-02	0.629	0.002	97
trimethylamine	6.935e-02	-9.790e-02	2.366e-01	0.408	0.015	49	-2.564e-03	-6.178e-03	1.050e-03	0.162	0.021	94
tryptophan	4.098e-02	-6.294e-02	1.449e-01	0.434	0.009	70	-1.122e-03	-3.319e-03	1.074e-03	0.314	0.008	126
tyrosine	1.101e+00	1.201e-01	2.083e+00	0.029	0.083	58	3.266e-03	-1.931e-02	2.585e-02	0.775	0.001	105
uracil	7.340e-01	-3.426e-02	1.502e+00	0.061	0.062	57	7.567e-03	-8.635e-03	2.377e-02	0.356	0.009	102
valine	1.258e+00	-3.894e-01	2.905e+00	0.132	0.040	58	1.094e-02	-2.477e-02	4.666e-02	0.545	0.004	106
xanthine	6.871e-02	-1.929e-01	3.303e-01	0.596	0.009	32	1.516e-03	-3.814e-03	6.846e-03	0.572	0.005	67
lactate	-1.918e+00	-7.399e+00	3.562e+00	0.487	0.008	66	1.801e-01	4.419e-03	3.559e-01	0.045	0.034	119

Note: Bolded rows in red text are metabolites that passed the X to M and M to Y criteria for mediation. In each cell, the letter "e" denotes powers of 10 (for example, 1.23e-01 means 1.23 multipled by 10^{-1} or 1.23 X 10^{-1}).

Table 3.19. Identifying mediators from infant gut microbiome at 4 months data, that mediate the association between (i) maternal atopy and male infant gut microbes (M) and (ii) male infant gut microbes (M) and male infant motor scores at 2 years of age (Y).

Infant Gut Bacteria	Linear Regression Results of the Association between Maternal Atopy (*X*) and Infant Gut Microbiome (*M*) *X -> M*						Linear Regression Results of the Association between Infant Gut Microbiome (*M*) and Male Infant Motor Score at 2 Years (Y) *M -> Y*					
	β-coefficient	**[95% CI]**		**p-value**	**R^2**	**N**	**β-coefficient**	**[95% CI]**		**p-value**	**R^2**	**N**
p__Actinobacteriac__A	1.24E-02	-4.17E-02	6.66E-02	0.651	0.001	172	3.38E-04	-2.30E-03	2.98E-03	0.801	0	172
p__Actinobacteriac__C	9.10E-04	-6.18E-03	8.00E-03	0.8	0	172	-1.02E-04	-4.47E-04	2.44E-04	0.562	0.002	172
p__Bacteroidetesc__Ba	-3.87E-02	-1.39E-01	6.18E-02	0.448	0.003	172	2.56E-03	-2.34E-03	7.45E-03	0.303	0.006	172
p__Firmicutesc__Bacil	-3.47E-03	-1.91E-02	1.21E-02	0.661	0.001	172	-2.26E-04	-9.86E-04	5.34E-04	0.558	0.002	172
p__Firmicutesc__Clost	-1.60E-02	-9.17E-02	5.98E-02	0.677	0.001	172	**-3.64E-03**	**-7.29E-03**	**1.10E-05**	**0.041****	**0.022**	**172**
p__Firmicutesc__Erysi	-8.16E-03	-1.98E-02	3.49E-03	0.169	0.011	172	1.68E-04	-4.03E-04	7.38E-04	0.562	0.002	172
p__Proteobacteriac__B	1.26E-03	-8.13E-03	1.06E-02	0.792	0	172	-1.79E-04	-6.36E-04	2.78E-04	0.44	0.004	172
p__Proteobacteriac__D	9.73E-04	-3.46E-03	5.40E-03	0.665	0.001	172	7.56E-05	-1.40E-04	2.91E-04	0.49	0.003	172
p__Proteobacteriac__E	8.17E-06	-1.02E-03	1.04E-03	0.987	0	172	-1.45E-05	-6.45E-05	3.56E-05	0.568	0.002	172
p__Proteobacteriac__G	3.50E-02	-3.64E-02	1.07E-01	0.335	0.005	172	-4.73E-04	-3.97E-03	3.02E-03	0.79	0	172
p__Verrucomicrobiac__	1.30E-02	-2.72E-02	5.32E-02	0.525	0.002	172	1.44E-03	-5.05E-04	3.39E-03	0.145	0.012	172
o__Actinomycetales	3.32E-03	-2.96E-03	9.60E-03	0.298	0.006	172	-1.48E-04	-4.54E-04	1.58E-04	0.342	0.005	172
o__Bifidobacteriales	9.10E-03	-4.33E-02	6.15E-02	0.732	0.001	172	4.86E-04	-2.07E-03	3.04E-03	0.708	0.001	172
o__Coriobacteriales	9.10E-04	-6.18E-03	8.00E-03	0.8	0	172	-1.02E-04	-4.47E-04	2.44E-04	0.562	0.002	172
o__Bacteroidales	-3.87E-02	-1.39E-01	6.18E-02	0.448	0.003	172	2.56E-03	-2.34E-03	7.45E-03	0.303	0.006	172
o__Bacillales	2.65E-04	-8.79E-04	1.41E-03	0.648	0.001	172	2.66E-05	-2.91E-05	8.22E-05	0.347	0.005	172
o__Gemellales	-2.96E-05	-3.44E-04	2.85E-04	0.853	0	172	6.36E-06	-8.92E-06	2.16E-05	0.413	0.004	172
o__Lactobacillales	-3.72E-03	-1.89E-02	1.15E-02	0.631	0.001	172	-2.59E-04	-1.00E-03	4.83E-04	0.492	0.003	172
o__Clostridiales	-1.60E-02	-9.17E-02	5.98E-02	0.677	0.001	172	**-3.64E-03**	**-7.29E-03**	**1.10E-05**	**0.018****	**0.022**	**172**
o__Erysipelotrichales	-8.16E-03	-1.98E-02	3.49E-03	0.169	0.011	172	1.68E-04	-4.03E-04	7.38E-04	0.562	0.002	172
o__Fusobacteriales	1.31E-04	-2.29E-04	4.91E-04	0.475	0.003	172	4.83E-06	-1.27E-05	2.24E-05	0.588	0.002	172
o__Burkholderiales	1.25E-03	-8.14E-03	1.06E-02	0.793	0	172	-1.81E-04	-6.38E-04	2.76E-04	0.435	0.004	172
o__Desulfovibrionales	9.73E-04	-3.46E-03	5.40E-03	0.665	0.001	172	7.56E-05	-1.40E-04	2.91E-04	0.49	0.003	172
o__Campylobacterales	8.17E-06	-1.02E-03	1.04E-03	0.987	0	172	-1.45E-05	-6.45E-05	3.56E-05	0.568	0.002	172
o__Enterobacteriales	3.81E-02	-3.31E-02	1.09E-01	0.292	0.007	172	-5.19E-04	-4.00E-03	2.96E-03	0.769	0.001	172
cdifflog_3m	4.01E-01	-6.61E-01	1.46E+00	0.457	0.004	158	**-4.10E-02**	**-9.00E-02**	**8.10E-03**	**0.024****	**0.017**	**158**
cdifflog_1y	1.45E-01	-1.34E+00	1.63E+00	0.847	0	133	**-8.14E-02**	**-1.49E-01**	**-1.37E-02**	**0.019****	**0.041**	**133**
g_Bacteroides_3_12_mos	-1.55E-02	-1.07E-01	7.63E-02	0.74	0.001	172	2.12E-03	-2.35E-03	6.58E-03	0.35	0.005	172
g_Bac_1yr	-2.17E-02	-1.07E-01	6.40E-02	0.618	0.002	133	4.82E-04	-3.51E-03	4.47E-03	0.811	0	133

*Note: Bolded rows are pathways that have statistically significant association; ** = $p < 0.05$*

Table 3.20. Identifying mediators from infant gut microbiome at 4 months data, that mediate the association between (i) maternal asthma and male infant gut microbes (M) and (ii) male infant gut microbes (M) and male infant motor scores at 2 years of age (Y).

Infant Gut Bacteria	Linear Regression Results of the Association between Maternal Asthma (*X*) and Infant Gut Microbiome (*M*) *X -> M*						Linear Regression Results of the Association between Infant Gut Microbiome (*M*) and Male Infant Motor Score at 2 Years (Y) *M -> Y*					
	β-coefficient	[95% CI]		p-value	R^2	N	β-coefficient	[95% CI]		p-value	R^2	N
p__Actinobacteriac__A	1.03E-02	-4.88E-02	6.95E-02	0.73	0.001	172	3.38E-04	-2.30E-03	2.98E-03	0.801	0	172
p__Actinobacteriac__C	1.24E-03	-6.50E-03	8.98E-03	0.751	0.001	172	-1.02E-04	-4.47E-04	2.44E-04	0.562	0.002	172
p__Bacteroidetesc__Ba	-3.24E-02	-1.42E-01	7.74E-02	0.561	0.002	172	2.56E-03	-2.34E-03	7.45E-03	0.303	0.006	172
p__Firmicutesc__Bacil	-4.80E-03	-2.18E-02	1.22E-02	0.579	0.002	172	-2.26E-04	-9.86E-04	5.34E-04	0.558	0.002	172
p__Firmicutesc__Clost	3.77E-02	-4.49E-02	1.20E-01	0.369	0.005	172	**-3.64E-03**	**-7.29E-03**	**1.10E-05**	**0.041****	**0.022**	**172**
p__Firmicutesc__Erysi	-4.47E-03	-1.72E-02	8.30E-03	0.49	0.003	172	1.68E-04	-4.03E-04	7.38E-04	0.562	0.002	172
p__Proteobacteriac__B	8.68E-03	-1.49E-03	1.88E-02	0.094	0.016	172	-1.79E-04	-6.36E-04	2.78E-04	0.44	0.004	172
p__Proteobacteriac__D	-1.31E-03	-6.15E-03	3.53E-03	0.593	0.002	172	7.56E-05	-1.40E-04	2.91E-04	0.49	0.003	172
p__Proteobacteriac__E	8.04E-04	-3.11E-04	1.92E-03	0.156	0.012	172	-1.45E-05	-6.45E-05	3.56E-05	0.568	0.002	172
p__Proteobacteriac__G	-1.19E-02	-9.01E-02	6.64E-02	0.765	0.001	172	-4.73E-04	-3.97E-03	3.02E-03	0.79	0	172
p__Verrucomicrobiac__	-1.11E-02	-5.50E-02	3.28E-02	0.618	0.001	172	1.44E-03	-5.05E-04	3.39E-03	0.145	0.012	172
o__Actinomycetales	4.72E-04	-6.40E-03	7.35E-03	0.892	0	172	-1.48E-04	-4.54E-04	1.58E-04	0.342	0.005	172
o__Bifidobacteriales	9.87E-03	-4.73E-02	6.71E-02	0.734	0.001	172	4.86E-04	-2.07E-03	3.04E-03	0.708	0.001	172
o__Coriobacteriales	1.24E-03	-6.50E-03	8.98E-03	0.751	0.001	172	-1.02E-04	-4.47E-04	2.44E-04	0.562	0.002	172
o__Bacteroidales	-3.24E-02	-1.42E-01	7.74E-02	0.561	0.002	172	2.56E-03	-2.34E-03	7.45E-03	0.303	0.006	172
o__Bacillales	-3.89E-04	-1.64E-03	8.59E-04	0.539	0.002	172	2.66E-05	-2.91E-05	8.22E-05	0.347	0.005	172
o__Gemellales	-6.38E-05	-4.07E-04	2.79E-04	0.714	0.001	172	6.36E-06	-8.92E-06	2.16E-05	0.413	0.004	172
o__Lactobacillales	-4.34E-03	-2.10E-02	1.23E-02	0.607	0.002	172	-2.59E-04	-1.00E-03	4.83E-04	0.492	0.003	172
o__Clostridiales	3.77E-02	-4.49E-02	1.20E-01	0.369	0.005	172	**-3.64E-03**	**-7.29E-03**	**1.10E-05**	**0.018****	**0.022**	**172**
o__Erysipelotrichales	-4.47E-03	-1.72E-02	8.30E-03	0.49	0.003	172	1.68E-04	-4.03E-04	7.38E-04	0.562	0.002	172
o__Fusobacteriales	1.15E-04	-2.78E-04	5.08E-04	0.564	0.002	172	4.83E-06	-1.27E-05	2.24E-05	0.588	0.002	172
o__Burkholderiales	8.64E-03	-1.52E-03	1.88E-02	0.095	0.016	172	-1.81E-04	-6.38E-04	2.76E-04	0.435	0.004	172
o__Desulfovibrionales	-1.31E-03	-6.15E-03	3.53E-03	0.593	0.002	172	7.56E-05	-1.40E-04	2.91E-04	0.49	0.003	172
o__Campylobacterales	8.04E-04	-3.11E-04	1.92E-03	0.156	0.012	172	-1.45E-05	-6.45E-05	3.56E-05	0.568	0.002	172
o__Enterobacteriales	-1.91E-02	-9.70E-02	5.88E-02	0.629	0.001	172	-5.19E-04	-4.00E-03	2.96E-03	0.769	0.001	172
cdifflog_3m	3.96E-01	-7.16E-01	1.51E+00	0.483	0.003	158	**-4.10E-02**	**-9.00E-02**	**8.10E-03**	**0.024****	**0.017**	**158**
cdifflog_1y	-3.96E-01	-2.02E+00	1.23E+00	0.63	0.002	133	**-8.14E-02**	**-1.49E-01**	**-1.37E-02**	**0.019****	**0.041**	**133**
g_Bacteroides_3_12_mos	-1.86E-02	-1.19E-01	8.16E-02	0.715	0.001	172	2.12E-03	-2.35E-03	6.58E-03	0.35	0.005	172
g_Bac_1yr	-4.26E-02	-1.36E-01	5.10E-02	0.37	0.006	133	4.82E-04	-3.51E-03	4.47E-03	0.811	0	133

*Note: Bolded rows are pathways that have statistically significant association; ** = $p < 0.05$*

Table 3.21 Interaction term results between maternal atopy status and infant sex

Motor Scores at 2 Years		Coef.	[95% Conf	Interval]	p-value	Sig
Interaction						
Combined atopy	**infant sex**	0	.	.	.	
None	Female	.016	-3.541	3.573	.993	
Present	Male	-3.168	-6.182	-.153	.04	**
Present	Female	.507	-2.531	3.545	.743	
Cognitive Scores at 2 Years		Coef.	[95% Conf	Interval]	p-value	Sig
Interaction						
Combined atopy	**infant sex**	0	.	.	.	
None	Female	-.066	-5.082	4.951	.98	
Present	Male	-3.789	-8.04	.462	.08	*
Present	Female	4.149	-.135	8.434	.058	*
Socioemotional Scores at 2 Years		Coef.	[95% Conf	Interval]	p-value	Sig
Interaction						
Maternal Asthma	**infant sex**	0	.	.	.	
None	Female	3.117	-.72	6.953	.111	
Present	Male	-5.826	-11.294	-.357	.037	**
Present	Female	-1.25	-7.328	4.828	.686	
Language Scores at 1 Year		Coef.	[95% Conf	Interval]	p-value	Sig
Interaction						
Maternal Asthma	**infant sex**	0	.	.	.	
None	Female	6.847	3.921	9.773	0	***
Present	Male	5.039	.892	9.185	.017	**
Present	Female	5.265	.614	9.915	.027	**

*Note: *** p<.01, ** p<.05, * p<.1*

CHAPTER 4: Conclusions

The purpose of this thesis is to investigate the associations between both infant and maternal sensitization and infant neurodevelopmental outcomes at 1 and 2 years of age. Chapter 2 describes the association between infant atopic sensitization at 1 year and infant neurodevelopmental outcomes at 1 and 2 years. Chapter 3 covers maternal atopic status and asthma and its impact on infant neurodevelopmental scores at 1 and 2 years. The major findings for each chapter will be summarized, followed by a discussion of the strengths and limitations of the CHILD Cohort Study. The final section of Chapter 4 will cover the implications and future directions for future research.

4.1 Key findings and general conclusions

Research Study I: The main finding of the first research study is the cross-sectional and sex-specific associations found between infant atopic sensitization at 1 year and subsequent decrease in socioemotional scores at 1 year of infant age. Specifically, this decrease in socio-emotional scores at 1 year was observed in the male infant group. Although temporal associations were analyzed, neither infant food nor atopic sensitization at 1 year predicted infant neurodevelopmental scores at 2 years of age. Mounting research evidence supports that immune dysregulation and inflammation as an effect of IgE-mediated sensitization arises in parallel with infant neurodevelopmental challenges (45). However, since none of our study covariates were associated with these effects, we believe the association we found possibly acted through covariates we were not able to measure in the CHILD study. The first potential explanation has to do with parental stress associated with raising children living with food challenges, as parents often need to more vigilant in closely monitoring their infant's diet. Stressful post-pregnancy experiences harm the bond between mothers and babies, affecting their ability to form secure attachments, which in turn may impair the socio-emotional development of the child. On the other hand, we also propose the idea of a "reverse causation" hypothesis wherein socio-emotional impairment may be in the pathway to atopic or food sensitization. For example, when mothers experience a stressful post-pregnancy, it may lead to consequences including reduced breastfeeding duration which limits the child's access to essential nutrients during this critical period of their development. Therefore, the stress experienced by the child impairs their connection with their mothers and decreases their socio-emotional scores. Lastly, literature supports that an infant's socio-emotional impairments in response to a stressful environment may enhance existing inflammatory signals and stimulate immune-related conditions including atopic and food sensitization.

Research Study II: The main finding of research study II consists of three parts. First, maternal atopy is associated with a decrease in male motor scores at 2 years. Second, maternal asthma is associated with decreased socio-emotional scores at 2 years in all infants, and an increase in male language scores at 1 year. Third, phenylalanine and dimethylamine are key metabolites that mediate the pathway between maternal asthma and its associations with infant neurodevelopmental score. We proposed that our research reflects strong research evidence regarding the maternal immune activation (MIA) hypothesis that suggests maternal immune cells have the ability to cross the placental barrier, influence fetal brain programming which may include adverse effects on the developing infant brain. Furthermore, both phenylalanine and dimethylamine have been identified in the literature as metabolites suggested to interfere with normal development of infant brain. Phenylalanine was shown to have a strong effect on offspring cognitive outcomes at 1 year of age, and dimethylamine was identified as one of the potential biomarkers elevated in mothers exhibiting depressive disorders (39).

4.2 Study Strengths and Sources of Bias

The prospective and longitudinal nature of the CHILD Study, in addition to its high retention rate (92% retention rate), allows us access to extensive documented data on maternal and early childhood factors and covariates (55). Additionally, our large sample size was sufficient to be able to uncover and detect meaningful results in our fully-adjusted models. We were also able to further existing studies by not only testing cross-sectional, but also temporal associations between infant and maternal atopy and neurodevelopmental scores. However, we also recognize that there are potential sources of bias in our study:

Selection Bias

Our sample size consists of participants who are mostly White Caucasian and moderate-to-high income parents who live in urban centers in Canada. We recognize that this limits the generalizability of our studies to other population groups. Excluding infants from low income families may greatly reduce the sample size of infants with atopic sensitization and/or neurodevelopment impairment, leading to a biased comparison. However, the main justification of recruiting from urban centers is since 80% of the Canadian population is urban (75). Furthermore, compared to other historical birth cohorts, the recruited population of the CHILD study is more ethnically varied and diverse and children represented mixed ethnic populations to a greater degree compared to other studies (75).

Measurement Bias

Measurement bias happens when there are discrepancies in how certain variables were measured or collected between comparison groups. Infant atopic sensitization in research study I was measured using a standardized skin prick test (SPT); while maternal atopic sensitization and asthma were measured from self-report questionnaires in research study II. Although self-reported questionnaires may reduce systemic inconsistencies among mothers, the difference in how sensitization was assessed between infants and mothers may contribute to less validity in our comparison of the effect of sensitization to neurodevelopmental scores in mothers versus infants.

Despite this limitation, the CHILD study strived to minimize bias through standard operating procedures that uses the same recruitment and selection methods at all sites. Furthermore, the self-reported questionnaires that indicated maternal atopy and asthma status has been thoroughly validated in previous studies.

Confounding Bias

Our study also aimed to reduce confounding bias by using a Directed Acyclic Graph (DAG) to determine direct associations between covariates and their relationship with infant and maternal atopic status and neurodevelopmental scores. The DAG is a robust covariate selection method used in many epidemiological research studies that helps determine causal-relationships and properly identify a minimally sufficient adjustment set. This use of DAG, followed by additional statistical verification of true confounds using a 15% change in estimate method consisted our robust approach to model adjustment that helped us avoid over or under adjustment of our models.

4.3 Implications for future research

In conclusion, both research studies emphasize the importance of further research in exploring early antecedents that shape infant neurodevelopmental outcomes, as impact during this critical window may have lasting effects on infants that persist until later years and impair the quality of life of children and their families. In both of our research studies, finding an association between infant and maternal atopic status and infant neurodevelopment adds support to research evidence highlighting the role of infant and maternal immune-related conditions and its potential ability to program fetal development. Moreover, the emergence of the potential role of metabolites points to promising future research that may uncover more mechanistic pathways that will provide us with insights on how infant and maternal atopy impact child neurodevelopmental outcomes. Furthermore, sex-specific associations in our study encourages additional research that further investigates the role of certain biological sex differences in infant brain development.

Bibliography

1. Wang L-J, Mu S-C, Lin M-I, Sung · Tseng-Chen, Chiang B-L, Lin · Cheng-Hui. Clinical Manifestations of Pediatric Food Allergy: a Contemporary Review. 2016 [cited 2022 Feb 6]; Available from: https://doi.org/10.1007/s12016-021-08895-w

2. Hartvigsson O, Barman M, Rabe H, Sandin A, Wold AE, Brunius C, et al. Associations of maternal and infant metabolomes with immune maturation and allergy development at 12 months in the Swedish NICE-cohort. Scientific Reports | [Internet]. 123AD [cited 2022 Feb 8];11:12706. Available from: https://doi.org/10.1038/s41598-021-92239-3

3. Nwaru BI, Hickstein L, Panesar SS, Muraro A, Werfel T, Cardona V, et al. The epidemiology of food allergy in Europe: a systematic review and meta-analysis. Allergy [Internet]. 2014 Jan 1 [cited 2022 Feb 1];69(1):62–75. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/all.12305

4. Liu AH, Jaramillo R, Sicherer SH, Wood RA, Bock SA, Burks AW, et al. National prevalence and risk factors for food allergy and relationship to asthma: Results from the National Health and Nutrition Examination Survey 2005-2006. Journal of Allergy and Clinical Immunology. 2010 Oct 1;126(4):798-806.e14.

5. Tran MM, Lefebvre DL, Dharma C, Dai D, Lou WYW, Subbarao P, et al. Predicting the atopic march: Results from the Canadian Healthy Infant Longitudinal Development Study. The Journal of allergy and clinical immunology [Internet]. 2018 Feb 1 [cited 2022 Feb 8];141(2):601-607.e8. Available from: https://pubmed.ncbi.nlm.nih.gov/29153857/

6. Valenta R, Hochwallner H, Linhart B, Pahr S. Food allergies: the basics. Gastroenterology [Internet]. 2015 May 1 [cited 2022 Feb 8];148(6):1120-1131.e4. Available from: https://pubmed.ncbi.nlm.nih.gov/25680669/

7. Penders J, Gerhold K, Thijs C, Zimmermann K, Wahn U, Lau S, et al. Gut Microbes New

insights into the hygiene hypothesis in allergic diseases Mediation of sibling and birth mode effects by the gut microbiota. 2014 [cited 2022 Feb 9]; Available from: https://www.tandfonline.com/action/journalInformation?journalCode=kgmi20

8. Dierick BJH, van der Molen T, Flokstra-De Blok BMJ, Muraro A, Postma MJ, Kocks JWH, et al. Burden and socioeconomics of asthma, allergic rhinitis, atopic dermatitis and food allergy. 2020 [cited 2022 Feb 6]; Available from: https://www.tandfonline.com/action/journalInformation?journalCode=ierp20

9. Chad Z. Allergies in children. Paediatrics & Child Health [Internet]. 2001 [cited 2022 Feb 6];6(8):555. Available from: /pmc/articles/PMC2805592/

10. Iweala OI, Choudhary SK, Commins SP. Food Allergy. Current Gastroenterology Reports [Internet]. 2018 May 1 [cited 2022 Feb 6];20(5):1–6. Available from: https://link.springer.com/article/10.1007/s11894-018-0624-y

11. Nibbering B, Ubags NDJ. Microbial interactions in the atopic march. Clinical and experimental immunology [Internet]. 2020 Jan 1 [cited 2022 Feb 8];199(1):12–23. Available from: https://pubmed.ncbi.nlm.nih.gov/31777060/

12. Yang L, Fu J, Zhou Y. Research Progress in Atopic March. Frontiers in Immunology [Internet]. 2020 Aug 27 [cited 2022 Feb 6];11:1907. Available from: /pmc/articles/PMC7482645/

13. Wang L-J, Mu S-C, Lin M-I, Sung · Tseng-Chen, Chiang B-L, Lin · Cheng-Hui. Clinical Manifestations of Pediatric Food Allergy: a Contemporary Review. 2016 [cited 2022 Feb 1];1:3. Available from: https://doi.org/10.1007/s12016-021-08895-w

14. Koplin JJ, Wake M, Dharmage SC, Matheson M, Tang MLK, Gurrin LC, et al. Cohort Profile: The HealthNuts Study: Population prevalence and environmental/genetic predictors of food allergy. International Journal of Epidemiology [Internet]. 2015 Aug 1 [cited 2022 Feb 8];44(4):1161–71. Available from: https://academic.oup.com/ije/article/44/4/1161/667193

15. Alduraywish SA, Lodge CJ, Campbell B, Allen KJ, Erbas B, Lowe AJ, et al. The march from early life food sensitization to allergic disease: a systematic review and meta-analyses of birth cohort studies. Allergy [Internet]. 2016 Jan 1 [cited 2022 Feb 6];71(1):77–89. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/all.12784

16. DunnGalvin A, Hourihane JOB, Frewer L, Knibb RC, Oude Elberink JNG, Klinge I. Incorporating a gender dimension in food allergy research: A review. Allergy: European Journal of Allergy and Clinical Immunology. 2006 Nov;61(11):1336–43.

17. Løvik M, Namork E, Faeste C, Egaas E. The Norwegian National Reporting System and Register of Severe Allergic Reactions to Food. Norsk Epidemiologi [Internet]. 2004 Oct 13 [cited 2022 Feb 6];14(2):155–60. Available from: https://www.ntnu.no/ojs/index.php/norepid/article/view/238

18. Lautenbacher S. Sex and gender differences in responses to experimentally induced pain in humans.

19. Pali-Schöll I, Jensen-Jarolim E. Gender aspects in food allergy. Current opinion in allergy and clinical immunology [Internet]. 2019 Jun 1 [cited 2022 Feb 9];19(3):249–55. Available from: https://pubmed.ncbi.nlm.nih.gov/30893085/

20. Kelly C, Gangur V. Sex Disparity in Food Allergy: Evidence from the PubMed Database. Journal of Allergy [Internet]. 2009 Jul 2 [cited 2022 Feb 6];2009:1–7. Available from: /pmc/articles/PMC2957586/

21. Barbee RA, Halonen M, Lebowitz M, Burrows B. Distribution of IgE in a community population sample: correlations with age, sex, and allergen skin test reactivity.

22. Golding MA, Simons E, Abrams EM, Gerdts J, Protudjer JLP. The excess costs of childhood food allergy on Canadian families: a cross-sectional study. Allergy Asthma Clin Immunol [Internet]. 2021 [cited 2022 Feb 6];17:28. Available from: https://doi.org/10.1186/s13223-021-00530-9

23. Thörnqvist V, Middelveld R, Wai HM, Ballardini N, Nilsson E, Strömquist J, et al. Health-related quality of life worsens by school age amongst children with food allergy. Clinical and translational allergy [Internet]. 2019 Feb 7 [cited 2022 Feb 6];9(1). Available from: https://pubmed.ncbi.nlm.nih.gov/30774928/

24. Penner Protudjer JL, Middelveld R, Dahlén S-E, Ahlstedt S. Food allergy-related concerns during the transition to self-management on behalf of FoodHE Investigators. Allergy Asthma Clin Immunol [Internet]. 2019 [cited 2022 Feb 6];15:54. Available from: https://doi.org/10.1186/s13223-019-0370-1

25. DunnGalvin A, Koman E, Raver E, Frome H, Adams M, Keena A, et al. An Examination of the Food Allergy Quality of Life Questionnaire Performance in a Countrywide American Sample of Children: Cross-Cultural Differences in Age and Impact in the United States and Europe. The journal of allergy and clinical immunology In practice [Internet]. 2017 Apr 1 [cited 2022 Feb 9];5(2):363-368.e2. Available from: https://pubmed.ncbi.nlm.nih.gov/28017626/

26. Dubois J, Alison M, Counsell SJ, Hertz-Pannier L, Hüppi PS, Benders MJNL. MRI of the Neonatal Brain: A Review of Methodological Challenges and Neuroscientific Advances. Journal of Magnetic Resonance Imaging. 2021 May 1;53(5):1318–43.

27. Lewis AJ, Austin E, Knapp R, Vaiano T, Galbally M. Perinatal Maternal Mental Health, Fetal Programming and Child Development. Healthcare [Internet]. 2015 Dec 1 [cited 2022 Feb 6];3(4):1212. Available from: /pmc/articles/PMC4934640/

28. Ratsika A, Codagnone MC, O'mahony S, Stanton C, Cryan JF. Priming for Life: Early Life Nutrition and the Microbiota-Gut-Brain Axis. Nutrients [Internet]. 2021 Feb 1 [cited 2022 Feb 8];13(2):1–33. Available from: /pmc/articles/PMC7912058/

29. Aita M, De G, Faugère C, Lavallée A, Feeley N, Stremler R, et al. Effectiveness of interventions on early neurodevelopment of preterm infants: a systematic review and meta-analysis. [cited 2022 Feb 6]; Available from: https://doi.org/10.1186/s12887-021-02559-6

30. Lach LM, Kohen DE, Garner RE, Brehaut JC, Miller AR, Klassen AF, et al. The health and psychosocial functioning of caregivers of children with neurodevelopmental disorders. https://doi.org/101080/08916930802354948 [Internet]. 2009 [cited 2022 Feb 6];31(9):741–52. Available from: https://www.tandfonline.com/doi/abs/10.1080/08916930802354948

31. Brown RH, Eisner M, Walker S, Tomlinson M, Fearon P, Dunne MP, et al. The impact of maternal adverse childhood experiences and prenatal depressive symptoms on foetal attachment: Preliminary evidence from expectant mothers across eight middle-income countries. Journal of Affective Disorders. 2021 Dec 1;295:612–9.

32. Perone S, Gartstein MA. Mapping cortical rhythms to infant behavioral tendencies via baseline EEG and parent-report. Developmental Psychobiology [Internet]. 2019 Sep 1 [cited 2022 Feb 6];61(6):815–23. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/dev.21867

33. Chua RXY, Tay MJY, Ooi DSQ, Siah KTH, Tham EH, Shek LPC, et al. Understanding the Link Between Allergy and Neurodevelopmental Disorders: A Current Review of Factors and Mechanisms. Frontiers in Neurology. 2021 Feb 15;11:1965.

34. Guo MMH, Wang LJ, Hsu TY, Yang KD, Kuo HC. Peanut Sensitivity and Allergic Rhinitis in Young Children are Associated with Attention-Deficit Hyperactivity Disorder Symptoms in Adolescence. Neuropsychiatric Disease and Treatment [Internet]. 2020 [cited 2022 Feb 8];16:1349. Available from: /pmc/articles/PMC7263365/

35. Meldrum SJ, D'Vaz N, Dunstan JA, Mori TA, Hird K, Simmer K, et al. Allergic disease in the first year of life is associated with differences in subsequent neurodevelopment and behaviour. Early human development [Internet]. 2012 Jul [cited 2022 Feb 8];88(7):567–73. Available from: https://pubmed.ncbi.nlm.nih.gov/22284984/

36. Bertelsen RJ, Rava M, Carsin AE, Accordini S, Benediktsdóttir B, Dratva J, et al. Clinical markers of asthma and IgE assessed in parents before conception predict asthma and hayfever in the offspring. Clinical & Experimental Allergy [Internet]. 2017 May 1 [cited 2022 Feb 9];47(5):627–38. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/cea.12906

37. Cook-Mills JM. Maternal Influences over Offspring Allergic Responses. Current Allergy and Asthma Reports 2015 15:2 [Internet]. 2015 Jan 23 [cited 2022 Feb 9];15(2):1–10. Available from: https://link.springer.com/article/10.1007/s11882-014-0501-1

38. Tuokkola J, Luukkainen P, Kaila M, Takkinen HM, Niinistö S, Veijola R, et al. Maternal dietary folate, folic acid and vitamin D intakes during pregnancy and lactation and the risk of cows' milk allergy in the offspring. British Journal of Nutrition [Internet]. 2016 Aug 28 [cited 2022 Feb 9];116(4):710–8. Available from: https://www.cambridge.org/core/journals/british-journal-of-nutrition/article/maternal-dietary-folate-folic-acid-and-vitamin-d-intakes-during-pregnancy-and-lactation-and-the-risk-of-cows-milk-allergy-in-the-offspring/7075AE63D0C30E01995D678AFBE98B29

39. Alford SH, Zoratti E, Peterson EL, Maliarik M, Ownby DR, Johnson CC. Parental history of atopic disease: Disease pattern and risk of pediatric atopy in offspring. Journal of Allergy and Clinical Immunology. 2004 Nov 1;114(5):1046–50.

40. Blümer N, Herz U, Wegmann M, Renz H. Prenatal lipopolysaccharide-exposure prevents allergic sensitization and airway inflammation, but not airway responsiveness in a murine model of experimental asthma. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology [Internet]. 2005 Mar [cited 2022 Feb 8];35(3):397–402. Available from: https://pubmed.ncbi.nlm.nih.gov/15784121/

41. Devereux G, Barker RN, Seaton A. Antenatal determinants of neonatal immune responses to allergens. Clinical and Experimental Allergy. 2002;32(1):43–50.

42. Uthoff H, Spenner A, Reckelkamm W, Ahrens B, Wölk G, Hackler R, et al. Critical role of preconceptional immunization for protective and nonpathological specific immunity in murine neonates. Journal of immunology (Baltimore, Md : 1950) [Internet]. 2003 Oct 1 [cited 2022 Feb 8];171(7):3485–92. Available from: https://pubmed.ncbi.nlm.nih.gov/14500644/

43. Lim RH, Kobzik L. Maternal transmission of asthma risk. American journal of reproductive immunology (New York, NY : 1989) [Internet]. 2009 [cited 2022 Feb 8];61(1):1–10. Available from: https://pubmed.ncbi.nlm.nih.gov/19007349/

44. Sonnenschein-van der Voort AMM, Jaddoe VWV, Moll HA, Hofman A, van der Valk RJP, de Jongste JC, et al. Influence of maternal and cord blood C-reactive protein on childhood respiratory symptoms and eczema. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology [Internet]. 2013 Aug [cited 2022 Feb 8];24(5):469–75. Available from: https://pubmed.ncbi.nlm.nih.gov/23773138/

45. Giwercman C, Halkjaer LB, Jensen SM, Bønnelykke K, Lauritzen L, Bisgaard H. Increased risk of eczema but reduced risk of early wheezy disorder from exclusive breast-feeding in high-risk infants. The Journal of allergy and clinical immunology [Internet]. 2010 Apr [cited 2022 Feb 8];125(4):866–71. Available from: https://pubmed.ncbi.nlm.nih.gov/20236698/

46. Al-Tamprouri C, Malin B, Bill H, Lennart B, Anna S. Cat and dog ownership during/after the first year of life and risk for sensitization and reported allergy symptoms at age 13. Immunity, Inflammation and Disease [Internet]. 2019 Dec 1 [cited 2022 Feb 8];7(4):250. Available from: /pmc/articles/PMC6842813/

47. Litonjua AA, Carey VJ, Burge HA, Weiss ST, Gold DR. Parental history and the risk for childhood asthma. Does mother confer more risk than father? American journal of respiratory and critical care medicine [Internet]. 1998 [cited 2022 Feb 8];158(1):176–81. Available from: https://pubmed.ncbi.nlm.nih.gov/9655726/

48. Wright AL, Holberg CJ, Taussig LM, Martinez FD. Factors influencing the relation of infant feeding to asthma and recurrent wheeze in childhood. Thorax [Internet]. 2001 [cited 2022 Feb 8];56(3):192–7. Available from: https://pubmed.ncbi.nlm.nih.gov/11182011/

49. Hartvigsson O, Barman M, Rabe H, Sandin A, Wold AE, Brunius C, et al. Associations of maternal and infant metabolomes with immune maturation and allergy development at 12 months in the Swedish NICE-cohort. Scientific Reports | [Internet]. 123AD [cited 2022 Feb 8];11:12706. Available from: https://doi.org/10.1038/s41598-021-92239-3

50. Fujimura T, Lum SZC, Nagata Y, Kawamoto S, Oyoshi MK. Influences of Maternal Factors Over Offspring Allergies and the Application for Food Allergy. Frontiers in Immunology [Internet]. 2019 [cited 2022 Feb 8];10(AUG):1933. Available from: /pmc/articles/PMC6716146/

51. Prins JR, Eskandar S, Eggen BJL, Scherjon SA. Microglia, the missing link in maternal immune activation and fetal neurodevelopment; and a possible link in preeclampsia and disturbed neurodevelopment? Journal of Reproductive Immunology. 2018 Apr 1;126:18–22.

52. Patel S, Cooper MN, Jones H, Whitehouse AJO, Dale RC, Guastella AJ. Maternal immune-related conditions during pregnancy may be a risk factor for neuropsychiatric problems in offspring throughout childhood and adolescence. Psychological medicine [Internet]. 2020 Dec 1 [cited 2022 Feb 8];51(16):2904–14. Available from: https://pubmed.ncbi.nlm.nih.gov/32476637/

53. Joseph CLM, Sitarik AR, Kim H, Huffnagle G, Fujimura K, Yong GJM, et al. Infant gut bacterial community composition and food-related manifestation of atopy in early childhood. Pediatric Allergy and Immunology. 2022 Jan 1;33(1).

54. Huang YJ, Marsland BJ, Bunyavanich S, O'Mahony L, Leung DYM, Muraro A, et al. The microbiome in allergic disease: Current understanding and future opportunities-2017 PRACTALL document of the American Academy of Allergy, Asthma & Immunology and the European Academy of Allergy and Clinical Immunology. The Journal of allergy and clinical immunology [Internet]. 2017 Apr 1 [cited 2022 Feb 6];139(4):1099–110. Available from: https://pubmed.ncbi.nlm.nih.gov/28257972/

55. Łoś-Rycharska E, Gołębiewski M, Grzybowski T, Rogalla-Ładniak U, Krogulska A. The microbiome and its impact on food allergy and atopic dermatitis in children. Advances in Dermatology and Allergology/Postępy Dermatologii i Alergologii [Internet]. 2020 [cited 2022 Feb 6];37(5):641. Available from: /pmc/articles/PMC7675070/

56. Canani RB, Sangwan N, Stefka AT, Nocerino R, Paparo L, Aitoro R, et al. Lactobacillus rhamnosus GG-supplemented formula expands butyrate-producing bacterial strains in food allergic infants. The ISME Journal 2016 10:3 [Internet]. 2015 Sep 22 [cited 2022 Feb 6];10(3):742–50. Available from: https://www.nature.com/articles/ismej2015151

57. Hua X, Goedert JJ, Pu A, Yu G, Shi J. Allergy associations with the adult fecal microbiota: Analysis of the American Gut Project. EBioMedicine [Internet]. 2015 Jan 1 [cited 2022 Feb 6];3:172–9. Available from: https://pubmed.ncbi.nlm.nih.gov/26870828/

58. Thompson-Chagoyan OC, Vieites JM, Maldonado J, Edwards C, Gil A. Changes in faecal microbiota of infants with cow's milk protein allergy – a Spanish prospective case–control 6-month follow-up study. Pediatric Allergy and Immunology [Internet]. 2010 Mar 1 [cited 2022 Feb 6];21(2p2):e394–400. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1399-3038.2009.00961.x

59. Tun HM, Peng Y, Chen B, Konya TB, Morales-Lizcano NP, Chari R, et al. Ethnicity Associations With Food Sensitization Are Mediated by Gut Microbiota Development in the First Year of Life. Gastroenterology [Internet]. 2021 Jul 1 [cited 2022 Feb 8];161(1):94–106. Available from: https://pubmed.ncbi.nlm.nih.gov/33741316/

60. Battersby AJ, Gibbons DL. The gut mucosal immune system in the neonatal period. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology [Internet]. 2013 Aug [cited 2022 Feb 8];24(5):414–21. Available from: https://pubmed.ncbi.nlm.nih.gov/23682966/

61. Allan Walker W. Initial intestinal colonization in the human infant and immune homeostasis. Annals of nutrition & metabolism [Internet]. 2013 Nov [cited 2022 Feb 8];63 Suppl 2(SUPPL.2):8–15. Available from: https://pubmed.ncbi.nlm.nih.gov/24217032/

62. Brandtzaeg P. Secretory IgA: Designed for Anti-Microbial Defense. Frontiers in immunology [Internet]. 2013 [cited 2022 Feb 8];4(AUG). Available from: https://pubmed.ncbi.nlm.nih.gov/23964273/

63. Patel S, Cooper MN, Jones H, Whitehouse AJO, Dale RC, Guastella AJ. Maternal immune-related conditions during pregnancy may be a risk factor for neuropsychiatric problems in offspring throughout childhood and adolescence. Psychological medicine [Internet]. 2020 Dec 1 [cited 2022 Feb 9];51(16):2904–14. Available from: https://pubmed.ncbi.nlm.nih.gov/32476637/

64. Malan-Muller S, Valles-Colomer M, Raes J, Lowry CA, Seedat S, Hemmings SMJ. The Gut Microbiome and Mental Health: Implications for Anxiety- and Trauma-Related Disorders. Omics : a journal of integrative biology [Internet]. 2018 Feb 1 [cited 2022 Feb 9];22(2):90–107. Available from: https://pubmed.ncbi.nlm.nih.gov/28767318/

65. Malan-Muller S, Valles-Colomer M, Raes J, Lowry CA, Seedat S, Hemmings SMJ. The gut microbiome and mental health: Implications for anxiety- and trauma-related disorders. OMICS A Journal of Integrative Biology. 2018 Feb 1;22(2):90–107.

66. Mayer EA, Tillisch K, Gupta A. Gut/brain axis and the microbiota. The Journal of Clinical Investigation. 2015 Mar 2;125(3):926–38.

67. Bercik P, Collins SM, Verdu EF. Microbes and the gut-brain axis. Neurogastroenterology & Motility [Internet]. 2012 May 1 [cited 2022 Feb 9];24(5):405–13. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1365-2982.2012.01906.x

68. Cryan JF, O'riordan KJ, Cowan CSM, Sandhu K v., Bastiaanssen TFS, Boehme M, et al. The microbiota-gut-brain axis. Physiological Reviews [Internet]. 2019 [cited 2022 Feb 9];99(4):1877–2013. Available from: https://journals.physiology.org/doi/abs/10.1152/physrev.00018.2018

69. Rosin S, Xia K, Azcarate-Peril MA, Carlson AL, Propper CB, Thompson AL, et al. A preliminary study of gut microbiome variation and HPA axis reactivity in healthy infants. Psychoneuroendocrinology. 2021 Feb 1;124:105046.

70. Johnson EO, Kamilaris TC, Chrousos GP, Gold PW. Mechanisms of stress: A dynamic overview of hormonal and behavioral homeostasis. Neuroscience and Biobehavioral Reviews. 1992;16(2):115–30.

71. Taylor JL, Corbett BA. A review of rhythm and responsiveness of cortisol in individuals with autism spectrum disorders. Psychoneuroendocrinology [Internet]. 2014 [cited 2022 Feb 8];49(1):207–28. Available from: https://pubmed.ncbi.nlm.nih.gov/25108163/

72. Bradley AJ, Dinan TG. A systematic review of hypothalamic-pituitary-adrenal axis function in schizophrenia: implications for mortality. Journal of psychopharmacology

(Oxford, England) [Internet]. 2010 [cited 2022 Feb 8];24(4 Suppl):91–118. Available from: https://pubmed.ncbi.nlm.nih.gov/20923924/

73. Sudo N, Chida Y, Aiba Y, Sonoda J, Oyama N, Yu XN, et al. Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice. The Journal of physiology [Internet]. 2004 Jul 1 [cited 2022 Feb 8];558(Pt 1):263–75. Available from: https://pubmed.ncbi.nlm.nih.gov/15133062/

74. Clarke G, Grenham S, Scully P, Fitzgerald P, Moloney RD, Shanahan F, et al. The microbiome-gut-brain axis during early life regulates the hippocampal serotonergic system in a sex-dependent manner. Molecular psychiatry [Internet]. 2013 Jun [cited 2022 Feb 8];18(6):666–73. Available from: https://pubmed.ncbi.nlm.nih.gov/22688187/

75. Crumeyrolle-Arias M, Jaglin M, Bruneau A, Vancassel S, Cardona A, Daugé V, et al. Absence of the gut microbiota enhances anxiety-like behavior and neuroendocrine response to acute stress in rats. Psychoneuroendocrinology [Internet]. 2014 [cited 2022 Feb 8];42:207–17. Available from: https://pubmed.ncbi.nlm.nih.gov/24636517/

76. Messaoudi M, Lalonde R, Violle N, Javelot H, Desor D, Nejdi A, et al. Assessment of psychotropic-like properties of a probiotic formulation (Lactobacillus helveticus R0052 and Bifidobacterium longum R0175) in rats and human subjects. The British journal of nutrition [Internet]. 2011 Mar 14 [cited 2022 Feb 8];105(5):755–64. Available from: https://pubmed.ncbi.nlm.nih.gov/20974015/

77. Schmidt K, Cowen PJ, Harmer CJ, Tzortzis G, Errington S, Burnet PWJ. Prebiotic intake reduces the waking cortisol response and alters emotional bias in healthy volunteers. Psychopharmacology [Internet]. 2015 May 1 [cited 2022 Feb 8];232(10):1793–801. Available from: https://pubmed.ncbi.nlm.nih.gov/25449699/

78. Hantsoo L, Jašarević E, Criniti S, McGeehan B, Tanes C, Sammel MD, et al. Childhood

adversity impact on gut microbiota and inflammatory response to stress during pregnancy. Brain, Behavior, and Immunity. 2019 Jan 1;75:240–50.

79. Michels N, van de Wiele T, Fouhy F, O'Mahony S, Clarke G, Keane J. Gut microbiome patterns depending on children's psychosocial stress: Reports versus biomarkers. Brain, Behavior, and Immunity. 2019 Aug 1;80:751–62.

80. Goyal DK, Miyan JA. Neuro-immune abnormalities in autism and their relationship with the environment: a variable insult model for autism. Frontiers in endocrinology [Internet]. 2014 [cited 2022 Feb 6];5(MAR). Available from: https://pubmed.ncbi.nlm.nih.gov/24639668/

81. Bilbo SD, Nevison CD, Parker W. A model for the induction of autism in the ecosystem of the human body: the anatomy of a modern pandemic? Microbial Ecology in Health & Disease [Internet]. 2015 Jan 28 [cited 2022 Feb 9];26(0). Available from: https://www.tandfonline.com/action/journalInformation?journalCode=zmeh20

82. Carlson AL, Xia K, Azcarate-Peril MA, Goldman BD, Ahn M, Styner MA, et al. Infant Gut Microbiome Associated With Cognitive Development. Biological Psychiatry. 2018 Jan 15;83(2):148–59.

83. Sordillo JE, Korrick S, Laranjo N, Carey V, Weinstock GM, Gold DR, et al. Association of the Infant Gut Microbiome With Early Childhood Neurodevelopmental Outcomes: An Ancillary Study to the VDAART Randomized Clinical Trial. JAMA network open [Internet]. 2019 Mar 1 [cited 2022 Feb 6];2(3):e190905. Available from: https://pubmed.ncbi.nlm.nih.gov/30901046/

84. Tamana SK, Tun HM, Konya T, Chari RS, Field CJ, Guttman DS, et al. Bacteroides-dominant gut microbiome of late infancy is associated with enhanced neurodevelopment. Gut microbes [Internet]. 2021 [cited 2022 Feb 6];13(1):1–17. Available from:

https://pubmed.ncbi.nlm.nih.gov/34132157/

85. Litonjua AA. Dietary Factors and the Development of Asthma. Immunology and Allergy Clinics of North America. 2008 Aug 1;28(3):603–29.

86. Maslova E, Hansen S, Strøm M, Halldorsson TI, Olsen SF. Maternal intake of vitamins A, E and K in pregnancy and child allergic disease: a longitudinal study from the Danish National Birth Cohort. British Journal of Nutrition [Internet]. 2014 Mar 28 [cited 2022 Feb 8];111(6):1096–108. Available from: https://www.cambridge.org/core/journals/british-journal-of-nutrition/article/maternal-intake-of-vitamins-a-e-and-k-in-pregnancy-and-child-allergic-disease-a-longitudinal-study-from-the-danish-national-birth-cohort/221C01A4F3ADA86FCF661AAD0E2EFC17

87. Nwaru BI, Ahonen S, Kaila M, Erkkola M, Haapala AM, Kronberg-Kippilä C, et al. Maternal diet during pregnancy and allergic sensitization in the offspring by 5 yrs of age: </br>a prospective cohort study. Pediatric Allergy and Immunology [Internet]. 2010 Feb 1 [cited 2022 Feb 8];21(1-Part-I):29–37. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1399-3038.2009.00949.x

88. Miyake Y, Sasaki S, Tanaka K, Hirota Y. Consumption of vegetables, fruit, and antioxidants during pregnancy and wheeze and eczema in infants. Allergy [Internet]. 2010 Jun 1 [cited 2022 Feb 8];65(6):758–65. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1398-9995.2009.02267.x

89. Smith PK, Masilamani M, Li XM, Sampson HA. The false alarm hypothesis: Food allergy is associated with high dietary advanced glycation end-products and proglycating dietary sugars that mimic alarmins. Journal of Allergy and Clinical Immunology. 2017 Feb 1;139(2):429–37.

90. Venter C, Pickett K, Starling A, Maslin K, Smith PK, Palumbo MP, et al. Advanced glycation end product intake during pregnancy and offspring allergy outcomes: A Prospective cohort study. Clinical & Experimental Allergy [Internet]. 2021 Nov 1 [cited 2022 Feb 8];51(11):1459–70. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/cea.14027

91. Garcia-Larsen V, Ierodiakonou D, Jarrold K, Cunha S, Chivinge J, Robinson Z, et al. Diet during pregnancy and infancy and risk of allergic or autoimmune disease: A systematic review and meta-analysis. PLoS Medicine. 2018 Feb 1;15(2).

92. Sunde RB, Thorsen J, Pedersen C-ET, Stokholm J, Bønnelykke K, Chawes B, et al. Prenatal tobacco exposure and risk of asthma and allergy outcomes in childhood. European Respiratory Journal [Internet]. 2021 Jul 8 [cited 2022 Feb 8];2100453. Available from: https://erj.ersjournals.com/content/early/2021/06/25/13993003.00453-2021

93. Hossenbaccus L, Linton S, Ramchandani R, Gallant MJ, Ellis AK. Insights into allergic risk factors from birth cohort studies. Annals of Allergy, Asthma & Immunology. 2021 Sep 1;127(3):312–7.

94. Ekblad M, Korkeila J, Lehtonen L. Smoking during pregnancy affects foetal brain development. Acta Paediatrica [Internet]. 2015 Jan 1 [cited 2022 Feb 8];104(1):12–8.

Available from: https://onlinelibrary-wiley-com.login.ezproxy.library.ualberta.ca/doi/full/10.1111/apa.12791

95. Magnusson CGM. Maternal smoking influences cord serum IgE and IgD levels and increases the risk for subsequent infant allergy. Journal of Allergy and Clinical Immunology. 1986 Nov 1;78(5):898–904.

96. Thacher JD, Gruzieva O, Pershagen G, Neuman, van Hage M, Wickman M, et al. Parental smoking and development of allergic sensitization from birth to adolescence. Allergy [Internet]. 2016 Feb 1 [cited 2022 Feb 8];71(2):239–48. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/all.12792

97. Barrero-Castillero A, Pierce LJ, Urbina-Johanson SA, Pirazzoli L, Burris HH, Nelson CA. Perinatal and early childhood biomarkers of psychosocial stress and adverse experiences. Pediatric Research 2022 [Internet]. 2022 Jan 28 [cited 2022 Feb 8];1–10. Available from: https://www.nature.com/articles/s41390-022-01933-z

98. Rajasekera TA, Gur TL. Maternal Exposure to Adversity: Impact on the Microbiota-Gut-Brain Axis, Inflammation and Offspring Psychiatric Outcomes. 2021;32:26–39.

99. DeSocio JE. Epigenetics, maternal prenatal psychosocial stress, and infant mental health. Archives of Psychiatric Nursing. 2018 Dec 1;32(6):901–6.

100. Coussons-Read ME, Okun ML, Nettles CD. Psychosocial stress increases inflammatory markers and alters cytokine production across pregnancy. Brain, Behavior, and Immunity. 2007 Mar 1;21(3):343–50.

101. Olvera Alvarez HA, Kubzansky LD, Campen MJ, Slavich GM. Early life stress, air pollution, inflammation, and disease: An integrative review and immunologic model of social-environmental adversity and lifespan health. Neuroscience and biobehavioral

reviews [Internet]. 2018 Sep 1 [cited 2022 Feb 8];92:226–42. Available from: https://pubmed.ncbi.nlm.nih.gov/29874545/

102. Pedersen JM, Mortensen EL, Christensen DS, Rozing M, Brunsgaard H, Meincke RH, et al. Prenatal and early postnatal stress and later life inflammation. Psychoneuroendocrinology [Internet]. 2018 Feb 1 [cited 2022 Feb 8];88:158–66. Available from: https://pubmed.ncbi.nlm.nih.gov/29291495/

103. Slopen N, Loucks EB, Appleton AA, Kawachi I, Kubzansky LD, Non AL, et al. Early origins of inflammation: An examination of prenatal and childhood social adversity in a prospective cohort study. Psychoneuroendocrinology [Internet]. 2015 Jan 1 [cited 2022 Feb 8];51:403–13. Available from: https://pubmed.ncbi.nlm.nih.gov/25462912/

104. Kang LJ, Vu KN, Koleva PT, Field CJ, Chow A, Azad MB, et al. Maternal psychological distress before birth influences gut immunity in mid-infancy. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology [Internet]. 2020 Feb 1 [cited 2022 Feb 8];50(2):178–88. Available from: https://pubmed.ncbi.nlm.nih.gov/31845414/

105. Rodriguez N, Tun HM, Field CJ, Mandhane PJ, Scott JA, Kozyrskyj AL. Prenatal Depression, Breastfeeding, and Infant Gut Microbiota. Frontiers in Microbiology [Internet]. 2021 Jul 30 [cited 2022 Feb 8];12. Available from: /pmc/articles/PMC8363245/

106. Picó C, Palou M, Pomar CA, Palou A. Benefits of breastfeeding in infant health: a role for milk signaling peptides. Molecular Nutrition: Mother and Infant. 2021 Jan 1;29–56.

107. Louis-Jacques AF, Stuebe AM. Enabling Breastfeeding to Support Lifelong Health for Mother and Child. Obstetrics and Gynecology Clinics of North America. 2020 Sep 1;47(3):363–81.

108. Gould JF. Complementary Feeding, Micronutrients and Developmental Outcomes of Children. Nestle Nutrition Institute workshop series [Internet]. 2017 [cited 2022 Feb 9];87:13–28. Available from: https://pubmed.ncbi.nlm.nih.gov/28315884/

109. Zhong C, Guo J, Tan T, Wang H, Lin L, Gao D, et al. Increased food diversity in the first year of life is inversely associated with allergic outcomes in the second year. Pediatric Allergy and Immunology. 2022 Jan 1;33(1).

110. Caffarelli C, di Mauro D, Mastrorilli C, Bottau P, Cipriani F, Ricci G. Solid Food Introduction and the Development of Food Allergies. Nutrients 2018, Vol 10, Page 1790 [Internet]. 2018 Nov 17 [cited 2022 Feb 9];10(11):1790. Available from: https://www.mdpi.com/2072-6643/10/11/1790/htm

111. Karmaus W. Does a higher number of siblings protect against the development of allergy and asthma? A review. J Epidemiol Community Health [Internet]. 2002 [cited 2022 Feb 9];56:209–17. Available from: http://jech.bmj.com/

112. Leadbitter P, Pearce N, Cheng S, Sears MR, Holdaway MD, Flannery EM, et al. Relationship between fetal growth and the development of asthma and atopy in childhood. Thorax [Internet]. 1999 [cited 2022 Feb 9];54(10):905–10. Available from: https://pubmed.ncbi.nlm.nih.gov/10491453/

113. Rona RJ, Hughes JM, Chinn S. Association between asthma and family size between 1977 and 1994. Journal of epidemiology and community health [Internet]. 1999 [cited 2022 Feb 9];53(1):15–9. Available from: https://pubmed.ncbi.nlm.nih.gov/10326047/

114. Wickens KL, Crane J, Kemp TJ, Lewis SJ, D'Souza WJ, Sawyer GM, et al. Family size, infections, and asthma prevalence in New Zealand children. Epidemiology (Cambridge,

Mass) [Internet]. 1999 [cited 2022 Feb 9];10(6):699–705. Available from: https://pubmed.ncbi.nlm.nih.gov/10535783/

115. Okada H, Kuhn C, Feillet H, Bach JF. The 'hygiene hypothesis' for autoimmune and allergic diseases: an update. Clinical and Experimental Immunology [Internet]. 2010 Apr [cited 2022 Feb 9];160(1):1. Available from: /pmc/articles/PMC2841828/

116. Seiskari T, Kondrashova A, Viskari H, Kaila M, Haapala AM, Aittoniemi J, et al. Allergic sensitization and microbial load − a comparison between Finland and Russian Karelia. Clinical and Experimental Immunology [Internet]. 2007 [cited 2022 Feb 9];148(1):47. Available from: /pmc/articles/PMC1868862/

117. Ben-Itzchak E, Zukerman G, Zachor DA. Having Older Siblings is Associated with Less Severe Social Communication Symptoms in Young Children with Autism Spectrum Disorder. Journal of Abnormal Child Psychology [Internet]. 2016 Nov 1 [cited 2022 Feb 9];44(8):1613–20. Available from: https://link.springer.com/article/10.1007/s10802-016-0133-0

118. Pyrhönen K, Kulmala P. Delivery mode and the incidence of atopic sensitization and food allergy in a Finnish child population. Pediatr Allergy Immunol [Internet]. 2022 [cited 2022 Feb 9];33. Available from: https://doi.org/10.1111/pai.13584wileyonlinelibrary.com/journal/pai

119. Almqvist C, Cnattingius S, Lichtenstein P, Lundholm C. The impact of birth mode of delivery on childhood asthma and allergic diseases-a sibling study. Clinical and Experimental Allergy. 2012 Sep;42(9):1369–76.

120. Jakobsson HE, Abrahamsson TR, Jenmalm MC, Harris K, Quince C, Jernberg C, et al. Decreased gut microbiota diversity, delayed Bacteroidetes colonisation and reduced Th1

responses in infants delivered by caesarean section. Gut [Internet]. 2014 [cited 2022 Feb 9];63(4):559–66. Available from: https://pubmed.ncbi.nlm.nih.gov/23926244/

121. Wiguna T, Khoe LC. The impact of Caesarean delivery mode towards brain and neurodevelopment among children. World Nutrition Journal [Internet]. 2020 Oct 1 [cited 2022 Feb 9];4(1–2):32–7. Available from: https://worldnutrijournal.org/OJS/index.php/WNJ/article/view/V04.S2.0005

122. Kenkel W. Birth signalling hormones and the developmental consequences of caesarean delivery. Journal of Neuroendocrinology [Internet]. 2021 Jan 1 [cited 2022 Feb 9];33(1):e12912. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/jne.12912

123. May T, Adesina I, McGillivray J, Rinehart NJ. Sex differences in neurodevelopmental disorders. Current Opinion in Neurology [Internet]. 2019 Aug 1 [cited 2022 Feb 9];32(4):622–6. Available from: https://journals.lww.com/co-neurology/Fulltext/2019/08000/Sex_differences_in_neurodevelopmental_disorders.18.aspx

124. Ferri SL, Abel T, Brodkin ES. Sex Differences in Autism Spectrum Disorder: a Review. Current Psychiatry Reports [Internet]. 2018 Feb 1 [cited 2022 Feb 9];20(2):1–17. Available from: https://link.springer.com/article/10.1007/s11920-018-0874-2

125. Ji Y, Hong X, Wang G, Chatterjee N, Riley AW, Lee LC, et al. A Prospective Birth Cohort Study on Early Childhood Lead Levels and Attention Deficit Hyperactivity Disorder: New Insight on Sex Differences. The Journal of pediatrics [Internet]. 2018 Aug 1 [cited 2022 Feb 9];199:124-131.e8. Available from: https://pubmed.ncbi.nlm.nih.gov/29752174/

126. Murray AL, Booth T, Eisner M, Auyeung B, Murray G, Ribeaud D. Sex differences in ADHD trajectories across childhood and adolescence. Developmental Science [Internet]. 2019 Jan 1 [cited 2022 Feb 9];22(1):e12721. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/desc.12721

127. Becklake MR, Kauffmann F. Gender differences in airway behaviour over the human life span. Thorax [Internet]. 1999 [cited 2022 Feb 9];54(12):1119–38. Available from: https://pubmed.ncbi.nlm.nih.gov/10567633/

128. Williams TC, Bach CC, Matthiesen NB, Henriksen TB, Gagliardi L. Directed acyclic graphs: a tool for causal studies in paediatrics. Pediatric Research 2018 84:4 [Internet]. 2018 Jun 4 [cited 2022 Feb 8];84(4):487–93. Available from: https://www.nature.com/articles/s41390-018-0071-3

129. Weng HY, Hsueh YH, Messam LLM v., Hertz-Picciotto I. Methods of covariate selection: directed acyclic graphs and the change-in-estimate procedure. American journal of epidemiology [Internet]. 2009 May [cited 2022 Feb 8];169(10):1182–90. Available from: https://pubmed.ncbi.nlm.nih.gov/19363102/

130. Peters RL, Koplin JJ, Allen KJ, Lowe AJ, Lodge CJ, Tang MLK, et al. The Prevalence of Food Sensitization Appears Not to Have Changed between 2 Melbourne Cohorts of High-Risk Infants Recruited 15 Years Apart. The journal of allergy and clinical immunology In practice [Internet]. 2018 Mar 1 [cited 2022 Feb 8];6(2):440-448.e2. Available from: https://pubmed.ncbi.nlm.nih.gov/29248387/

131. Bayley Scales of Infant & Toddler Development Ed 3 [Internet]. [cited 2022 Feb 6]. Available from: https://www.pearsonassessments.com/store/usassessments/en/Store/Professional-

Assessments/Behavior/Adaptive/Bayley-Scales-of-Infant-and-Toddler-Development-%7C-Third-Edition/p/100000123.html

132. Albers CA, Grieve AJ. Test Review: Bayley, N. (2006). Bayley Scales of Infant and Toddler Development– Third Edition. San Antonio, TX: Harcourt Assessment: http://dx.doi.org/101177/0734282906297199 [Internet]. 2016 Aug 19 [cited 2022 Feb 6];25(2):180–90. Available from: https://journals.sagepub.com/doi/abs/10.1177/0734282906297199

133. Baron RM, Kenny DA. The Moderator-Mediator Variable Distinction in Social Psychological Research. Conceptual, Strategic, and Statistical Considerations. Journal of Personality and Social Psychology [Internet]. 1986 Dec [cited 2022 Feb 6];51(6):1173–82. Available from: /record/1987-13085-001

134. Straughen JK, Sitarik AR, Johnson CC, Wegienka G, Ownby DR, Johnson-Hooper TM, et al. Prenatal IgE as a Risk Factor for the Development of Childhood Neurodevelopmental Disorders. Frontiers in pediatrics [Internet]. 2021 May 14 [cited 2022 Feb 8];9. Available from: https://pubmed.ncbi.nlm.nih.gov/34055677/

135. Hadders-Algra M, Tacke U, Pietz J, Rupp A, Philippi H. Standardized Infant NeuroDevelopmental Assessment developmental and socio-emotional scales: reliability and predictive value in an at-risk population. Developmental Medicine & Child Neurology [Internet]. 2020 Jul 1 [cited 2022 Feb 8];62(7):845–53. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/dmcn.14423

136. Brito NH, Fifer WP, Amso D, Barr R, Bell MA, Calkins S, et al. Beyond the Bayley: Neurocognitive Assessments of Development During Infancy and Toddlerhood. https://doi.org/101080/8756564120181564310 [Internet]. 2019 Feb 17 [cited 2022 Feb

8];44(2):220–47. Available from: https://www.tandfonline.com/doi/abs/10.1080/87565641.2018.1564310

137. Mikkelsen A, Borres MP, Björkelund C, Lissner L, Oxelmark L. The Food hypersensitivity famiLy ImPact (FLIP) questionnaire - development and first results. Pediatric Allergy and Immunology [Internet]. 2013 Sep 1 [cited 2022 Feb 8];24(6):574–81. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/pai.12105

138. Treyvaud K, Anderson VA, Howard K, Bear M, Hunt RW, Doyle LW, et al. Parenting behavior is associated with the early neurobehavioral development of very preterm children. Pediatrics [Internet]. 2009 Feb [cited 2022 Feb 8];123(2):555–61. Available from: https://pubmed.ncbi.nlm.nih.gov/19171622/

139. Karam F, Sheehy O, Huneau MC, Chambers C, Fraser WD, Johnson D, et al. Impact of maternal prenatal and parental postnatal stress on 1-year-old child development: results from the OTIS antidepressants in pregnancy study. Archives of Women's Mental Health [Internet]. 2016 Oct 1 [cited 2022 Feb 8];19(5):835–43. Available from: https://link.springer.com/article/10.1007/s00737-016-0624-6

140. Letourneau NL, Kozyrskyj AL, Cosic N, Ntanda HN, Anis L, Hart MJ, et al. Maternal sensitivity and social support protect against childhood atopic dermatitis. Allergy, Asthma & Clinical Immunology 2017 13:1 [Internet]. 2017 May 26 [cited 2022 Feb 8];13(1):1–14. Available from: https://aacijournal.biomedcentral.com/articles/10.1186/s13223-017-0199-4

141. Panza R, Baldassarre ME, di Mauro A, Cervinara A, Capozza M, Laforgia N. Infantile Functional Gastrointestinal Disorders and Maternal Psychological Status: A Narrative

Review. Current pediatric reviews [Internet]. 2021 Feb 9 [cited 2022 Feb 8];17(2):111–9. Available from: https://pubmed.ncbi.nlm.nih.gov/33557737/

142. Browne PD, Aparicio M, Alba C, Hechler C, Beijers R, Rodríguez JM, et al. Human milk microbiome and maternal postnatal psychosocial distress. Frontiers in Microbiology. 2019;10(OCT):2333.

143. Kawano A, Emori Y. The Relationship Between Maternal Postpartum Psychological State and Breast Milk Secretory Immunoglobulin A Level. Journal of the American Psychiatric Nurses Association [Internet]. 2015 Jan 17 [cited 2022 Feb 8];21(1):23–30. Available from: https://journals.sagepub.com/doi/full/10.1177/1078390314566882?casa_token=wPAEaak mrmEAAAAA%3A-ANMqBSnlcgfCyxRJiPBARhAN0xvKCtWgKLmayuVJrhgBR0PqQdYXhlwJGT_fQ6uP 3bc3EZfGhTf

144. Kingston D, Tough S, Whitfield H. Prenatal and postpartum maternal psychological distress and infant development: A systematic review. Child Psychiatry and Human Development [Internet]. 2012 Oct 10 [cited 2022 Feb 8];43(5):683–714. Available from: https://link.springer.com/article/10.1007/s10578-012-0291-4

145. Yang X, Liang R, Xing Q, Ma X. Fighting Food Allergy by Inducing Oral Tolerance: Facts and Fiction. International Archives of Allergy and Immunology. 2021 Sep 1;182(9):852–62.

146. Osborne NJ, Koplin JJ, Martin PE, Gurrin LC, Lowe AJ, Matheson MC, et al. Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants. J Allergy Clin Immunol. (2011) 127:668–76. doi: 10.1016/j.jaci.2011.01.039

147. Valenta R, Hochwallner H, Linhart B. Food allergies: the basics. Gastroenterology. (2015) 148:1120–31. doi: 10.1053/j.gastro.2015.02.006

148. Theoharides TC, Tsilioni I. Mast cells, neuroinflammation and pain in fibromyalgia syndrome. Front Cell Neurosci. (2019) 13:353. doi: 10.3389/fncel.2019.00353

149. 4. Nibbering B. Microbial interactions in the atopic march. Clin Exp Immunol. (2020) 199:12–23. doi: 10.1111/cei.13398

150. 5. Liu AH, Jaramillo R, Sicherer SH, Wood RA, Bock SA, Burks A, et al. National prevalence and risk factors for food allergy and relationship to asthma: results from the National Health and Nutrition Examination Survey 2005- 2006. J Allergy Clin Immunol. (2010) 126:798–806. doi: 10.1016/j.jaci.2010. 07.026

151. 6. Tran MM, Lefebvre DL, Dharma C, Dai D, Lou WY, Subbarao P, et al. Predicting the atopic march: results from the canadian healthy infant longitudinal development study. J Allergy Clin Immunol. (2018) 141:601– 7. doi: 10.1016/j.jaci.2017.08.024

152. 7. Koplin JJ, Wake M, Dharmage SC, Matheson M, Tang ML, Gurrin LC, et al. Cohort profile: the HealthNuts study: population prevalence and environmental/genetic predictors of food allergy. Int J Epidemiol. (2015) 44:1161– 71. doi: 10.1093/ije/dyu261

153. 8. Alduraywish SA, Lodge CJ, Vicendese D, Lowe AJ, Erbas B, Matheson M, et al. Sensitization to milk, egg and peanut from birth to 18 years: a longitudinal study of a cohort at risk of allergic disease. Pediatr Allergy Immunol. (2016) 27:83–91. doi: 10.1111/pai.12480

154. 9. Ratsika A, Codagnone MC, O’Mahony S, Stanton C. Priming for life: early life nutrition and the microbiota-gut-brain axis. Nutrients. (2021) 13:423. doi: 10.3390/nu13020423

155. 10. Chua RXY, Tay MJY, Ooi DSQ, Siah KTH, Tham EH, Shek LP, et al. Understanding the link between allergy and neurodevelopmental disorders: a current review of factors and mechanisms. Front Neurol. (2021) 11:1965. doi: 10.3389/fneur.2020.603571

156. 11. Jyonouchi H. Autism spectrum disorders and allergy: observation from a pediatric allergy/immunology clinic. Expert Rev Clin Immunol. (2010) 6:397– 411. doi: 10.1586/eci.10.18

157. 12. Guo MMH, Wang LJ, Hsu TY, Yang KD. Peanut sensitivity and allergic rhinitis in young children are associated with attention-deficit hyperactivity disorder symptoms in adolescence. Neuropsychiatr Dis Treat. (2020) 16:1349. doi: 10.2147/NDT.S232299

158. 13. Meldrum SJ, D'Vaz N, Dunstan JA, Mori TA, Hird K, Simmer K, et al. Allergic disease in the first year of life is associated with differences in subsequent neurodevelopment and behaviour. Early Hum Dev. (2012) 88:567– 73. doi: 10.1016/j.earlhumdev.2011.12.032

159. 14. Qu X, Lee LC, Ladd-Acosta C, Hong X, Ji Y, Kalb LG, et al. Association between atopic diseases and neurodevelopmental disabilities in a longitudinal birth cohort. Autism Res. (2022) 15:740–50. doi: 10.1002/aur.2680

160. 15. Kristal AR, Vizenor NC, Patterson RE, Neuhouser ML, Shattuck AL. Precision and bias of food frequency-based measures of fruit and vegetable intakes. Cancer Epidemiol Biomarkers Prev. (2000) 9:939–44.

161. 16. Bolduc FV, Lau A, Rosenfelt CS, Langer S, Wang N, Smithson L, et al. Cognitive enhancement in infants associated with increased maternal fruit intake during pregnancy: results from a birth cohort study with validation in an animal model. EBioMed. (2016) 8:331–40. doi: 10.1016/j.ebiom.2016. 04.025

162. 17. Williams TC, Bach CC, Matthiesen NB, Henriksen TB. Directed acyclic graphs: a tool for causal studies in paediatrics. Pediatr Res. (2018) 84:487– 93. doi: 10.1038/s41390-018-0071-3

163. 18. Weng HY, Hsueh YH, Messam LLM. Methods of covariate selection: directed acyclic graphs and the change-in-estimate procedure. Am J Epidemiol. (2009) 169:1182–90. doi: 10.1093/aje/kwp035

164. 19. Tun HM, Peng Y, Chen B, Konya TB, Morales-Lizcano NP, Chari R, et al. Ethnicity associations with food sensitization are mediated by gut microbiota development in the first year of life. Gastroenterology. (2021) 161:94– 106. doi: 10.1053/j.gastro.2021.03.016

165. 20. Peters RL, Koplin JJ, Allen KJ, Lowe AJ, Lodge CJ, Tang M, et al. The prevalence of food sensitization appears not to have changed between 2 Melbourne cohorts of high-risk infants recruited 15 years apart. J Allergy Clin Immunol. (2018) 6:440–8. doi: 10.1016/j.jaip.2017.11.018

166. 21. Heinzerling L, Mari A, Bergmann KC, Bresciani M, Burbach G, Darsow U, et al. The skin prick test–European standards. Clin Transl Allergy. (2013) 3:1–10. doi: 10.1186/2045-7022-3-3

167. 22. Bayley N. Bayley Scales of Infant and Toddler Development. San Antonio, TX: PsychCorp. (2006). doi: 10.1037/t14978-000

168. 23. Albers CA. (2007). Test review: Bayley N. Bayley scales of infant and toddler development–third edition. San Antonio, TX: Harcourt assessment. J Psychoeduc Assess. (2006) 25:180–90. doi: 10.1177/0734282906297199

169. 24. Tede Z, Cohen MO, Riskin A. The reliability and validity of the Greenspan Social Emotional Growth Chart (GSEGC) in Israeli children with developmental delay and autism—A pilot study. Res Dev Disabil. (2016) 55:226– 34. doi: 10.1016/j.ridd.2016.04.013

170. 25. Straughen JK, Sitarik AR, Johnson CC, Wegienka G, Ownby DR, Johnson-Hooper T, et al. Prenatal IgE as a risk factor for the development of childhood neurodevelopmental disorders. Front Pediatr. (2021) 9. doi: 10.3389/fped.2021.601092

171. 26. Hadders-Algra M, Tacke U, Pietz J, Rupp A, Philippi H. Standardized infant neurodevelopmental assessment developmental and socio-emotional scales: reliability and predictive value in an at-risk population. Dev Med Child Neurol. (2020) 62:845–53. doi: 10.1111/dmcn.14423

172. 27. Brito NH, Fifer WP, Amso D, Barr R, Bell MA, Calkins S, et al. Beyond the Bayley: neurocognitive assessments of development during infancy and toddlerhood. Dev Neuropsychol. (2019) 44:220– 47. doi: 10.1080/87565641.2018.1564310

173. 28. Mikkelsen A, Borres MP, Björkelund C, Lissner L. The food hypersensitivity famiLy ImPact (FLIP) questionnaire-development and first results. Pediatr Allergy Immunol. (2013) 24:574–81.

doi: 10.1111/pai.12105

174. 29. Treyvaud K, Anderson VA, Howard K, Bear M, Hunt RW, Doyle L, et al. Parenting behavior is associated with the early neurobehavioral development of very preterm children. Pediatrics. (2009) 123:555–61. doi: 10.1542/peds.20 8-0477

175. 30. Karam F, Sheehy O, Huneau MC, Chambers C, Fraser WD, Johnson D, et al. Impact of maternal prenatal and parental postnatal stress on 1-yearold child development: results from the OTIS antidepressants in pregnancy study. Archiv Womens Mental Health. (2016) 19:835–43. doi: 10.1007/s00737-01 6-0624-6

176. 31. Letourneau NL, Kozyrskyj AL, Cosic N, Ntanda HN, Anis L, Hart M, et al. Maternal sensitivity and social support protect against childhood atopic dermatitis. Allergy Asthma Clin Immunol. (2017) 13:1–14. doi: 10.1186/s13223-01 7-0199-4

177. 32. Panza R, Baldassarre ME, Di Mauro A, Cervinara A, Capozza M, Laforgia N. Infantile functional gastrointestinal disorders and maternal psychological status: a narrative review. Curr Pediatr Rev. (2021) 17:111–19. doi: 10.2174/1573396317666210208155106

178. 33. Browne PD, Aparicio M, Alba C, Hechler C, Beijers R, Rodríguez J, et al. Human milk microbiome and maternal postnatal psychosocial distress. Front Microbiol. (2019) 10:2333. doi: 10.3389/fmicb.2019.02333

179. 34. Kawano A. The relationship between maternal postpartum psychological state and breast milk secretory immunoglobulin A level. J Am Psychiatr Nurses Assoc. (2015) 21:23–30. doi: 10.1177/1078390314566882

180. 35. Kang LJ, Vu KN, Koleva PT, Field CJ, Chow A, Azad MB, et al. Maternal psychological distress before birth influences gut immunity in mid-infancy. Clin Exp Allergy. (2020) 50:178–88. doi: 10.1111/cea.13551

181. 36. Kingston D, Tough S. Prenatal and postpartum maternal psychological distress and infant

development: a systematic review. Child Psychiatry Hum Dev. (2012) 43:683–714. doi: 10.1007/s10578-012-0291-4

182. 37. Yang X, Liang R, Xing Q, Ma X. Fighting Food Allergy by Inducing Oral Tolerance: Facts and Fiction. International archives of allergy and immunology. (2021) 1–11. doi: 10.1159/000515292

183. 38. Perone S. Mapping cortical rhythms to infant behavioral tendencies via baseline EEG and parent-report. Dev Psychobiol. (2019) 61:815–23. doi: 10.1002/dev.21867

184. 39. Muntoni F. At their children's expense: how parents' gender stereotypes affect their children's reading outcomes. Learn Instr. (2019) 60:95–103. doi: 10.1016/j.learninstruc.2018.12.002

185. 40. Begum L, Grossman PJ. Parental gender bias and investment in children's health and education: evidence from Bangladesh. Oxf Econ Pap. (2022) 1– 18. doi: 10.1093/oep/gpac006

186. 41. Abramishvili Z, Appleman W. Parental Gender Preference in the Balkans and Scandinavia: Gender Bias or Differential Costs?. CERGE-EI Working Paper Series, No. 623. (2019). Available online at: https://papers.ssrn.com/sol3/papers. cfm?abstract_id=3448492

187. Wang L-J, Mu S-C, Lin M-I, Sung · Tseng-Chen, Chiang B-L, Lin · Cheng-Hui. Clinical Manifestations of Pediatric Food Allergy: a Contemporary Review. 2016 [cited 2022 Feb 6]; Available from: https://doi.org/10.1007/s12016-021-08895-w

188. Hartvigsson O, Barman M, Rabe H, Sandin A, Wold AE, Brunius C, et al. Associations of maternal and infant metabolomes with immune maturation and allergy development at 12 months in the Swedish NICE-cohort. Scientific Reports | [Internet]. 123AD [cited 2022 Feb 8];11:12706. Available from: https://doi.org/10.1038/s41598-021-92239-3

189. Nwaru BI, Hickstein L, Panesar SS, Muraro A, Werfel T, Cardona V, et al. The epidemiology of food allergy in Europe: a systematic review and meta-analysis. Allergy [Internet]. 2014 Jan 1 [cited 2022 Feb 1];69(1):62–75. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/all.12305

190. Liu AH, Jaramillo R, Sicherer SH, Wood RA, Bock SA, Burks AW, et al. National prevalence and risk factors for food allergy and relationship to asthma: Results from the National Health and Nutrition Examination Survey 2005-2006. Journal of Allergy and Clinical Immunology. 2010 Oct 1;126(4):798-806.e14.

191. Tran MM, Lefebvre DL, Dharma C, Dai D, Lou WYW, Subbarao P, et al. Predicting the atopic march: Results from the Canadian Healthy Infant Longitudinal Development Study. The Journal of allergy and clinical immunology [Internet]. 2018 Feb 1 [cited 2022 Feb 8];141(2):601-607.e8. Available from: https://pubmed.ncbi.nlm.nih.gov/29153857/

192. Valenta R, Hochwallner H, Linhart B, Pahr S. Food allergies: the basics. Gastroenterology [Internet]. 2015 May 1 [cited 2022 Feb 8];148(6):1120-1131.e4. Available from: https://pubmed.ncbi.nlm.nih.gov/25680669/

193. Penders J, Gerhold K, Thijs C, Zimmermann K, Wahn U, Lau S, et al. Gut Microbes New insights into the hygiene hypothesis in allergic diseases Mediation of sibling and birth mode effects by the gut microbiota. 2014 [cited 2022 Feb 9]; Available from: https://www.tandfonline.com/action/journalInformation?journalCode=kgmi20

194. Dierick BJH, van der Molen T, Flokstra-De Blok BMJ, Muraro A, Postma MJ, Kocks JWH, et al. Burden and socioeconomics of asthma, allergic rhinitis, atopic dermatitis and food allergy. 2020 [cited 2022 Feb 6]; Available from: https://www.tandfonline.com/action/journalInformation?journalCode=ierp20

195. Chad Z. Allergies in children. Paediatrics & Child Health [Internet]. 2001 [cited 2022 Feb 6];6(8):555. Available from: /pmc/articles/PMC2805592/

196. Iweala OI, Choudhary SK, Commins SP. Food Allergy. Current Gastroenterology Reports [Internet]. 2018 May 1 [cited 2022 Feb 6];20(5):1–6. Available from: https://link.springer.com/article/10.1007/s11894-018-0624-y

197. Nibbering B, Ubags NDJ. Microbial interactions in the atopic march. Clinical and experimental immunology [Internet]. 2020 Jan 1 [cited 2022 Feb 8];199(1):12–23. Available from: https://pubmed.ncbi.nlm.nih.gov/31777060/

198. Yang L, Fu J, Zhou Y. Research Progress in Atopic March. Frontiers in Immunology [Internet]. 2020 Aug 27 [cited 2022 Feb 6];11:1907. Available from:

199. /pmc/articles/PMC7482645/

200. Wang L-J, Mu S-C, Lin M-I, Sung · Tseng-Chen, Chiang B-L, Lin · Cheng-Hui. Clinical Manifestations of Pediatric Food Allergy: a Contemporary Review. 2016 [cited 2022 Feb 1];1:3. Available from: https://doi.org/10.1007/s12016-021-08895-w

201. Koplin JJ, Wake M, Dharmage SC, Matheson M, Tang MLK, Gurrin LC, et al. Cohort Profile: The HealthNuts Study: Population prevalence and environmental/genetic predictors of food allergy. International Journal of Epidemiology [Internet]. 2015 Aug 1 [cited 2022 Feb 8];44(4):1161–71. Available from: https://academic.oup.com/ije/article/44/4/1161/667193

202. Alduraywish SA, Lodge CJ, Campbell B, Allen KJ, Erbas B, Lowe AJ, et al. The march from early life food sensitization to allergic disease: a systematic review and meta-analyses of birth cohort studies. Allergy [Internet]. 2016 Jan 1 [cited 2022 Feb 6];71(1):77–89. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/all.12784

203. DunnGalvin A, Hourihane JOB, Frewer L, Knibb RC, Oude Elberink JNG, Klinge I. Incorporating a gender dimension in food allergy research: A review. Allergy: European Journal of Allergy and Clinical Immunology. 2006 Nov;61(11):1336–43.

204. Løvik M, Namork E, Faeste C, Egaas E. The Norwegian National Reporting System and Register of Severe Allergic Reactions to Food. Norsk Epidemiologi [Internet]. 2004 Oct 13 [cited 2022 Feb 6];14(2):155–60. Available from:

https://www.ntnu.no/ojs/index.php/norepid/article/view/238

205. Lautenbacher S. Sex and gender differences in responses to experimentally induced pain in humans.

206. Pali-Schöll I, Jensen-Jarolim E. Gender aspects in food allergy. Current opinion in allergy and clinical immunology [Internet]. 2019 Jun 1 [cited 2022 Feb 9];19(3):249–55. Available from: https://pubmed.ncbi.nlm.nih.gov/30893085/

207. Kelly C, Gangur V. Sex Disparity in Food Allergy: Evidence from the PubMed Database

208. Journal of Allergy [Internet]. 2009 Jul 2 [cited 2022 Feb 6];2009:1–7. Available from:

209. /pmc/articles/PMC2957586/

210. Barbee RA, Halonen M, Lebowitz M, Burrows B. Distribution of IgE in a community population sample: correlations with age, sex, and allergen skin test reactivity.

211. Golding MA, Simons E, Abrams EM, Gerdts J, Protudjer JLP. The excess costs of childhood food allergy on Canadian families: a cross-sectional study. Allergy Asthma Clin Immunol [Internet]. 2021 [cited 2022 Feb 6];17:28. Available from: https://doi.org/10.1186/s13223-021-00530-9

212. Thörnqvist V, Middelveld R, Wai HM, Ballardini N, Nilsson E, Strömquist J, et al.

213. Health-related quality of life worsens by school age amongst children with food allergy. Clinical and translational allergy [Internet]. 2019 Feb 7 [cited 2022 Feb 6];9(1). Available from: https://pubmed.ncbi.nlm.nih.gov/30774928/

214. Penner Protudjer JL, Middelveld R, Dahlén S-E, Ahlstedt S. Food allergy-related concerns during the transition to self-management on behalf of FoodHE Investigators. Allergy Asthma Clin Immunol [Internet]. 2019 [cited 2022 Feb 6];15:54. Available from: https://doi.org/10.1186/s13223-019-0370-1

215. DunnGalvin A, Koman E, Raver E, Frome H, Adams M, Keena A, et al. An Examination

of the Food Allergy Quality of Life Questionnaire Performance in a Countrywide American Sample of Children: Cross-Cultural Differences in Age and Impact in the United States and Europe. The journal of allergy and clinical immunology In practice [Internet]. 2017 Apr 1 [cited 2022 Feb 9];5(2):363-368.e2. Available from: https://pubmed.ncbi.nlm.nih.gov/28017626/

216. Dubois J, Alison M, Counsell SJ, Hertz-Pannier L, Hüppi PS, Benders MJNL. MRI of the Neonatal Brain: A Review of Methodological Challenges and Neuroscientific Advances. Journal of Magnetic Resonance Imaging. 2021 May 1;53(5):1318–43.

217. Lewis AJ, Austin E, Knapp R, Vaiano T, Galbally M. Perinatal Maternal Mental Health, Fetal Programming and Child Development. Healthcare [Internet]. 2015 Dec 1 [cited 2022 Feb 6];3(4):1212. Available from: /pmc/articles/PMC4934640/

218. Ratsika A, Codagnone MC, O'mahony S, Stanton C, Cryan JF. Priming for Life: Early Life Nutrition and the Microbiota-Gut-Brain Axis. Nutrients [Internet]. 2021 Feb 1 [cited 2022 Feb 8];13(2):1–33. Available from: /pmc/articles/PMC7912058/

219. Aita M, De G, Faugère C, Lavallée A, Feeley N, Stremler R, et al. Effectiveness of interventions on early neurodevelopment of preterm infants: a systematic review and meta-analysis. [cited 2022 Feb 6]; Available from: https://doi.org/10.1186/s12887-021-02559-6

220. Lach LM, Kohen DE, Garner RE, Brehaut JC, Miller AR, Klassen AF, et al. The health and psychosocial functioning of caregivers of children with neurodevelopmental disorders. https://doi.org/101080/08916930802354948 [Internet]. 2009 [cited 2022 Feb 6];31(9):741–52. Available from: https://www.tandfonline.com/doi/abs/10.1080/08916930802354948

221. Brown RH, Eisner M, Walker S, Tomlinson M, Fearon P, Dunne MP, et al. The impact of

maternal adverse childhood experiences and prenatal depressive symptoms on foetal attachment: Preliminary evidence from expectant mothers across eight middle-income countries. Journal of Affective Disorders. 2021 Dec 1;295:612–9.

222. Perone S, Gartstein MA. Mapping cortical rhythms to infant behavioral tendencies via baseline EEG and parent-report. Developmental Psychobiology [Internet]. 2019 Sep 1 [cited 2022 Feb 6];61(6):815–23. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/dev.21867

223. Chua RXY, Tay MJY, Ooi DSQ, Siah KTH, Tham EH, Shek LPC, et al. Understanding the Link Between Allergy and Neurodevelopmental Disorders: A Current Review of Factors and Mechanisms. Frontiers in Neurology. 2021 Feb 15;11:1965.

224. Guo MMH, Wang LJ, Hsu TY, Yang KD, Kuo HC. Peanut Sensitivity and Allergic Rhinitis in Young Children are Associated with Attention-Deficit Hyperactivity Disorder Symptoms in Adolescence. Neuropsychiatric Disease and Treatment [Internet]. 2020 [cited 2022 Feb 8];16:1349. Available from: /pmc/articles/PMC7263365/

225. Meldrum SJ, D'Vaz N, Dunstan JA, Mori TA, Hird K, Simmer K, et al. Allergic disease in the first year of life is associated with differences in subsequent neurodevelopment and behaviour. Early human development [Internet]. 2012 Jul [cited 2022 Feb 8];88(7):567–

226. 73. Available from: https://pubmed.ncbi.nlm.nih.gov/22284984/

227. Bertelsen RJ, Rava M, Carsin AE, Accordini S, Benediktsdóttir B, Dratva J, et al. Clinical markers of asthma and IgE assessed in parents before conception predict asthma and hayfever in the offspring. Clinical & Experimental Allergy [Internet]. 2017 May 1 [cited 2022 Feb 9];47(5):627–38. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/cea.12906

228. Cook-Mills JM. Maternal Influences over Offspring Allergic Responses. Current Allergy

and Asthma Reports 2015 15:2 [Internet]. 2015 Jan 23 [cited 2022 Feb 9];15(2):1–10. Available from: https://link.springer.com/article/10.1007/s11882-014-0501-1

229. Tuokkola J, Luukkainen P, Kaila M, Takkinen HM, Niinistö S, Veijola R, et al. Maternal dietary folate, folic acid and vitamin D intakes during pregnancy and lactation and the risk of cows' milk allergy in the offspring. British Journal of Nutrition [Internet]. 2016 Aug 28 [cited 2022 Feb 9];116(4):710–8. Available from: https://www.cambridge.org/core/journals/british-journal-of-nutrition/article/maternal-dietary-folate-folic-acid-and-vitamin-d-intakes-during-pregnancy-and-lactation-and-the-risk-of-cows-milk-allergy-in-the-offspring/7075AE63D0C30E01995D678AFBE98B29

230. Alford SH, Zoratti E, Peterson EL, Maliarik M, Ownby DR, Johnson CC. Parental history of atopic disease: Disease pattern and risk of pediatric atopy in offspring. Journal of Allergy and Clinical Immunology. 2004 Nov 1;114(5):1046–50.

231. Blümer N, Herz U, Wegmann M, Renz H. Prenatal lipopolysaccharide-exposure prevents allergic sensitization and airway inflammation, but not airway responsiveness in a murine model of experimental asthma. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology [Internet]. 2005 Mar [cited 2022 Feb 8];35(3):397–402. Available from: https://pubmed.ncbi.nlm.nih.gov/15784121/

232. Devereux G, Barker RN, Seaton A. Antenatal determinants of neonatal immune responses to allergens. Clinical and Experimental Allergy. 2002;32(1):43–50.

233. Uthoff H, Spenner A, Reckelkamm W, Ahrens B, Wölk G, Hackler R, et al. Critical role of preconceptional immunization for protective and nonpathological specific immunity in murine neonates. Journal of immunology (Baltimore, Md : 1950) [Internet]. 2003 Oct 1 [cited 2022 Feb 8];171(7):3485–92. Available from: https://pubmed.ncbi.nlm.nih.gov/14500644/

234. Lim RH, Kobzik L. Maternal transmission of asthma risk. American journal of reproductive immunology (New York, NY : 1989) [Internet]. 2009 [cited 2022 Feb 8];61(1):1–10. Available from: https://pubmed.ncbi.nlm.nih.gov/19007349/

235. Sonnenschein-van der Voort AMM, Jaddoe VWV, Moll HA, Hofman A, van der Valk RJP, de Jongste JC, et al. Influence of maternal and cord blood C-reactive protein on childhood respiratory symptoms and eczema. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology [Internet]. 2013 Aug [cited 2022 Feb 8];24(5):469–75. Available from: https://pubmed.ncbi.nlm.nih.gov/23773138/

236. Giwercman C, Halkjaer LB, Jensen SM, Bønnelykke K, Lauritzen L, Bisgaard H. Increased risk of eczema but reduced risk of early wheezy disorder from exclusive breast-feeding in high-risk infants. The Journal of allergy and clinical immunology [Internet]. 2010 Apr [cited 2022 Feb 8];125(4):866–71. Available from: https://pubmed.ncbi.nlm.nih.gov/20236698/

237. Al-Tamprouri C, Malin B, Bill H, Lennart B, Anna S. Cat and dog ownership during/after the first year of life and risk for sensitization and reported allergy symptoms at age 13. Immunity, Inflammation and Disease [Internet]. 2019 Dec 1 [cited 2022 Feb 8];7(4):250. Available from: /pmc/articles/PMC6842813/

238. Litonjua AA, Carey VJ, Burge HA, Weiss ST, Gold DR. Parental history and the risk for childhood asthma. Does mother confer more risk than father? American journal of respiratory and critical care medicine [Internet]. 1998 [cited 2022 Feb 8];158(1):176–81. Available from: https://pubmed.ncbi.nlm.nih.gov/9655726/

239. Wright AL, Holberg CJ, Taussig LM, Martinez FD. Factors influencing the relation of infant feeding to asthma and recurrent wheeze in childhood. Thorax [Internet]. 2001 [cited 2022 Feb 8];56(3):192–7. Available from: https://pubmed.ncbi.nlm.nih.gov/11182011/

240. Hartvigsson O, Barman M, Rabe H, Sandin A, Wold AE, Brunius C, et al. Associations of maternal and infant metabolomes with immune maturation and allergy development at 12 months in the Swedish NICE-cohort. Scientific Reports | [Internet]. 123AD [cited 2022 Feb 8];11:12706. Available from: https://doi.org/10.1038/s41598-021-92239-3

241. Fujimura T, Lum SZC, Nagata Y, Kawamoto S, Oyoshi MK. Influences of Maternal Factors Over Offspring Allergies and the Application for Food Allergy. Frontiers in Immunology [Internet]. 2019 [cited 2022 Feb 8];10(AUG):1933. Available from:

242. /pmc/articles/PMC6716146/

243. Prins JR, Eskandar S, Eggen BJL, Scherjon SA. Microglia, the missing link in maternal immune activation and fetal neurodevelopment; and a possible link in preeclampsia and disturbed neurodevelopment? Journal of Reproductive Immunology. 2018 Apr 1;126:18– 22.

244. Patel S, Cooper MN, Jones H, Whitehouse AJO, Dale RC, Guastella AJ. Maternal immune-related conditions during pregnancy may be a risk factor for neuropsychiatric problems in offspring throughout childhood and adolescence. Psychological medicine [Internet]. 2020 Dec 1 [cited 2022 Feb 8];51(16):2904–14. Available from: https://pubmed.ncbi.nlm.nih.gov/32476637/

245. Joseph CLM, Sitarik AR, Kim H, Huffnagle G, Fujimura K, Yong GJM, et al. Infant gut bacterial community composition and food-related manifestation of atopy in early childhood. Pediatric Allergy and Immunology. 2022 Jan 1;33(1).

246. Huang YJ, Marsland BJ, Bunyavanich S, O'Mahony L, Leung DYM, Muraro A, et al. The microbiome in allergic disease: Current understanding and future opportunities-2017 PRACTALL document of the American Academy of Allergy, Asthma & Immunology and the European Academy of Allergy and Clinical Immunology. The Journal of allergy and clinical

immunology [Internet]. 2017 Apr 1 [cited 2022 Feb 6];139(4):1099–110. Available from: https://pubmed.ncbi.nlm.nih.gov/28257972/

247. Łoś-Rycharska E, Gołębiewski M, Grzybowski T, Rogalla-Ładniak U, Krogulska A. The microbiome and its impact on food allergy and atopic dermatitis in children. Advances in Dermatology and Allergology/Postępy Dermatologii i Alergologii [Internet]. 2020 [cited 2022 Feb 6];37(5):641. Available from: /pmc/articles/PMC7675070/

248. Canani RB, Sangwan N, Stefka AT, Nocerino R, Paparo L, Aitoro R, et al. Lactobacillus rhamnosus GG-supplemented formula expands butyrate-producing bacterial strains in food allergic infants. The ISME Journal 2016 10:3 [Internet]. 2015 Sep 22 [cited 2022 Feb 6];10(3):742–50. Available from: https://www.nature.com/articles/ismej2015151

249. Hua X, Goedert JJ, Pu A, Yu G, Shi J. Allergy associations with the adult fecal microbiota: Analysis of the American Gut Project. EBioMedicine [Internet]. 2015 Jan 1 [cited 2022 Feb 6];3:172–9. Available from: https://pubmed.ncbi.nlm.nih.gov/26870828/

250. Thompson-Chagoyan OC, Vieites JM, Maldonado J, Edwards C, Gil A. Changes in faecal microbiota of infants with cow's milk protein allergy – a Spanish prospective case–control 6-month follow-up study. Pediatric Allergy and Immunology [Internet]. 2010 Mar 1 [cited 2022 Feb 6];21(2p2):e394–400. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1399-3038.2009.00961.x

251. Tun HM, Peng Y, Chen B, Konya TB, Morales-Lizcano NP, Chari R, et al. Ethnicity Associations With Food Sensitization Are Mediated by Gut Microbiota Development in the First Year of Life. Gastroenterology [Internet]. 2021 Jul 1 [cited 2022 Feb 8];161(1):94–106. Available from: https://pubmed.ncbi.nlm.nih.gov/33741316/

252. Battersby AJ, Gibbons DL. The gut mucosal immune system in the neonatal period.

253. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology [Internet]. 2013 Aug [cited 2022 Feb 8];24(5):414–21. Available from: https://pubmed.ncbi.nlm.nih.gov/23682966/

254. Allan Walker W. Initial intestinal colonization in the human infant and immune homeostasis. Annals of nutrition & metabolism [Internet]. 2013 Nov [cited 2022 Feb 8];63 Suppl 2(SUPPL.2):8–15. Available from: https://pubmed.ncbi.nlm.nih.gov/24217032/

255. Brandtzaeg P. Secretory IgA: Designed for Anti-Microbial Defense. Frontiers in immunology [Internet]. 2013 [cited 2022 Feb 8];4(AUG). Available from: https://pubmed.ncbi.nlm.nih.gov/23964273/

256. Patel S, Cooper MN, Jones H, Whitehouse AJO, Dale RC, Guastella AJ. Maternal immune-related conditions during pregnancy may be a risk factor for neuropsychiatric problems in offspring throughout childhood and adolescence. Psychological medicine [Internet]. 2020 Dec 1 [cited 2022 Feb 9];51(16):2904–14. Available from: https://pubmed.ncbi.nlm.nih.gov/32476637/

257. Malan-Muller S, Valles-Colomer M, Raes J, Lowry CA, Seedat S, Hemmings SMJ. The Gut Microbiome and Mental Health: Implications for Anxiety- and Trauma-Related Disorders. Omics: a journal of integrative biology [Internet]. 2018 Feb 1 [cited 2022 Feb 9];22(2):90–107. Available from: https://pubmed.ncbi.nlm.nih.gov/28767318/

258. Malan-Muller S, Valles-Colomer M, Raes J, Lowry CA, Seedat S, Hemmings SMJ. The gut microbiome and mental health: Implications for anxiety- and trauma-related disorders. OMICS A Journal of Integrative Biology. 2018 Feb 1;22(2):90–107.

259. Mayer EA, Tillisch K, Gupta A. Gut/brain axis and the microbiota. The Journal of Clinical Investigation. 2015 Mar 2;125(3):926–38.

260. Bercik P, Collins SM, Verdu EF. Microbes and the gut-brain axis. Neurogastroenterology & Motility [Internet]. 2012 May 1 [cited 2022 Feb 9];24(5):405–13. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1365-2982.2012.01906.x

261. Cryan JF, O'riordan KJ, Cowan CSM, Sandhu K v., Bastiaanssen TFS, Boehme M, et al.

262. The microbiota-gut-brain axis. Physiological Reviews [Internet]. 2019 [cited 2022 Feb 9];99(4):1877–2013. Available from:

https://journals.physiology.org/doi/abs/10.1152/physrev.00018.2018

263. Rosin S, Xia K, Azcarate-Peril MA, Carlson AL, Propper CB, Thompson AL, et al. A preliminary study of gut microbiome variation and HPA axis reactivity in healthy infants. Psychoneuroendocrinology. 2021 Feb 1;124:105046.

264. Johnson EO, Kamilaris TC, Chrousos GP, Gold PW. Mechanisms of stress: A dynamic overview of hormonal and behavioral homeostasis. Neuroscience and Biobehavioral Reviews. 1992;16(2):115–30.

265. Taylor JL, Corbett BA. A review of rhythm and responsiveness of cortisol in individuals with autism spectrum disorders. Psychoneuroendocrinology [Internet]. 2014 [cited 2022 Feb 8];49(1):207–28. Available from: https://pubmed.ncbi.nlm.nih.gov/25108163/

266. Bradley AJ, Dinan TG. A systematic review of hypothalamic-pituitary-adrenal axis function in schizophrenia: implications for mortality. Journal of psychopharmacology

267. (Oxford, England) [Internet]. 2010 [cited 2022 Feb 8];24(4 Suppl):91–118. Available from: https://pubmed.ncbi.nlm.nih.gov/20923924/

268. Sudo N, Chida Y, Aiba Y, Sonoda J, Oyama N, Yu XN, et al. Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice. The Journal of physiology [Internet]. 2004 Jul 1 [cited 2022 Feb 8];558(Pt 1):263–

269. 75. Available from: https://pubmed.ncbi.nlm.nih.gov/15133062/

270. Clarke G, Grenham S, Scully P, Fitzgerald P, Moloney RD, Shanahan F, et al. The microbiome-gut-brain axis during early life regulates the hippocampal serotonergic system in a sex-dependent manner. Molecular psychiatry [Internet]. 2013 Jun [cited 2022 Feb 8];18(6):666–73. Available from: https://pubmed.ncbi.nlm.nih.gov/22688187/

271. Crumeyrolle-Arias M, Jaglin M, Bruneau A, Vancassel S, Cardona A, Daugé V, et al.

272. Absence of the gut microbiota enhances anxiety-like behavior and neuroendocrine response to acute stress in rats. Psychoneuroendocrinology [Internet]. 2014 [cited 2022 Feb 8];42:207–17. Available from: https://pubmed.ncbi.nlm.nih.gov/24636517/

273. Messaoudi M, Lalonde R, Violle N, Javelot H, Desor D, Nejdi A, et al. Assessment of psychotropic-like properties of a probiotic formulation (Lactobacillus helveticus R0052 and Bifidobacterium longum R0175) in rats and human subjects. The British journal of nutrition [Internet]. 2011 Mar 14 [cited 2022 Feb 8];105(5):755–64. Available from: https://pubmed.ncbi.nlm.nih.gov/20974015/

274. Schmidt K, Cowen PJ, Harmer CJ, Tzortzis G, Errington S, Burnet PWJ. Prebiotic intake reduces the waking cortisol response and alters emotional bias in healthy volunteers. Psychopharmacology [Internet]. 2015 May 1 [cited 2022 Feb 8];232(10):1793–801. Available from: https://pubmed.ncbi.nlm.nih.gov/25449699/

275. Hantsoo L, Jašarević E, Criniti S, McGeehan B, Tanes C, Sammel MD, et al. Childhood adversity impact on gut microbiota and inflammatory response to stress during pregnancy. Brain, Behavior, and Immunity. 2019 Jan 1;75:240–50.

276. Michels N, van de Wiele T, Fouhy F, O'Mahony S, Clarke G, Keane J. Gut microbiome patterns depending on children's psychosocial stress: Reports versus biomarkers. Brain, Behavior, and Immunity. 2019 Aug 1;80:751–62.

277. Goyal DK, Miyan JA. Neuro-immune abnormalities in autism and their relationship with the environment: a variable insult model for autism. Frontiers in endocrinology [Internet]. 2014 [cited 2022 Feb 6];5(MAR). Available from: https://pubmed.ncbi.nlm.nih.gov/24639668/

278. Bilbo SD, Nevison CD, Parker W. A model for the induction of autism in the ecosystem of the human body: the anatomy of a modern pandemic? Microbial Ecology in Health & Disease [Internet]. 2015 Jan 28 [cited 2022 Feb 9];26(0). Available from: https://www.tandfonline.com/action/journalInformation?journalCode=zmeh20

279. Carlson AL, Xia K, Azcarate-Peril MA, Goldman BD, Ahn M, Styner MA, et al. Infant Gut Microbiome Associated With Cognitive Development. Biological Psychiatry. 2018 Jan 15;83(2):148–59.

280. Sordillo JE, Korrick S, Laranjo N, Carey V, Weinstock GM, Gold DR, et al. Association of

the Infant Gut Microbiome With Early Childhood Neurodevelopmental Outcomes: An Ancillary Study to the VDAART Randomized Clinical Trial. JAMA network open [Internet]. 2019 Mar 1 [cited 2022 Feb 6];2(3):e190905. Available from: https://pubmed.ncbi.nlm.nih.gov/30901046/

281. Tamana SK, Tun HM, Konya T, Chari RS, Field CJ, Guttman DS, et al. Bacteroides-dominant gut microbiome of late infancy is associated with enhanced neurodevelopment. Gut microbes [Internet]. 2021 [cited 2022 Feb 6];13(1):1–17. Available from: https://pubmed.ncbi.nlm.nih.gov/34132157/

282. Litonjua AA. Dietary Factors and the Development of Asthma. Immunology and Allergy Clinics of North America. 2008 Aug 1;28(3):603–29.

283. Maslova E, Hansen S, Strøm M, Halldorsson TI, Olsen SF. Maternal intake of vitamins A, E and K in pregnancy and child allergic disease: a longitudinal study from the Danish National Birth Cohort. British Journal of Nutrition [Internet]. 2014 Mar 28 [cited 2022 Feb 8];111(6):1096–108. Available from: https://www.cambridge.org/core/journals/british-journal-of-nutrition/article/maternal- intake-of-vitamins-a-e-and-k-in-pregnancy-and-child-allergic-disease-a-longitudinal- study-from-the-danish-national-birth-cohort/221C01A4F3ADA86FCF661AAD0E2EFC17

284. Nwaru BI, Ahonen S, Kaila M, Erkkola M, Haapala AM, Kronberg-Kippilä C, et al.

285. Maternal diet during pregnancy and allergic sensitization in the offspring by 5 yrs of age: </br>a prospective cohort study. Pediatric Allergy and Immunology [Internet]. 2010 Feb 1 [cited 2022 Feb 8];21(1-Part-I):29–37. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1399-3038.2009.00949.x

286. Miyake Y, Sasaki S, Tanaka K, Hirota Y. Consumption of vegetables, fruit, and antioxidants during pregnancy and wheeze and eczema in infants. Allergy [Internet]. 2010 Jun 1 [cited 2022 Feb 8];65(6):758–65. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1398-9995.2009.02267.x

287. Smith PK, Masilamani M, Li XM, Sampson HA. The false alarm hypothesis: Food allergy is associated with high dietary advanced glycation end-products and proglycating dietary sugars that mimic alarmins. Journal of Allergy and Clinical Immunology. 2017 Feb 1;139(2):429–37.

288. Venter C, Pickett K, Starling A, Maslin K, Smith PK, Palumbo MP, et al. Advanced glycation end product intake during pregnancy and offspring allergy outcomes: A Prospective cohort study. Clinical & Experimental Allergy [Internet]. 2021 Nov 1 [cited 2022 Feb 8];51(11):1459–70. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/cea.14027

289. Garcia-Larsen V, Ierodiakonou D, Jarrold K, Cunha S, Chivinge J, Robinson Z, et al. Diet during pregnancy and infancy and risk of allergic or autoimmune disease: A systematic review and meta-analysis. PLoS Medicine. 2018 Feb 1;15(2).

290. Sunde RB, Thorsen J, Pedersen C-ET, Stokholm J, Bønnelykke K, Chawes B, et al.

291. Prenatal tobacco exposure and risk of asthma and allergy outcomes in childhood. European Respiratory Journal [Internet]. 2021 Jul 8 [cited 2022 Feb 8];2100453. Available from: https://erj.ersjournals.com/content/early/2021/06/25/13993003.00453- 2021

292. Hossenbaccus L, Linton S, Ramchandani R, Gallant MJ, Ellis AK. Insights into allergic risk factors from birth cohort studies. Annals of Allergy, Asthma & Immunology. 2021 Sep 1;127(3):312–7.

293. Ekblad M, Korkeila J, Lehtonen L. Smoking during pregnancy affects foetal brain development. Acta Paediatrica [Internet]. 2015 Jan 1 [cited 2022 Feb 8];104(1):12–8.

294. Available from: https://onlinelibrary-wiley-com.login.ezproxy.library.ualberta.ca/doi/full/10.1111/apa.12791

295. Magnusson CGM. Maternal smoking influences cord serum IgE and IgD levels and increases the risk for subsequent infant allergy. Journal of Allergy and Clinical Immunology. 1986 Nov 1;78(5):898–904.

296. Thacher JD, Gruzieva O, Pershagen G, Neuman, van Hage M, Wickman M, et al. Parental

smoking and development of allergic sensitization from birth to adolescence. Allergy [Internet]. 2016 Feb 1 [cited 2022 Feb 8];71(2):239–48. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/all.12792

297. Barrero-Castillero A, Pierce LJ, Urbina-Johanson SA, Pirazzoli L, Burris HH, Nelson CA. Perinatal and early childhood biomarkers of psychosocial stress and adverse experiences. Pediatric Research 2022 [Internet]. 2022 Jan 28 [cited 2022 Feb 8];1–10. Available from: https://www.nature.com/articles/s41390-022-01933-z

298. Rajasekera TA, Gur TL. Maternal Exposure to Adversity: Impact on the Microbiota-Gut-Brain Axis, Inflammation and Offspring Psychiatric Outcomes. 2021;32:26–39.

299. DeSocio JE. Epigenetics, maternal prenatal psychosocial stress, and infant mental health.

300. Archives of Psychiatric Nursing. 2018 Dec 1;32(6):901–6.

301. Coussons-Read ME, Okun ML, Nettles CD. Psychosocial stress increases inflammatory markers and alters cytokine production across pregnancy. Brain, Behavior, and Immunity. 2007 Mar 1;21(3):343–50.

302. Olvera Alvarez HA, Kubzansky LD, Campen MJ, Slavich GM. Early life stress, air pollution, inflammation, and disease: An integrative review and immunologic model of social-environmental adversity and lifespan health. Neuroscience and biobehavioral

303. reviews [Internet]. 2018 Sep 1 [cited 2022 Feb 8];92:226–42. Available from: https://pubmed.ncbi.nlm.nih.gov/29874545/

304. Pedersen JM, Mortensen EL, Christensen DS, Rozing M, Brunsgaard H, Meincke RH, et al. Prenatal and early postnatal stress and later life inflammation. Psychoneuroendocrinology [Internet]. 2018 Feb 1 [cited 2022 Feb 8];88:158–66. Available from: https://pubmed.ncbi.nlm.nih.gov/29291495/

305. Slopen N, Loucks EB, Appleton AA, Kawachi I, Kubzansky LD, Non AL, et al. Early origins of inflammation: An examination of prenatal and childhood social adversity in a prospective cohort study. Psychoneuroendocrinology [Internet]. 2015 Jan 1 [cited 2022 Feb

8];51:403–13. Available from: https://pubmed.ncbi.nlm.nih.gov/25462912/

306. Kang LJ, Vu KN, Koleva PT, Field CJ, Chow A, Azad MB, et al. Maternal psychological distress before birth influences gut immunity in mid-infancy. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology [Internet]. 2020 Feb 1 [cited 2022 Feb 8];50(2):178–88. Available from: https://pubmed.ncbi.nlm.nih.gov/31845414/

307. Rodriguez N, Tun HM, Field CJ, Mandhane PJ, Scott JA, Kozyrskyj AL. Prenatal Depression, Breastfeeding, and Infant Gut Microbiota. Frontiers in Microbiology [Internet]. 2021 Jul 30 [cited 2022 Feb 8];12. Available from: /pmc/articles/PMC8363245/

308. Picó C, Palou M, Pomar CA, Palou A. Benefits of breastfeeding in infant health: a role for milk signaling peptides. Molecular Nutrition: Mother and Infant. 2021 Jan 1;29–56.

309. Louis-Jacques AF, Stuebe AM. Enabling Breastfeeding to Support Lifelong Health for Mother and Child. Obstetrics and Gynecology Clinics of North America. 2020 Sep 1;47(3):363–81.

310. Gould JF. Complementary Feeding, Micronutrients and Developmental Outcomes of Children. Nestle Nutrition Institute workshop series [Internet]. 2017 [cited 2022 Feb 9];87:13–28. Available from: https://pubmed.ncbi.nlm.nih.gov/28315884/

311. Zhong C, Guo J, Tan T, Wang H, Lin L, Gao D, et al. Increased food diversity in the first year of life is inversely associated with allergic outcomes in the second year. Pediatric Allergy and Immunology. 2022 Jan 1;33(1).

312. Caffarelli C, di Mauro D, Mastrorilli C, Bottau P, Cipriani F, Ricci G. Solid Food Introduction and the Development of Food Allergies. Nutrients 2018, Vol 10, Page 1790 [Internet]. 2018 Nov 17 [cited 2022 Feb 9];10(11):1790. Available from: https://www.mdpi.com/2072-6643/10/11/1790/htm

313. Karmaus W. Does a higher number of siblings protect against the development of allergy and asthma? A review. J Epidemiol Community Health [Internet]. 2002 [cited 2022 Feb

9];56:209–17. Available from: http://jech.bmj.com/

314. Leadbitter P, Pearce N, Cheng S, Sears MR, Holdaway MD, Flannery EM, et al.

315. Relationship between fetal growth and the development of asthma and atopy in childhood. Thorax [Internet]. 1999 [cited 2022 Feb 9];54(10):905–10. Available from: https://pubmed.ncbi.nlm.nih.gov/10491453/

316. Rona RJ, Hughes JM, Chinn S. Association between asthma and family size between 1977 and 1994. Journal of epidemiology and community health [Internet]. 1999 [cited 2022 Feb 9];53(1):15–9. Available from: https://pubmed.ncbi.nlm.nih.gov/10326047/

317. Wickens KL, Crane J, Kemp TJ, Lewis SJ, D'Souza WJ, Sawyer GM, et al. Family size, infections, and asthma prevalence in New Zealand children. Epidemiology (Cambridge,

318. Mass) [Internet]. 1999 [cited 2022 Feb 9];10(6):699–705. Available from: https://pubmed.ncbi.nlm.nih.gov/10535783/

319. Okada H, Kuhn C, Feillet H, Bach JF. The 'hygiene hypothesis' for autoimmune and allergic diseases: an update. Clinical and Experimental Immunology [Internet]. 2010 Apr [cited 2022 Feb 9];160(1):1. Available from: /pmc/articles/PMC2841828/

320. Seiskari T, Kondrashova A, Viskari H, Kaila M, Haapala AM, Aittoniemi J, et al. Allergic sensitization and microbial load − a comparison between Finland and Russian Karelia. Clinical and Experimental Immunology [Internet]. 2007 [cited 2022 Feb 9];148(1):47. Available from: /pmc/articles/PMC1868862/

321. Ben-Itzchak E, Zukerman G, Zachor DA. Having Older Siblings is Associated with Less Severe Social Communication Symptoms in Young Children with Autism Spectrum Disorder. Journal of Abnormal Child Psychology [Internet]. 2016 Nov 1 [cited 2022 Feb 9];44(8):1613–20. Available from: https://link.springer.com/article/10.1007/s10802-016-0133-0

322. Pyrhönen K, Kulmala P. Delivery mode and the incidence of atopic sensitization and food allergy in a Finnish child population. Pediatr Allergy Immunol [Internet]. 2022 [cited 2022

Feb 9];33. Available from:
https://doi.org/10.1111/pai.13584wileyonlinelibrary.com/journal/pai

323. Almqvist C, Cnattingius S, Lichtenstein P, Lundholm C. The impact of birth mode of delivery on childhood asthma and allergic diseases-a sibling study. Clinical and Experimental Allergy. 2012 Sep;42(9):1369–76.

324. Jakobsson HE, Abrahamsson TR, Jenmalm MC, Harris K, Quince C, Jernberg C, et al.

325. Decreased gut microbiota diversity, delayed Bacteroidetes colonisation and reduced Th1

326. responses in infants delivered by caesarean section. Gut [Internet]. 2014 [cited 2022 Feb 9];63(4):559–66. Available from: https://pubmed.ncbi.nlm.nih.gov/23926244/

327. Wiguna T, Khoe LC. The impact of Caesarean delivery mode towards brain and neurodevelopment among children. World Nutrition Journal [Internet]. 2020 Oct 1 [cited 2022 Feb 9];4(1–2):32–7. Available from: https://worldnutrijournal.org/OJS/index.php/WNJ/article/view/V04.S2.0005

328. Kenkel W. Birth signalling hormones and the developmental consequences of caesarean delivery. Journal of Neuroendocrinology [Internet]. 2021 Jan 1 [cited 2022 Feb 9];33(1):e12912. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/jne.12912

329. May T, Adesina I, McGillivray J, Rinehart NJ. Sex differences in neurodevelopmental disorders. Current Opinion in Neurology [Internet]. 2019 Aug 1 [cited 2022 Feb 9];32(4):622–6. Available from: https://journals.lww.com/co-neurology/Fulltext/2019/08000/Sex_differences_in_neurodevelopmental_disorders.18.asp x

330. Ferri SL, Abel T, Brodkin ES. Sex Differences in Autism Spectrum Disorder: a Review.

331. Current Psychiatry Reports [Internet]. 2018 Feb 1 [cited 2022 Feb 9];20(2):1–17. Available from: https://link.springer.com/article/10.1007/s11920-018-0874-2

332. Ji Y, Hong X, Wang G, Chatterjee N, Riley AW, Lee LC, et al. A Prospective Birth Cohort Study on Early Childhood Lead Levels and Attention Deficit Hyperactivity Disorder: New Insight on Sex Differences. The Journal of pediatrics [Internet]. 2018 Aug 1 [cited 2022 Feb

9];199:124-131.e8. Available from: https://pubmed.ncbi.nlm.nih.gov/29752174/

333. Murray AL, Booth T, Eisner M, Auyeung B, Murray G, Ribeaud D. Sex differences in ADHD trajectories across childhood and adolescence. Developmental Science [Internet]. 2019 Jan 1 [cited 2022 Feb 9];22(1):e12721. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/desc.12721

334. Becklake MR, Kauffmann F. Gender differences in airway behaviour over the human life span. Thorax [Internet]. 1999 [cited 2022 Feb 9];54(12):1119–38. Available from: https://pubmed.ncbi.nlm.nih.gov/10567633/

335. Williams TC, Bach CC, Matthiesen NB, Henriksen TB, Gagliardi L. Directed acyclic graphs: a tool for causal studies in paediatrics. Pediatric Research 2018 84:4 [Internet]. 2018 Jun 4 [cited 2022 Feb 8];84(4):487–93. Available from: https://www.nature.com/articles/s41390-018-0071-3

336. Weng HY, Hsueh YH, Messam LLM v., Hertz-Picciotto I. Methods of covariate selection: directed acyclic graphs and the change-in-estimate procedure. American journal of epidemiology [Internet]. 2009 May [cited 2022 Feb 8];169(10):1182–90. Available from: https://pubmed.ncbi.nlm.nih.gov/19363102/

337. Peters RL, Koplin JJ, Allen KJ, Lowe AJ, Lodge CJ, Tang MLK, et al. The Prevalence of Food Sensitization Appears Not to Have Changed between 2 Melbourne Cohorts of High-Risk Infants Recruited 15 Years Apart. The journal of allergy and clinical immunology In practice [Internet]. 2018 Mar 1 [cited 2022 Feb 8];6(2):440-448.e2. Available from: https://pubmed.ncbi.nlm.nih.gov/29248387/

338. Bayley Scales of Infant & Toddler Development Ed 3 [Internet]. [cited 2022 Feb 6]. Available from: https://www.pearsonassessments.com/store/usassessments/en/Store/Professional-Assessments/Behavior/Adaptive/Bayley-Scales-of-Infant-and-Toddler-Development-

339. %7C-Third-Edition/p/100000123.html

340. Albers CA, Grieve AJ. Test Review: Bayley, N. (2006). Bayley Scales of Infant and Toddler Development– Third Edition. San Antonio, TX: Harcourt Assessment: http://dx.doi.org/101177/0734282906297199 [Internet]. 2016 Aug 19 [cited 2022 Feb 6];25(2):180–90. Available from: https://journals.sagepub.com/doi/abs/10.1177/0734282906297199

341. Baron RM, Kenny DA. The Moderator-Mediator Variable Distinction in Social Psychological Research. Conceptual, Strategic, and Statistical Considerations. Journal of Personality and Social Psychology [Internet]. 1986 Dec [cited 2022 Feb 6];51(6):1173–82. Available from: /record/1987-13085-001

342. Straughen JK, Sitarik AR, Johnson CC, Wegienka G, Ownby DR, Johnson-Hooper TM, et al. Prenatal IgE as a Risk Factor for the Development of Childhood Neurodevelopmental Disorders. Frontiers in pediatrics [Internet]. 2021 May 14 [cited 2022 Feb 8];9. Available from: https://pubmed.ncbi.nlm.nih.gov/34055677/

343. Hadders-Algra M, Tacke U, Pietz J, Rupp A, Philippi H. Standardized Infant NeuroDevelopmental Assessment developmental and socio-emotional scales: reliability and predictive value in an at-risk population. Developmental Medicine & Child Neurology [Internet]. 2020 Jul 1 [cited 2022 Feb 8];62(7):845–53. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/dmcn.14423

344. Brito NH, Fifer WP, Amso D, Barr R, Bell MA, Calkins S, et al. Beyond the Bayley: Neurocognitive Assessments of Development During Infancy and Toddlerhood. https://doi.org/101080/8756564120181564310 [Internet]. 2019 Feb 178];44(2):220–47. Available from: https://www.tandfonline.com/doi/abs/10.1080/87565641.2018.1564310

345. Mikkelsen A, Borres MP, Björkelund C, Lissner L, Oxelmark L. The Food hypersensitivity famiLy ImPact (FLIP) questionnaire - development and first results. Pediatric Allergy and Immunology [Internet]. 2013 Sep 1 [cited 2022 Feb 8];24(6):574–

346. 81. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/pai.12105

347. Treyvaud K, Anderson VA, Howard K, Bear M, Hunt RW, Doyle LW, et al. Parenting behavior is associated with the early neurobehavioral development of very preterm children. Pediatrics [Internet]. 2009 Feb [cited 2022 Feb 8];123(2):555–61. Available from: https://pubmed.ncbi.nlm.nih.gov/19171622/

348. Karam F, Sheehy O, Huneau MC, Chambers C, Fraser WD, Johnson D, et al. Impact of maternal prenatal and parental postnatal stress on 1-year-old child development: results from the OTIS antidepressants in pregnancy study. Archives of Women's Mental Health [Internet]. 2016 Oct 1 [cited 2022 Feb 8];19(5):835–43. Available from: https://link.springer.com/article/10.1007/s00737-016-0624-6

349. Letourneau NL, Kozyrskyj AL, Cosic N, Ntanda HN, Anis L, Hart MJ, et al. Maternal sensitivity and social support protect against childhood atopic dermatitis. Allergy, Asthma & Clinical Immunology 2017 13:1 [Internet]. 2017 May 26 [cited 2022 Feb 8];13(1):1–14. Available from: https://aacijournal.biomedcentral.com/articles/10.1186/s13223-017-0199- 4

350. Panza R, Baldassarre ME, di Mauro A, Cervinara A, Capozza M, Laforgia N. Infantile Functional Gastrointestinal Disorders and Maternal Psychological Status: A Narrative

351. Review. Current pediatric reviews [Internet]. 2021 Feb 9 [cited 2022 Feb 8];17(2):111–9. Available from: https://pubmed.ncbi.nlm.nih.gov/33557737/

352. Browne PD, Aparicio M, Alba C, Hechler C, Beijers R, Rodríguez JM, et al. Human milk microbiome and maternal postnatal psychosocial distress. Frontiers in Microbiology. 2019;10(OCT):2333.

353. Kawano A, Emori Y. The Relationship Between Maternal Postpartum Psychological State and Breast Milk Secretory Immunoglobulin A Level. Journal of the American Psychiatric Nurses Association [Internet]. 2015 Jan 17 [cited 2022 Feb 8];21(1):23–30. Available from: https://journals.sagepub.com/doi/full/10.1177/1078390314566882?casa_token= wPAEaak mrmEAAAAA%3A- ANMqBSnlcgfCyxRJiPBARhAN0xvKCtWgKLmayuVJrhgBR0PqQdYXhlwJG

T_fQ6uP 3bc3EZfGhTf

354. Kingston D, Tough S, Whitfield H. Prenatal and postpartum maternal psychological distress and infant development: A systematic review. Child Psychiatry and Human Development [Internet]. 2012 Oct 10 [cited 2022 Feb 8];43(5):683–714. Available from: https://link.springer.com/article/10.1007/s10578-012-0291-4

355. Yang X, Liang R, Xing Q, Ma X. Fighting Food Allergy by Inducing Oral Tolerance: Facts and Fiction. International Archives of Allergy and Immunology. 2021 Sep 1;182(9):852–62.

Appendix A

Table B1. Unique adjustment sets for each multivariable regression model.

Atopic Sensitization Multivariate Model Adjustments								
Cognitive Covariate	Language 1-Year	Motor 1-Year	Social-Emoti 1-Year	onal 1-Year	Cognitive 2-Year	Language 2-Year	Motor 2-Year	Social-Emotio nal 2-Year
Maternal Age								
Maternal Ethnicity								
Maternal Prenatal Diet Fruit Intake								
Maternal Prenatal Smoking								
Maternal Prenatal Depression								
Maternal Asthma								
Siblings								
Infant Diet (Solids)								
Breastfeeding Duration								
Mode of Birth								
Gestational Age								

Food Sensitization Multivariate Model Adjustments

Cognitive Covariate	Language 1-Year	Motor 1-Year	Social-Emoti 1-Year	onal 1-Year	Cognitive 2-Year	Language 2-Year	Motor 2-Year	Social-Emotio nal 2-Year
Maternal Age		(pink)			(pink)	(pink)		
Maternal Ethnicity	(pink)	(pink)	(pink)	(pink)	(pink)	(pink)	(pink)	(pink)
Maternal Prenatal Diet Fruit Intake		(pink)			(pink)	(pink)	(pink)	
Maternal Prenatal Smoking		(pink)	(pink)		(pink)	(pink)	(pink)	
Maternal Prenatal Depression	(pink)	(pink)	(pink)		(pink)	(pink)	(pink)	
Maternal Asthma	(pink)	(pink)			(pink)	(pink)	(pink)	
Siblings		(pink)			(pink)		(pink)	
Infant Diet (Solids)		(pink)	(pink)		(pink)	(pink)	(pink)	
Breastfeeding Duration		(pink)			(pink)	(pink)	(pink)	
Mode of Birth	(pink)	(pink)	(pink)		(pink)		(pink)	(pink)
Gestational Age	(pink)	(pink)	(pink)		(pink)	(pink)	(pink)	

Note: Variables identified as potential covariates from the DAG (Figure 1) were individually tested for a greater than 15% change to the estimate. Only covariates that were identified in both the DAG and caused a greater than 10% change to the estimate (shown in pink) were added to the minimal adjustment set for the corresponding multivariable model.

Table B2. Frequency characteristics for categorical variables in the study sample of infants with atopic and food sensitization at 1 year and neurodevelopmental data at 1 and 2 years of age (n=537)

Maternal characteristics	Total N	n (%)	Infant characteristics	Total N	n (%)
Family Income	488		**Atopic Sensitization**	537	
Less than 39,999		26 (5.3)	Yes		88 (16.4)
40,000 to 79,999		121 (24.8)	No		449 (83.6)
80,000 to 99,999		79 (16.2)	**Food Sensitization**	537	
Exceeds 100,000		262 (53.7)	Yes		72 (13.4)
Maternal Education	515		No		456 (86.6)
Some/finished high school		36 (7.0)	**Child Sex**	537	
Some university/college		193 (37.5)	Boys		279 (52.0)
University degree		286 (55.5)	Girls		258 (48.0)
Maternal Asthma	519		**Breastfeeding 3 Months**	535	
Yes		123 (23.7)	None		77 (14.4)
No		396 (76.7)	Partial		146 (27.3)
Prenatal Smoking	519		Exclusive		312 (58.4)
Yes		19 (3.7)	**Birthmode**	532	
No		500 (96.3)	Vaginal no IAP		277 (52.1)
Maternal Depression	483		Vaginal IAP		127 (23.9)
Yes		96 (19.9)	CS-Elective		58 (10.9)
No		387 (80.1)	CS-Emergency		70 (13.2)
Maternal Age	537		**Gestational Age**	537	
18-29		150 (27.9)	37 weeks+		506 (5.8)
30-39		366 (68.2)	34-36 weeks		31 (5.6)
40+		21 (3.9)	**Siblings**	535	
Maternal Ethnicity	533		Yes		302 (56.5)
White Caucasian		420 (78.8)	No		233 (43.5)
Asian		51 (9.6)			
Other		62 (11.6)			

Table B3. Frequency characteristics for continuous variables in the study sample of infants with atopic and food sensitization at 1 year and neurodevelopmental data at 1 and 2 years of age (n=537)

Continuous variables	Total N	Mean (SD)	Min	Max
BSID-III Cognitive 1 Year	537	110.04 (10.3)	75	145
Missing, n (%)	0 (0)			
BSID-III Language 1 Year	536	107.9 (11.9)	65	147
Missing, n (%)	1 (0.2)			
BSID-III Motor 1 Year	535	102.8 (13.6)	70	154
missing, n (%)	2 (0.4)			
BSID-III Social-Emotional 1 Year	519	102.6 (13.8)	60	145
Missing, n (%)	18 (3)			
BSID-III Cognitive 2 Year	537	105.7 (14.3)	70	145
Missing, n (%)	0 (0)			
BSID-III Language 2 Year	536	100.2 (12.0)	68	135
Missing, n (%)	1 (0.2)			
BSID-III Motor 2 Year	537	98.9 (9.5)	67	127
Missing, n (%)	0 (0.0)			
BSID-III Social-Emotional 2 Year	527	108.7 (15.7)	60	145
Missing, n (%)	10 (1.9)			
Maternal Pregnancy Fruit Intake	508	3.2 (2.0)	0.14	13.4
Missing, n (%)	29 (5.4)			
Breastfeeding Duration	517	10.2 (6.7)	0	25
Missing, n (%)	10.2 (6.7)			

Table B4. Percentage distribution of food and atopic sensitization at 1 year across candidate covariates (n=537)

Categorical variables	Atopic Sensitization 1YR (**YES**) (16.4% overall) N[c] (%)	Atopic Sensitizationon 1YR (**NO**) (83.6% overall) N[c] (%)	p-value	Food sensitization(**YES**) (13.4% overall) N[c] (%)	Sensitization on 1YR (**NO**) (86.6%) N[c] (%)	p-value
Maternal Characteristics						
CESD			0.386[a]			0.553[a]
Never	77 (16.8)	382 (83.2)		64 (13.9)	395 (86.1)	
Prenatal	7 (23.6)	24 (77.4)		5 (16.1)	26 (83.9)	
Postnatal	4 (10.3)	35 (89.7)		3 (7.7)	36 (92.3)	
Persistent	0 (0.0)	8 (100)		0 (0.0)	8 (100.0)	
Maternal age			0.638[a]			0.294[a]
18 to 29	21 (14.0)	129 (86.0)		15 (10.0)	135 (90.0)	
30 to 39	64 (17.6)	302 (82.5)		55 (15.0)	311 (85.0)	
Over 40	3 (14.3)	18 (85.7)		2 (9.5)	19 (90.5)	
Maternal education			**0.038[a]**			**0.010[a]**
Some/finished high school	4 (11.1)	32 (88.9)		3 (8.3)	33 (91.7)	
Some university/ college	23 (11.9)	170 (88.1)		16 (8.3)	177 (91.7)	
University degree	58 (20.3)	228 (79.7)		50 (17.5)	236 (82.5)	
Prenatal smoking			0.223[a]			0.091[a]
Yes	1 (5.3)	18 (94.7)		0 (0.0)	19 (100.0)	
No	86 (17.2)	414 (82.8)		71 (14.2)	429 (85.8)	
Maternal ethnicity			**<0.001**			**<0.001**
White Caucasian	53 (12.6)	367 (87.4)		43 (10.2)	377 (89.8)	
Asian	19 (37.3)	32 (62.8)		15 (29.4)	36 (70.6)	
Other	15 (24.2)	47 (75.8)		13 (21.0)	49 (79.0)	
Maternal asthma			0.838			0.822
Yes	20 (23.0)	95 (22.0)		15 (13.0)	100 (87.0)	
No	67 (77.0)	337 (83.4)		56 (12.9)	348 (86.1)	
Infant characteristics						
Child sex			0.595			0.095
Boys	48 (17.2)	231 (82.8)		44 (15.8)	235 (84.2)	
Girls	40 (15.5)	218 (84.5)		28 (10.9)	230 (89.2)	
Older siblings			0.529			0.236

Yes	47 (53.4)	255 (57.1)		36 (15.5)	266 (88.1)	
No	41 (46.6)	192 (82.4)		36 (11.9)	197 (84.6)	
Birth mode			0.593			0.958
Vaginal-noIAP	43 (15.5)	234 (84.5)		37 (13.4)	240 (86.6)	
Vaginal-IAP	19 (15.0)	108 (85.0)		15 (11.8)	112 (88.2)	
CS-elective	13 (22.4)	45 (77.6)		8 (13.8)	50 (86.2)	
CS-emergency	11 (15.7)	59 (84.3)		10 (14.3)	60 (85.7)	
Infant diet - solids at 3M			0.704			1.000[a]
Yes	1 (7.7)	12 (92.3)	1 (7.7)		12 (92.3)	
No	86 (16.6)	432 (83.4)	70 (13.5)		448 (86.5)	
Infant breastfeeding duration (months)			0.220		0.200	
85(16.4%)		432 (83.6%)		70 (13.54%)	447 (86.46%)	
Maternal prenatal fruit intake			0.086			0.059
83 (16.34%)		425 (83.66%)		68 (13.39%)	440 (86.61%)	
Gestational age (in weeks)						
88 (16.54%)		444 (83.46%)	0.097	72 (13.53%)	460 (86.47%)	0.1713

[a]Fisher's exact test
[b]Bold values are statistically significant
[c]Total number of observations (N) is based per column per atopy/food sensitizatio yes/no

Table B5. Distribution of 1-year BSID-III neurodevelopment subscale scores across candidate study covariates (N=537).

		Neurodevelopmental Scores at 1 YR							
Covariates	N (%)	Cognitive Score Mean *(SD)*	*P* Value	Language Score Mean *(SD)*	*P* Value	Motor Score Mean *(SD)*	*P* Value	Socio Emotional Score Mean *(SD)*	*P* Value
Maternal Categorical Factors – Mean (SD)[a]									
CESD			0.463		0.739		0.470		0.409
Never	459 (85.5)	110.03(10.20)		107.85 (12.18)		102.64 (14.71)		102.99 (13.96)	
Prenatal	31 (5.8)	108.23 (11.07)		106.10 (10.59)		99.13 (13.40)		99.35 (10.23)	
Postnatal	39 (7.3)	110.77 (9.97)		109.33 (10.95)		104.38 (15.82)		101.43 (14.78)	
Persistent	8 (1.5)	114.38 (14.50)		107.88 (10.26)		105 (9.09)		98.57 (15.20)	
Maternal Age			0.595		0.118		0.118		0.595
18 to 29	150 (27.9)	109.35 (9.79)		107.94 (12.16)		103.74 (13.52)		103.60 (14.65)	
30 to 39	366 (68.2)	110.40 (10.46)		107.90 (11.93)		101.85 (15.20)		102.22 (13.54)	
Over 40	21 (3.9)	108.67 (11.24)		106.43 (11.71)		107.57 (11.45)		102.25 (13.33)	
Prenatal Smoking			0.783		0.039		0.275		0.748
Yes	19 (3.7)	110.79 (9.02)		113.53 (11.03)		106.05 (13.75)		101.39 (10.12)	
No	500 (96.3)	110.12 (10.36)		107.69 (12.13)		102.32 (14.66)		102.45 (13.87)	
Maternal ethnicity			0.001		0.001		0.137		0.007
White Caucasian	420 (78.8)	110.47 (9.99)	108.71 (11.80)	102.66 (15.15)	103.13 (13.64)				
Asian	51 (9.6)	105.10 (11.02)	101.94 (13.01)	99.29 (13.50)	99.26 (16.05)				
Other	62 (11.6)	111.21 (11.08)	106.92 (11.31)	104.81 (12.06)	101.55 (13.19)				
Infant Categorical Factors – Mean (SD)[a]									
Child Sex									
			0.217		0.000		0.436		0.406
Males	279 (52.0)	109.51 (10.73)		106.08 (12.04)		102.13 (14.25)		103.09 (14.29)	
Females	258 (48.0)	110.61 (9.78)		109.76 (11.62)		103.12 (15.09)		102.08 (13.34)	
Breastfeeding at 3 months			0.549		0.278		0.265		0.503
Exclusive	312 (58.3)	109.29 (9.79)		107.25 (11.78)		101.49 (11.71)		100.97 (14.88)	
Partial	146 (27.3)	109.60 (11.34)		106.74 (13.28)		101.32 (17.52)		102.53 (13.27)	
None	77 (14.4)	110.46 (9.94)		108.57 (11.37)		103.47 (13.84)		103.07 (13.86)	
Birth mode									
Vaginal-no IAP	277 (52.1)	110.56 (10.58)	0.342	107.98 (12.50)	0.881	101.79 (15.74)	0.099	102.90 (13.88)	0.943
Vaginal-IAP	127 (23.9)	110.16 (10.35)		107.83 (10.57)		102.61 (13.58)		101.97 (13.12)	
CS-elective	58 (10.9)	108.79 (8.90)		106.71 (13.21)		100.78 (13.73)		102.68 (15.43)	
CS-emergency	70 (13.2)	108.39 (10.36)		108.31 (11.35)		106.33 (11.85)		102.46 (14.00)	
Introduced to Solids			0.144		0.115		0.864		0.111
No	518 (97.6)	109.40 (10.36)		108.33 (11.76)		102.79 (14.39)		100.85 (13.01)	
Yes	13 (2.4)	110.50 (10.27)		107.53 (12.13)		102.43 (14.91)		103.91 (14.34)	
Older siblings			0.220		0.443		0.779		0.012
No	233 (43.6)	109.40 (10.36)		107.53 (12.13)		102.79 (14.39)		100.85 (13.01)	
Yes	302 (56.4)	110.50 (10.27)		108.13 (12.25)		102.43 (14.91)		103.91 (14.34)	
Neurodevelopmental Outcomes – or β (95% CI)[b]									
Breastfeeding duration	10.16 (6.69)[c]	0.18 (0.05, 0.31)	0.007	0.08 (-0.069, 0.24)	0.281	0.14 (-0.05, 0.32)	0.157	0.21 (0.03, 0.39)	0.023
Maternal fruit intake	3.16 (1.99)[c]	0.14 (-0.30, 0.59)	0.531	0.263 (-0.26, 0.79)	0.326	0.03(-0.61, 0.67)	0.924	0.57(-0.04, 1.17)	0.068
Gestational age (in weeks)	39.11 (1.39)[c]	1.13 (0.50, 1.76)	0.000	0.67 (-0.05, 1.42)	0.067	1.05 (0.15,1.95)	0.022	0.59(-0.28, 1.46)	0.182

Note: BISD-III=Bayley Infant Scales of Development Third Edition; SD=standard deviation; *β=Coefficient.* Total number of observations (N) is based per column covariate and it's corresponding categories

[a]Analyzed by *t*test or one-way analysis of variance, [b]Analyzed by linear regression, [c] Reported in means (standard deviation). Gestational age is measured in weeks and maternal

prenatal fruit intake assessed using the Healthy Eating Index (HEI)

Table B6. Distribution of 2-year BSID-III neurodevelopment subscale scores across candidate study covariates (N=537).

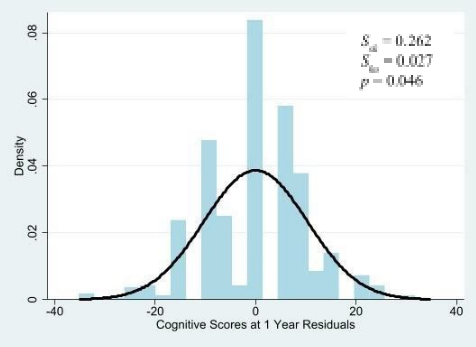
		Neurodevelopmental Scores at 2 YRs							
Covariates	**N (%)**	**Cognitive Score Mean *(SD)***	***P* Value**	**Language Score Mean *(SD)***	***P* Value**	**Motor Score Mean *(SD)***	***P* Value**	**Socio Emotional Score Mean *(SD)***	***P* Value**
Maternal Categorical Factors – Mean (SD)[a]									
CESD	459 (85.5)	106.09 (14.42)	0.364	100.40 (11.86)	0.105	99.03 (9.45)	0.915	109.34(15.73)	0.015
Never	31 (5.8)	104.52 (13.87)		100.84 (12.88)		98.13 (10.64)		102.67 (14.49)	
Prenatal	39 (7.3)	104.23 (14.80)		98.90 (13.22)		98.26 (8.77)		108.29 (15.65)	
Postnatal	8 (1.5)	98.13		90.25 (9.45)		98.13 (11.89)		95.01 (11.55)	
Persistent		(5.94)							
Maternal Age									
18 to 29	150 (27.9)	107.33 (15.12)	0.226	101.52 (11.35)	0.153	99.65 (9.27)	0.512	109.18 (15.18)	0.856
30 to 39	366 (68.2)	105.02 (13.94)		99.48 (12.24)		98.59 (9.64)		108.57 (16.04)	
Over 40	21 (3.9)	107.14 (15.13)		102.33 (12.60)		99.10 (8.50)		107.38 (14.72)	
Prenatal Smoking			0.135		0.358		0.664		0.274
Yes	19 (3.7)	100.79 (13.15)	97.63 (9.62)	98 (8.02)	104.74 (16.79)				
No	500 (96.3)	105.77 (14.30)	100.23 (12.15)	98.98 (9.66)	108.76 (15.67)				
Maternal ethnicity									
White Caucasian	420 (78.8)	106.90 (14.41)	0.002	101.45 (11.39)	0.000	98.98 (9.33)	0.528	109.40 (15.77)	0.201
Asian	51 (9.6)	101.27 (13.30)	93.02 (13.31)	97.53 (10.35)	105.60 (15.41)				
Other	62 (11.6)	101.81 (13.77)	97.63 (12.93)	99.44 (10.19)	107.25 (15.42)				
Infant Categorical Factors – Mean (SD)[a]									
Child Sex	279 (52.0)	103.36 (13.41)	0.000	97.18 (11.86)	0.000	98.02 (9.45)	279 (52.0)	103.36 (13.41)	0.000
Males	258 (48.0)	108.33 (14.88)		103.41 (11.38)		99.87 (9.46)	258 (48.0)	108.33 (14.88)	
Females			0.018		0.002				0.018
Breastfeeding at 3 months	312 (58.1)	102.86 (10.71)		98.05 (10.48)		97 .66(8.29)	312 (58.1)	102.86 (10.71)	
Exclusive	146 (27.2)	104.25 (13.23)		97.94 (11.13)		98.4 (9.45)	146 (27.2)	104.25 (13.23)	
Partial	77 (14.3)	107.23 (15.45)		101.71 (12.56)		99.4 (9.80)	77 (14.3)	107.23 (15.45)	
None			0.068		0.082				0.068
Birth mode	277 (52.1)	107.03 (15.14)		101.12 (11.16)		99.58 (9.01)	277 (52.1)	107.03 (15.14)	
Vaginal-no IAP	127 (23.9)	104.53 (12.35)	100.08 (12.67)	98.29 (9.14)			127 (23.9)	104.53 (12.35)	100.08 (12.67)
Vaginal-IAP	58 (10.9)	101.98 (14.23)	96.78 (13.18)	97.05 (10.87)			58 (10.9)	101.98 (14.23)	96.78 (13.18)
CS-elective	70 (13.2)	105.86 (14.17)	99.26 (12.99)	98.91 (10.49)			70 (13.2)	105.86 (14.17)	99.26 (12.99)
CS-emergency			0.423		0.386				0.423
Introduced to Solids	518 (97.6)	105.93 (14.47)		100.31 (11.93)		98.97 (9.42)	518 (97.6)	105.93 (14.47)	
No	13 (2.4)	102.69 (9.04)		97.38 (15.63)		97.77 (12.62)	13 (2.4)	102.69 (9.04)	
Yes			0.931		0.596				0.931
Older siblings	233 (43.6)	105.64 (14.73)	100.44 (12.00)	97.58 (9.33)			233 (43.6)	105.64 (14.73)	100.44 (12.00)
No	302 (56.4)	105.75 (14.05)	99.88 (12.08)	99.91 (9.51)			302 (56.4)	105.75 (14.05)	99.88 (12.08)
Yes	279 (52.0)	103.36 (13.41)	0.000	97.18 (11.86)	0.000	98.02 (9.45)	279 (52.0)	103.36 (13.41)	0.000
Neurodevelopmental Outcomes – or β (95% CI)[b]									
Breastfeeding duration									
	10.16 (6.69)[c]	0.26 (0.08, 0.44)	0.006	0.30 (0.14, 0.45)	0.000	0.07 (-0.05, 0.20)	10.16 (6.69)[c]	0.26 (0.08, 0.44)	0.006
Maternal fruit intake	3.16 (1.99)[c]	-0.39 (-1.01, 0.23)	0.217	0.39 (-0.13, 0.92)	0.144	0.17 (-0.25, 0.59)	3.16 (1.99)[c]	-0.39	0.217
Gestational age (in weeks)	39.11 (1.39)[c]	1.12 (0.25, 2.00)	0.012	1.13 (0.40, 1.86)	0.002	0.82(0.24, 1.40)	39.11 (1.39)[c]	1.12	0.012

Note: BISD-III=Bayley Infant Scales of Development Third Edition; SD=standard deviation; β=*Coefficient.* Total number of observations (N) is based per column covariate and it's corresponding categories
[a]Analyzed by *t*test or one-way analysis of variance, [b]Analyzed by linear regression, [c] Reported in means (standard deviation). Gestational age is measured in weeks and maternal prenatal fruit intake assessed using the Healthy Eating Index (HEI)

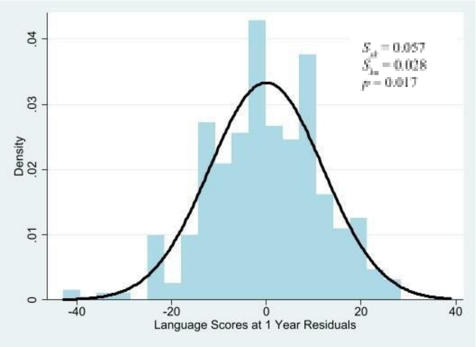
Figure B1. Residuals resulting from regressing neurodevelopmental scores at 1 year (A-D) and 2 years (E-H) of infant age against infant atopic sensitization status.

Note: S_{kw} = skewness; S_{ku} = kurtosis; p = p value

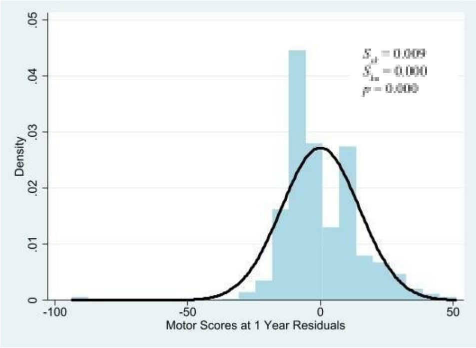
A.



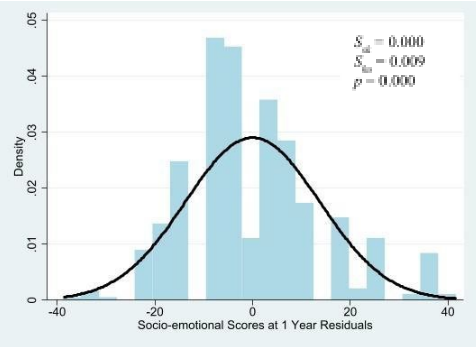
B.



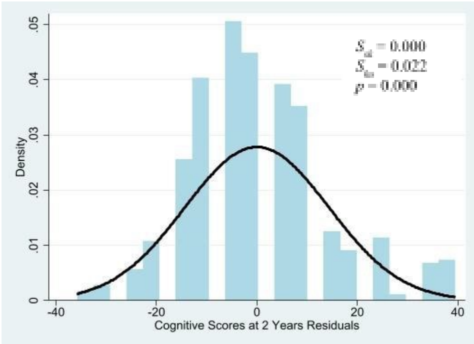
C.



D.

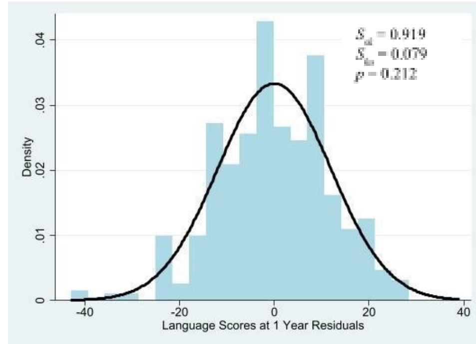


E.



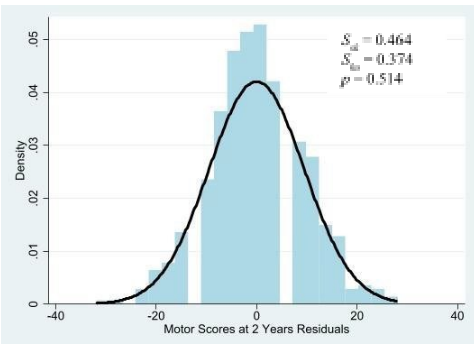
S_{sk} = 0.000
S_{ku} = 0.022
p = 0.000
Density
0
.01
.02
.03
.04
.05
-40
-20
0
20
40
Cognitive Scores at 2 Years Residuals

F.



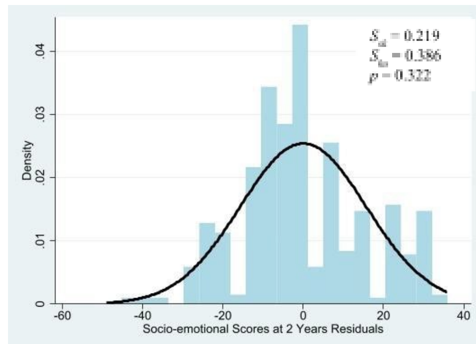
S_{sk} = 0.919
S_{ku} = 0.079
p = 0.212
Density
0
.01
.02
.03
.04
-40
-20
0
20
40
Language Scores at 1 Year Residuals

G.



S_{sk} = 0.464
S_{ku} = 0.374
p = 0.514
Density
0
.01
.02
.03
.04
.05
-40
-20
0
20
40
Motor Scores at 2 Years Residuals

H.

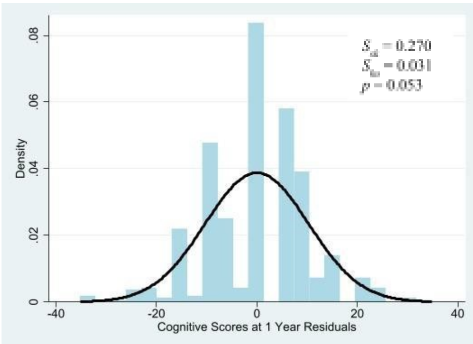


S_{sk} = 0.219
S_{ku} = 0.386
p = 0.322
Density
0
.01
.02
.03
.04
-60
-40
-20
0
20
40
Socio-emotional Scores at 2 Years Residuals

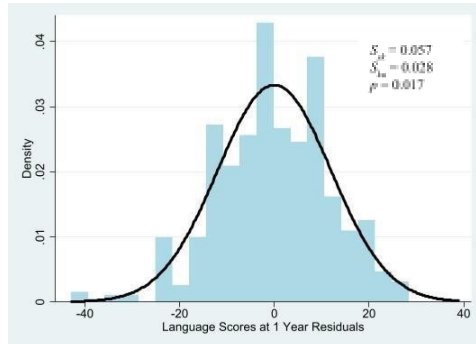
Figure B2. Residuals resulting from regressing neurodevelopmental scores at 1 year (A-D) and 2 years (E-H) of infant age against infant food sensitization status.

Note: S_{kw} = skewness; S_{ku} = kurtosis; p = p value

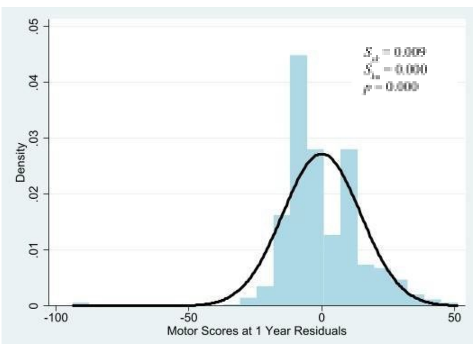
A.



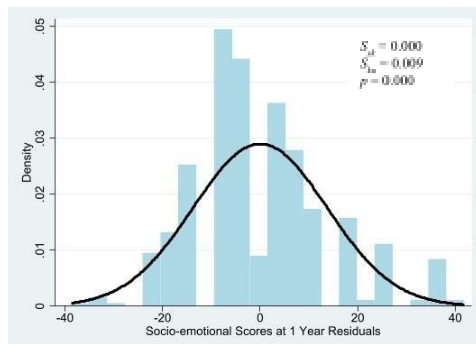
B.



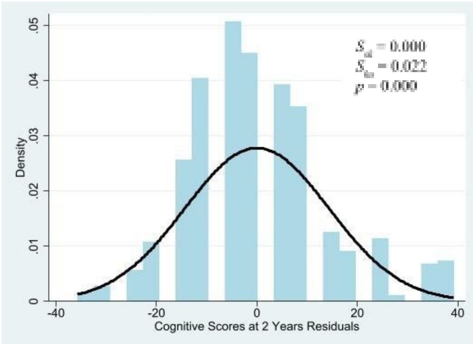
C.



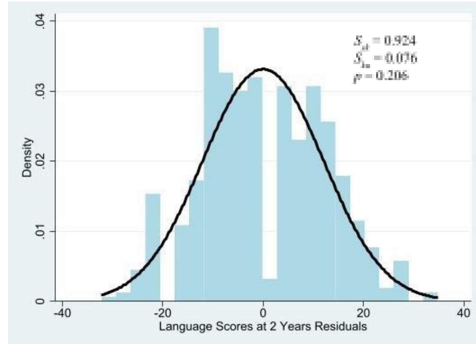
D.



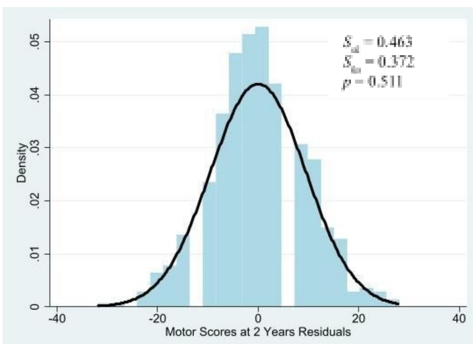
E.


S_{sk} = 0.000
S_{ku} = 0.022
p = 0.000
Density
Cognitive Scores at 2 Years Residuals

F.


S_{sk} = 0.924
S_{ku} = 0.076
p = 0.206
Density
Language Scores at 2 Years Residuals

G.


S_{sk} = 0.463
S_{ku} = 0.372
p = 0.511
Density
Motor Scores at 2 Years Residuals

H.

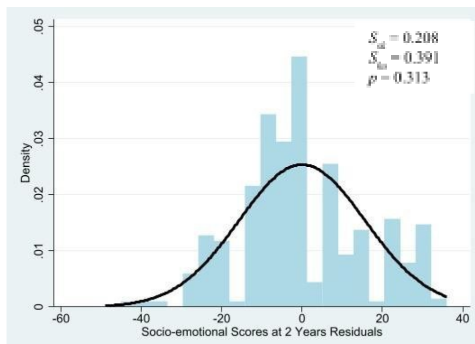

S_{sk} = 0.208
S_{ku} = 0.391
p = 0.313
Density
Socio-emotional Scores at 2 Years Residuals

Table B1. Frequency characteristics for continuous variables in the study sample of maternal atopic status at 1 year and neurodevelopmental data at 1 and 2 years of age (n=335)

Continuous variables	Total N	Mean (SD)	Min	Max
BSID-III Cognitive 1 Year	335	110.58 (10.51)	75	145
Missing, n (%)	0 (0)			
BSID-III Language 1 Year	334	108.71 (12.31)	68	147
Missing, n (%)	1 (0.2)			
BSID-III Motor 1 Year	335	103.02 (15.97)	9	154
missing, n (%)	0 (0)			
BSID-III Social-Emotional 1 Year	324	102.22 (13.31)	70	140
Missing, n (%)	11 (0.03)			
BSID-III Cognitive 2 Year	335	105.30 (13.80)	70	145
Missing, n (%)	0 (0)			
BSID-III Language 2 Year	334	100.19 (11.71)	74	129
Missing, n (%)	1 (0.2)			
BSID-III Motor 2 Year	335	98.56 (9.65)	70	127
Missing, n (%)	0 (0.0)			
BSID-III Social-Emotional 2 Year	331	108.32 (15.82)	60	145
Missing, n (%)	4 (1.2)			
Maternal Pregnancy Fruit Intake	325	3.2 (2.14)	0.44	13.42
Missing, n (%)	10 (3.0)			
Breastfeeding Duration	327	9.56 (6.79)	0	24
Missing, n (%)	8 (2.4)			

Table B2. Linear regression results assessing the association between the exposure (*X*) or combined maternal atopy and the potential mediator (*M*) or infant gut microbiome abundance at 4 months of infant age.

	Testing *X* -> *M* Association in All Infants			
Infant gut microbe at 4 months of infant age	**β-coefficient**	**[95% Confidence Interval]**		**p-value**
p__Firmicutesc__Erysi	-0.009	-0.016	-0.002	**0.018**
o__Erysipelotrichales	-0.009	-0.016	-0.002	**0.018**
p__Actinobacteriac~A	-0.001	-0.04	0.038	0.969
p__Actinobacteriac~C	-0.003	-0.01	0.003	0.344
p__Bacteroidetesc_~a	-0.013	-0.086	0.059	0.715
p__Firmicutesc__Ba~l	-0.012	-0.01	0.01	0.992
p__Firmicutesc__Cl~t	0.01	-0.045	0.065	0.727
p__Proteobacteriac~B	0	-0.009	0.009	0.955
p__Proteobacteriac~D	0.001	-0.002	0.004	0.579
p__Proteobacteriac~E	0	0	0.001	0.845
p__Proteobacteriac~G	-0.004	-0.054	0.047	0.892
p__Verrucomicrobia~_	0.018	-0.01	0.046	0.212
o__Actinomycetales	0.001	-0.002	0.005	0.48
o__Bifidobacteriales	-0.002	-0.04	0.036	0.912
o__Coriobacteriales	-0.003	-0.01	0.003	0.344
o__Bacteroidales	-0.013	-0.086	0.059	0.715
o__Bacillales	0	-0.001	0.001	0.869
o__Gemellales	0	0	0	0.963
o__Lactobacillales	0	-0.01	0.01	1
o__Clostridiales	0.01	-0.045	0.065	0.727
o__Fusobacteriales	0	-0.001	0	0.4
o__Burkholderiales	0	-0.008	0.009	0.949
o__Desulfovibriona~s	0.001	-0.002	0.004	0.579
o__Campylobacterales	0	0	0.001	0.845
o__Enterobacteriales	0.005	-0.046	0.055	0.852
cdifflog_3m	0.4	-0.367	1.167	0.306
cdifflog_1y	0.323	-0.649	1.296	0.513

Note: Bolded p-values indicate statistical significance

Table B3 Linear regression results assessing the association between the exposure (*X*) or maternal asthma and the potential mediator (*M*) or infant gut metabolite abundance at 4 months of infant age.

	Linear Regression Results of the Association between Combined Maternal Atopy (*X*) and Metabolite (*M*)						Linear Regression Results of the Association between and Metabolite (*M*) and Female Infant Cognitive Scores at 2 Years					
	X -> *M*						*M* -> *Y*					
Metabolite	**β-coefficient**	**[95% CI]**		**p-value**	**R^2**	**N**	**β-coefficient**	**[95% CI]**		**p-value**	**R^2**	**N**
formate	-3.51E+00	-8.01E+00	9.96E-01	0.124	0.049	50	9.43E-02	-6.11E-02	2.50E-01	0.229	0.03	50
acetate	**3.69E+01**	**5.67E+00**	**6.82E+01**	**0.021**	**0.07**	**60**	**5.37E-02**	**6.89E-03**	**1.0E-01**	**0.023**	**0.08**	**60**
butyrate	3.30E+00	-1.25E+00	7.85E+00	0.152	0.035	60	-1.02E-01	-2.59E-01	5.47E-02	0.197	0.028	60
propionate	6.15E+00	-2.06E+00	1.44E+01	0.139	0.037	60	-5.41E-02	-3.41E-01	2.33E-01	0.707	0.002	60
valerate	6.88E-01	-4.97E-01	1.87E+00	0.25	0.023	60	-1.21E-02	-5.32E-02	2.89E-02	0.556	0.006	60
isobutyrate	4.20E-01	-1.38E-01	9.79E-01	0.137	0.038	60	-5.32E-03	-2.48E-02	1.42E-02	0.587	0.005	60
isovalerate	7.67E-01	-1.15E-01	1.65E+00	0.087	0.05	60	-1.51E-02	-4.59E-02	1.58E-02	0.332	0.016	60
lactate	-5.99E-01	-1.14E+01	1.02E+01	0.912	0	56	3.84E-01	2.27E-02	7.46E-01	0.038	0.078	56
succinate	-4.27E+00	-2.22E+01	1.36E+01	0.635	0.004	60	6.17E-01	2.20E-02	1.21E+00	0.042	0.069	60
hydroxyglutarate	4.01E+00	-3.54E+01	4.34E+01	0.419	0.626	3	-1.97E-01	-1.46E+00	1.07E+00	0.298	0.797	3
aminobutyrate	9.20E-01	-2.06E+00	3.90E+00	0.533	0.014	30	1.12E-01	3.30E-03	2.21E-01	0.044	0.137	30
hydroxyphenylacetate	7.13E-02	-2.74E-01	4.17E-01	0.677	0.005	34	-8.66E-03	-2.36E-02	6.30E-03	0.247	0.042	34
aminopentanoate	6.61E-01	-2.87E+00	4.19E+00	0.704	0.006	28	-5.57E-02	-1.94E-01	8.23E-02	0.415	0.026	28
acetoin	1.10E+00	-8.39E-01	3.04E+00	0.253	0.054	26	2.61E-02	-5.33E-02	1.06E-01	0.504	0.019	26
alanine	1.57E+00	-2.33E+00	5.46E+00	0.423	0.013	50	1.05E-01	-2.60E-02	2.35E-01	0.114	0.051	50
aspartate	1.55E+00	-3.20E-01	3.42E+00	0.102	0.056	49	1.79E-02	-4.75E-02	8.33E-02	0.585	0.006	49
betaalanine	2.63E-01	-2.12E+00	2.65E+00	0.796	0.012	8	-1.78E-02	-9.29E-02	5.73E-02	0.583	0.053	8
cadaverine	-2.28E+00	-5.94E+00	1.39E+00	0.214	0.048	34	-1.20E-01	-2.79E-01	3.97E-02	0.136	0.068	34
choline	-1.76E-01	-5.54E-01	2.02E-01	0.354	0.019	47	2.63E-02	1.58E-02	3.67E-02	0	0.362	47

creatine	1.22E-01	-2.94E-01	5.38E-01	0.556	0.008	46	1.32E-02	-8.58E-04	2.73E-02	0.065	0.075	46
creatinine	6.27E-02	-2.55E-01	3.81E-01	0.693	0.003	49	1.38E-02	3.24E-03	2.43E-02	0.011	0.128	49
dimethylamine	6.41E-03	-8.25E-02	9.54E-02	0.884	0.001	33	-2.56E-03	-5.83E-03	7.09E-04	0.12	0.076	33
ethanol	5.81E-01	-2.45E+00	3.61E+00	0.7	0.003	45	1.33E-01	3.86E-02	2.27E-01	0.007	0.158	45
fucose	3.08E+00	-1.30E+01	1.92E+01	0.699	0.005	34	2.24E-01	-3.78E-01	8.26E-01	0.454	0.018	34
fumarate	2.11E-01	-9.93E-02	5.22E-01	0.178	0.038	49	3.05E-03	-7.68E-03	1.38E-02	0.57	0.007	49
galactose	2.59E+00	-3.29E+00	8.47E+00	0.378	0.022	37	2.07E-01	-1.89E-02	4.32E-01	0.071	0.09	37
glucose	3.74E+00	-1.57E+00	9.05E+00	0.163	0.04	50	2.92E-01	1.27E-01	4.57E-01	0.001	0.209	50
glutamate	-3.55E+00	-1.54E+01	8.29E+00	0.549	0.008	47	1.22E-01	-2.76E-01	5.21E-01	0.54	0.008	47
glycerol	-1.01E+00	-2.03E+00	9.49E-03	0.052	0.104	37	2.27E-02	-1.94E-02	6.47E-02	0.281	0.033	37
glycine	-1.07E+00	-3.94E+00	1.79E+00	0.455	0.012	49	1.07E-02	-8.76E-02	1.09E-01	0.828	0.001	49
histidine	3.35E-01	-6.94E-01	1.37E+00	0.506	0.021	23	-1.54E-02	-4.63E-02	1.55E-02	0.311	0.049	23
hypoxanthine	1.78E+00	-2.02E-01	3.76E+00	0.074	0.262	13	-2.26E-02	-9.00E-02	4.48E-02	0.476	0.047	13
isoleucine	1.18E+00	-1.98E-01	2.56E+00	0.091	0.058	50	5.91E-03	-4.27E-02	5.45E-02	0.808	0.001	50
leucine	1.72E+00	-4.58E-01	3.90E+00	0.119	0.05	50	-1.96E-02	-9.58E-02	5.67E-02	0.608	0.006	50
lysine	4.21E+00	-3.40E+00	1.18E+01	0.267	0.044	30	-1.45E-02	-2.61E-01	2.32E-01	0.905	0.001	30
malonate	**1.64E+00**	**-2.98E-02**	**3.31E+00**	**0.054**	**0.075**	**50**	**4.95E-02**	**-8.14E-03**	**1.07E-01**	**0.091**	**0.058**	**50**
methanol	-3.45E-01	-1.18E+00	4.85E-01	0.408	0.014	50	-2.11E-02	-4.90E-02	6.83E-03	0.135	0.046	50
methionine	8.51E-01	8.07E-02	1.62E+00	0.031	0.093	50	3.03E-03	-2.46E-02	3.07E-02	0.826	0.001	50
methylamine	**9.35E-02**	**-3.64E-03**	**1.91E-01**	**0.059**	**0.111**	**33**	**-3.91E-03**	**-8.24E-03**	**4.26E-04**	**0.075**	**0.098**	**33**
methylhistidine	-5.17E-01	-1.16E+00	1.25E-01	0.109	0.118	23	-2.18E-03	-2.29E-02	1.86E-02	0.829	0.002	23
myoinositol	6.28E-01	-3.83E+00	5.08E+00	0.766	0.007	15	1.91E-01	2.59E-02	3.57E-01	0.027	0.324	15
pcresol	8.62E-02	1.53E-02	1.57E-01	0.028	0	5	-2.18E-03	-1.33E-02	8.89E-03	0.575	0.116	5
phenylacetate	3.25E-01	-7.11E-01	1.36E+00	0.504	0.042	13	-3.09E-02	-5.51E-02	-6.72E-03	0.017	0.418	13
phenylalanine	6.33E-01	-3.61E-01	1.63E+00	0.207	0.034	49	8.87E-03	-2.50E-02	4.27E-02	0.6	0.006	49

proline	-1.95E+00	-6.00E+00	2.11E+00	0.3	0.133	10	5.32E-02	-6.90E-02	1.75E-01	0.345	0.112	10
propyleneglycol	-1.52E+00	-5.75E+00	2.71E+00	0.474	0.011	47	1.53E-01	1.80E-02	2.88E-01	0.027	0.104	47
putrescine	-3.41E-01	-1.29E+00	6.10E-01	0.465	0.025	24	-6.88E-03	-4.32E-02	2.94E-02	0.698	0.007	24
pyroglutamate	9.41E-02	-1.40E+00	1.59E+00	0.894	0.001	16	2.83E-04	-7.60E-02	7.66E-02	0.994	0	16
pyruvate	-1.39E+00	-3.80E+00	1.03E+00	0.255	0.027	49	8.66E-02	8.37E-03	1.65E-01	0.031	0.095	49
serine	1.96E-01	-2.71E+00	3.11E+00	0.891	0.001	25	6.07E-02	-2.29E-02	1.44E-01	0.147	0.089	25
taurine	4.46E-01	-6.11E-01	1.50E+00	0.394	0.027	29	7.23E-03	-3.27E-02	4.72E-02	0.713	0.005	29
threonine	-5.17E-01	-2.50E+00	1.47E+00	0.603	0.006	48	-6.67E-03	-7.38E-02	6.05E-02	0.842	0.001	48
trimethylamine	6.87E-02	-9.69E-02	2.34E-01	0.408	0.015	47	9.35E-04	-4.52E-03	6.39E-03	0.732	0.003	47
tryptophan	4.05E-02	-7.02E-02	1.51E-01	0.467	0.009	59	-3.31E-03	-7.01E-03	3.92E-04	0.079	0.053	59
tyrosine	9.17E-01	-2.12E-01	2.05E+00	0.109	0.054	49	1.05E-02	-2.83E-02	4.93E-02	0.589	0.006	49
uracil	3.50E-01	-3.76E-01	1.08E+00	0.336	0.021	47	7.40E-03	-1.75E-02	3.23E-02	0.552	0.008	47
valine	1.67E+00	-3.27E-01	3.66E+00	0.099	0.056	50	1.40E-02	-5.61E-02	8.40E-02	0.69	0.003	50
xanthine	1.23E-01	-1.33E-01	3.80E-01	0.336	0.027	36	-5.61E-05	-1.03E-02	1.02E-02	0.991	0	36
lactate	-5.99E-01	-1.14E+01	1.02E+01	0.912	0	56	3.84E-01	2.27E-02	7.46E-01	0.038	0.078	56

Note: Bolded rows are metabolites that passed the criteria for mediation.