PERINATAL DETERMINANTS OF OFFSPRING NEURODEVELOPMENT

PRENATAL AND POSTNATAL DETERMINANTS OF OFFSPRING NEURODEVELOPMENT: UNDERSTANDING EARLY NEURODEVELOPMENT AND ASSESSING THE EFFECTIVNESS OF A PREGNANCY NUTRITION AND EXERCISE INTERVENTION

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Lay Abstract

Early brain development is crucial for shaping the cognition, behaviour, and emotions of individuals. Pregnancy is an important time to improve and prevent problems with offspring brain development, and lifestyle factors such as mother's diet and exercise levels may have a meaningful impact on the developing offspring. Therefore, the objectives of this thesis were to i) identify modifiable risk factors during pregnancy that may affect offspring cognitive and emotion regulation development, ii) understand how these risk factors may affect offspring cognitive and emotion regulation development, and iii) test the effectiveness of interventions aimed at reducing risk factors and improving offspring cognitive and emotion regulation development. Results from this thesis show that improving mother's diet quality and/or exercise levels during pregnancy may lead to better cognitive and emotion regulation development in offspring during infancy and the preschool years. This thesis suggests that identifying and intervening on risk factors during pregnancy may benefit early brain development in offspring.

Abstract

Objectives: To understand the preventive potential of the Developmental Origins of Health and Disease (DOHaD) hypothesis in improving fetal and offspring cognitive and emotion regulation (ER) development by: i) identifying modifiable risk factors during pregnancy that may affect offspring cognitive and ER development, ii) understanding the mechanisms involved in altering offspring cognitive and ER development, and iii) testing the effectiveness of interventions aimed at reducing risk factors and improving offspring cognitive and ER development

Methods: Study 1 used data from the Maternal-Infant Research on Environmental Chemicals (MIREC) cohort to examine the effect of prenatal diet quality on executive function (EF) and/or behavioral development in children raised in suboptimal home environments. Studies 2, 3, and 4 are sub-studies of the original Be Health In Pregnancy (BHIP) trial. These studies used a randomized controlled trial (RCT) to test the effectiveness of a pregnancy nutrition and exercise intervention on improving offspring cognitive and ER development at 12 and 36 months of age.

Results: Study 1 suggested that healthier maternal diet quality could potentially benefit child executive function and behaviour in 3–4-year-old children from suboptimal home environments. Studies 2, 3, and 4 found that using an experimental approach, the BHIP maternal nutrition and exercise intervention improved various offspring cognitive and ER outcomes across infancy (12-months) and early childhood (36-months).

Conclusion: The studies in this thesis highlight the importance of modifiable risk factors introduced during the prenatal period, and their benefits on fetal and child development, and provide the scientific foundation for larger more diverse RCTs to build upon. If results of future RCTs are similar, the BHIP intervention could represent a significant component of the next successfully implemented research-enabled public health strategy aimed at improving offspring neurodevelopment.

Key words: Pregnancy nutrition, pregnancy exercise, fetal neurodevelopment, cognitive development, emotion regulation development, Developmental Origins of Health and Disease (DOHaD), early childhood

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None.

List of Abbreviations

ADHD: Attention-deficit / hyperactivity disorder

ANOVA: Analysis of variance

ANS: Autonomic nervous system

BASC-2: Behavior Assessment System for Children– 2nd Edition

BSID-III: Bayley Scale of Infant and Toddler Development- 3rd Edition

BDNF: Brain-derived neurotrophic factor

BHIP: Be healthy in pregnancy

BMI: Body mass index

BRIEF-P: Behavior Rating Inventory of Executive Functioning– Preschool Edition

CBQ: Child Behavior Questionnaire

CES-D-10, 10-item version of the Center for Epidemiological Studies–Depression

COVID-19: Coronavirus disease 2019

DHA: Docosahexaenoic acid

DOHaD: Developmental Origins of Health and Disease

ECG: Electrocardiography

EEG: Electroencephalography

EF: Executive function

EMI: Emergent metacognition index

EPA: Eicosapentaenoic acid

EPDS: Edinburgh Postnatal Depression Scale

ER: Emotion regulation

FAA: Frontal alpha asymmetry

FFQ: Food frequency questionnaire

FI: Flexibility index

FKBP5: FK506 binding protein 5

fNIRS: Functional near infrared spectroscopy

GAC: General adaptive composite

GDM: Gestational diabetes mellitus

GWG: Gestational weight gain
HEI: Healthy Eating Index
HOME: Home Observation for Measurement of the Environment
HPA: Hypothalamic-pituitary-adrenal
HF-HRV: High frequency heart rate variability
HRV: Heart rate variability
IBQ-R SF: Infant Behavior Questionnaire- Revised short form
IGF: Insulin-like growth factor
ISCI: Inhibitory self control index
IQ: Intelligence quotient
MIREC-CD Plus, Maternal-Infant Research on Environmental Chemicals–Child Development
$\eta^{2}p$: Partial eta squared
PFC: Pre-frontal cortex
PNS: Parasympathetic nervous system
RCT: Randomized controlled trial
RMSSD: Root mean square of successive differences
SD: Standard deviation
SDNN: Standard deviation of N-N intervals
SES: Socioeconomic status
SNS: sympathetic nervous system
SPSS: Statistical package for the social sciences
UC: Usual care
UPC: Usual prenatal care
VEGF: Vascular endothelial growth factor
VIF: Variance inflation factor

Declaration of Academic Achievement

This sandwich thesis comprises of 4 studies, each written by the student. She led all formal data acquisition procedures and helped with data collection (studies 2-4). The student cleaned all physiological data pertaining to the studies, conducted all statistical analyses, prepared the initial draft of each manuscript, and revised each paper based on edits from the co-authors. This work was completed between September 2018 and May 2023, therefore, the studies in this thesis meet requirements for inclusion in the text. In accordance with the McMaster School of Graduate Studies requirements, contributions made by each co-author for each study are outlined below.

Study 1 examined the effect of prenatal diet quality on Executive function and/or behavioral development in children raised in suboptimal home environments. Neda Mortaji interpreted the study findings, wrote the first draft of the manuscript and incorporated subsequent edits and revisions, and approved the final manuscript as submitted; Dr. John Krzeczkowski conceptualized the idea for this study and its design, analyzed the data, and provided feedback and interpretation of the data; Dr. Khrista Boylan supported data extraction procedures, provided feedback and interpretation of the data, and reviewed and critically evaluated the intellectual content of the manuscript; Dr. Linda Booij contributed to design of the MIREC and cohort study, provided support in the interpretation of findings, and reviewed and revised the manuscript, Dr. Maude Perreault critically evaluated the content of the manuscript and provided feedback and interpretation of the data; and Dr. Ryan Van Lieshout aided in the conceptualization of the idea for the project, helped design the study, provided data analysis and interpretation, critically reviewed and revised the manuscript, and approved the final manuscript form submission.

Study 2 and 3 examined whether fetal exposure to a maternal nutrition and exercise intervention lead to better cognition (and physical, communication, social/emotional, and adaptive functioning) and emotion regulation at 12 months of age. Neda Mortaji acquired the data, analyzed all data, interpreted findings, wrote the first draft of the manuscript and incorporated subsequent edits and revisions. Dr. John Krzeczkowski and Dr. Bahar Amani helped with data collection and provided feedback and interpretation of the data; Dr. Stephanie Atkinson contributed to data interpretation and to the intellectual content of the article and provided feedback on subsequent versions of the article; Dr. Louis A. Schmidt supported data interpretation, provided intellectual support for the content of the article and critically evaluated subsequent drafts of the article; and Dr. Ryan Van Lieshout helped conceptualize the idea for the study and interpret the data, provided feedback on intellectual content and on subsequent drafts of the manuscript.

Study 4 examined whether fetal exposure to a maternal nutrition and exercise intervention lead to better emotion regulation in children at 36 months of age. Neda Mortaji helped with data collection, acquired the data, analyzed all data, interpreted findings, wrote the first draft of the manuscript and incorporated subsequent edits and revisions. Dr. John Krzeczkowski helped with data collection and provided feedback and interpretation of the data; Dr. Stephanie Atkinson contributed to data interpretation and to the intellectual content of the article and provided feedback on subsequent versions of the article; Dr. Louis A. Schmidt supported data interpretation, provided intellectual support for the content of the article and critically evaluated subsequent drafts of the article; and Dr. Ryan Van Lieshout helped conceptualize the idea for the study and interpret the data, provided feedback on intellectual content and on subsequent drafts of the manuscript.

Chapter 1: Background

1. Prevalence and origins of cognitive, emotional, and behavioural problems across the lifespan

Early brain development is crucial for shaping the cognition, behaviour, and emotions of individuals, and significantly influences one's lifelong health and success (Fitzgerald., 2022). In Canada, up to 20% of children are affected by problems of cognition, behaviour, and emotion (Frances et al., 2020). Since up to 70% of these problems have their onset in infancy or early childhood, prevention, along with early detection and intervention is critical to optimizing neurodevelopmental outcomes (Kessler., 2007).

Normal brain development is dependent on prenatal and early postnatal conditions (Dyck & Morrow., 2017). Research suggests that the first "1000 days" of life (beginning at conception) are a critically important period that sets the foundation for healthy brain development across the lifespan (Likhar et al., 2022). This period is also characterized by substantial developmental change and heightened neuroplasticity (Cusick et al., 2016). During this time, the brain is highly responsive to environmental cues that influence neural network development. Such exposures include maternal nutrition, stress, infection and the home environment, among others (Fitzgerald., 2022). Advances in neuroimaging have established that numerous mental and neurological disorders are due to altered prenatal brain development (Vasung et al., 2019). The perinatal period, and more specifically the prenatal period is therefore a key time to intervene and potentially prevent and/or reduce the impact of adverse experiences on the development of cognitive, behavioural, and emotional problems (which are more difficult and expensive to address later) (Howard et al., 2020)).

1.2 The developmental origins of health and disease (DOHaD) hypothesis

Formal recognition of DOHaD became much more widespread in the 1990s as epidemiological studies reported associations between geographic locations with high infant mortality and high adult mortality from heart disease (Mandy et al., 2018). This observation was made by Dr. David Barker, which is why the DOHaD hypothesis was often referred to as the Barker hypothesis earlier in its emergence (Wadhwa et al., 2009). From this observation, Dr. Barker defined the DOHaD hypothesis as environmental exposures during sensitive periods of fetal development can influence health and susceptibility to disease later in life (Hoffman et al., 2017). The hypothesis posits that environmental conditions such as maternal nutrition, obesity, stress, or infection can have programming effects on multiple fetal organ systems (Fitzgerald et al., 2020). However, it was later better appreciated that both adverse prenatal <u>and</u> early postnatal conditions can influence susceptibility to disease later in life.

Initially, the DOHaD field focused primarily on outcomes related to cardiovascular and metabolic health, diabetes and obesity (Heindel et al., 2015). However, the DOHaD hypothesis has now broadened to more frequently examine neurodevelopmental outcomes such as cognitive, behavioural and emotional outcomes.

The past few decades of evidence have now supported a link between perinatal exposures and child neurodevelopmental outcomes. It has been hypothesized that developmental plasticity underlies the longer-term impacts of fetal and early postnatal life exposures on brain development and its associated disorders. Developmental plasticity is the ability for a phenotype to change depending on environmental cues during sensitive periods such as the prenatal and early postnatal periods (Lea et al., 2017). The phenotypic outcomes that develop during these periods are considered to remain throughout one’s life (Monoghan et al, 2008). Therefore, adverse environmental conditions during these periods may lead to altered phenotypes and lifelong neurodevelopmental problems.

Therefore, perinatal exposures during sensitive periods of development can affect cognitive and ER development, and lead to lifelong susceptibility to problems and disease. However, although brain plasticity decreases with age and prenatal interventions may provide the best means of reducing neurodevelopmental problems, the majority of research in the DOHaD field is observational in nature. In order to unlock the clinical potential of the DOHaD hypothesis and test its scientific validity, more rigorous experimental studies in humans (i.e., RCTs) are needed.

1.3 Cognitive and Behavioural Problems and their Development

Cognition has been defined as the ability to acquire, process and store the information required to understand and effectively interact with one's environment. Cognition is a complex and multifaceted concept that is central to other processes such as behaviour and emotion regulation (Arioli et al., 2018). Cognition includes functions like attention and memory, as well as higher order mental processes referred to as executive functions (Khera & Rangasamy., 2021). Executive function is required for the cognitive control of behaviour and consists of factors such as working memory, planning, flexibility, and inhibition (Friedman et al., 2022). These skills are central to daily functioning, academic success, social relationships, and self regulation (Reilly & Downer, 2020). Behaviour is defined as observable actions one takes or a reaction in response to their environment (Jhangiani et al., 2022). Both cognitive and behavioural development are core to shaping interpersonal relationships, academic success, and subsequent mental health, and predict overall health as well including premature mortality (Pietromonco & Collins., 2018). Since the overall architecture of the brain has developed by 6 months of gestation, it is important to understand the development of cognition and behaviour prenatally so that we can determine how to prevent problems and optimize functioning (Baburamani et al., 2019).

1.3.1 Prenatal Development

The early stages of cognitive and behavioural development in the first trimester involve neural tube formation (Singh et al., 2022). The neural tube eventually forms into the brain and spinal cord which sets the foundation for processes such as neurogenesis to occur (Prado et al., 2014). Neurogenesis involves the process of cell division in the brain to lead the growth and interplay of various brain regions such as the limbic system (which includes the hippocampus, hypothalamus and amygdala), the prefrontal cortex (PFC) and cerebral cortex (Bremner et al., 2006). These brain regions begin to develop via the processes of neural proliferation, differentiation, migration and circuit formation (Hwang et al., 2019).

During the second trimester of pregnancy, a set number of neurons and glial cells then migrate to the different regions of the brain in response to chemical signals that ensure cell movement to correct locations in the brain (Molnar et al., 2015). The number of cells that migrate to each brain region influences the function, size and connectivity of the region (Belmonte-Mateos et al., 2019), and so the fewer neural cells that migrate to brain regions associated with cognition and behaviour, the more cognitive and behavioural deficits can develop (Hwang et al., 2019). Once neural cell migration is complete, brain regions begin forming neural circuits by creating synaptic connections between neural cells in order to communicate with different brain regions (Tau et al. 2010). The strength of these neural circuits is influenced by the number of neural cells at each brain region as well as the number of neural connections they form (Daught et al., 2017).

Multiple neural circuits are important to the development of normative cognitive and behavioural functioning, and they are primarily established in utero (Tau et al., 2010). First, in the second trimester, the sensory circuits between the visual and auditory cortex form in the superior temporal sulcus (Hickok et al., 2009). These circuits begin to develop and activate in the fetus in response to external stimuli such as sound and light (Fagard et al., 2018). When these circuits are activated, they are strengthened and begin to form neural circuits with other brain regions (hippocampus, amygdala, PFC, temporal lobe) important for additional cognitive functions such as memory, attention, and perception (McEwen et al., 2016). Therefore, these sensory experiences shape fetal cognitive development by strengthening sensory circuits and creating additional circuits that are needed for more complex cognitive development (Tierney et al., 2009).

Language circuits involved in the comprehension (Wernicke's area) and production (Broca's area) of language also begin to develop in the second trimester (Kunert et al., 2015). The arcuate fasciculus (bundle of nerves that goes through the frontal and temporal lobes) connects Broca's and Wernicke's areas (Catani et al., 2008). The arcuate fasciculus in the fetus is activated in response to language exposure (from the second trimester) which strengthens and matures the circuits between Broca's and Wernicke's areas (Romeo et al., 2018). This may be the reason that studies have found that fetuses who were exposed to more language in utero develop more advanced language abilities in infancy and childhood (Moon et al., 2013). Similarly, the maturation of language circuits leads to the development of additional neural circuits responsible for motor coordination and memory (Goto et al., 2022).

Lastly, the hippocampal-PFC-amygdala circuit is important for a variety of cognitive and higher-order cognitive development (i.e., problem solving, memory formation, learning, emotional processing) (Tyng et al., 2017). This circuit begins to develop in the second to third trimester and is strengthened by sensory inputs as well as maternal nutrition (Smic et al., 2021). Like other circuits, it is activated and strengthened by external inputs such as voices, sounds, and tastes (the last of which is particularly sensitive to nutritional inputs (Tau et al., 2010)).

Good maternal nutrition leads to better growth and development of these brain regions and the synaptic connections between them, and in turn strengthens the hippocampal-PFC-amygdala circuit (Zimmerman et al., 2019). Likewise, poor maternal nutrition can disrupt the development of this circuit and lead to numerous cognitive deficits (Cortés-Albornoz et al., 2021). Therefore, the development and strengthening of neural circuits involved in cognitive development can lead to the formation of additional circuits between many brain regions important to cognition (Khalil et al., 2019). In turn, the fetus develops a larger and more complex functional connectome (network of neural connections between brain regions) (Turk et al., 2019). Research has suggested that the fetal connectome can provide significant insight on the cognitive development of offspring postnatally, such that larger connectomes may lead to better cognitive development in offspring (Cao et al., 2017).

In the third trimester, the rapid development of the cerebral cortex begins which is the outermost layer of the brain, and is important for higher-order cognitive and behavioural processes such as decision making and problem solving (Vasung et al. 2019). Since the cerebral cortex consists of the frontal, parietal, occipital, and temporal lobes, its development (specifically the frontal lobe) prenatally is key to cognitive and behavioural development (Tierny et al., 2009). The frontal lobe is important to cognitive and behavioural development and is related to functions such as adaptive behaviour, social interactions, problems solving and executive functions (Rabinovici et al., 2015). Adverse prenatal exposures such as poor nutrition, stress and substance abuse can disrupt the synaptic connections within the frontal lobe and its connections with the parietal (attention and special processing), occipital (motivation and memory), and temporal lobes (language and facial processing) (Arain et al. 2013). These synaptic connections are key to integrating information between different brain regions, which is required for higher order cognitive processes (Bassi et al., 2019). Therefore, positive prenatal exposures such as healthy maternal nutrition can strengthen synaptic connections within the frontal lobe and across the other lobes in the cerebral cortex (as well as form additional connections within the cerebral cortex) (Franke et al., 2020). Research has also suggested that increased synaptic connections between the lobes can lead to better cognitive and behavioural performance later in life (Kolb et al., 2011). Therefore, it may be implied that cognitive and behavioural development begin prenatally, and set the foundation for brain development postnatally.

1.3.2 Postnatal Development

Cognitive and behavioural development is a continuous process that continues to develop from birth through adulthood, but during the first three years of life, the most rapid brain growth and development occur (Tierney et al., 2009). At this time, cognitive and behavioural development is influenced by experiences and external stimuli that form new neural connections and strengthen prior connections between brain regions (Kolb et al., 2011). Experiences such as stimulating home environments, parental support and caregiving, as well as stress, abuse and social relationships affect brain development, and can have long-term implications (Ilyka et al. 2021). Positive experiences increase neural connectivity and activation in brain regions associated with cognitive and behavioural development, and strengthen neural connections so that they become more effective and efficient (Tierney et al., 2009). Additionally, the early postnatal period is characterized by a period of synaptic pruning, where weaker neural connections are discarded, and the remaining neural connections are strengthened to facilitate the development of higher order mental processes (Cardozo et al., 2019). Therefore, providing positive and enriching prenatal and postnatal environments can ensure the proper development of cognitive and behavioural outcomes across the lifespan.

1.4 Problems with emotion regulation and its development

Emotion regulation (ER) is defined as the ability to modify one's emotions in response to ongoing demands (McRae et al, 2020) and its application has been hypothesized to occur in two ways. The first way is referred to as top-down ER, which refers to the conscious use of cognitive functions (i.e., distraction, mindfulness) and thinking to regulate emotions and physiological responses in response to a stimulus (Guendelman et al., 2017). Top-down activation of ER is often associated with the activation of brain regions such as the PFC and the anterior cingulate cortex (Chisea et al., 2013). These brain regions underlie cognitive functions such as attention and problem solving which may be involved in regulating an emotional response (Friedman et al., 2022). The second way refers to bottom-up ER, which refers to the unconscious and often immediate physiological response towards a stimulus (i.e., instant fear) (McRae et al., 2012). Bottom-up activation of ER often involves the amygdala (key brain region for emotional processing) and the hypothalamus (aids in regulating the stress response to a stimulus) (Simic et al., 2021). These regions help regulate heart rate and breathing, which are important aspects of bottom-up ER (Ikeda et al., 2017). Both top-down and bottom-up ER are often used in combination with one another, however, researchers suggest that bottom-up ER often occurs first (unconscious response to a stimulus), followed by top-down ER once the individual has had time to process the physiological response.

Historically, it was assumed that ER developed only after birth, but more contemporary evidence suggests that ER development begins in utero (Allen et al., 2015). One study found that the fetus can portray facial expressions such as disgust or sadness in response to stimuli in the second and third trimesters using 4D ultrasound technology (Abo Ellail et al., 2018). Other work suggested that the fetus can exhibit different heart rate patterns and movement in response to different stimuli (Marx et al., 2015). These studies led to the discovery and understanding that fetuses have ER abilities, and that prenatal exposures can affect fetal and later offspring ER development (Ross et al., 2015). This is not surprising since prenatal exposures have been found to affect the development of brain regions such as the amygdala and the PFC which are involved in ER development in the fetus and later in life (Pulli et al., 2019). The prenatal and postnatal development of ER will be discussed in sections 1.4.1 and 1.4.2. Problems with ER very early in life have been linked to an increased risk of substance misuse, criminal conviction, mental health problems, risk-taking behaviour and physical health problems including cardiovascular disease (Bradizza et al., 2018).

1.4.1 Prenatal Development

Similar to cognitive and behavioural development, ER begins to emerge prenatally in the first trimester through the process of neurulation which forms the neural tube to develop into the brain later (Chhetri et al., 2021). During the second trimester, processes such as neural cell proliferation, migration and synaptic connections form between key brain regions (Kolk et al., 2022). Such regions include the limbic system, PFC, insula and the anterior cingulate (Teffer et al., 2012). However, the development of ER is also dependent on a series of other processes such as the balance of neurotransmitters, epigenetic modifications of genes, and the development of the somatosensory system involved in regulating emotions (Simic et al., 2021).

Neurotransmitters such as serotonin, dopamine, GABA and glutamate are critical in preparing the brain for postnatal life (Bolneo et al., 2022). First, they aid in the development of plasticity in brain regions, allowing them to accommodate to changing experiences and environments (Egerton et al., 2020). Second, these neurotransmitters play a key role in the regulation of fetal breathing, heart rate and movement, factors that are believed to mediate ER (Sarawagi et al., 2021). Third, they support the formation of neural circuits involved in ER such as the amygdala-PFC-insula circuit that connects through the corticolimbic network (Qui et al., 2015). This circuit involves brain regions key to emotional processing and regulation, and disruptions to the neurotransmitter systems (serotonergic, noradrenergic, dopaminergic) from adverse prenatal exposures (i.e., maternal stress, poor nutrition), can alter and weaken this circuit (Godoy et al., 2018). This circuit is important for prenatal ER development as it may help the fetus regulate emotional responses from external and internal stimuli which they are able to process from the second trimester (Ross et al., 2015). Lastly, neurotransmitter system support the expression of genes involved in ER and the stress response through epigenetic processes (Sarawagi et al., 2021).

Epigenetics is the study of how external influences can affect gene expression without altering the DNA sequence (Al Aboud et al., 2022). These changes in gene expression may be caused by modifications in DNA that regulate when genes are turned “on” or “off” (Handy et al., 2011). Epigenetic modifications in response to external stimuli may play an important role in how genes are expressed and regulated, and may have a strong impact on fetal and offspring neurodevelopment (Kundakovic et al. 2017). The most studied epigenetic modifications include DNA methylation (adding or removing a methyl group from DNA or proteins) and histone modifications (modulation of chromatin structure that affect DNA processes) (Banik et al., 2017). These epigenetic modifications occur in response to prenatal exposures such as maternal nutrition or stress (Li et al., 2019). Adverse prenatal conditions have been suggested to alter DNA methylation and histone modifications and affect gene expression related to neural differentiation, synaptic plasticity, neurotransmitter signalling, and the stress response in brain regions such as the PFC and amygdala (Matosin et al., 2017). The most well studied genes affected by these epigenetic modifications are genes FK506 binding protein 5 (FKBP5) and brain-derived neurotrophic factor (BDNF) which are involved in ER (Mourtzi et al., 2021). The FKBP5 gene is involved in the regulation of the stress hormone cortisol (and the stress response system), and studies have suggested that prenatal exposures such as maternal stress or undernutrition can lead to changes in DNA methylation in this gene which can lead to a decrease in expression of the FKBP5 gene and increased cortisol signalling in the fetus which can alter the fetal stress response system both prenatally and postnatally (Zannas et al., 2016). Studies have suggested increased cortisol signalling prenatally may be associated with greater emotional reactivity later in life (McGowen et al., 2018). On the other hand, histone modifications may alter the BDNF gene (a protein important for the growth and development of neurons in the brain) in brain regions such as the hippocampus (involved in ER) (Kowianski et al., 2018). Adverse prenatal conditions may lead to changes in histone modifications that decrease levels of the BDNF gene in the hippocampal tissue, which can alter emotional responses in the fetus and later in life (Kundakovic et al., 2017). Therefore, epigenetic modifications in response to adverse prenatal exposures may be involved in the development of emotion regulation and dysregulation and lead to long lasting changes in gene expression that may affect ER (Jiang et al., 2019).

During the second and third trimesters, the development of the somatosensory system also begins, which permits the fetus to process and respond to various stimuli such as maternal touch which may optimize emotional regions of the brain such as the amygdala (emotional center of the brain) and improve the function of the stress response system (Simic et al., 2021). Non-human animal studies have suggested that maternal touch during pregnancy led to an increased number of neurons and synapses in the amygdala (which optimizes the development of the amygdala and strengthens its connections with other brain regions to further improve ER) (Stoye et al., 2020). Additionally, maternal touch led to an increase in the expression of genes such as BDNF genes involved in synaptic plasticity in the amygdala (Colucci-D'Amato et al., 2020). Synaptic plasticity in the amygdala is important for the adaptation of emotional responses to changing environments, which is a key construct of ER (Bathina et al., 2015). Lastly, maternal touch may lead to a decrease in the (hypothalamic-pituitary-adrenal) HPA axis activity and cortisol levels which can reduce the stress response and prevent hyperactivity in the amygdala (Herman et al., 2016). Therefore, positive prenatal exposures may affect the development and functioning of the amygdala and improve the stress response system, in turn optimizing ER development. However, studies also support that adverse prenatal exposures such as the emotional state of the mother can affect fetal ER and the somatosensory system by exposing the fetus to increased levels of cortisol (stress hormone) which hinders their development (Glover et al., 2015). Increased levels of cortisol can cause hyperactivity of the HPA axis system and the amygdala, leading to dysregulation in emotions (Sheng et al., 2021).

A range of other external factors also influence the development of ER prenatally, such as maternal stress, mood disorders, sub-optimal nutrition, physical inactivity, and substance misuse (Lewis et al., 2014). These maternally mediated exposures affect the development of gray matter volume in brain regions such as the PFC, anterior cingulate and insula, key regions that facilitate fetal ER, as well as its markers including heart rate variability (HRV) (Marečková et al., 2019).

HRV is a measure of fetal autonomic nervous system regulation and is one of the earliest emerging markers of later stress reactivity (Pham et al., 2021). Reduced fetal gray matter volume in these brain regions has been linked to poorer emotion regulatory capacity in infancy and early childhood (Marečková et al., 2019). Therefore, the prenatal development of ER can set the foundation for emotional processing and control after birth through these exposures and their resultant epigenetic changes (Kundakovic et al., 2017).

1.4.2 Postnatal Development

The first three postnatal years provide an important window for the continued development of ER by providing opportunities for the learning and teaching of emotional abilities to infants and children (Nelson et al., 2019). The development of ER during infancy and early childhood generally consists of several different factors. During infancy, ER is developed primarily through the quality of caregiver regulation and attachment style (Fernandes et al., 2021). Caregivers (still most frequently mothers) are the main source of emotion regulation for infants, and this is optimally accomplished by responding appropriately and sensitively to cues of distress in their infant. When caregivers effectively calm their infants, infants can develop a secure attachment style and are better able to independently regulate their emotions both during infancy, and later in life (Taipale et al., 2016).

As infants enter early childhood, the primary influences on ER development shift from caregivers to themself (Perry et al., 2018). Neuroanatomically, ER development in early childhood is characterized by the maturation of the PFC, a key brain region in shaping ER (Hodel et al., 2018). During the maturation of the PFC, functions critical to ER such as working memory, inhibition of impulsive behaviour, cognitive flexibility, and regulatory strategies such as distraction begin to emerge and contribute to ER development and optimal social interactions.

Another important influence on ER development in early childhood is socialization and modelling. As children socialize with others, they learn to respond in emotionally appropriate ways, especially if they observed positive behaviours from caregivers (Ornaghi et al., 2021).

2. Key Factors Affecting cognitive, behavioural and emotional development in offspring

2.1 Prenatal Determinants

Maternal nutrition: prenatal nutrients provide the building blocks needed for optimal brain development to occur (Kadosh et al., 2021). These include fatty acids, amino acids, vitamins, and minerals. Deficiencies and/or imbalances in these can contribute to problems with the development of the systems underlying cognition, behaviour and emotions (Cusick et al., 2016). Although every nutrient plays an important role in the developing fetal brain, a list of the crucial and well-studied nutrients will be described in this section. First, adequate maternal nutrition is required for the development of the brain's structure and its neural processes that initiate brain development (Cheatham et al., 2019). Very early in fetal brain development, nutrients such as folate are required for neural proliferation and differentiation, guiding neural tube formation - the first step in brain development (Balashova et al., 2018). Neural tube defects occurring as a result of a lack of folate, may lead to abnormalities in brain development present in conditions such as spina bifida (Greene et al., 2014). Processes such as myelination and synaptic formation require nutrients such as iron and omega-3 fatty acids respectively (Tardy et al., 2020). Iron is important for myelin development which is necessary for efficient neuronal transmission of neurons (Mills et al., 2010), and omega-3 fatty acids aid in the formation of synaptic connections between neurons of brain regions (Dyall et al., 2015). However, a combination of nutrients is required for optimal development of the structure of the brain. Adequate nutrient consumption, specifically protein intake, can determine the size and function of brain regions important for cognitive and emotional development such as the PFC and amygdala (Kadosh et al., 2021).

Maternal nutrition can also affect fetal cognitive and emotional development by influencing gene expression and epigenetic modifications that alter the expression of genes (Banik et al. 2017). Nutrients such as choline and protein can enhance gene expression and alter DNA methylation patterns of genes involved in the development of cognitive and emotional brain structures and their functions (Thorsell et al., 2016). Third, non-human animal studies have reported that poor maternal nutrition consisting of a diet high in fat and sugars have been suggested to impact neural circuitry important for cognition and ER, and lead to problems like cognitive impairments and mood disorders later in childhood. Moreover, such a diet can lead to additional problems such as inflammation and obesity (discussed later in this section) which can affect fetal cognition and ER (Parlee et al., 2014).

Maternal exercise: exercise during pregnancy can provide benefits to the fetus that may improve cognitive and emotion regulation development. The primary benefit of maternal prenatal exercise includes supporting the development of the placenta (Chae et al., 2022). The placenta is responsible for blood, oxygen and nutrient delivery to the fetus, and exercise can enhance the blood flow of oxygen and nutrients to the developing brain regions so they can optimally develop and form synaptic connections (Gaccioli et al., 2016). Another benefit of maternal exercise is that it can result in an increase in levels of neurotrophic factors in the brain such as BDNF and vascular endothelial growth factor (VEGF) (Cho et al., 2022). These neurotrophic factors support the development and survival of neurons and have been linked to improved cognitive and emotion regulation development (Sleiman et al., 2016). Lastly, exercise during pregnancy can prevent or reduce complications such as gestational diabetes mellitus

(GDM), preeclampsia, inflammation, or stress in pregnant women, which have been linked to adverse fetal cognitive and emotional development (Wang et al., 2016). However, exercise during pregnancy must be monitored and controlled by health care providers as elevated, excessive levels of exercise (e.g., intense stair running) may lead to adverse effects on the fetus, specifically later in pregnancy (Cooper et al., 2022).

Maternal inflammation: prenatal inflammation can adversely affect both maternal and fetal health. Specifically, maternal inflammation interrupts the process of neurogenesis, which involves the formation of new neurons in different regions of the brain (Kohman et al, 2013). Dysregulation of neurogenesis may lead to cognitive and emotional deficits as there are fewer neurons available (Leuner et al. 2016). Maternal inflammation can also increase oxidative stress in the fetal brain by increasing the number of reactive oxygen species molecules that harm cells in the brain and interfere with neuronal connections (Mannaerts et al., 2016). Lastly, inflammation may also alter gene expression in brain regions core to cognition and emotion regulation, thereby altering their developing size and function (Gyllenhammer et al., 2022).

Maternal gestational weight gain (GWG): excessive maternal GWG has been linked to several mechanisms underlying adverse fetal cognitive and emotional development. First, maternal obesity may lead to the dysregulation in the expression of hormones such as insulin and leptin in brain regions such as the limbic system and cortex, regions heavily involved in cognition and ER (Hasebe et al., 2021). Abnormal insulin and leptin signaling in the fetal brain may also lead to poor neuronal differentiation and development (Valleau et al., 2014). Second, maternal obesity may interfere with the development of serotonergic and dopaminergic systems that have been implicated in many neurodevelopmental disorders (Shook et al, 2020). Reduced serotonin synthesis may impact neuronal processes such as neurogenesis and neuronal migration, as well as the initial development of the central nervous system (Hwang et al., 2019). Similarly, dysregulation of the dopaminergic system can lead to altered expression and signaling of dopamine in brain regions such as the PFC and lead to reduced synaptic connections between the PFC and other regions key in cognition and ER (Hanswijk et al, 2020). Lastly, maternal obesity is characterized by chronic inflammation throughout pregnancy which can adversely affect oxidative stress, expression of pro-inflammatory cytokines and reduced neurotrophic levels in the fetal brain (Parisi et al., 2021).

Maternal infection: an infection during pregnancy may have direct and indirect effects on cognitive and ER development in the fetus. Directly, maternal infection may impair cells in brain regions and cause significant changes to the function and structure of these regions (Jash et al., 2022). Indirectly, maternal infection may lead to placental aberrations and reduce the delivery of nutrients and oxygen available to the fetal brain (Estes et al., 2016). Additionally, infection may lead to an increase in maternal inflammatory cytokines which are particles that disrupt brain cell formation (Elgueta et al., 2022).

Maternal distress: maternal distress refers to feelings of stress, depression and anxiety can alter fetal brain structure (Wu et al., 2022). Since maternal distress is characterized by elevated levels of glucocorticoids that may enter the fetal brain through the placenta, it may impact neurotransmission and cell structure of regions important to cognition and ER (Miranda et al. 2018). Additionally, maternal distress is associated with white matter changes in the fetal brain, which are important for neuronal communication between brain regions and synaptic formations (Demers et al., 2021). White matter structures begin to develop in the second trimester and the majority of its structures are developed by birth (Wilson et al., 2021). Therefore, maternal distress may compromise white matter integrity during a period where it is rapidly developing and forming connections between key cognitive and ER circuits (Martínez-García et al, 2021).

2.2 Postnatal Determinants

The postnatal environment introduces a variety of experiences and stimuli that are important for rapidly developing brain, and that can interact with postnatal factors to shape cognition and behaviour.

The home environment: the home environment provides infants and children with exposures to many factors that influence cognitive and ER development. First, the quality of caregiver relationships can directly shape ER abilities in infants and children (Karakas et al., 2019). Responsive and predictable caregivers promote the development of secure attachment styles in their children which will promote a healthy stress response (Benoit et al., 2004). Second, the availability of resources and stimulation for the child such as playing, reading, and providing a variety of toys may enable their cognitive development by forming and improving neural connections between cognitive brain regions such as the hippocampus and PFC (Gee et al, 2021).

Socioeconomic status (SES): children raised in households marked by socioeconomic disadvantage may also be at risk for poorer cognitive and ER development (Blair et al., 2016). Lower SES may influence the quality of stimulation and support available to the child (Schmidt et al, 2021), and since stimulation and support from caregivers is important for the development of cognitive-based neural circuits, lower SES may have a negative impact on cognitive development (Noble et al., 2015). Additionally, lower SES has been linked in studies with additional challenges such as abuse and familial disharmony. These exposures can negatively impact ER development by causing an overactive stress response and deficits in brain regions such as the amygdala (Johnson et al., 2016). Additionally, the chronic exposure to these challenges can lead to problems with anxiety and depression in children that may impact their ER development and abilities (Franke et al., 2014).

Child diet/breastfeeding: Breastfeeding in infancy has also been linked to cognitive and emotion regulation development in children. Breastmilk provides essential nutrients such as long-chain polyunsaturated fatty acids that are only found in breastmilk and can improve cognitive development (Krol et al., 2018). Breastfeeding may also improve emotion regulation development by promoting a secure attachment style between mother and infant and increasing hormones such as oxytocin that promote bonding necessary for secure attachments (Bigelow et al., 2022). Similar to prenatal diet, an overall healthy child diet is required to continue the development of brain regions and neuronal connections between regions key to cognition and ER (Irvine et al., 2022).

3. Modifiable lifestyle interventions and offspring cognitive and ER development

3.1 Nutrition during pregnancy

Following nutritional recommendations during pregnancy is important for both fetal and maternal health. The current nutritional recommendations for pregnant people include guidance on caloric intake, as well as that of key vitamins and minerals, macronutrients and weight gain (Jouanne et al., 2021). Since pregnancy produces extra demands on the body, it is recommended that pregnant people consume an additional 350 calories per day starting in the second trimester and increasing calories by 500 in the third trimester per fetus (Kominarek et al., 2016). Consuming a variety of vitamins and nutrients is important for optimal fetal brain development, therefore, a prenatal multivitamin supplying all key vitamins and minerals needed during pregnancy is crucial. Deficits in vitamins or minerals, or too much of certain vitamins can be harmful to fetal brain development (Mousa et al., 2019). For example, folic acid is a vitamin that is essential for the development of the fetal spine and brain. However, the recommended dosage of folic acid (600 micrograms) during pregnancy is difficult to obtain from food alone, and so a prenatal supplement is often recommended for the prevention of neural tube defects (Balashova et al., 2018). Additional vitamins that are required for a healthy pregnancy and fetus include iron (27 milligrams), calcium (1000 milligrams), iodine (220 micrograms), choline (450 milligrams), vitamin C (85 milligrams), vitamin D (600 international units) and omeg-3 fatty acids (200 milligrams) (Brown et al., 2020).

In addition to vitamins and minerals, macronutrient consumption, specifically protein intake is crucial to infant brain development during pregnancy (Mousa et al., 2019). Protein provides the amino acids that comprise fetal cells and is especially important in the second and third trimester as the fetal brain is rapidly developing (Murphy et al., 2021). Protein intake recommendations during pregnancy consist of 20-25% of caloric intake (Herring et al., 2018). It is important that a combination of micronutrients and macronutrients be consumed during pregnancy to receive the range of benefits they offer fetal brain development.

Lastly, to ensure a healthy and safe pregnancy for both the mother and the fetus, and reduce complications throughout pregnancy, appropriate GWG is recommended. the recommended GWG during pregnancy is dependent on weight prior to conception. For example, underweight woman (BMI <18.5 kg/m^2) are recommended to gain more weight during pregnancy than normal weight woman (BMI 18.5-24.9 kg/m^2), and overweight/obese woman (BMI >25 kg/m^2) are recommended to gain less weight (Sun et al., 2020). The recommended

GWG guidelines for normal weight woman are half-pound to 1 pound per week from the second trimester to the end of pregnancy (Gilmore et al., 2015). These values increase or decrease if woman are underweight or overweight/obese respectively.

3.1.2 Studies examining maternal nutrition and offspring cognitive and ER development and their limitations

Maternal nutrition and offspring cognitive and ER development have been extensively reviewed in the literature. Decades of observational studies have found links between maternal nutrient intake and cognitive and ER development. For example, higher maternal choline intake has been associated with impaired executive function, verbal and visual memory, memory and attention, lower risk of attention-deficit / hyperactivity disorder (ADHD), and better HRV from 3 months of age to 7 years of age (Boeke et al,. 2013; Pugh et al., 2016; Fuemmeler et al., 2019). Greater maternal omega-3 fatty acid intake has been associated with better problem solving and language abilities, improved planning and organization skills, and improved HRV from 2 months of age to 8 years of age (Baumann et al., 2018; Christensen et al., 2011; Jackson et al., 2018). Other studies have examined the associations between greater maternal fruit and vegetable intake during pregnancy and reduced hyperactivity and aggression, and better receptive and expressive language in children aged 2 to 7 years of age (Murphy et al., 2014; Polanska et al., 2021; Miyake et al., 2020) . In terms of macronutrient consumption during pregnancy, studies have found associations between higher maternal protein intake and language development, problem solving skills, better HRV, and less hyperactivity and aggression in 6 months olds to 3 year olds (Taylor et al., 2021; Mahmassani et al., 2022; Wang et al., 2021). However, two major limitations exist in the literature of maternal nutrition and offspring neurodevelopment. First, the majority of studies examining maternal nutrition and child neurodevelopmental outcomes have examined single nutrients (as opposed to overall diet) which is not representative of human diets. Since nutrients do not act in isolation, but synergistically, good overall diet quality provides various benefits from the consumption of different micro and macronutrients, and thus has the ability to maximize fetal and child neurodevelopmental outcomes (Cheatham et al, 2015). Additionally, overall diet quality may improve maternal health outcomes such as prevention of GDM, obesity, and hypertension (all of which adversely affect fetal neurodevelopment), while single nutrients are limited in their ability to do so (Dierlein et al., 2021). Second, most of the studies in the literature are observational in nature and limit our ability to establish causal relationships. Since diet quality is modifiable, and easily implementable during pregnancy, RCTs examining overall diet quality and offspring neurodevelopment are extensively needed to bridge the gap between the complex interactions between nutrients and their effects on fetal neurodevelopment.

3.2 Exercise during pregnancy

Exercise during pregnancy may offer multiple additive benefits to maternal and fetal health if performed safely. The current exercise guidelines recommend 150 minutes of moderate-intensity aerobic exercise weekly (Yang et al., 2019). Although walking is the safest and most recommended form of exercise, other exercises may include swimming, yoga, or activities such as gardening (Bull et al., 2022). However, less than 15% of pregnant woman follow the recommended guidelines for exercise due to the fear of exercise related complications during pregnancy (Connell et al., 2021).

Research suggests that exercise during pregnancy has not been associated with adverse pregnancy complications, rather, exercise has prevented or improved pregnancy complications such as obesity, GDM, hypertension, and fetal neurodevelopmental outcomes (Parikh et al., 2021). Exercise intensity should be reduced as pregnancy progresses, specially in the third trimester as fetal demands have increased and require greater oxygen delivery (Beetham et al., 2019). Although exercise offers numerous benefits during pregnancy, it is important to discuss exercise plans with health care professionals as there are certain contraindications to exercise such as woman with pre-eclampsia, pregnancies with more than one fetus (twins, triplets), or have placenta previa in the third trimester (Evenson et al., 2014).

3.2.1 Studies examining maternal exercise and offspring cognitive and ER development and their limitations

Research examining the effects of maternal exercise on fetal and child cognitive and ER outcomes is limited. Observational studies have reported links between women who exercise during pregnancy and child cognitive outcomes such as improved attention, working memory, executive function, and language abilities from 4-5 years of age, compared to non-exercising woman (Robinson et al., 2012; Di Liegro et al., 2019; Dalile et al., 2022). Observational studies have also reported pregnancy exercise is associated with improved emotion regulation abilities such as better self-soothing abilities, self-control, fewer negative emotions, and more positive affect in 6 month to 5 year olds compared to non exercising woman (Penner et al., 2022; Zhang et al., 2019). The majority of RCTs examining exercise and child emotion regulation utilize HRV as the only measure of ER. Two RCTs reported women who performed moderate-intensity aerobic exercise had offspring with better HRV at 1 month (May et al., 2013) and 1 year of age (May et al., 2014). However, fetal HRV can also be measured during gestation using fetal electrocardiography, and RCTs have reported improved fetal HRV from 28 to 35 weeks gestation in response to maternal exercise (Bauer et al., 2020). Nonetheless, limitations in the field of pregnancy exercise and offspring neurodevelopment still exist. First, very few RCTs have been conducted, limiting our understanding of causality. Second, the majority of studies have used only a single physiological measure to measure ER (HRV) which is not a comprehensive and recommended approach to measuring ER. Therefore, RCTs using multiple approaches to test offspring cognition and ER are still needed. Additionally, maternal exercise has not been examined in combination with other modifiable risk factors such as maternal nutrition to improve offspring neurodevelopment. Since maternal nutrition and exercise are both modifiable and easily implementable during pregnancy, it may be important to examine their synergistic benefits on offspring neurodevelopment.

3.3 Potential synergistic effect of nutrition + exercise

While observational studies examining the impact of pregnancy nutrition and exercise on child cognition and ER are extremely rare, no RCTs examining these effects exist. One observational study reported that infants who had mothers that exercised during pregnancy and took an omega-3 fatty acid supplement had better cognitive scores such as language scores at 1 and 6 months of age, compared to infants born to women who only exercised or only took an omega-3 supplement (Braarud et al., 2018).

However, the combination of good nutrition and exercise during pregnancy offers many maternal and fetal benefits. First, women are more likely to achieve the recommended GWG, and reduce the risk of pregnancy complications such as GDM, hypertension, inflammation, and obesity if they consume a healthy diet and exercise (Lewandowska et al., 2020). These complications may also lead to adverse development of the fetal brain (Zheng et al., 2019). Second, the combination of good nutrition and exercise during pregnancy may lead to better postpartum health and recovery. Pregnant people who combine a healthy diet and exercise report better mood during postpartum, such as less anxious and depressive symptoms, and return to pre-pregnancy weight faster (Evenson et al., 2014). These effects can have important implications for infant cognitive and emotional development as maternal mood disorders have been linked to poorer child cognitive and ER development during the early postnatal period (Slomian et al., 2019). Lastly, since maternal nutrition provides important nutrients required for fetal brain development, and maternal exercise improves the placental delivery of these nutrients to the fetus, the combination of nutrition and exercise ensures optimal absorption of nutrients (Sebastiani et al., 2019). Therefore, the synergistic effects of maternal nutrition and exercise throughout pregnancy can potentially create a ceiling effect, where the fetus has the most optimal prenatal conditions to grow and develop, whereas without one of these conditions the foundation for optimal fetal brain development may be comprised.

3.4 The importance of modifiable prenatal factors

Since brain plasticity decreases with age, prenatal interventions represent the most efficient and effective means by which child cognition and ER can be optimized (Oberman et al., 2013). Further, even economists have reported that investments in the development of fetal and early child outcomes are one of the most cost-effective public expenses (Bono et al., 2016). Additionally, a growing body of evidence has shown that improving prenatal factors (i.e., nutrition and exercise) during pregnancy may have protective effects against postnatal adversity (Moyer et al., 2016; Cattane et al., 2021). By optimizing fetal brain development and creating an optimal foundation for brain development postnatally, offspring may be more resilient to postnatal adversity. Longitudinal studies have also supported that improving prenatal factors such as nutrition, exercise, stress and exposure to toxins can improve cognition and ER from infancy into adolescence, suggesting the long-lasting benefits of improved prenatal conditions (Campbelle et al., 2012; Lumey et al., 2011; Eskenazi et al., 2006). In order to reduce the risk of early cognitive and ER problems, and reduce the economical costs to correct such problems, improving modifiable prenatal factors is of great importance.

3.5 Lifestyle interventions during pregnancy and their potential to improve maternal and fetal/child health

Lifestyle interventions such as nutrition and exercise interventions are ideal for optimizing child cognition and ER for several practical reasons. First, women are most motivated to make healthy changes during pregnancy than at any other time in their lives (Bagherzadeh et al., 2021). Second, this is a time when women regularly interact with healthcare providers, increasing compliance of such interventions (Sword et al., 2012). Third, women prefer lifestyle to pharmacological treatments (including herbal supplements) (Jarbol et al., 2017). Fourth, women may be more able to fully engage in interventions prenatally as opposed to after delivery (Sword et al., 2012). Fifth, significant public health infrastructure exists in Canada to deliver programming related to prenatal nutrition (Canada Prenatal Nutrition Program). Finally, cognitive and self-regulatory problems are important precursors to substance use disorders and school problems, two of parents' most significant concerns for their children (Griffen et al., 2010). However, although prenatal nutrition and exercise interventions hold immense promise for improving maternal and fetal outcomes, there are a lack of studies examining the combined effects of nutrition and exercise on fetal cognition and ER using RCTs. Since prenatal factors have shown to lead to improved cognitive and ER outcomes in children, they could provide the scope for the primary prevention or amelioration of cognitive and ER problems early in life. Additionally, investigating the impact of prenatal factors such as nutrition and exercise on cognition and ER would enable us to further test the preventative potential of the DOHaD hypothesis by examining the plasticity of brain regions and systems core to cognition and ER.

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Chapter 2: Maternal pregnancy diet, postnatal home environment and executive function and behavior in 3- to 4-y-olds (Study 1)

Study 1 Overview

Title: Maternal pregnancy diet, postnatal home environment and executive function and behavior in 3- to 4-y-olds

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Context and Implications of this study: The first study examined the effects of prenatal diet quality on Executive function (EF) and/or behavioral development in children raised in suboptimal home environments. Maternal diet quality is a modifiable risk factor during pregnancy that has not been extensively examined in relation to offspring ER and behaviour, which may limit our understanding of the preventative potential of the DOHaD hypothesis.

This was the first study to show the positive associations between a prenatal exposure (maternal diet quality) in the presence of increased postnatal adversity. We found that healthier maternal diet quality appears to potentially benefit child EF and behavioural development in children from suboptimal home environments.

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Abstract

Background: Optimal maternal nutrition during pregnancy has been linked to better cognitive and behavioral development in children. However, its influence on the effects of suboptimal postnatal exposures like reduced stimulation and support in the home is not known.

Objectives: To examine the effect of maternal pregnancy diet on executive function and/or behavioral development in children raised in suboptimal home environments.

Methods: Data were provided by 808 mother–infant dyads from the Canadian Maternal-Infant Research on Environmental Chemicals–Child Development study. Maternal pregnancy diet was self-reported using the Healthy Eating Index 2010 questionnaire. Stimulation and support in the home was assessed using the Home Observation for Measurement of the Environment (HOME) when children were 3–4 y old. Child executive function was reported by mothers at this age using the Behavior Rating Inventory of Executive Functioning–Preschool Edition, and child behavior was assessed using the Behavior Assessment System for Children–2nd Edition. We examined the interaction of maternal pregnancy diet and postnatal HOME scores on child executive function and behavior using linear regression adjusted for maternal education, postpartum depression, pre-pregnancy BMI, and smoking.

Results: Maternal pregnancy diet was associated with an increasingly positive association with child working memory (β: 0.21; 95% CI: 0.82, 3.41; *P* = 0.001), planning (β: 0.17; 95% CI: 0.38, 2.84; *P* = 0.007), and adaptability (β: –0.13; 95% CI: –1.72, –0.08; *P* = 0.032) as levels of postnatal stimulation decreased.

Conclusions: The positive association of maternal pregnancy diet quality and executive function and adaptability in 3- to 4-y-olds appeared to increase with decreasing levels of postnatal

stimulation and support. These results suggest that overall maternal pregnancy diet could be linked to better child neurodevelopment in families experiencing barriers to providing stimulation and support to children in their home.

Introduction

Difficulties in cognition and behavior affect 1 in 5 children globally (1). Executive function (EF), the processes involved in goal-targeted and purposeful behavior (2), can be an important contributor to these problems. Understanding the factors influencing EF in children is important given its role in academic functioning (3), interpersonal relations (4), and psychopathology across the life span (5, 6). Observable aspects of EF emerge in the preschool years (7) when children have to regulate emotions and attend to others (8) and are the building blocks for problem solving and decision making (9).

Adverse prenatal exposures, such as maternal infection and suboptimal nutrition, can negatively affect neurodevelopment (10, 11), whereas more favorable intrauterine conditions like good nutrition (12) and exercise (13–15) can improve these processes. Although individual nutrients (i.e., iron, zinc, folate) are important, overall high-quality diet is key to cognitive and behavioral development (16).

More than 60% of women of childbearing age in North America consume an unhealthy "Western diet" (17, 18) consisting of an excess of foods that are high in fats and sugar and low in nutrients (17). Consumption of this type of diet during pregnancy can adversely alter the fetal brain (19), including development of the hippocampus (20), a structure critical to cognitive functioning and behavioral regulation (21). Because maternal pregnancy diet is modifiable (22), improving maternal gestational diet quality could be capable of optimizing brain development and function (22).

One of the most powerful postnatal factors affecting cognitive and behavioral development is the rearing environment in the home (23–29). Stimulation and support at home provide the basis for cognitive and behavioral functioning (30) and the foundation that later environments (e.g., school) build upon (31). Home environments lacking these features can adversely affect brain regions core to healthy cognitive and behavioral functioning (23), including the prefrontal cortex (PFC) and its associated connections with the hippocampus (32). Positive and supportive experiences in the home can enable optimal EF and behavioral development and functioning (33).

Maternal diet quality during pregnancy may be one modifiable way to mitigate the adverse effects of suboptimal postnatal home environments. Proper dietary intake during pregnancy can ensure that synaptogenesis and neuronal and glial cell proliferation occur optimally during gestation (34), promote healthy neurodevelopment, and reduce the impact of postnatal adversities like deprived home environments (35). It is therefore important to examine associations between maternal diet during pregnancy and offspring cognition and behavior in home environments marked by less stimulation and support.

To our knowledge, no studies have examined how maternal pregnancy diet quality and postnatal adversity interact to influence offspring EF and behavior. As a result, it remains unclear if maternal diet quality can benefit EF and behavioral development in children who experience postnatal adversity.

Methods

Sample

Participants in this study were initially enrolled in the Canadian Maternal-Infant Research on Environmental Chemicals (MIREC) cohort, a longitudinal pregnancy cohort that recruited 2001 women from across Canada (Vancouver, Edmonton, Winnipeg, Sudbury, Toronto, Hamilton, Kingston, Ottawa, Montreal, and Halifax) before 14 wk of gestation and between 2008 and 2011. The current study used data from the MIREC–Child Development (CD Plus) cohort (a substudy of the original MIREC cohort) to assess the neurodevelopment of 808 children aged 3–4 y and who were selected to complete the Behavior Rating Inventory of Executive Functioning–Preschool Edition (BRIEF-P; a measure of child executive functioning) and the Behavior Assessment System for Children–2nd Edition (BASC-2; an assessment of emotions and behavior) (please refer to Supplemental Figure 1 for the participant flowchart). To improve efficiency and reduce costs, the MIREC-CD Plus study was restricted to the 6 recruitment sites of MIREC that had the most births: Vancouver, Toronto, Hamilton, Montreal, Kingston, and Halifax.

Mothers of singleton children aged 3–4 y, born at a gestational age >28 wk, and without major congenital anomalies or a history of convulsions or major neurologic disorders during the data collection period were invited to take part in the children's neurobehavioral assessment phase of the study.

This research was approved by Health Canada's Research Ethics Board and by ethics committees of each participating hospital. Each participant signed an informed consent form at recruitment and before the follow-up for cognitive and behavioral assessment of children.

Predictors

Maternal diet quality during pregnancy

Maternal pregnancy diet quality was defined using 2 measures. At 16–21 wk of gestation, mothers completed an FFQ (36). This semiquantitative measure assessed the frequency (daily, weekly, or monthly) and portion size (small, average, or large) intake of 46 foods across 8 subgroups (fruit, vegetables, poultry, meat, fish and alternatives, grains, dairy, and commonly consumed composite foods, i.e., desserts, pasta, pizza) (36). This FFQ was developed to obtain information about nutrients critical to a healthy pregnancy consumed in the prior month. Serving sizes for each of the 46 items were converted to servings per day. A 33% inflation factor was used for large servings and a 33% reduction factor for small servings. Serving size, gram weights, and nutrient amounts were obtained for each food item using the 2010 Canadian Nutrient File [national nutrition database supported by Health Canada (37)]. For composite foods (e.g., "pizza"), the Canadian Community Health Survey, Cycle 2.2 [a nationally representative Canadian survey on the nutrition of pregnant and nonpregnant women (38)] was used to rank the popularity and the weighted average of amounts of nutrients per serving of foods.

The validity of the FFQ was examined by administering a second FFQ to a subset of 115 participants 2 wk following administration of the first, and 24-h dietary recalls were also used. Results from Pearson product-moment correlations and Spearman rank-order correlations indicated that the FFQ was valid in assessing absolute amounts of foods (in grams) and absolute intake of nutrients (all correlations were statistically significant). Other short-form versions of the FFQ have been shown to be useful in assessing average food group intake (39), as well as an acceptable tool for assessing nutrition in large epidemiologic studies (40).

The Healthy Eating Index (HEI) 2010 used data from this FFQ to provide an estimate of overall prenatal maternal diet quality. It converted dietary intake information from the FFQ into a single score capturing overall maternal diet quality during pregnancy. The following 3 steps were carried out to convert FFQ data to HEI 2010 scores. First, for each FFQ item, a composite score was created based on the frequency and serving sizes of each food item for each participant. Second, each FFQ item was matched to the corresponding food within the Food Patterns

Equivalents Database (41). Information on sodium and fatty acids was obtained from a USDA food compositions data set. Composite FFQ scores were multiplied by each food's nutrient components to obtain food pattern scores for each participant based on the amount of each food item they consumed. Finally, this information was inputted into the HEI 2010 macros to obtain estimates of total diet quality. These macros are freely available from the Epidemiology and Genetics Research Program (42). The HEI has been found to be a reliable and valid measure of diet quality for pregnant women (43) and provides a valid means by which short-form FFQs can be converted to a single diet quality score (44).

The HEI generates 9 dietary "adequacy" components (total fruit, whole fruit, total vegetables, greens and beans, whole grains, dairy, total protein, seafood and plant proteins, and fatty acids). Higher scores for each of these components is consistent with better diet quality. The HEI also consists of 3 "moderation" dietary components (refined grains, sodium, and empty calories from fats and sugars), things that are best consumed in moderation. These moderation items are reverse scored, so that higher scores in these dietary components indicate poorer diet quality (43). The sum of the adequacy and moderation dietary components results in a single HEI score up to 100, with higher scores indicating better diet quality. This HEI total score was used to determine overall diet quality in this study. HEI scores were also categorized so that HEI scores >80 were considered "good," HEI scores <50 were considered "poor," and HEI scores between 50 and 80 were considered "needing improvement" (45).

Quality of home environment

The quality of the child's home environment was assessed when children were aged 3–4 y using the observer-rated Home Observation for Measurement of the Environment (HOME) scale. The HOME scale is the most commonly used assessment of the home environment in developmental research and is used to assess the quality of stimulation and support provided to the child in a naturalistic environment (46). It has been shown to be reliable and valid (47) and was administered by trained research staff.

Its scoring involves both observation of the home environment as well as a semi-structured interview with the mother. During the observational component of this measure, interviewers used a binary (yes/no) scale to observe *1*) the presence of stimulating resources such as books, toys, and games in the home; *2*) maternal–child interactive behaviors; and *3*) the absence of harmful aspects such as hazards. During the semistructured interview, mothers were asked to focus on a specific day of the week and recall their child's experience at home. The HOME scale consists of 45 items and took ∼1 h to administer. Total HOME scores were calculated (maximum of 55 points), with lower scores indicating less optimal home environments (48).

Child Outcomes

Child executive function (BRIEF-P)

The BRIEF-P provides a measure of EF using parental reports in children (7) and yields an internally consistent ($r = 0.80–0.90$), valid, and temporally stable score ($r = 0.90+$) for assessing EF (49, 50). The scale consists of 63 items comprising 5 subscales that are standardized across children aged 2–5 y to assess working memory (difficulties retaining information needed to complete a task), planning/organizing (difficulties preparing for future events), inhibition (difficulties with controlling impulses), shift (difficulties moving from one situation/activity to another), and emotional control (difficulties with modifying emotions) (51). Mothers were then asked to respond to each item as “never” (0), “sometimes” (1), or “often”

(2). *Higher* scores on the BRIEF-P indicate *more problems* with executive functioning (50). Given the multiple objectives and wide-ranging data collection procedures in the MIREC-CD Plus study, mothers were asked to complete only items for the BRIEF-P working memory and planning/organizing scales.

Child behavior (BASC-2)

The BASC-2 is based on a multidimensional system used to understand the behaviors and emotions of children from the perspectives of parents, teachers, and the self (52). The parent-reported preschool form of the BASC-2 was used in this study. It is a comprehensive, psychometrically sound 134- to 160-item scale that is standardized to assess child behavior at 2–5 y of age (53).

In the present study, mothers were asked to respond to each item based on a 4-point Likert scale (0 = never to 3 = almost always). The BASC-2 generates 16 scales (hyperactivity, aggression, conduct problems, anxiety, learning problems, depression, somatization, atypicality, withdrawal, attention problems, study skills, adaptability, social skills, leadership, activities of daily living, and functional communication) and 5 composite scales including adaptive skills (ability to adapt to surroundings), externalizing problems (impulsive and uncontrolled behaviors), internalizing problems (sadness and withdrawal behaviors), behavioral symptoms index (overall level of behavioral problems), and school problems (areas of attention problems and learning problems) (54), with higher scores indicating greater levels of adaptability (55).

In keeping with most previous research, T scores for each of the composite scales were used in this analysis (55). T scores indicate the distance of scores from the norm-group mean

(mean ± SD: 50 ± 10) (56). Because they capture the broadest aspects of child behavior at 3–4 y of age, we examined internalizing, externalizing, and adaptability outcomes in the present study.

Both early executive functioning and behavioral development are critical to adaptive functioning across the life span. Therefore, our primary outcome variables included both working memory and planning scales of the BRIEF-P, as well as the adaptability, internalizing, and externalizing scales of the BASC-2. Given the exploratory nature of the study, we did not adjust for multiple comparisons.

Covariates

To examine the interaction of maternal pregnancy diet quality and postnatal home environment on EF and behavior in 3- to 4-y-old children, and in order to attempt to isolate the association of these predictors individually and jointly on our outcomes, we adjusted for covariates. Our covariates were selected a priori based on previous evidence reporting consistent associations of our covariates with our predictors (home environment and prenatal diet) and offspring cognitive and behavioral outcome variables (57–60).

Maternal educational attainment

Research has shown a strong link between maternal education and the development of EF and adaptive behavioral functioning in children (61, 62). Mothers who have completed a higher level of education tend to interact more with their child (63), as well as provide more stimulating resources in the home environment (64). In addition, women with more education tend to have better dietary patterns (65). Therefore, in this study, we adjusted for self-reported maternal education (high school or less compared with postsecondary education or greater) in our statistical analyses.

Maternal postpartum depression

Studies have consistently reported that mothers who have depressive symptoms are more likely to struggle with parenting (66) and be less warm, sensitive, and supportive toward their children (67). Such exposures have been linked to poor EF development and an early onset of behavioral problems (68). Therefore, maternal depressive symptoms were adjusted for statistically in this study. It was assessed at 6 mo postpartum using the 10-item version of the Center for Epidemiological Studies–Depression (CES-D-10) scale. The CES-D-10 has been shown to be both reliable and valid (68). Mothers were asked to rate any depressive symptoms experienced the previous week on a 4-point scale (1 = rarely to 4 = all of the time). A score of 10 or higher on the scale indicates a possible presence of major depressive disorder symptoms (69).

Maternal prepregnancy BMI

Maternal prepregnancy BMI can affect fetal neurodevelopment (70), as well as the behavioral and neurocognitive development of the fetus (71–73), and has been linked to poorer pregnancy diet quality (74). Maternal prepregnancy BMI (normal: BMI 18.5 to <25 compared with overweight/obese: BMI >25) was obtained by dividing self-reported prepregnancy weight (kg) by height (m^2) measured at the first-trimester study visit.

Maternal smoking during pregnancy

Extensive research also supports links between maternal prenatal smoking and altered child neurocognitive and neurobehavioral development (75), and maternal prenatal smoking has been linked to maternal pregnancy diet (76) and home environment (60). Self-reported maternal prenatal smoking patterns were obtained at the third prenatal visit by asking mothers if they "never smoked," "formerly smoked" (quit smoking before knowledge of pregnancy), or "quit during pregnancy" (smoked during part of pregnancy but quit smoking at some point during pregnancy).

Statistical analyses

The characteristics of the study sample were described using means and SDs for continuous variables and frequencies for categorical variables. Multiple linear regression models were used to assess the relation between our 2 predictors and 5 child outcomes. We did not observe any evidence of violations to the assumptions of multiple linear regression models [i.e., all data were visually inspected for normality, and we statistically tested for this using the Shapiro–Wilk test ($P > 0.05$), data were independent, there was no evidence of heteroscedasticity, and so we assumed and examined linear relations]. These models were then adjusted for our covariates (maternal educational attainment, maternal depression at 6 mo, maternal prepregnancy BMI, and maternal prenatal smoking). The presence of multicollinearity was examined in our adjusted models using variance inflation factors (VIFs). All VIF values were <10; therefore, no multicollinearity was observed. Standardized βs were reported and show how many SDs the outcome variable changes per SD increase in a predictor.

Diet and home variables were centered at the mean prior to the creation of our interaction variable (mean-centered diet quality score was multiplied by mean-centered HOME scale scores). Also, to better illustrate the impact of maternal pregnancy diet quality in home environments marked by less or more stimulation and/or support, we dichotomized HOME scores at the median for the current sample.

Listwise deletion was used to account for any missing data. A missing values analysis was conducted on predictor, outcome, and covariate variables and revealed that the Little test of missing completely at random was not significant ($\chi^2 = 134.9$, $df = 123$, $P = 0.218$), suggesting data are missing completely at random. All analyses were performed using SPSS statistics 23 (SPSS, Inc.) and were 2-tailed with significance levels set at $P < 0.05$.

Results

The characteristics of the MIREC-CD Plus sample involved in the present study are presented in Table 1. The mean ± SD age of mothers was 32.8 ± 4.8 y at enrollment, and 57.4% had a BMI in the normal range at the first pregnancy study visit. Most mothers had completed college or above (89.3%). The majority of women were married/common law (96%) and born in Canada (81.7%). Maternal characteristics from our sample were comparable to maternal characteristics from other large, representative Canadian pregnancy cohorts (77). HOME total scale scores ranged from 27 to 55. The mean ± SD total HEI score was 72.2 ± 7.9 (minimum: 40.7; maximum: 92.7), with the majority of women consuming diets that need improvement (79%), 7% of women consuming poor diets, and 14% of women consuming good diets. HEI data from our sample are comparable to HEI data in other Canadian samples of pregnant women (78). However, the total HEI score in our study was moderately higher than mean HEI scores among current nonpregnant Canadian adults (mean: 50.9) (79), but this may be due to the fact that pregnant women consume healthier overall diets compared with nonpregnant women (80). Infants were born at a mean ± SD of 38.9 ± 1.7 wk of gestation and provided EF and behavioral data at 3.4 ± 0.31 y. Most infants were breastfed for 6 mo or less (83.3%). Most of the mothers in our sample used a multivitamin supplement during pregnancy (86%). Women participating in the MIREC-CD Plus subsample differed from the women participating in the original MIREC study on maternal age, total HEI score, gestational age of child (weeks), birthweight of child (g), education level, and pregnancy smoking status.

Table 1: Child and Maternal Characteristics of MIREC-CD Plus Sample (n=808) vs. original MIREC cohort (n=1983)

	MIREC CD-Plus (n=808)[3]	Original MIREC (n=1983)[4]	
	M± SD	**M±SD**	***P*** [2]
Children:			
Birthweight (g)	3442.1±529.9	3384.9±649.10	0.03
Gestational age (weeks)	38.9±1.7	38.0±4.62	<0.01
Mothers:			
Maternal age (years)	32.8±4.8	31.8±5.24	<0.01
Maternal depression (CES-D-10 score)	5.8±3.7	[1]	
HOME Total Score	47.3±4.3	[1]	
HEI Total Score	72.2±7.9	71.4±8.82	0.01
	n (%)	**n (%)**	***P*** [2]
Maternal Education			<0.01
Less than high school	8 (1)	39 (3.3)	
High school graduate	75 (9.2)	158 (13.4)	
College or trade school graduate	172 (21.2)	295 (25.1)	
University graduate or above	551 (68.1)	683 (58.1)	
Marital Status			0.62
Married/common-law	777 (96)	1120 (95.3)	
Divorced/separated/single	30 (3.7)	54 (4.6)	
Country of Birth			0.64
Canada	661 (81.7)	951 (80.9)	
Outside of Canada	147 (18.2)	224 (19.1)	
Maternal BMI (kg/m^2)			0.34
Normal	464 (57.4)	642 (54.6)	
Overweight	153 (18.9)	251 (21.4)	
Obese	120 (14.8)	97 (8.3)	
Maternal Pregnancy Smoking			<0.01
Never	529 (65.4)	673 (57.3)	
Former	212 (26.2)	332 (28.3)	
Quit during pregnancy	67 (8.3)	170 (14.5)	
Maternal HEI Score (Diet Quality)			0.07
Poor	58 (7)	107 (10.3)	
Needs improvement	622 (79)	780 (75.1)	
High	111 (14)	151 (14.6)	
Maternal Multivitamin Usage			0.15
Yes	694 (86)	1037 (88.3)	
No	113 (14)	138 (11.7)	
Duration of Breastfeeding			
≤than 6 months	457 (83.3)	[1]	
>than 6 months	91 (16.7)	[1]	

[1]=The CES-D, HOME score and duration of breastfeeding measures were not obtained as part of the original MIREC sample

[2]= Differences between categorical variables between each cohort were examined using chi-squared tests. Differences in continuous variables were tested using independent samples t-tests. The MIREC CD-Plus subsample is independent of the Original MIREC cohort

[3]=For the MIREC CD-Plus sample, maternal education is only reported for 806 women, marital status is reported for 807 women, BMI is reported for 737 women, maternal HEI score is reported for 791 women, multivitamin usage is reported for 807 women, and breastfeeding duration is reported for 548 women.

[4]=For the Original MIREC sample, maternal education is only reported for 1175 women, marital status is reported for 1174 women, country of birth is reported for 1175 women, BMI is reported for 990 women, maternal smoking is reported for 1175 women, maternal HEI score is reported for 1038 women and multivitamin usage is reported for 1175 women.

BMI= Body mass index
CES-D-10= Center for Epidemiologic Studies Depression Scale-10 Item Version
g= grams
HEI, Healthy Eating Index
HOME= Home Observation for the Measurement of the Environment Scale
M= mean
SD= standard deviation

A statistically significant interaction was observed between maternal diet quality during pregnancy and HOME scale scores on the working memory (β: 0.13; 95% CI: 0.52, 2.32; $P < 0.001$) and planning (β: 0.11; 95% CI: 0.27, 2.00; $P = 0.006$) scales of the BRIEF-P (Table 2). There was also a statistically significant interaction between maternal diet quality and HOME scores on the child adaptability composite of the BASC-2 (β: –0.14; 95% CI: –1.38, –0.13; $P < 0.001$) but not for internalizing or externalizing problems (Table 2).

Table 2: Unadjusted associations between maternal pregnancy diet, HOME scores, EF (BRIEF-P) and behavior (BASC-2) outcomes in children at 3-4 years of age[1].

BRIEF-P (n=698)	**R^2**	**Standardized β**	**95% CI**	***P***
Working Memory	0.08			
Total HOME scores		-0.23	(-0.71, -0.31)	<0.001
Total diet quality score (HEI)		0.01	(-0.11, 0.12)	0.829
Diet x Home		0.13	(0.52, 2.32)	<0.001
Planning (n=699)	0.06			
Total HOME scores		-0.21	(-0.64, -0.24)	<0.001
Total diet quality score (HEI)		-0.01	(-0.12, 0.09)	0.944
Diet x Home		0.11	(0.27, 2.00)	0.006
BASC-2				
Internalizing (n=693)	0.01			
Total HOME scores		-0.06	(-0.29, 0.04)	0.145

Total diet quality score (HEI)		0.07	(-0.01, 0.16)	0.100
Diet x Home		-0.05	(-1.15, 0.29)	0.242
Externalizing (n=699)	0.06			
Total HOME scores		-0.24	(-0.60, -0.29)	<0.001
Total diet quality score (HEI)		0.03	(-0.06, 0.11)	0.539
Diet x Home		0.07	(-0.13, 1.23)	0.115
Adaptability (n=700)	0.03			
Total HOME scores		0.07	(0.26, 0.54)	0.088
Total diet quality score (HEI)		0.01	(-0.02, 0.13)	0.757
Diet x Home		-0.14	(-1.38, -0.13)	<0.001

[1]= Linear regression model was used to analyze the data
BASC-2, Behavioral Assessment of Children- 2nd Edition
BRIEF-P, Behavior Rating Inventory of Executive Function- Preschool version
EF, Executive function
HEI, Healthy Eating Index
HOME, Home Observation Measurement of the Environment

After adjusting for maternal BMI, education, depression, and smoking, statistically significant interactions remained between overall maternal diet quality during pregnancy and HOME scale scores on child working memory (β: 0.21; 95% CI: 0.82, 3.41; *P* < 0.001) and planning (β: 0.17; 95% CI: 0.38, 2.84; *P* = 0.007) of the BRIEF-P, as well as adaptability (β: –0.13; 95% CI: –1.72, –0.08; *P* = 0.032) on the BASC-2. These results are summarized in Table 3. The covariates that accounted for significant variance in the adjusted model were maternal postpartum depression (statistically significant for all 3 outcomes) and maternal smoking during pregnancy (statistically significant for the BASC-2 adaptability outcome) (Supplemental Table 1).

Table 3: Adjusted associations between maternal pregnancy diet quality, HOME scores, EF (BRIEF-P) and behavior (BASC-2) outcomes in children at 3-4 years of age[1]

BRIEF-P (n=698)	**R^2**	**Standardized β**	**95% CI**	***P***
Working Memory Scale	0.12			
Total HOME scores		-0.18	(-0.77, -0.04)	0.006
Total diet quality scores (HEI)		0.12	(-0.02, 0.34)	0.064
Diet x Home		0.21	(0.82, 3.41)	0.001
Planning Scale (n=699)	0.10			
Total HOME scores		-0.16	(-0.68, -0.38)	0.015

Total diet quality scores (HEI)		0.12	(-0.02, 0.32)	0.060
Diet x Home		0.17	(0.38, 2.84)	0.007
BASC-2				
Adaptability Composite (n=700)	0.10			
Total HOME scores		0.17	(0.08, 0.51)	0.008
Total diet quality scores (HEI)		0.07	(-0.05, 0.18)	0.277
Diet x Home		-0.13	(-1.72, -0.08)	0.032

[1]=Multiple linear regression models are adjusted for: maternal BMI, years of education, depression at 6-months and prenatal smoking.

BASC-2, Behavioral Assessment of Children- 2nd Edition
BRIEF-P, Behavior Rating Inventory of Executive Function- Preschool version
EF, Executive function
HEI, Healthy Eating Index
HOME, Home Observation Measurement of the Environment

To better understand the impact of maternal pregnancy diet quality in home environments marked by less or more stimulation and/or support, we dichotomized HOME scores at the median for the current sample. For each of the statistically significant interactions noted, associations between prenatal maternal diet quality and child EF and behavior scores were examined in less (below median split) or more (above median split) stimulating/supportive home environments (Supplemental Figure 2).

These analyses suggest that increased prenatal maternal diet quality in our sample was associated with better working memory (β: –0.17; 95% CI: –0.57, –0.10; *P* = 0.007), planning (β: –0.09; 95% CI: –0.48, –0.08; *P* = 0.006), and adaptability (β: 0.18; 95% CI: 0.01, 0.35; *P* = 0.044) in less stimulating home environments. In more stimulating home environments, associations between pregnancy diet quality in mothers and working memory (β: 0.06; 95% CI: –0.07, 0.28; *P* = 0.173), planning (β: 0.02; 95% CI: –0.13, 0.24; *P* = 0.452), or adaptability (β: –0.06; 95% CI: –0.19, 0.07; *P* = 0.345) were not statistically significant.

Although not as consistently linked to our predictors and outcomes in the literature as our a priori covariates, we did conduct a series of post hoc sensitivity analyses to examine potential associations with other variables of interest. Maternal multivitamin usage, exclusive breastfeeding duration, maternal age, marital status, gestational age, and birthweight were added individually to our adjusted models to avoid overfitting our data. However, the results of our interactions were unchanged when these variables were examined. Finally, we also examined if diet quality moderated the links between home environment and our outcomes in children, as well as links between home environment and each of our outcomes in children at both high and low levels of diet quality (assessed by a median split of the data set). Home environment was statistically significantly associated with each of our outcome variables at both high and low levels of diet quality (Supplemental Figure 2).

Discussion

This study used data from a large Canadian birth cohort to investigate whether maternal pregnancy diet quality moderated the association between postnatal caregiving environment and offspring executive function and behavior in 3- to 4-y-old children. Our findings suggest that associations between better overall diet quality during pregnancy and offspring working memory, planning, and adaptability are stronger as stimulation in the home decreases. These findings raise the possibility that interventions aimed at optimizing pregnancy diet could be associated with improved offspring executive function and behavior in those at higher risk (i.e., less optimal home environments), in developed countries at least.

Previous studies have examined the joint effects of prenatal exposures and postnatal adversity on child neurodevelopment [e.g., Nomura et al. (81) and Ezpeleta et al. (82)], but these studies have generally reported cumulative risk effects. Indeed, Nomura et al. (81) reported that in 212 preschool children, the joint effect of maternal prenatal gestational diabetes mellitus (GDM) and low socioeconomic status postnatally on child attention-deficit/hyperactivity disorder at 6 y of age was greater than in those with GDM and less socioeconomic disadvantage. However, the findings presented here show not only that an absence of gestational adversity (poorer diet) is ideal but that the presence of better diet may actually be associated with more benefit in increasingly poor conditions. To our knowledge, this is the first study to show the positive associations between a prenatal exposure in the presence of increased postnatal adversity, suggesting that healthier prenatal diet quality could have the potential to benefit children from suboptimal home environments, one of the best validated predictors of poor school and behavioral performance in children.

Working memory and planning are the aspects of executive functioning that require the ability to hold onto information during a task and the prediction of future tasks/events, respectively (82). Adaptability, on the other hand, is a behavioral regulatory skill that requires the ability to adapt to changing environmental and socioemotional conditions (83). Despite different definitions, these skills share common neural underpinnings and rely largely on optimal functioning within the PFC, as well as its connections to subcortical areas such as the hippocampus (84, 85). It has been established that the hippocampal-PFC circuit is involved in working memory (86), planning (87), and adaptability/flexibility skills (88). This circuit supports cognition and behavior by allowing information to be relayed bidirectionally between these coactivated brain regions (85, 89). Therefore, optimal development of the foundations for this circuit during the prenatal period could be one mechanism by which optimal pregnancy diet can buffer associations between less stimulating postnatal home environments and child executive function and behavior.

Prenatal maternal diet quality is important for fetal neurodevelopment, and evidence suggests that it can adversely affect the development of the hippocampus and its associated connections (90). The hippocampus is a region that is sensitive to nutritional insults and undergoes rapid development prenatally (91, 92). Poorer prenatal nutrition has been linked to modified gene expression of genes critical for hippocampal development, function, and volume (93). Furthermore, synapses in the hippocampus of individuals exposed to poorer prenatal diets exhibit weaker connectivity with the PFC postnatally (94). Thomas et al. (95) have reported that provision of a combination of choline and DHA to female rats during gestation resulted in pups with significantly higher numbers of neurons in the hippocampus compared with a control group who did not receive the nutritional supplement or who received only a single nutrient supplement. Therefore, optimal prenatal development of the PFC-hippocampal circuit may depend on the synergistic effect of exposure to multiple nutrients (as might be present in good overall diet). As a result, good prenatal diet may play a role in altering hippocampal-PFC circuitry, which could result in improvements in cognitive and behavioral deficits, including working memory, cognitive flexibility, adaptability, emotion regulation, and planning (96).

Regardless, it is important that our results suggest that better pregnancy diet quality may be associated with beneficial effects in families and children who may be more vulnerable to problems with cognition and behavior be replicated given the massive potential public health potential of these findings. We should also note that we did not observe associations between maternal diet quality and behavior (internalizing and externalizing) problems in offspring at ages 3–4 y. This may be explained by a lower sensitivity to behavioral vulnerabilities in offspring at this age. The BASC-2 could also lack the sensitivity needed to detect these interactions. However, reassessment of behavioral outcomes later in life may demonstrate a different finding. Finally, because children exposed to poorer home environments appear to exhibit problems with executive function, this may increase the risk of emotional and behavioral outcomes later in life.

However, it is important to view the results of this work with the following limitations in mind. First, only the home environment was used as a marker of postnatal adversity in this study. Although there are other forms of adversity, we chose home environment because it is one of the best understood factors affecting child EF and behavioral development (97). However, given its correlation with other forms of adversity (91), it may be a reasonable proxy for this construct as a whole. Another limitation is that we did not have a measure of children's postnatal nutrition, which can affect brain development postnatally. However, other groups [e.g., Jacka et al. (98)] have reported that maternal gestational diet can predict behavioral and emotional problems in offspring independent of postnatal child diet. Third, the study used a short-form (46-item) version of the FFQ to estimate overall dietary intake, which may have limited the extent of our dietary assessment. Although other short-form versions of the FFQ (i.e., 52-item) are validated measures of dietary intake (39), future studies could use more comprehensive versions of the FFQ or other measures of pregnancy diet. Fourth, although we did adjust for maternal education, this is not likely to be able to completely control for the impact of maternal EF. Fifth, given that this was an exploratory study, future studies that include more diverse samples of mother–child dyads are needed. Sixth, although our study adjusted for variables with associations between each of our covariates and our child outcome variables, future studies could examine additional covariates that may influence the results. Last, our findings require replication before informing public health efforts because our (Canadian) sample appeared well educated and potentially well supported. For context, we compared our demographics to data reported by Statistics Canada (99) on mother and childbirth outcomes in 2019. The average age of mothers at birth was 30.7 years, 62% of mothers were married, 35% of mothers had a university degree, average birthweight of infants was 3315 g, and 91% of infants were born at gestational ages 37–41 wk.

As a result, the present results may only be generalizable to similar groups, namely those in Western nations, and mothers who may be relatively less socioeconomically disadvantaged. Confirmation of these findings in more diverse areas and samples is required to assess the full potential for pregnancy diet to improve executive function and behavior, particularly in more vulnerable families.

In this study, we used data from a large Canadian cohort to show that better maternal pregnancy diet quality may be associated with better working memory, planning, and adaptability in children, an association that was stronger with decreasing levels of stimulation and support present in the home. Because pregnancy diet is potentially modifiable, public health has the mandate and capacity to introduce broad and targeted interventions, and given that women are more motivated to make healthy changes during pregnancy than at any other time in their lives, improving maternal diet quality during pregnancy could represent an important potential future means by which public health units in Western countries could positively affect child neurodevelopment, particularly for families that face challenges to providing optimally stimulating home environments for their children.

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Chapter 3: Early Neurodevelopment in the Offspring of Women Enrolled in a Randomized Controlled Trial Assessing the Effectiveness of a Nutrition + Exercise Intervention for Optimizing Gestational Weight Gain During Pregnancy (Study 2)

Study 2 Overview

Title: Early Neurodevelopment in the Offspring of Women Enrolled in a Randomized Controlled Trial Assessing the Effectiveness of a Nutrition + Exercise Intervention for Optimizing Gestational Weight Gain During Pregnancy

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Context and Implications of this study: The second study examined whether fetal exposure to the Be Healthy in Pregnancy (BHIP) nutrition+exercise intervention lead to better cognition, physical, communication, social/emotional, and adaptive functioning at 12 months of age. We found that using an experimental approach, the BHIP maternal nutrition+exercise intervention improved expressive language and general adaptive functioning, but not cognitive, receptive language, motor, or socioemotional functioning in infants at 12 months of age. Although this is the first study to examine the effects of a combined nutrition and exercise intervention during pregnancy on offspring cognition, further research is needed to determine the clinical utility of nutrition+exercise interventions for optimizing infant neurodevelopment.

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Abstract

Experimental data on the effects of lifestyle interventions on fetal neurodevelopment in humans remain scarce. This study assessed the impact of a pregnancy nutrition+exercise intervention on offspring neurodevelopment at 12 months of age. The Be Healthy in Pregnancy (BHIP) randomized controlled trial (RCT) randomly assigned pregnant persons with stratification by site and body mass index (BMI) to bi-weekly nutrition counselling and high dairy protein diet, walking goal of 10,000 steps/day plus usual prenatal care (UPC; intervention group) or UPC alone (control group). This study examined a subset of these mothers (>18 years, singleton pregnancy, BMI<40 kg/m^2, and enrolled by ≤12 weeks gestation) and their infants (intervention= 42, control= 32), assessing cognition, language, motor, social-emotional and adaptive functioning at 12 months using the *Bayley Scales of Infant and Toddler Developmental* third edition (BSID-III). We also examined if maternal factors (pre-pregnancy BMI, gestational weight gain (GWG)) moderated associations. Expressive language (MD=9.62, 95% CI=(9.05-10.18), p= 0.03, $\eta^2 p=0.07$) and general adaptive composite (GAC) scores (MD=103.97, 95% CI=(100.31-107.63), p=0.04, $\eta^2 p=0.06$) were higher in infants of mothers in the intervention group. Effect sizes were medium. However, mean cognitive, receptive language, motor, and social-emotional scale scores did not differ between groups. A structured and monitored nutrition+exercise intervention during pregnancy led to improved expressive language and general adaptive behaviour in 12-month-olds, but not cognitive, receptive language, motor, or socioemotional functioning. While these experimental data are promising, further research is needed to determine the clinical utility of nutrition+exercise interventions for optimizing infant neurodevelopment.

Keywords: cognitive development, pregnancy nutrition, fetal development, pregnancy exercise, lifestyle intervention, neurodevelopment

Clinical Trial Registration (if any): The analyses presented here were preregistered at ClinicalTrials.gov, NCT01689961 on September 21, 2012. The preregistration is available at the following URL: Be Healthy in Pregnancy (BHIP) With Nutrition and Exercise - Full Text View - ClinicalTrials.gov

Introduction

Optimal early brain development is vital to health and success in life[1]. Problems with neurodevelopment affect up to 20% of children[2] and portend some of the most chronic and costly problems facing society today[3]. However, the plasticity of the brain during gestation affords a tremendous opportunity for early intervention to optimize neurodevelopment and improve a wide range of outcomes across the lifespan[4].

Prenatal nutrients provide the building blocks for neuronal proliferation, patterning and function, and neurotransmitter metabolism in the brain[5]. Research from observational studies of maternal nutritional status has long supported a link between maternal nutrient deficiencies and reduced cognitive functioning in offspring[6-9]. The majority of RCTs that have examined the impact of maternal nutrient supplementation in western countries on children's cognitive functioning have supplemented individual nutrients and found very few positive effects[10]. Since human diets contain a variety of nutrients, examining the impact of overall diet could represent a more promising approach to optimizing neurodevelopment[11]. One observational study of the offspring of pregnant persons who had five or more nutrients supplemented had better cognition than when single nutrients were supplemented alone[12]. Another observational report supported the importance of choline, Docosahexaenoic acid (DHA), and uridine synergism in the support of plasticity in the brain[13]. Since nutrients work in a synergistic manner to benefit the fetus[14], lifestyle interventions that attempt to optimize overall diet may represent the best chance to optimize offspring cognition.

Exercise during pregnancy may also positively influence fetal brain development[15]. However, studies examining associations between maternal exercise during pregnancy and offspring cognitive function are rare. In a series of three observational studies, Clapp and colleagues compared the offspring of pregnant persons who had been active prior to pregnancy and then reduced their level of exercise during gestation, and a group who remained active[16-18]. They found that participants who remained active had infants with improved early motor skills at one year of age and improved general intelligence/oral language skills at five years of age. In another observational study, Jukic and colleagues examined the effects of exercise during pregnancy on language and IQ at 15 months and eight years of age in children living in the United Kingdom. Exercise during pregnancy was associated with an increased likelihood of higher language scores at 15 months of age but not at eight years of age[19]. Lastly, in two small RCTs, pregnant persons who exercised during pregnancy had infants with higher heart rate variability[20], and infants with superior auditory memory at 8-12 days of age compared to non-exercising women[21]. Although these studies support the potential beneficial effects of pregnancy exercise on offspring neurodevelopment, existing RCTs are small, contain only very young infants, and assess the effects of exercise on individual aspects of neurodevelopment.

Despite their potential, there appear to be no experimental human studies that have tested the effects of a combined diet and exercise intervention on offspring neurodevelopment. Since lifestyle interventions are acceptable to the majority of pregnant persons, if they can improve offspring neurodevelopment, they could have significant clinical and population health implications. Given this background, the present study followed the offspring of pregnant persons enrolled in an RCT of a nutrition and exercise intervention to examine its impact on offspring neurodevelopment at 12 months of age.

Method

Trial Design and Procedures

This study was a follow-up of the 12 month old offspring of mothers enrolled in the original BHIP RCT[22] for which the primary objective was to determine if introducing a nutrition and exercise program (intervention group) in early pregnancy plus usual prenatal care (UPC) increased the likelihood of attaining gestational weight gain within the Institute of Medicine guidelines[22] more than UPC alone (control group) In the original BHIP RCT, pregnant persons (n=241) living in Hamilton, Ontario area were recruited at 12-17 weeks gestation, and randomized to intervention or control groups in a 1:1 allocation ratio (by a research assistant) after informed consent was obtained with stratification by pre-pregnancy BMI category (i.e., normal (BMI=18.50-24.99), overweight (BMI=25.00-29.99) and obese (BMI>30)) and study site. Ethical approval was granted by the Hamilton Integrated Research Ethics Board at McMaster University (REB Project#12-469) and Joseph Brant Hospital, Burlington (JBH 000-018-14) in Ontario, Canada. The trial was registered at www.clinicaltrials.gov (NCT01689961).

During the first study visit (occurring at 12-17 weeks gestation), participant eligibility was confirmed and baseline data were collected. Block randomization to the two study arms was conducted at the second visit to the study centre and was stratified by study site and BMI category as detailed previously[22]. The study was open-label with blinded endpoints due to the nature of the intervention[22], therefore, participants were aware of their group status but research personnel and outcome analysists were blinded to group status. Analyses were performed on an intention-to-treat basis.

Participants

Study recruitment for the original BHIP RCT took place from January 2013 to April 2018. Follow-up of mothers and their infants continued until 6 months after delivery and was completed in March 2019. For the present study, pregnant persons recruited at the McMaster site were informed of the 12-month follow-up study at their 6-month visit. Participants (n=113) who signed consent to contact forms received a follow-up phone call that outlined study guidelines and expectations. Of the 113 participants who were eligible and consented to the neurodevelopmental follow-up study, 39 participants were lost to follow-up (see Figure 1); 74 participants were eligible and agreed to participate at 12 months of age. The study took place at McMaster University[22-23].

Inclusion Criteria: Healthy pregnant persons >18 years old with singleton pregnancies, pre-pregnancy BMI<40 kg/m^2, ≤12 weeks gestation at enrollment, approval of primary health care provider to participate, and the ability to understand English and provide informed consent.

Exclusion Criteria: Contraindications to exercise, significant heart, kidney, or liver disease, refusal to consume dairy products, pre-existing diabetes mellitus, smoking, or a baseline score ≥12 on the Edinburgh Postnatal Depression Scale (EPDS) at recruitment.

Intervention

Individuals in the intervention group received usual prenatal care (UPC) from their healthcare providers plus the BHIP nutrition+exercise intervention. Usual prenatal care in Ontario consists of universally available healthcare, and routine prenatal visits with a healthcare provider every one to four weeks (depending on the stage of pregnancy). The nutritional component of the intervention was comprised of an individualized nutrition plan with a high protein intake (~25% of energy needs) primarily provided by dairy products. Participants visited the study site biweekly to receive their dairy products and see the study nutritionist, who provided them with strategies to reach their nutritional goals.

The exercise component of the intervention consisted of a controlled walking program, starting at 25 minutes 3-4 times per week, and increasing in duration by 2 minutes per session to a maximum of 40 minutes daily until delivery. In addition, participants maintained 10,000 steps per day, using a pedometer and exercise logs to track their progress each day.

Those in the intervention group were to complete the intervention from enrolment during early pregnancy (<12 weeks gestation) and throughout gestation. Additional information on the nutritional and exercise components of the intervention are reported by Perreault and colleagues[22].

Participants randomized to the control group received UPC from their health care practitioner(s) plus the provision of the most recent guidance on pregnancy nutrition from Health Canada[24]. The effectiveness of this nutrition+exercise intervention was assessed on the cognitive development of 12-month-old infants born to women in the study.

Outcome Measure: Bayley Scales of Infant and Toddler Development-3rd Edition

The BSID-III is the most widely used measure of cognition in infants and children aged 0-42 months and a common assessment of early child development[25]. The BSID-III was administered by two trained psychometrists blind to offspring group status.

The BSID-III generates scores for five major areas of development: cognition, language (receptive and expressive), motor (fine and gross motor), social-emotional functioning, and adaptive behavior (which utilizes parent reports of 10 skills: communication, community use, leisure, self-care, pre-academic, social, health and safety, self direction, home living, and motor function). Scores for these 10 skills are then combined to form a GAC score. Higher scores on all BSID-III scales are indicative of better performance.

In keeping with previous studies[26], we used scaled scores in our statistical analyses. The advantages of scaled scores are that they provide greater accuracy by comparing scores of children of the same age group, which can enhance clinical utility of the measure. Scaled scores range from 1-19, with a mean of 10 and standard deviation of 3[27]. However, GAC scores are only reported as composite scores, and these scores range from 40-160, with a mean of 100 and standard deviation of 15[27].

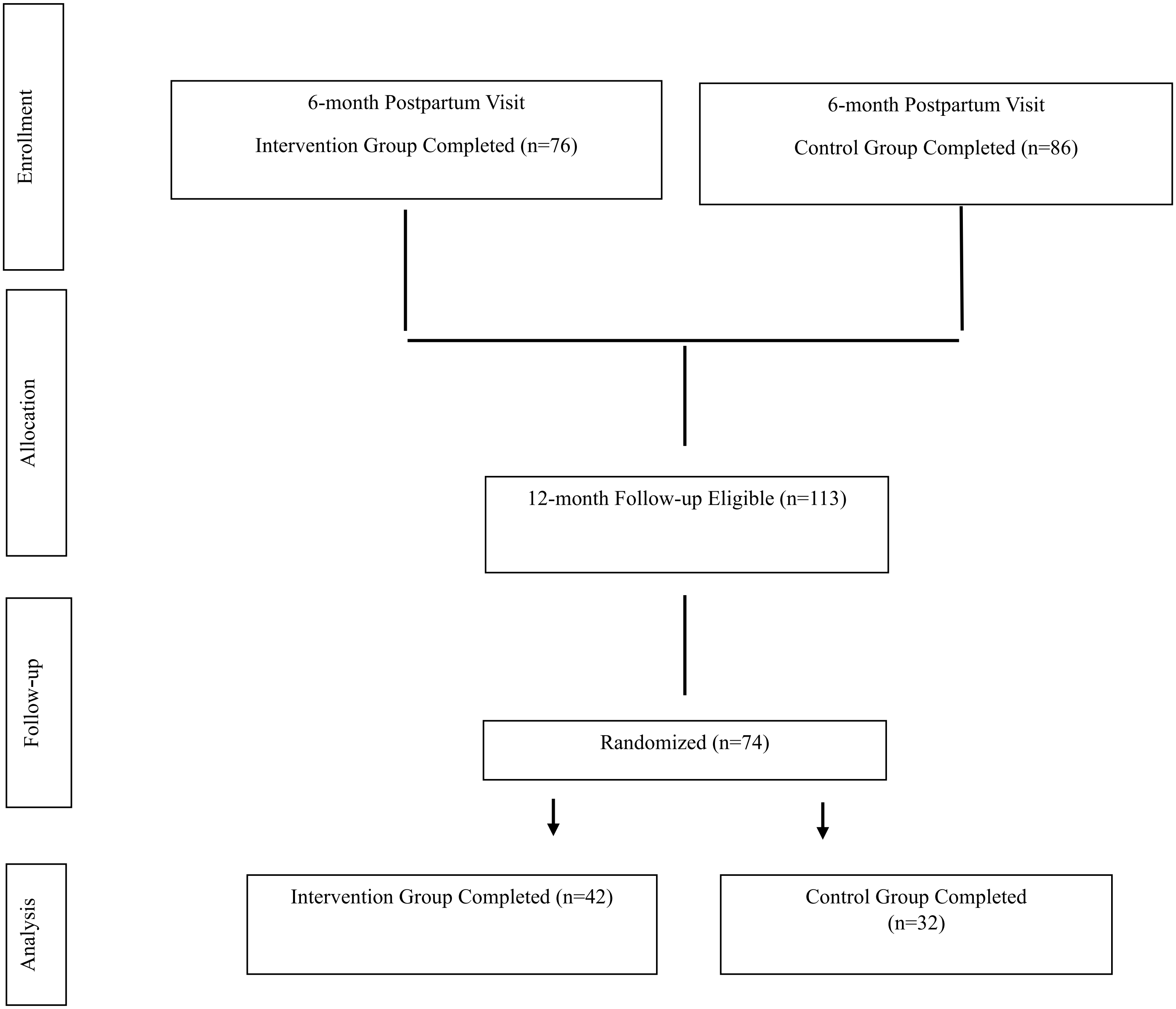
Statistical Analysis

Maternal baseline characteristics were summarized using descriptive statistics: mean (SD) for continuous variables and n (%) for categorical variables. This information was also compared between groups using *t*-tests (continuous data) and Chi squared –tests (categorical data). Statistical tests were performed using two-sided tests at with statistical significance set at 0.05. One-way analysis of variance (ANOVA) was used to determine the mean difference in BSID-III scores in the intervention and control group. Reported effect sizes followed partial eta-squared criteria for ANOVAs (small= 0.01, medium=0.06 and large=0.14).

Analysis of covariance (ANCOVA) was used to determine if select baseline factors (pre-pregnancy adiposity (BMI), gestational weight gain, obstetrical complications) moderated associations between treatment status and outcome. Equality of variances was tested through Levene′s test, and in all cases, data met assumption criteria. Additionally, independent samples t-tests were used to examine sex differences in this sample. All analyses were accounted for stratification by including participant BMI category in each model. All analyses were conducted using SPSS Statistics 23.

Results

Figure 1. Flow of Participants Through the BHIP Trial



Participant recruitment and eligibility criteria in Figure 1 are detailed in the manuscript outlining the original BHIP RCT[23]. The characteristics of the BHIP 12-month subsample (intervention=42, control=32) involved in the present study are presented in Table 1. Baseline median maternal age$_{\text{years}}$ (intervention=30.5, control=32.0) and median pre-pregnancy BMI (intervention= 24.1, control=24.4) were similar between the original sample and the 12-month subsample. Maternal characteristics were also comparable for maternal parity, education level, marital status, ethnicity, household income, and obstetrical complications. Birth and early life characteristics of infants in the intervention and control group did not differ on median birthweight (3607.0 vs. 3572.0 grams) and most infants were exclusively breastfed at 6 months of age. Characteristics of pregnant persons participating in this BHIP 12 subsample did not differ from those in the original BHIP RCT.

Table 1. Maternal characteristics at enrollment and infant characteristics at birth and six months

Variables	Intervention n=42	Standard care n=32	p-value
Maternal Characteristics			
Maternal age (y) median (Q1, Q3)	30.5 (28.8, 34.0)	32.0 (30.0, 33.0)	0.95
Gestational age at randomisation (wk) median (Q1, Q3)	13 (12.0, 14.0)	13 (12.0, 14.0)	0.92
Maternal education level n (%)			0.72
Education above Bachelor's degree	37 (88.0)	26 (81.0)	
Pre-pregnancy BMI (kg/m^2) median (Q1, Q3)	24.1 (22.1, 26.3)	24.4 (21.8, 27.7)	0.95
Pre-pregnancy BMI (kg/m^2) category n (%)			0.53
Underweight (<18.5)	0 (0.0)	0 (0.0)	
Normal weight (18.5-24.9)	26 (62.0)	18 (56.0)	
Overweight (25.0-29.9)	12 (29.0)	8 (25.0)	
Obese (≥30)	4 (9.0)	6 (19.0)	
Race/ethnicity n (%)			0.51
European descent	37 (88.0)	30 (94.0)	
Mixed/Other	5 (12.0)	2 (6.0)	
Total family income n (%)			0.51
<$45,000	2 (5.0)	1 (3.0)	
$45,000-$74,999	5 (12.0)	3 (9.0)	
>$75,000	34 (81.0)	26 (82.0)	
Unknown	1 (2.0)	2 (6.0)	

Married/living with significant other n (%)	41 (98.0)	32 (100.0)	0.58
Complications during pregnancy Yes No	 5 (12.0) 31 (74.0)	 4 (13.0) 18 (56.0)	0.72
Nulliparous n (%)	21 (50.0)	17 (53.0)	0.71
Infant Characteristics			

Abbreviations: BMI, Body mass index; y, year; wk, week; g, grams, EPDS, Edinburgh Postnatal Depression Scale
Mixed, combination of exclusive breastfeeding and formula

BSID-III scaled and composite test scores from infants at 12 months of age are reported in Table 2. Mean scores of infants from the intervention and control group did not differ on the cognitive (p=0.53), receptive language (p=0.71), fine motor (p=0.91), gross motor (p=0.16), or social-emotional (p=0.19) scales. However, infants in the intervention group had statistically significantly higher scores on the expressive language (M=9.62, 95% CI 9.05-10.18, p= 0.03, η^2p=0.07) and GAC (M=103.97, 95% CI=(100.31-107.63), p=0.04, η^2p=0.06) scales compared to infants in the control group. There were no statistically significant sex differences for the expressive language (t (df)= 61, p=0.16) and GAC (t (df)= 66, p=0.29) outcomes.

Table 2: Influence of the intervention on infant scaled and composite Bayley-III scores at 12 months of age

	Intervention (n=42)		Control (n=32)			
BSID-III	Mean	95% CI	Mean	95% CI	p-value	η^2p
Scaled Scores:						
Cognitive	9.62	(9.03-10.20)	9.34	(8.71-9.98)	0.53	0.02
Receptive language	9.54	(8.57-10.50)	9.28	(8.33-10.23)	0.71	0.02
Expressive language	9.62	(9.05-10.18)	8.72	(7.83-9.61)	0.03	0.07
Fine motor	10.32	(9.54-11.09)	10.38	(9.67-11.08)	0.91	0.03

Gross motor	10.23 (9.23-11.35)	9.16 (7.90-10.41)	0.16	0.04
Social-Emotional	12.39 (11.51-13.28)	11.41 (10.07-12.75)	0.19	0.03
Composite Score:				
GAC	103.97 (100.31-107.63)	98.90 (95.76-102.05)	0.04	0.06

BSID-III, Bayley's Scale of Infant and Toddler Development- 3rd Edition; GAC, general adaptive composite

A one-way ANCOVA found no evidence for moderating effects of pre-pregnancy BMI, GWG, or obstetrical complications on the relations between treatment group and any BSID-III outcome. These results are summarized in Supplementary Table S1.

Discussion

The present RCT tested the effect of a nutrition+exercise intervention during pregnancy on offspring neurodevelopment at 12 months of age using the BSID-III. We found that the offspring of pregnant persons in the intervention group had higher expressive language and overall adaptive behavior scores, but not of cognitive, receptive language, motor, or social-emotional functioning. Differences between the intervention and control group for expressive language and overall adaptive behavior were of medium effect size.

Since this is the first known RCT to examine the effects of a combined nutrition+exercise intervention as well as examine overall diet during pregnancy on fetal neurodevelopment at 12 months of age, comparable studies are lacking. However, one previous RCT of pregnancy B12 supplementation in India was associated with higher expressive language scores in children at 30 months[28]. Another recent observational study by He and colleagues reported that prenatal micronutrient supplementation during pregnancy was associated with overall language development in Chinese children less than two years of age, but not of cognitive, motor and social-emotional functioning[29]. In terms of the impact of pregnancy exercise, one observational study suggested that exercise during pregnancy was associated with higher language scores at 15 months of age in a sample of British children[19]. Clapp also reported that children of exercising mothers scored higher on oral language skills at five years of age compared to children from inactive mothers in the US[18]. Non-human animal studies have also shown that the pups of exercising rat mothers had better memory and spatial learning, as well as increased synaptic density and cerebral maturation[21]. Such learning abilities are important components of language acquisition and could be one mechanism which exercise during pregnancy can enhance expressive language development.

Studies examining infant adaptive behavior in response to pregnancy nutrition or exercise interventions are also rare. One RCT found no differences in infant adaptive behavior at 12 months of age between American mothers taking an omega-3 fatty acid (300 mg n-3 DHA and 67 mg Eicosapentaenoic acid (EPA)) daily and a control group[30]. In an observational study, Bolduc also reported associations between higher fruit and lycopene consumption during pregnancy and infant adaptive development at 12 months in the offspring of Canadian mothers[31].

While it appears as if intervening prenatally could optimize infant expressive language and adaptive functioning at 12 months of age, the mechanisms underlying these changes are not known. Expressive language refers to the use of words, gestures and sentences to communicate with others[32], while adaptive behavior refers to skills (conceptual, social and practical) that affect the ways individuals meet their personal and environmental needs[33]. However, both of these domains of the BSID-III are heavily dependent on frontal lobe development and functioning[34], and sub-optimal maternal nutrition has been linked to structural abnormalities in brain regions such as the frontal lobe[35]. Indeed, the thickness of the frontal cortex and greater gray matter volume has previously been positively and strongly correlated with infants’ expressive language ability at 12 months of age, and associated with better social competence (a key component of adaptive behavior) in early childhood[36]. Non-human animal studies have also shown that cortical thickness and volume in rat pups from mothers with a protein deficient diet was significantly less than pups from mothers consuming a high protein diet[37]. It is therefore possible that a high protein diet during pregnancy (as with BHIP) may contribute to greater cortical thickness and gray matter volume in the frontal lobe[37]. Although the direct mechanisms underlying maternal exercise and fetal neurodevelopment are unclear, studies have hypothesized that infants of exercising mothers received more blood and nutrients through the placenta[20]. Perhaps the nutrients required for brain development are provided by improved diet while exercise during pregnancy may increase placental absorption of those nutrients. Other studies have reported that maternal exercise during pregnancy may improve neurogenesis[19] and increase neurotrophic factor expression[21] in various brain regions.

However, it is unclear why the intervention did not have an impact on the other BSID-III scales. These results are comparable to several studies that have failed to observe an effect of maternal nutrition or exercise on these other components of the BSID-III. One RCT found no difference between the 24-month-old offspring of pregnant Bangladeshi persons who received a multiple micronutrient or iron-folic acid supplement[10]. In another RCT conducted in New Zealand, the infants of pregnant persons who were given an iodine supplement did not improve on any BSID-III outcome at 18 months of age[6]. Furthermore, the absence of statistically significant results may also be due to the limited statistical power of the study.

Although this study did not observe moderating effects of pre-pregnancy BMI, GWG and maternal complications during pregnancy on the relation between treatment group and the BSID-III outcomes, it is important that these potential effects not be dismissed. The absence of these moderating effects may be due to the very low observed power in the study (Supplementary Table 1), that reduced the likelihood of detecting effects[38].

The following study limitations should also be acknowledged. The sample size was relatively small and attrition (owing to multiple factors including the COVID-19 pandemic) was elevated, both of which may have interfered with our ability to detect some effects. Second, the use of a single-centre design and recruitment of an ethnically homogenous (i.e., white) group who were educated and unlikely to be facing significant socioeconomic disadvantage. Third, the reliability and stability of scores of these BSID-III outcomes increase as children get older, which may have interfered with our ability to detect potential effects of the current intervention in early infancy[39]. Fourth, the sample consisted of individuals living in a country where severe nutrient deficiencies are not common. Fifth, adaptive behavior was maternally reported. Sixth, data on postnatal factors including postnatal home environment were not collected. However, infants were balanced on all other characteristics at baseline and randomized to treatment or control group. Seventh, maternal compliance with the intervention was not assessed. However, several strategies were used throughout both components of the intervention to improve compliance. Finally, this sample consisted of pregnant persons living in a country with universal access to healthcare, where they may already have been advised by healthcare professionals to maintain an optimal diet and exercise regimen, reducing the potential impact of the intervention. Such limitations may limit generalizability, hence studies including pregnant persons from different countries with larger samples are required to determine the potential impact of this intervention.

In conclusion, given that this intervention had medium-sized effects on expressive language and adaptive functioning, since pregnancy nutrition and exercise are modifiable, and given that pregnant persons are motivated to make healthy changes during pregnancy, future studies should examine the impact of combined nutrition and exercise interventions during pregnancy in larger and more diverse samples, and follow offspring beyond 12 months of age to determine their potential impact in public health settings.

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Chapter 4: Preliminary Findings of Emotion Regulation in 12-Month Old Infants of Mothers Enrolled in a Randomized Controlled Trial Assessing a Nutrition + Exercise Intervention (Study 3)

Study 3 Overview

Title: Preliminary Findings of Emotion Regulation in 12-Month Old Infants of Mothers Enrolled in a Randomized Controlled Trial Assessing a Nutrition + Exercise Intervention

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Context and Implications of this study: The third study extended the second study by examining whether fetal exposure to the Be Healthy in Pregnancy (BHIP) nutrition+exercise intervention led to better emotion regulation (ER) at 12 months of age. We found that using an experimental approach, as well as a multimethod assessment of infant ER, the BHIP maternal nutrition+exercise intervention improved parasympathetic nervous system function (high frequency heart rate variability (HF-HRV) and root mean square of successive differences (RMSSD)), as well as maternal reports of infant temperament (Infant Behavior Questionnaire-Revised short form) in infants at 12 months of age. Although this study and study 2 suggest that this nutrition+exercise intervention may lead to improvements in both language, adaptive behaviour, and ER, further research with larger sample sizes are needed to determine the clinical utility of nutrition+exercise interventions for optimizing infant neurodevelopment.

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Conflicts of interest: None

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Abstract:

Background: Improved offspring emotion regulation (ER) has been associated with maternal intake of single nutrients or exercise during pregnancy but has not been examined in randomized trials. We investigated the impact of a maternal nutrition+exercise intervention during pregnancy on offspring ER at 12 months of age.

Methods: Mothers in the Be Healthy In Pregnancy (BHIP) randomized controlled trial were randomly assigned to an individualized nutrition+exercise intervention plus usual care (UC) or UC alone (control group). A multimethod assessment of infant ER using parasympathetic nervous system function (high frequency heart rate variability (HF-HRV) and root mean square of successive differences (RMSSD)), as well as maternal reports of infant temperament (Infant Behavior Questionnaire- Revised short form) was completed with a sub-sample of infants of enrolled mothers (intervention=9, control=8).

Results: We observed greater HF-HRV (M=4.63, SD=0.50, p=0.04, η^2p=0.25) and RMSSD (M=24.25, SD=6.15, p=0.04, η^2p=0.25) in infants of mothers in the intervention vs. control group. Intervention group infants also had higher maternally-rated surgency/extraversion (M=5.54, SD=0.38, p=0.00, η^2p=0.65) and regulation/orienting (M=5.46, SD=0.52, p=0.02, η^2p=0.81), and lower negative affectivity (M=2.70, SD=0.91, p=0.03, η^2p=0.52).

Conclusions: These preliminary results suggest that pregnancy nutrition+exercise interventions could improve infant ER but these findings require replication in larger, more diverse samples. The trial was registered at www.clinicaltrials.gov (NCT01689961).

Key words: Emotion regulation, prenatal diet, prenatal exercise, infant heart rate variability, infant temperament, pregnancy interventions, infant physiology

Introduction

Emotion regulation (ER) refers to the processes involved in modifying emotions in the service of future goals[1]. Such regulation begins to develop in infancy and is central to adaptive functioning across cognitive, emotional and behavioral domains throughout life[2]. Early problems with ER are associated with an increased risk of academic and learning difficulties[3], behavioral problems[4], criminal conviction[5], and are involved in the development of most forms of psychopathology[6].

The Developmental Origins of Health and Disease (DoHaD) hypothesis posits that adverse prenatal conditions can affect the function and structure of key physiological systems, including those involved in ER[7]. Poorer maternal nutrition and suboptimal levels of physical activity during pregnancy have been hypothesized to adversely impact offspring cognition and behavior, as well as physiological systems linked to emotion regulatory capacity[8]. As a result, intervening on these exposures through maternal lifestyle interventions could represent effective early approaches to improving offspring ER and subsequent functioning.

Lower high frequency heart rate variability (HF-HRV) is among the earliest emerging markers of poor ER later in life[9], and links between deficiencies in specific nutrients in pregnancy and HF-HRV have been reported in humans[10]. For example, low maternal levels of vitamin B12 in pregnancy have been linked to reduced HF-HRV in 3-8 year old children[11], and higher maternal pregnancy omega-3 consumption was associated with higher HF-HRV in infants at 2 weeks, and four and six months of age[12]. Maternal zinc deficiency during pregnancy has also been linked with lower fetal HRV at 34-36 weeks gestation[13]. Given the observational nature of these studies, randomized controlled trials (RCTs) are now required to better understand the clinical potential of intervening on maternal diet to improve infant ER.

Research examining the impact of maternal physical activity during pregnancy on offspring ER is rarer[14]. Two small RCTs found that the offspring of mothers who engaged in aerobic exercise had higher fetal HF-HRV at 36 weeks gestation[15] and at one-month postpartum[16] compared to those born to non-exercising mothers. In an observational study, offspring of mothers who did aerobic exercise were better able to calm themselves and orient to environmental stimuli five days after birth[17] than those born to those who did not engage in regular exercise. However, the offspring in these studies were very young, and so examining the impact of maternal interventions on infants within developmental windows where infants begin to implement greater levels of ER capacities is important.

Given that maternal diet and exercise during pregnancy have been independently associated with improvements in infant ER, it is important to determine synergistic effects of diet and exercise during pregnancy. Given existing knowledge gaps, we examined a subset of infants of mothers enrolled in an RCT of a pregnancy nutrition+exercise intervention to determine their impact on offspring ER at 12-months of age.

Materials & Methods

Trial Design and Participants

Participants in this study were the 12-month-old offspring of mothers enrolled in the Be Health In Pregnancy (BHIP) RCT[18]. Briefly, 241 pregnant persons living in Hamilton, Ontario, Canada were recruited by 12 weeks gestation, stratified by pre-pregnancy BMI category (normal, overweight and obese) and allocated to treatment or control groups in a 1:1 ratio. Healthy pregnant persons >18 years old with singleton pregnancies, pre-pregnancy BMI<40 kg/m^2, and the ability to understand English and provide informed consent were eligible. Those with contraindications to exercise, health problems (heart, liver, or kidney disease), an inability to consume dairy products, who were smoking cigarettes, had pre-existing diabetes mellitus, or a baseline score ≥12 on the Edinburgh Postnatal Depression Scale (EPDS) at the recruitment were excluded.

A sub-sample of 74 participants were then recruited from the remaining BHIP participants at 6 months of age to participate in a study that assessed the cognitive outcomes of 12-month-old offspring (manuscript under review). Additional funding enabled us to complete the present study which utilized a subset of 17 of these 12-month-old participants to also assess emotion regulation. Given that opportunities to assess the neurodevelopment of the offspring of women who have participated in diet+exercise interventions are rare, we assessed emotion regulation in this subset of participants. Informed consent was obtained prior to study participation. Ethical approval was granted by the Hamilton Integrated Research Ethics Board at McMaster University (REB Project#12-469) and Joseph Brant Hospital, Burlington (JBH 000-018-14) in Ontario, Canada.

Intervention

The details of the BHIP pregnancy nutrition+exercise intervention have been reported in detail previously[19]. Briefly, those in the intervention group received usual care (UC) from their health care providers in addition to the BHIP nutrition+exercise intervention (from study enrollment at 12 weeks gestation to birth). The nutrition component of the intervention consisted of an individualized diet plan that prioritized protein intake (~25% of energy needs) largely from dairy products. Participants received their dairy products biweekly by visiting the study site and consulting with the study nutritionist. The exercise component of the intervention consisted of 10,000 steps daily, tracked using a pedometer and exercise log, and a walking program starting at 25 minutes (increasing duration by two minutes each session) 3-4 times a week.

Participants in the control group received UC from their healthcare providers and the most recent guidance on pregnancy nutrition from Health Canada[20].

Randomization/Group Allocation

Due to the nature of the intervention the study was open-label with blinded endpoints[18].

Infant Outcomes

As ER is best measured using a combination of physiological measures and informant reports,[21] this study collected physiological and maternal report data. Our physiological measure of EF was HF-HRV[21]. HF-HRV has been linked to parasympathetic nervous system functioning, and greater HF-HRV is related to more adaptive control and flexibility in times of stress[22] (and is reflective of better ER). Informant reports of infant temperament were collected from mothers using the IBQ-R short-form[23]. Infants were followed up at 12 months of age, as brain regions underlying ER (e.g., the prefrontal cortex (PFC)) play an increasingly crucial role in directing emerging ER capacity at that age[24].

Time Domain Heart Rate Variability (HRV): Infants were seated in a highchair facing their mothers and research assistant prior to completing their cognitive testing (e.g., the Bayley Scale of Infant and Toddler Development 3rd Edition (BSID-III)) for approximately 30 minutes. Two pediatric electrodes were placed on the infants' right shoulder blade and lower-most left back. Data were continuously acquired throughout the task using the Biolab Software (version 3.2.3, Mindware Technologies Ltd. Gahanna, OH). Data were then inspected for artifacts using the Mindware HRV software. Activity within the infant respiratory sinus arrythmia frequency band (0.24 to 1.04 Hz) were extracted. In keeping with contemporary recommendations, we also considered HRV assessed in the time domain (Standard deviation of N-N intervals (SDNN) and root mean square of successive differences between heartbeats (RMSSD)). While RMSSD data provide a primary time domain measure of the parasympathetic influences which is reflective of a calm state[25], SDNN is a gold standard measure of the responses to environmental demands and has more sympathetic influences on HRV, reflective of a more aroused state[26]. Therefore, greater RMSSD values are reflective of better ER.

Temperament: Infant Behavior Questionnaire- Revised (IBQ-R) Short Form

Mothers completed the 91-item IBQ-R short form, which assesses infant behavior over the past week using a seven-point scale (1=never, 7=always). The IBQ-R consists of 14 scales that create three broad factors of infant temperament including Orienting/Regulation (low intensity pleasure, cuddliness, soothability, duration of orienting scales), Surgency/Extraversion (consisting of approach, high intensity pleasure, smiling/laughing, vocal reactivity, activity level scales), and Negative Affectivity (sadness, distress, fear, falling reactivity scales)[23]. Higher scores indicate greater levels of each factor and all three broad factors were examined in this study.

Statistical Analysis

Maternal and infant baseline characteristics were summarized and compared between intervention and control groups, and between our sub-sample of participants and the original BHIP sample. One way analysis of variance (ANOVA) was used to calculate the mean differences between HRV metrics and temperament between intervention and control groups at 12 months of age. Correlation analyses were also conducted to assess the statistical relationship between our two ER measures. All analyses included stratification by participant BMI category. Analyses were performed using SPSS statistics 23 (IBM).

Results

Maternal and infant baseline characteristics are presented in Table 1. There were no statistically significant differences in maternal demographic data between intervention and control groups in the current study sub-sample nor in the core study[19]. For infants, median birthweight (3539g vs. 3690g, p=0.45) and breastfeeding practice at 6 months (exclusively breast fed (3 vs. 3), mixed breastfeeding and formula fed (6 vs. 5), and exclusively formula fed (0 vs. 0), p=0.63) did not differ between intervention and control groups.Demographic characteristics of the complete BHIP sample are presented elsewhere[19], however, there were no statistically differences between this sub-sample and the original BHIP sample.

Table 1. Maternal and Infant Baseline Characteristics

Variables	**Intervention n=9**	**Standard care n=8**	**p-value**
Maternal Demographics M (SD), N (%)			
Maternal age (y) median (Q1, Q3)	30.2 (28.6, 33.8)	31.5 (30, 32.8)	0.57
Gestational age at randomization (wk) median (Q1, Q3)	13 (12, 14)	13 (12, 14)	0.29
Maternal education level HS and below College/Bachelor Above Bachelor	 0 (0%) 6 (67%) 3 (33%)	 0 (0%) 5 (63%) 3 (37%)	0.62
Pre-pregnancy BMI (kg/m^2)	22.7 (1.9)	24.1 (3.6)	0.33
Pre-pregnancy BMI (kg/m^2) category n (%) Underweight (<18.5) Normal weight (18.5-24.9) Overweight (25.0-29.9) Obese (≥30)	 0 (0%) 7 (78%) 2 (22%) 0 (0%)	 0 (0%) 5 (63%) 2 (25%) 1 (12%)	0.53
Race/ethnicity n (%) European descent Mixed/Other	 9 (100%) 0 (0%)	 7 (88%) 1 (12%)	0.10

Total family income (in CAD) n (%)			0.53
<$45,000	0 (0%)	0 (0%)	
$45,000-$74,999	1 (11%)	1 (12%)	
>$75,000	8 (89%)	5 (62%)	
Unknown	0 (0%)	1 (12%)	
Complications during pregnancy			0.60
Yes	2 (22%)	1 (13%)	
No	7 (78%)	7 (87%)	
Nulliparous n (%)	5 (56%)	4 (50%)	0.71
Infant demographics			
Birthweight (g) median (Q1, Q3)	3539 (3234, 3792)	3690 (3347, 3912)	0.45
Breastfeeding 6 months			0.63
Exclusive	3 (33%)	3 (38%)	
Mixed	6 (67%)	5 (62%)	
Formula	0 (0%)	0 (0%)	

Abbreviations: BMI, Body mass index; y, year; wk, week; g, grams; EPDS, Edinburgh Postnatal Depression Scale; Mixed, combination of exclusive breastfeeding and formula

It is important to note that although data on maternal compliance to the intervention is limited, we found that the 10,000 step goal was achieved by 20% of mothers in the second trimester and 10% of mothers in the third trimester. Therefore, step count did not differ between intervention and control group (p=0.27, n^{2}p=0.36) throughout pregnancy, as well as from pre-randomization throughout pregnancy. However, protein intake was statistically significantly higher in the intervention group (p=0.003, n^{2}p=0.66) compared to the control group from the second trimester to the end of pregnancy. Diet quality (using a shortform food frequency questionnaire (FFQ)- PrimeScreen) did not differ prior to randomization in the trial (p=0.63).

Infant 12-month time domain HRV metrics (estimates of parasympathetic and sympathetic activity) are reported in Table 2. Mean scores from infants in the intervention and control group did not differ on HR (p=0.15) and SDNN (p=0.35) metrics. However, infants in the intervention compared to control group had statistically significantly higher HF-HRV (p=0.04, η^{2}p=0.25) and RMSSD (p=0.04, η^{2}p=0.25), suggesting that infants in the intervention group had better ER because of greater parasympathetic influence (RMSSD). Differences between the intervention and control group for HF-HRV and RMSSD were of large effect size. No statistically significant sex differences for HF-HRV (t (df)= 10, p=0.06) and RMSSD (t (df)= 15, p=0.17) outcomes were found.

Table 2: 12 Month Infant Heart Rate Variability Metrics Scores

	Intervention (n=9)	Control (n=8)		
HRV metrics	Mean (SD)	Mean (SD)	*P*-value	η²p
HR	124.59 (9.17)	131.28 (8.78)	0.15	0.13
HF-HRV	4.63 (0.50)	3.91 (0.84)	0.04	0.25
RMSSD	24.25 (6.15)	17.31 (6.70)	0.04	0.25
SDNN	31.31 (6.64)	27.88 (8.21)	0.35	0.05

HR, heart rate; HF-HRV, high frequency heart rate variability; RMSSD, root mean square of successive differences; SDNN, standard deviation of NN intervals; SD, standard deviation; η²p, partial-eta squared

Maternally-reported infant temperament is reported in Table 3. Infants in the intervention compared to the control group scored higher in surgency/extraversion (p=0.00, η²p=0.81) and regulation/orienting (p=0.02, η²p=0.65), and statistically significantly lower in negative affectivity (p=0.03, η²p=0.52). Differences between the intervention and control group for all the IBQ-R short-form factors were of large effect size. Correlational analyses examining associations between HRV metrics and the IBQ-R short form did not note any statistically significant associations (Supplementary Table 1).

Tabel 3: Infant IBQ-R Short Form Scores

	Intervention (n=9)	Control (n=9)		
IBQ-R Factors	Mean (SD)	Mean (SD)	*P*-value	η²p
Regulation/Orienting	5.46 (0.52)	4.90 (0.42)	0.02	0.65
Surgency/Extraversion	5.54 (0.38)	4.94 (0.29)	<0.01	0.81
Negative Affectivity	2.70 (0.91)	3.75 (1.01)	0.03	0.52

IBQ-R, Infant behaviour Questionnaire-Revised; SD, standard deviation; η²p, partial-eta squared

Discussion

In this study, the 12-month-old infants of mothers who received a pregnancy nutrition+exercise intervention displayed better emotion regulatory capacity as evidenced by improved parasympathetic nervous system functioning (HF-HRV and RMSSD) and maternally-rated temperament relative to infants of mothers in the control group. The effect size of these differences was large, but our sample size was very small and so these results and their interpretation need to be viewed as preliminary in nature.

In terms of nutritional status of women during pregnancy, previous studies that have examined the effects of individual nutrient deficiencies during pregnancy and infant ER have reported associations between inadequate zinc and lower fetal HRV at 34-36 weeks gestation[13], and B12 and lower HRV in 3–8-year-old children[11]. In an observational study higher maternal omega-3 consumption was associated with greater HRV in two-week to 6-month-old infants[12]. However, these studies examined single nutrients and individual physiological measures of ER in isolation, and only HRV without the addition of time domain parameters. Another study reported a link between overall poor diet quality during pregnancy and lower HRV in infants at 6 months of age[27]. The results of the present study suggest that improving overall pregnancy diet along with the prescription of exercise could increase offspring HRV at 12 months of age.

The majority of mechanistic evidence for the effects of maternal diet and offspring ER is derived from non-human animal studies[28]. Poor overall maternal diet during pregnancy has been proposed to negatively affect the hypothalamic–pituitary–adrenal (HPA) axis feedback systems through alterations in glucocorticoid receptors[29]. Protein deficiency in rat dams increases fetal glucocorticoid production and sympathetic-adrenal responses to stress[30], and such changes could contribute to hyperactivity of the sympathetic nervous system (i.e., poorer ability to regulate emotions) and contribute to associations between maternal diet and behavioral regulatory outcomes in offspring (i.e., higher negative affectivity)[31]. In this sub-study of the BHIP trial, total protein intake was statistically significantly higher in the intervention group compared to the control group ($p=0.003$, $\eta^2p=0.66$) from the second trimester to the end of pregnancy as reported for the entire study group[19,32]. Therefore, it is possible that higher protein intake in the intervention group may have been one mechanism contributing to the improved ER observed in infants. Additionally, mothers in the intervention and control group did not differ in diet quality (using a shortform food frequency questionnaire (FFQ)-PrimeScreen) prior to randomization in the trial ($p=0.63$).

Although very limited data exist on the effects of maternal exercise during pregnancy and infant ER, two small RCTs have suggested that maternal aerobic exercise can lead to increased HRV at 36 weeks gestation[15] and one month of age[16]. The second of these RCTs found that maternal exercise during pregnancy (resistance or circuit training) improved HRV in 1-month old infants compared to the control group regardless of exercise type[16]. As for the primary trial, *Post-hoc* analysis of the mothers in our sample showed that step counts did not differ between intervention and control group in the sample during pregnancy ($p=0.27$, $\eta^2p=0.36$). Step count also did not differ from pre-randomization throughout pregnancy in either the intervention or control group, though step counts may not have captured all forms of physical activity completed by mothers. As a result, it is unclear what role physical activity may have played in contributing to the changes in HRV and temperament observed. Additionally, average step count in our sample was similar to other studies of sedentary pregnant women[33].

Maternal exercise during pregnancy has been proposed to affect neurotrophic factors that are key to the growth and plasticity of the fetal brain[34]. Maternal exercise increases neurotrophic factor levels such as BDNF and VEGF in the brain, which can lead to adaptive changes in brain regions such as the PFC and amygdala[35], which are involved in controlling stress and emotional responses[24]. Non-human animal studies have reported that low maternal protein intake decreases BDNF in the brains of neonatal rat offspring[36], and so perhaps higher maternal protein intake in this study in addition to exercise in the intervention group may have contributed to neurotrophic factor increases and a positive impact on infant ER.

Indeed, it is possible that the combination of nutrition+exercise interventions during pregnancy could act synergistically to benefit fetal brain development. Maternal diet during pregnancy is one of the most critical factors for optimal maternal and fetal health outcomes, and an overall healthy diet provides the essential nutrients needed for fetal brain development[37]. Maternal exercise during pregnancy could improve placental development and maintenance throughout pregnancy[38]. In terms of potential additive effects, maternal exercise could potentiate the positive effects of healthy maternal diet by optimizing fetal blood flow and nutrient delivery to various brain regions and physiological systems (PFC, amygdala, autonomic nervous system) associated with better maternal and fetal HRV and ER[38]. Fetal HRV is dependent on cardiac output, and a healthy maternal diet (consisting of proteins and fatty acids) promotes healthy development of the cardiac system[39], and maternal exercise could further improve fetal HRV and increase fetal cardiovascular adaptations postnatally[40]. For example, maternal exercise enhances amino acid transport pathways and genes associated with fatty acid metabolism which are both dietary factors involved in a healthy diet and that improve fetal HRV[39].

The following limitations of this study should be acknowledged. First, a single center design was utilized for this sub-study. Second, the sample size was very small and so our results are preliminary in nature. However, since we did observe statistically significant results (of large effect size) across both physiological and behavioral levels of analysis, we believe that this study could provide important preliminary evidence on the impact of prenatal diet and exercise on neurodevelopment, as well as estimates of effect to aid in the conduct of future larger randomized controlled trials. Third, the sample consisted mainly of an ethnically and socioeconomically homogenous group of mothers who were free of mental health problems and comfortable socioeconomically. It is important to note however that individuals in this sample did not differ from those in the original BHIP sample. Third, the study was an open-label study due to the nature of the intervention, though all research staff testing infants and outcome analysts were blinded to group status. Fourth, the IBQ-R Short-Form was used and it was maternally reported only, however mothers are typically the primary caregiver in Canada and spend more time with their offspring than their partners[41]. Fifth, saliva or blood samples measuring hypothalamic-pituitary-adrenal (HPA) axis function of infants were not reported, and since measures of the HPA axis can help us to better understand emotional development and stress reactivity in infants[42], future studies should consider including such measures. Sixth, limited data on maternal compliance to the intervention was reported. Lastly, while we expect the synergistic effects of both diet and exercise were needed to observe these results, it is not clear which had a greater impact than the other or if one alone was sufficient to produce the observed effects.

Conclusion

Our results suggest maternal use of the BHIP nutrition+exercise intervention during pregnancy may improve physiological and behavioral systems underlying offspring ER. However, it is important to note that these preliminary findings need to be replicated in larger more diverse samples and with offspring of different ages in order to assess the clinical utility of this intervention.

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Chapter 5: Effectiveness of a Pregnancy Nutrition + Exercise Intervention on Offspring Neurodevelopment at 36 Months of Age (Study 4)

Study 4 Overview

Title: Effectiveness of a Pregnancy Nutrition + Exercise Intervention on Offspring Neurodevelopment at 36 Months of Age

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Context and Implications of this study: The fourth study extendeds the third study by examining whether fetal exposure to the Be Healthy in Pregnancy (BHIP) nutrition+exercise intervention led to better emotion regulation (ER) at 36 months of age (early childhood). We found that using an experimental approach, as well as a multimethod assessment of ER (consisting of informant reports, observational tasks, and physiological measures), the BHIP maternal nutrition+exercise intervention improved select scales of the maternally reported Child Behavior Questionnaire (CBQ) and Behavior Rating Inventory of Executive Function-Preschool Edition (BRIEF-P), impulsivity scores using an observational task, and physiological measures of HRV at 36 months of age. Although studies 2-4 suggest that this nutrition+exercise intervention may lead to improvements in both cognitive and ER development from infancy to early childhood, further research with larger sample sizes are needed to determine the clinical utility of nutrition+exercise interventions for optimizing infant neurodevelopment.

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Abstract

Background: Pregnancy nutrition and exercise have been linked to improved offspring emotion regulation (ER) in observational studies, but this has not been examined in randomized controlled trials (RCTs). We investigated the impact of a maternal nutrition+exercise intervention during pregnancy on offspring ER at 36 months of age.

Methods: The Be Healthy in Pregnancy (BHIP) RCT randomly assigned consenting pregnant persons to a nutrition+exercise intervention or care as usual (CAU). This study examined a subset of these mothers and their offspring (intervention= 22, control= 20) and assessed emotion regulatory capacity at 36 months of age. This was assessed using a multimethod approach consisting of informant reports, observational tasks, and physiological measures.

Results: Children of those in the intervention group had better ER as indexed by parent reports on the approach, attentional focusing, soothability, and inhibitory control scales of the CBQ, and the inhibitory self-control and flexibility index of the BRIEF-P. They also performed better on an observed impulsivity task, and had better HRV at rest and during this task. Effects sizes were medium to large but attrition in the trial from enrolment to 36 months was high.

Conclusion: A structured and monitored nutrition+exercise lifestyle intervention during pregnancy led to improvements in ER in 36-month-olds. Larger RCTs containing more diverse samples are needed to better understand the clinical potential of intervening on maternal diet to improve infant cognition and ER.

Introduction

Emotion regulation (ER), the processes involved in modifying emotions in the service of future goals[6] begins to develop in infancy and is essential to adaptive functioning across behavioral, emotional and cognitive domains throughout life[7]. Indeed, problems with ER early in life are linked to a tripling risk of polysubstance dependence[2], criminal conviction[3], and income rates below the poverty line in adulthood[4].

The development of ER in early childhood is influenced by factors internal to the child, as well as those external to them. Internal factors include biological and behavioral traits such as temperament, innate differences in external reactivity to changing demands[8]. External factors such as caregiving style is also critical, with decrements in emotion regulatory capacity seen in those born to families experiencing high stress and/or socioeconomic disadvantage[8]. However, prenatal environmental exposures may also affect ER development[9]. The Developmental Origins of Health and Disease (DoHaD) hypothesis posits that suboptimal intrauterine environmental exposures can affect the function and structure of the brain, including key systems involved in ER development[10]. Conditions such as poor maternal diet, lack of exercise, stress, mood disorders and infection during pregnancy have all been hypothesized to affect the physiological systems linked to offspring ER[10]. However, maternal diet quality and exercise during pregnancy are among the only modifiable risk factors that affect offspring ER. Since brain plasticity decreases with age, prenatal nutrition and physical activity interventions could represent an effective means by which ER could be optimized[12].

The majority of studies that have examined the impact of prenatal exposures such as maternal diet and exercise on offspring ER in humans utilize observational study designs and have tended to examine single nutrients in isolation, as well as just one or two outcomes. In order to assess the full scope of ER in pediatric populations and minimize bias, robust multimethod assessments that include parent-reports, observed behavior, and physiological and behavioural assessment across both physiological and behavioral levels are required[13,14]. To date, very few observational studies have found that a better maternal diet during pregnancy is associated with a lower risk of aggressive behaviour, ADHD, and less emotional/behavioural problems in 7-10 year olds[19]. Conversely, a maternal diet high in sugar and fat was found to be related to emotional-behavioral dysregulation at 2, 4 and 7 years of age[20]. While few have examined physiological outcomes, work assessing the impact of lower maternal vitamin B12[16], zinc[17] and omega-3[18] during pregnancy has showed that they are associated with reduced HRV in children up to three years of age.

Studies examining maternal exercise during pregnancy are also rare. One observational study examining maternal aerobic exercise throughout pregnancy and its impact on infant emotion regulation at five days of age found that infants of mothers who exercised were better able to calm themselves than the infants of mothers who didn’t exercise during pregnancy. The two small RCTs that have assessed the effects of maternal aerobic exercise during pregnancy found that HRV increased in response to exercise at 36-38 weeks gestation[21] and the other study at one month of age[22].

To our knowledge only two studies have examined the impact of a combined diet+exercise intervention during pregnancy on infant ER. These are both sub-studies of the Canadian Be Healthy in Pregnancy (BHIP) RCT and found that a diet+exercise intervention starting in the second trimester of pregnancy improved expressive language and general adaptive functioning in infants at 12 months of age (manuscript under review), as well as multiple indices of emotion regulation including physiological (HRV) and informant-based (Infant Behavior

Questionnaire- Revised Short Form) measures. These studies have begun to suggest that the combination of healthy diet and exercise during pregnancy could act synergistically to benefit fetal brain development and improve infant ER. However, in order to assess the full potential of diet+exercise interventions to improve offspring ER, it is important to use multiple methods across measures and physiological systems over time.

Given these knowledge gaps, the objective of this study was to examine the effects of overall diet quality and exercise during pregnancy on infant ER using physiological, observational, and behavioural outcomes at three years of age. This age is an important period for emotional development as children enter preschool and begin to interact with others in a different social setting, their understanding of others' emotions and their own in response to emotional events is overtly displayed,[26] and ER at this age predicts later ER,[27] as well as multiple other outcomes like mental health, and educational and vocational attainment[28].

Methods

Trial Design and Procedures

This study followed the 36-month-old offspring of mothers and birthing parents enrolled in the original BHIP RCT that examined the impact of a diet+exercise intervention on parents' likelihood of attaining recommended gestational weight gain during pregnancy[29]. Pregnant persons (n=241) were originally recruited into BHIP from the Hamilton, Ontario, Canada region at 12-17 weeks gestation and randomized to intervention or control group in a 1:1 allocation ratio and further stratified by pre-pregnancy BMI category (normal, overweight, obese). Ethical approval was granted by the Hamilton Integrated Research Ethics Board at McMaster University (REB Project#12-469) and Joseph Brant Hospital, Burlington (JBH 000-018-14) in Ontario, Canada. The trial was registered at www.clinicaltrials.gov (NCT01689961). Baseline data were collected from mothers during the first study visit at 12-17 weeks gestation, and during their second study visit, block randomization of the study arms was conducted and stratified by BMI[28]. Due to the nature of the intervention, this study was an open-label format with blinded endpoints, so participants were aware of group status but staff and research analysists were blinded to group status. All analyses were performed on an intention-to-treat basis.

Participants

Participants were recruited by the original BHIP team between January 2013 to April 2018, and recruitment was complete by March 2019 when infants were six months old. A sub-sample of 74 participants were recruited from the remaining BHIP participants at six months of age to participate in a trial assessing the cognitive outcomes at 12 months of age (manuscript under review). The present study examines 42 participants of the 12-month follow-up. Informed consent was obtained prior to study participation and the study was conducted at McMaster University. Healthy pregnant persons >18 years old with singleton pregnancies, ≤12 weeks gestation at enrollment, approval of primary health care provider to participate, pre-pregnancy BMI<40 kg/m^2, and the ability to understand English and provide informed consent were eligible to participate. Those with contraindications to exercise, significant kidney, liver, or heart disease, pre-existing diabetes mellitus, refusal to consume dairy products, smoking, or a baseline score ≥12 on the Edinburgh Postnatal Depression Scale (EPDS) at recruitment were excluded.

Intervention

Individuals in the intervention group received usual care from their health care providers, which includes routine prenatal visits every one-to-four weeks[29], as well as the BHIP diet+exercise intervention. The diet component consisted of an individualized high protein diet (approximately 25% of energy needs) primarily from dairy products. Participants received their dairy products biweekly from the study nutritionist who also guided them through their nutritional goals. The exercise component of the intervention consisted of a monitored walking program three-to-four times per week for 25 minutes, and increasing in time by two minutes every session for up to 40 minutes daily until the end of pregnancy. Additionally, 10,000 steps per day were maintained by participants and tracked using a pedometer and exercise logs. Participants in the intervention group completed the intervention from enrollment (<12 weeks gestation) to the end of pregnancy. Additional details about the intervention is reported elsewhere[28]. Participants in the control group received usual care from their health care providers and updated guidelines on nutrition during pregnancy from Health Canada[30].

Infant Measures of Emotion Regulation:

Emotion is a combination of expression and physiology its regulation is best captured using multimethod assessments consisting of biological-physiological measures, observational and informant report measures[30].

Informant Reports

In this study, we used informant reports of child behavior to assess offspring temperament (child behaviour questionnaire (CBQ)), and executive function (Behavior Rating Inventory of Executive Function-Preschool Version (BRIEF-P)) as these constructs not only assess ER[31], but are also predictive of psychiatric problems in childhood and later in life[34].

Child Behavior Questionnaire (CBQ): The CBQ is a measure of child temperament in children aged 3-7 years of age. Temperament is fundamental to how children handle emotions and regulate their behaviour[38]. The CBQ consists of 195 questions which create fifteen temperament feature scales including Positive Anticipation, Smiling/Laughter, High Intensity Pleasure, Activity Level, Impulsivity, Shyness, Discomfort, Fear, Anger/Frustration, Sadness, Soothability, Inhibitory Control, Attentional Focusing, Low Intensity Pleasure, and Perceptual Sensitivity[38]. Mothers were asked to rate their child on a 7-point scale ranging from 1= extremely untrue to 7= extremely true, a not applicable option was also provided. Higher scores on these scales indicate better temperamental scores. In this study we chose to analyze temperament scales most closely related to child ER *a priori*[39] (Approach, Attentional Focusing, Falling Reactivity/Soothability, Impulsivity, and Inhibitory Control).

Behavior Rating Inventory of Executive Function-Preschool Version (BRIEF-P): The BRIEF-P is a standardized, validated and reliable measure of executive function (EF) in children aged two-to-five years of age. Problems with EF are associated with ER problems in children[40]. Since executive functions permit children to inhibit impulsive behaviour (inhibit scale), shift emotions in an appropriate manner (shift scale) and control their emotional responses (emotional control scale), EF is directly linked to ER[41]. The BRIEF-P includes 63 items and five scales including Inhibit, Shift, Emotional Control, Working Memory, and Plan/Organize. Mothers were asked to respond to each question as “never” (0), “sometimes” (1), or “often” (2). Higher scores on the BRIEF-P indexes indicate more problems with executive functioning. These scales form three separate indexes called Inhibitory Self-Control (ISCI) (inhibit and emotional control scales), Flexibility (Fl) (shift and emotional control scales), and Emergent Metacognition (EMI) (working memory and plan/organize scales)[40]. Based on the recommendations of Sherman and Brooks (2010) scores of all the indexes were reported[41].

Observational Measure: Objective Laboratory Task of Impulsivity (Snack Delay Task)

In the snack delay task, the child had to wait for the tester to say “go” before retrieving a treat (marshmallows) from the plate in front of them. Delays of 10, 20, 30, and 45 seconds were applied. Children were coded on their ability to wait until it was time to retrieve the treat, but scores were deducted if they moved their hands closer to the treat before the right time. This task was digitally recorded, and the research assistant who was trained on delivering and scoring this task timed the delays, as well as coded participants on a scale from 1= grabs treat before tester says “go” to 7=waits to retrieve treat until they are told “go”. Each time delay was scored from 1-7 and scores from each time were totalled to achieve a final overall score. Higher scores on the impulsivity task indicate less impulsivity.

Biological-Physiological Measures

Heart Rate Variability: HRV is one of the earliest emerging predictors of ER later in life and can predict later psychopathology[41]. Two ECG electrodes were placed on the child’s right shoulder blade and left lower back and data were acquired using Biolab Software (v.3.2.3 Mindware Ltd) during the five-minute resting state baseline task (watching a video clip from Finding Nemo), and during the impulsivity task. Mindware HRV software was then used to inspect data for artifacts and analyze data in the 0.24-1.04 Hz frequency domain[42]. Higher HF-HRV and RMSSD values indicate better heart rate variability and emotion regulatory abilities[31].

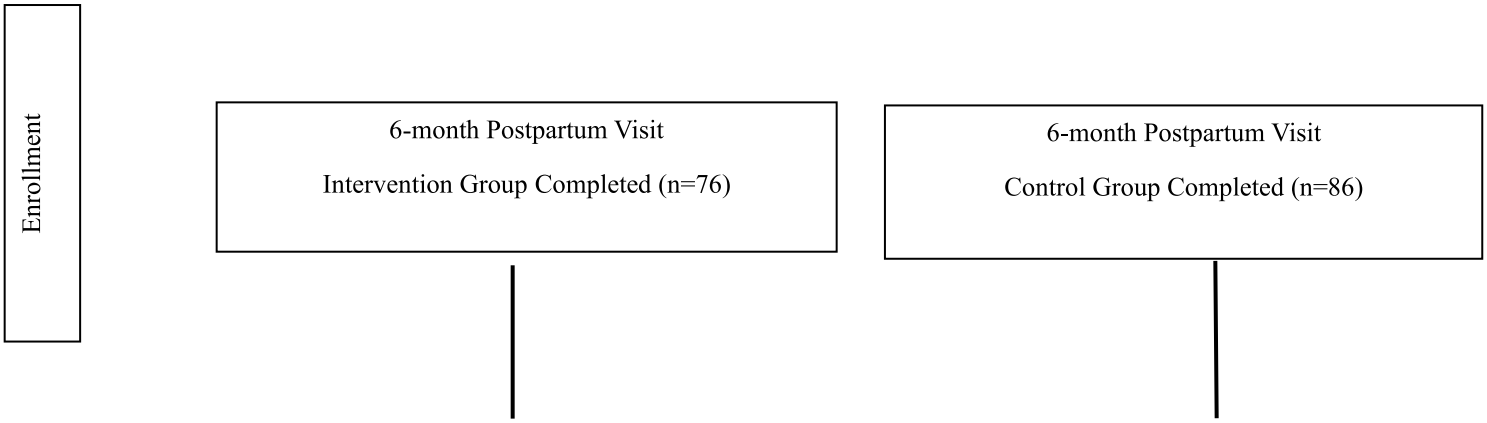
Frontal Alpha Asymmetry: EEG data were recorded using the Netstation (v.4.4.1) 128-electrode HydroCel sensor nets at 250 Hz and referenced to the vertex (EGI Inc). Data were collected during the impulsivity task, as FAA reflects task-specific neural processing[43]. Data was analyzed using EEGLab and underwent Fast Fourier Transformation to extract power within the 6-9 Hz alpha band. FAA was then calculated by subtracting the natural log transformed alpha power from the left hemisphere (F3) from the right hemisphere (F4). Greater left FAA is suggestive of better ER abilities[43].

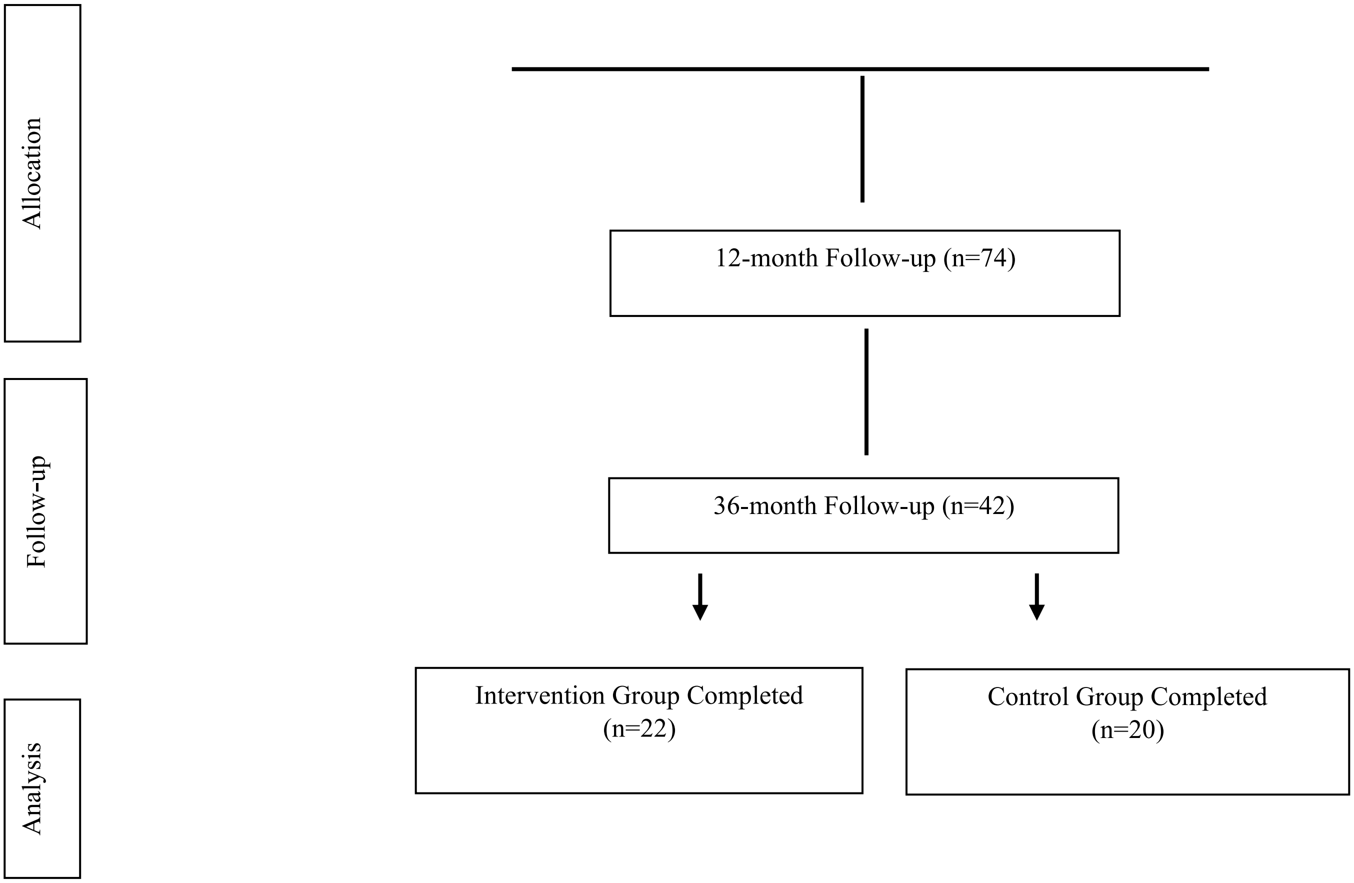
Statistical Analysis:

Maternal and infant demographic characteristics were summarized using descriptive summary measures: mean (SD) for continuous variables and n (%) for categorical variables. Demographic information was also compared between intervention and control groups and between our sub-sample and the original BHIP sample using *t*-tests (continuous data) and Chi squared –tests (categorical data). To calculate the mean differences between intervention and control groups at 36 months of age for the informant report, observational and biological-physiological measures, a one-way analysis of variance (ANOVA) was used. Given the exploratory nature of this study, we did not adjust for multiple comparisons. All analyses included stratification by participant BMI category. Analyses were performed using SPSS statistics 23 (IBM).

Results

Figure 1. Flow of Participants Through the BHIP Trial





Complete recruitment and eligibility criteria for the original BHIP RCT are detailed elsewhere[28]. The demographic characteristics of mothers and infants of our 36-month subsample (intervention=22, control=20) in the present study are presented in Table 1. Baseline maternal age (intervention=30.3 years, control=30.9) and pre-pregnancy BMI (intervention= 24.4, control=24.6) did not differ between the originally recruited BHIP sample (n=241), the BHIP 12-month follow-up (n=74), and this 36-month subsample. Maternal characteristics also did not differ for maternal education, ethnicity marital status, obstetrical complications, and household income. The age of three-year-old offspring of parents in the intervention and control group were not statistically significantly different (37.8 vs. 38.3 months), nor was birthweight (3611.0 vs. 3576.0 grams), and most children were exclusively breastfed at 6 months of age. The pregnancy characteristics of participants in this 36-month sample also did not differ from those in the original BHIP RCT.

Table 1. Demographic characteristics of participating mothers and children

Variables	**Intervention n=22**	**Standard care n=20**	**p-value**
Maternal Characteristics			
Maternal age (y) median (Q1, Q3)	30.3 (28.6, 33.9)	30.9 (28.1, 30.0)	0.93
Maternal education level n (%) Education above Bachelor's degree	17 (77.0)	15 (75.0)	0.69
Pre-pregnancy BMI (kg/m^2) median (Q1, Q3)	24.4 (22.2, 26.4)	24.6 (21.9, 27.8)	0.68
Pre-pregnancy BMI (kg/m^2) category n (%)			0.42
Underweight (<18.5)	0 (0.0)	0 (0.0)	
Normal weight (18.5-24.9)	15 (68.0)	12 (60.0)	
Overweight (25.0-29.9)	4 (18.0)	5 (25.0)	
Obese (≥30)	3 (13.0)	3 (15.0)	
Race/ethnicity n (%)			0.79
European descent	19 (86.0)	18 (90.0)	
Mixed/Other	3 (13.6)	2 (10.0)	
Total family income n (%)			0.82
<$45,000	1 (4.6)	0 (0.0)	
$45,000-$74,999	3 (13.6)	1 (5.0)	
>$75,000	17 (77.0)	18 (90.0)	
Unknown	1 (4.6)	1 (5.0)	
Married/living with significant other n (%)	22 (100.0)	20 (100.0)	0.95
Complications during pregnancy			0.76
Yes	2 (9.0)	1 (5.0)	
No	20 (91.0)	19 (95.0)	
Nulliparous n (%)	12 (55.0)	11 (55.0)	0.83
Infant Characteristics			
Child age (months) (SD)	37.8 (5.4)	38.3 (5.8)	0.81
Birthweight (g) median (Q1, Q3)	3611 (3298.0, 3971.0)	3576 (3266.0, 3792.0)	0.71
Breastfeeding 6 months	20 (91.0)	18 (90.0)	0.62
Exclusive	1 (4.5)	1 (5.0)	
Mixed	1 (4.5)	1 (5.0)	

Formula			

BMI, Body mass index; y, year; wk, week; SD, standard deviation; g, grams, EPDS, Edinburgh Postnatal Depression Scale
Mixed, combination of exclusive breastfeeding and formula

Maternally reported informant reports on the CBQ and BRIEF-P are reported in Table 2. For the CBQ, children in the intervention group scored statistically significantly higher in the approach ($p=0.02$, $\eta^2p=0.14$), attentional focusing ($p=0.02$, $\eta^2p=0.06$), falling reactivity/soothability ($p=0.04$, $\eta^2p=0.06$), and inhibitory control ($p=0.05$, $\eta^2p=0.10$) scales of the CBQ compared to children in the control group. Differences between the groups on these outcomes were of medium to large effect size. However, there were no statistically significant differences in the impulsivity scale between groups. For the BRIEF-P, mean scores from children in the intervention group were statistically significantly higher in the ISCI ($p=0.02$, $\eta^2p=0.15$) and FI ($p=0.05$, $\eta^2p=0.11$) indexes than children in the control group. Differences between the groups on these outcomes were also of medium to large size. There were no statistical differences between groups on the EMI index.

Table 2: Maternally Reported CBQ, and BRIEF-P Outcomes of Children at 36 Months of Age

	Intervention (n=22)		Control (n=20)			
Scales	Mean	95% CI	Mean	95% CI	p-value	η^2p
CBQ						
Approach	5.01	(4.69-5.33)	4.51	(4.20-4.83)	**0.02**	**0.14**
Attentional Focusing	4.91	(4.66-5.15)	4.38	(3.98-4.79)	**0.02**	**0.06**
Falling Reactivity/ Soothability	5.16	(4.73-5.58)	4.62	(4.34-4.90)	**0.04**	**0.06**
Impulsivity	4.13	(3.78-4.48)	4.18	(3.80-4.56)	0.84	0.01
Inhibitory Control	4.85	(4.47-5.22)	4.34	(3.95-4.73)	**0.04**	**0.10**

BRIEF-P				
ISCI	35.50 (32.42-38.57)	40.31 (37.32-43.30)	**0.02**	**0.15**
FI	27.05 (24.32-29.78)	31.18 (27.57-34.79)	**0.04**	**0.11**
EMI	38.73 (35.48-41.99)	38.81 (35.38-42.24)	0.97	0.00

CBQ, Children's Behavior Questionnaire; BRIEF-P, Behavior Rating Inventory of Executive Function-Preschool Edition; ISCI, Inhibitory self control index; FI, Flexibility index; EMI, Emergent metacognition index; η^2p, partial eta squared

Scores on the snack delay task are reported in Table 3. Children in the intervention group scored statistically significantly higher on the impulsivity task ($p=0.04$, $\eta^2p=0.15$), meaning they were less impulsive than children in the control group. Differences between the groups were of large effect size.

Table 3: Impulsivity task scores of children at 36 months of age

	Intervention (n=22)		Control (n=20)			
	Mean	95% CI	Mean	95% CI	p-value	η^2p
Impulsivity Score	26.41	(25.34-27.48)	24.10	(21.46-26.74)	**0.04**	**0.15**

η^2p, partial eta squared

HRV metrics of children at resting baseline and during the impulsivity task are reported in Table 4. Children in the intervention group had higher HF-HRV and RMSSD values at both baseline ($p=0.04$, $\eta^2p=0.25$; $p=0.03$, $\eta^2p=0.29$) and during the impulsivity task ($p=0.02$, $\eta^2p=0.27$; $p=0.04$, $\eta^2p=0.26$). These results suggest that infants in the intervention group had greater parasympathetic influence (RMSSD) during both tasks. Differences between groups for HF-HRV and RMSSD were of large effect size. Children in the two groups did not differ on FAA ($p=0.73$, $\eta^2p=0.18$).

Table 4: Biological-physiological outcomes of children during baseline and the impulsivity task

	Intervention (n=22)	Control (n=20)

Physiological metrics	Mean (SD)	Mean (SD)	*P*-value	η²p
Baseline HRV				
HR	108.29 (7.43)	114.18 (8.18)	0.21	0.14
HF-HRV	5.91 (1.20)	5.01 (1.03)	**0.04**	**0.25**
RMSSD	35.45 (8.15)	26.37 (7.10)	**0.03**	**0.29**
SDNN	41.21 (7.54)	37.32 (8.18)	0.42	0.07
Impulsivity Task HRV				
HR	121.21 (8.32)	127.83 (8.91)	0.34	0.16
HF-HRV	7.23 (3.54)	5.71 (2.73)	**0.02**	**0.27**
RMSSD	42.04 (8.95)	33.37 (7.87)	**0.04**	**0.26**
SDNN	44.24 (7.65)	39.94 (8.79)	0.51	0.05
Impulsivity Task FAA				
FAA	0.03 (0.13)	0.01 (0.11)	0.73	0.18

HR, heart rate; HF-HRV, high frequency heart rate variability; RMSSD, root mean square of successive differences; SDNN, standard deviation of NN intervals; SD, standard deviation; η²p, partial-eta squared

Discussion

In this RCT, the BHIP pregnancy diet+exercise intervention led to improvements in several informant-reported, observational, and biological-physiological measures of emotion regulatory capacity in children at 36 months of age. While the differences between intervention and control group for these measures ranged from medium to large effect sizes for all outcomes and the sample in this study did not differ from those enrolled in the original BHIP trial there has been significant attrition and the present findings are based on a small sub-sample.

To date, studies examining pregnancy diet and/or exercise interventions and child ER in humans are relatively rare. Observational studies that have assessed maternal nutrition during pregnancy and offspring ER abilities have shown that deficiencies of specific individual nutrients are associated with lower HRV in infants (Zn)[17] and children (B12)[16]. Another observational study examining the effects of an unhealthy maternal diet during pregnancy (western style diet) reported higher externalizing behavior and more aggression and attention problems in children up to 5 years of age[44].

Studies examining the effects of exercise during pregnancy and offspring ER are also very uncommon. Indeed, only two small RCTs have reported maternal aerobic exercise during pregnancy may lead to improved HRV at 36 weeks gestation[21] and 1 year of age[22].

Only two reports based on RCTs have examined the impact of a pregnancy diet+exercise intervention on offspring neurodevelopment and both emanated from the current sample and RCT[19,20]. These studies found improved expressive language and overall adaptive behavior in infants at 12 months of age, as well as improved HRV, RMSSD and parent-reported temperament at 12 months of age. This RCT will further contribute to the limitations of the field by assessing offspring ER development at 36 months of age (a critical age for observable aspects of ER) using a more comprehensive approach consisting of multiple ER measures, as opposed to a single physiological measure of ER.

The mechanisms underlying our findings of improved ER with a pregnancy diet+exercise intervention from the second trimester to the end of pregnancy are not known. However, research has suggested that poor overall diet quality and lower maternal protein intake during pregnancy is a source of prenatal fetal stress and can cause imbalances in the hypothalamic-pituitary-adrenal axis (HPA axis) of the offspring postnatally[51]. Stress induced imbalances in the HPA axis prenatally has been shown to alter glucocorticoid receptors in the amygdala, prefrontal cortex (PFC) and hippocampus, and lead to changes in the emotional reactivity of the offspring to stressful stimuli later in life[52] . Since the BHIP diet+exercise intervention began in the second trimester of pregnancy and pregnant persons in the intervention group consumed statistically significantly more protein in both the second and third trimester than the control group ($p=<0.001$, $n^2p=0.46$), as well as better diet quality overall during the second trimester, adequate protein intake and/or better overall quality may be plausible mechanisms for our results.

Brain regions such as the amygdala, PFC, and the hippocampus are highly involved in ER processes/development, and subject to heightened neuroplasticity during the second and third trimesters. These brain regions have also been found to be affected by maternal diet, specifically lower protein intake during pregnancy[47] which may decrease amygdala and hippocampal volume and contribute to behavioral and affective problems[48]. Since protein provides the amino acids essential for fetal development, an inadequate supply of any amino acid from maternal diet may impede protein synthesis by the fetus and result in adverse effects on fetal neurodevelopment[49,50]. However, a variety of nutrients such as omega-3 fatty acids, B-vitamins, and choline are also needed by the amygdala and hippocampus to develop optimally[51]. Therefore, a combination of good overall diet quality and higher protein intake during pregnancy are needed to potentially improve ER in offspring. Additionally, non-human animal studies report that poorer maternal protein intake leads to significant reductions in brain-derived neurotrophic factor (BDNF) levels in neonatal rat brains[54]. Given the key role BDNF plays in neuronal survival and growth, synaptogenesis, and neuronal/synaptic plasticity in the amygdala, PFC, and hippocampus[55], increased BDNF levels may be involved in our improved ER results.

Maternal exercise during pregnancy has also been found to increase BDNF and VEGF levels in the brain, leading to adaptive changes in the amygdala and PFC[58]. This may occur because maternal exercise optimizes fetal blood flow, as well as nutrient delivery to various brain regions and physiological systems that improve their development and function[59]. For example, maternal exercise during pregnancy is associated with greater neonatal cortical brain thickness,[60] an index of early brain development related to better behavioral and cognitive development in children[60]. However, step counts in the intervention group did not differ from the control group in the second (p=0.92, $n^2p=0.05$) or third trimester (p=0.58, $n^2p=0.13$). However, step count may not capture all of the exercise done by mothers and so it may also contribute, acting on its own or synergistically with diet to benefit fetal brain development in this study.

It is not known why improvements were not seen in FAA. One possibility is that the systems underlying FAA are influenced more by the postnatal social environment than the prenatal physical environment[61]. For example, one factor that has consistently shown to improve FAA (greater relative left frontal activity) is parent responsiveness and support in the home. Better sensitivity and responsiveness have led to improved FAA in offspring. Research has also suggested that prenatal interventions focused on maternal stress and mood disorders may have the greatest impact on FAA[62], since these factors can lead to greater right FAA (negative affective states)[63]. Since women in our sample were healthy and did not have any mood disorders, this intervention did not address one of the biggest predictors of FAA prenatally. However, studies have reported that HRV results may be enough to estimate emotion even without an EEG measure[62].

Despite the strengths of this study, the following limitations should be noted. First, attrition between study recruitment and 36 months postpartum was significant and the remaining sample size is quite small, and so these results need to be replicated in larger samples. However, since we did observe medium to large effect sizes for our statistically significant results across physiological, observational and behavioral levels of analysis, this study could provide important information on child ER and support future larger RCTs. Second, a single center design was used, and the sample consisted of a homogenous group of individuals who were healthy, educated, comfortable socioeconomically, and had access to universal healthcare. It is important to note however that participants in this sub-sample did not differ from participants in the original BHIP sample. Third, participants were aware of treatment group status. Fourth, limited data on maternal compliance to the intervention is available, which may limit our understanding of the mechanisms involved in our results. Additionally, we found that 18% of women in the second trimester achieved the 10,000 step count goal and only 9% of women in the third trimester. Fifth, child postnatal diet was not assessed, however, studies have supported that prenatal diet quality can lead to improvements in emotional and behavioural problems in offspring regardless of child diet postnatally[64]. Lastly, it is unknown whether the diet or exercise arm of the intervention had a greater impact on the results, or if the combination is required for positive effects.

This study utilized an RCT study design and found that the BHIP diet+exercise intervention applied during pregnancy improved multiple measures of ER across physiological, observational and behavioural levels of analysis. Although these results need to be replicated in larger and more diverse samples, this study utilized a modifiable, easily implementable, and widely accepted intervention to highlight the importance of investigating universal prenatal preventative interventions during periods of high neuroplasticity.

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Chapter 6: Conclusion

Summary

Nowhere is the importance of investing in health more apparent than in the developing child. The DOHaD hypothesis posits that prenatal and early postnatal exposures can negatively impact offspring neurodevelopment and lead to cognitive and emotional problems later in life (Mandy, 2018). To date, many observational studies have supported the tenets of the DOHaD hypothesis, but more methodologically rigorous experimental study designs (RCTs) have been lacking. Since early cognitive and ER difficulties place an enormous burden on children and families (Ennis et al., 2013), affect functioning at home and at school (Sandstrom et al., 2013), and retain strong continuities into adulthood (Spinelli et al, 2020), RCTs are needed to fully realize the DOHaD fields full clinical potential.

Since over half of pregnancies in Canada are unplanned (Black et al., 2015), examining modifiable risk factors that affect diverse populations, can be intervened upon, and that are cost-effective are crucial. Since brain plasticity decreases with age (Pauwels, 2018), prenatal interventions represent the most efficient and effective means by which child cognition and ER can be optimized (Abasi et al., 2021). Indeed, there are both economic and health care benefits of intervening early (Geelhoed et al., 2020). For example, every $1 invested in early child development interventions, generates a return of up to $17 per dollar invested (Heckman et al., 2013).

The studies included in this thesis are aimed at identifying risk and other modifying factors that may affect cognitive and emotional development in offspring, as well as testing interventions aimed at improving these outcomes. The results of study one found that better maternal diet quality was associated with improved executive function and behavioral outcomes in children raised in sub-optimal home environments. Problems with executive function and behaviour in children may lead to poor academic achievement, social problems and mental health disorders later in life (Andrews et al., 2021). Therefore, modifiable prenatal exposures (e.g., maternal diet quality) may have the potential to protect against later postnatal adversity such as poor home environments. However, adequately powered randomized controlled trials will be required to confirm these findings.

Studies two, three, and four used an experimental approach (i.e., an RCT) to examine the effects of a maternal nutrition and exercise intervention on offspring cognitive and ER development at different ages. In study two, the maternal nutrition and exercise intervention led to improved expressive language and adaptive behaviour scores on the BSID-III at 12 months of age. In study three, the intervention led to improved ER at 12 months of age, which was assessed across both physiological and behavioural levels. Lastly, in study four, the intervention led to improved ER at 36 months of age, which was assessed using physiological, observational and informant reported measures. These studies suggest maternal diet and/or exercise could have lasting effects on brain development, but also require replication in larger trials using different samples.

The studies in this thesis highlight the importance of identifying and intervening on modifiable risk factors during the prenatal period to potentially improve offspring cognition and ER, as well as moving the field closer to realizing the potential clinical utility of the DOHaD hypothesis as it pertains to optimizing offspring cognitive and ER development.

The Importance of Modifiable Prenatal Risk Factors and the DOHaD Hypothesis

The results of this thesis support the applicability of the DOHaD hypothesis to mental disorders and the importance of modifiable risk factors in optimizing offspring cognitive and ER development. To date, the majority of studies in the DOHaD field have been observational in nature, which has limited our understanding of causal mechanisms that underlie the DOHaD hypothesis (Mandy et al., 2018). Second, the majority of studies in the DOHaD field pertain to physical health problems like cardiovascular disease, kidney disease and diabetes (Arima et al., 2020). Studies examining offspring neurodevelopmental outcomes at critical periods in development are still largely lacking, particularly RCTs (Hanson et al., 2019). Third, studies that have examined modifiable risk factors such as diet or exercise during pregnancy have examined individual nutrients or nutrition and exercise independently for their impact on brain development (Sucharita et al., 2014; Spann et al., 2015; Gustafson at al., 2013). Given this background, the present thesis aimed to address some of the current gaps and limitations of the DOHaD hypothesis as it pertains to brain development, as well as provide preliminary recommendations for future studies. The results of this thesis suggest that a cost effective, easily implementable and comprehensive lifestyle intervention combining overall nutrition and exercise may be more effective in improving fetal and offspring cognition and ER development, and may have lasting results over years.

Mechanisms: How Combined Nutrition and Exercise During Pregnancy Impacts Offspring Cognition and ER From Infancy to Early Childhood

RCTs examining overall diet quality and/or exercise during pregnancy and offspring cognition and ER development are largely lacking. Observational studies looking at overall diet quality using birth cohorts have examined Mediterranean style diets (high in vegetables, fruits and lean proteins) during pregnancy and have found that they are associated with a reduction in the risk of offspring problems in communication, problem solving and personal-social domains at 12 months of age (Dai et al., 2023; House et al.; 2018). However, to date, RCTs addressing associations between pregnancy diet and offspring neurodevelopmental outcomes have largely examined the effects of micronutrient supplementation during pregnancy and offspring brain development. However, these studies have yielded inconsistent results (Zhou et al., 2018; Naninck et al., 2016; Larson et al., 2017). Additionally, very limited research exists in the field of maternal exercise during pregnancy and offspring cognitive and ER development. However, existing studies have suggested that maternal exercise may be associated with improved intelligence (Robinson et al., 2012), motor skills (Jones et at, 2021), attentional abilities (Balize et al., 2015), greater HRV (May et al., 2010), and reduced prevalence of ADHD later in life (Chan et al. 2022).

It is noteworthy to examine the potential mechanisms that lead to the persisting results of this prenatal intervention on later offspring neurodevelopment. Studies 2, 3, and 4 of this thesis suggests that the maternal diet and exercise intervention improved offspring cognitive and ER development from infancy to early childhood. One potential mechanism contributing to the lasting changes in cognition and ER that we observed is that maternal diet and exercise both gpromote neurogenesis and plasticity in the fetal and offspring brain (Kim et al., 2022). Enhanced neurogenesis and plasticity in the prenatal environment has a profound effect on fetal brain structure and function that may set the foundation and trajectory for later brain development postnatally (Pulli et al., 2019). Neurogenesis is critical for the development of neurons in the fetal brain and can optimize the development, size, and function of brain regions key to cognition and ER (i.e., PFC, amygdala, hippocampus). Neurogenesis is also involved in strengthening the neural connectivity between these regions that underlie important circuits for cognitive and ER performance in early childhood (Guadagno et al., 2021). Lastly, neurogenesis promotes brain plasticity (the brain's ability to adapt to changes/experiences) in the fetus and during early childhood. As new neurons that are generated are more malleable and responsive to stimuli (as opposed to mature neurons) and can form neural connections with additional neurons in response to stimuli or experiences (Tymofiyeva et al, 2021).

A second potential mechanism for these results may be that maternal diet and exercise have both been shown to reduce maternal health and metabolic conditions such as inflammation, oxidative stress, GDM, and obesity which may contribute to a wide range of fetal neurodevelopmental problems and reduce neurogenesis in the fetus (Han et al., 2021). A healthy maternal diet rich in protein can provide anti-inflammatory nutrients such as amino acids and omega-3 fatty acids to prevent or improve inflammation and reduce oxygen reactive species (Bordeleau et al., 2020), while maternal exercise prevents or reduces inflammation by increasing anti-inflammatory cytokines and improving insulin sensitivity (Calcaterra et al., 2022).

Another potential mechanism may be that maternal diet quality and exercise may improve maternal mental and physical health outcomes during the postnatal period. Since studies have suggested that diet quality and exercise during pregnancy can prevent or improve symptoms of depression, anxiety and stress in the postnatal period, this could have improved the quality of care and sensitivity, attention, and stimulation that mothers provided their offspring and further enhanced their cognitive and ER development in the postnatal period (Kołomańska et al., 2019). Additionally, introducing a comprehensive nutrition (overall diet quality) and exercise intervention could lead to healthy behavioural changes in women, where good nutrition and exercise becomes a part of their lifestyle (as opposed to introducing single nutrients only) (Anderson et al., 2016). If mothers consume a better diet quality and being active, they may be more likely to provide their children with the same diet quality and encourage physical activity, which are both important for cognitive and ER development (Mahmood et al., 2021).

One final mechanism that may emerge as a result of the intervention and function along with or in addition to those described above are epigenetic changes (e.g., DNA methylation) (Kundakovic et al., 2017). Maternal diet and exercise may promote DNA methylation and impact the expression of genes important to cognitive and ER development (i.e., BDNF, insulin-like growth factor (IGF)) and neurotransmitter production (i.e., serotonin, dopamine), which facilities the activity of brain regions such as the PFC and amygdala (Fernandes et al., 2017). Additionally, gene expression of BDNF and IGF have been suggested to improve neural plasticity in brain regions which may result in permanent changes to cognitive and ER development postnatally (Zuccarello et al., 2022).

Mechanisms: How Combined Nutrition and Exercise During Pregnancy Impacts Offspring HRV From Infancy to Early Childhood

Since the results of this thesis suggest persistent changes in ER, specifically HRV, it is important to discuss the potential mechanisms underlying these results. HRV is commonly used to measure autonomic nervous system (ANS) functioning in offspring as the ANS can reveal important information about how offspring regulate physiological processes such as heart rate and breathing, and their psychological state of health (Kim et al., 2018). Since HRV is one of the earliest emerging predictors of psychopathology later in life, prenatal factors such as maternal diet and exercise have been suggested to impact HRV (McCraty et al., 2015). Maternal exercise has been suggested to improve cardiovascular health and the functioning of the vagal tone (Witvrouwen et al., 2020). Vagal tone pertains to the activity of the vagus nerve which is an essential component of the Parasympathetic Nervous System (PNS) (Fields et al., 2008). PNS activity is indicative of a calm state while sympathetic nervous system (SNS) functioning is indicative of a stressed state (Sanghavi et al., 2014). Therefore, maternal exercise increases vagal tone and PNS functioning while decreasing SNS functioning, leading to better HRV and ER (White et al., 2014). Additionally, a healthy overall diet quality during pregnancy has also been suggested to increase PNS functioning and decrease SNS functioning (Krzeczkowski et al, 2020). A healthy diet has ant-inflammatory effects that can prevent or reduce maternal inflammation and oxidative stress (both of which can increase SNS activity and reduce PNS activity) (Iddir et al., 2020). Therefore, a diet consisting of a variety of nutrients can promote PNS functioning and improve HRV and ER in offspring (Young et al, 2018). The branches of the ANS are particularly sensitive to prenatal factors which may cause long-term changes to offspring ER (Perrera et al., 2011). For example, since the branches of the ANS are still under development prenatally, external factors (i.e., maternal diet quality, stress) can readily disrupt the balance between the PNS and SNS activity permanently (Mulkey et al., 2019).

Synergistic Effects of Nutrition and Exercise During Pregnancy on Postnatal Exposures That May Impact Offspring Cognition and ER

In addition to the positive prenatal effects maternal diet and exercise may have on fetal neurodevelopment, this intervention may have important implications for adverse postnatal exposures that may affect offspring neurodevelopment. One of the most commonly examined postnatal exposures affecting offspring neurodevelopment is SES (Hung et al., 2015). SES refers to an individuals social standing and often consists of the level of education, income and employment status (Darin-Mattsson et al., 2017). Research has suggested that offspring of lower SES households may be exposed to less stimulation, support, and resources needed for early childhood neurodevelopment (Bush et al., 2020). However, as study 1 of this thesis suggests, prenatal exposures such as good maternal diet quality may benefit offspring who face postnatal adversities such as poor SES. These results are consistent with other studies examining the potential protective effects of positive prenatal exposures against adverse postnatal exposures. One study reported that maternal exercise during pregnancy was associated with better cognitive and ER abilities in children at 10 years of age, these effects were stronger in children from low SES backgrounds (Labonete-Lemoyne & Cassidy, 2016). Similarly, another study reported that a maternal diet rich in nutrients (folate, omega-3, iron) was associated with better cognitive scores at 4.5 years of age, and these effects were also stronger in lower SES backgrounds (Julvez et al., 2016). Since optimal maternal diet and exercise may improve fetal neurodevelopmental processes (i.e., neuronal proliferation and differentiation, synaptogenesis) that aid in the development of brain regions and their synaptic connections with one another, this may lead optimal development of brain regions and circuits that make the offspring more resilient to postnatal adversity (Martinat et al., 2021). Resilience is defined as the ability to adapt to or recover from adversity (Southwick et al., 2014). Optimal fetal development of brain regions important to cognitive and ER development such as the PFC and amygdala, may lead to better decision making and stress management, as well as regulation of emotional responses in response to postnatal adversity respectfully (Bick et al., 2016). Additionally, greater fetal brain development through optimal maternal diet and exercise may lead to greater neuroplasticity which is the ability to change and adapt to stressful environments (Ho et al, 2021). Greater neuroplasticity may enable offspring to better cope and adjust to challenging situations such as poor SES (Noble et al., 2021). Ultimately, better prenatal exposures such as good maternal diet and exercise may result in less need for an optimal postnatal environment, whereas poorer prenatal exposures may result in greater need for positive postnatal environments (i.e., high SES) to compensate for poorer fetal neurodevelopment.

Limitations

The findings of this thesis should be viewed in light of their limitations. Study 1 was an observational study so we were unable to make causal inferences from this work. The primary limitation of studies 2, 3, and 4 were the sample size and lack of diversity in participant characteristics. Although these studies were RCTs, the sample sizes were small, so results of the studies must be interpreted with caution. The sample size was smaller than planned due to the effects of the COVID-19 pandemic and loss to follow-up of participants. However, we did observe medium to large effect sizes for the results of various measures which may enhance the clinical relevance of the study and aid in future larger RCTs. The sample characteristics in studies 2, 3, and 4 consisted of a homogenous group of women with higher education and SES. Therefore, this may limit the generalizability of these findings to other populations. Additionally, women in this sample had access to universal health care with no severe nutritional deficiencies present. Hence, the effects of this intervention may have been limited. It is therefore important for future RCTs to consist of a larger sample size, and include a diverse range of educational and SES backgrounds to reveal the potential of this intervention.

Additional limitations of studies 2, 3, and 4 include the lack of data on postnatal factors that may have improved child cognitive and ER abilities. For example, factors such as child diet and the home environment (stimulation and support in the home) may impact child cognition and ER development, however, we are unsure if these factors differed between groups. However, infants and children in the sample were balanced on all other characteristics at baseline. Further, since we did not examine mechanisms in women or their biology, we are unsure if our results may have resulted from improved maternal mental and physical health due to the effects of the intervention (leading to improved care and sensitivity towards their offspring), or if the intervention had direct effects on the fetus. Next, limited information on maternal adherence to the intervention was collected (only step count data collected). Lastly, although we observed improvements in outcomes such as ER, we are unaware which brain regions were underlying these improvements using only EEG and ECG measures.

Future Directions

Recommendations for Future RCTs Assessing Nutrition and Exercise Interventions and Offspring Cognition and ER Development

The results of the present thesis suggest that modifiable risk factors such as prenatal diet and exercise may improve offspring cognitive and ER development. However, it is important that future RCTs incorporate additional steps to improve the clinical potential and implications of the present RCT. Recommendations to improve the present RCT are outlined below.

First, larger RCTs using a heterogenous sample are required. If larger RCTs demonstrate similar results to the studies in this thesis, future RCTs can address numerous gaps in the field and use this intervention to potentially lead the DOHaD field forward.

For example, in addition to introducing this intervention to healthy women of various racial, educational, and SES backgrounds, extending this intervention to women with various mental and physical health problems to observe any effects this intervention has on the neurodevelopment of their offspring may be beneficial. Since research has suggested that maternal diet quality and exercise during pregnancy may improve maternal conditions such as depression, anxiety, stress, and diabetes (which are all associated with adverse fetal and offspring neurodevelopment (OuYang et al., 2021)), prenatally and during the postpartum period (Mate et al., 2021), it may be of interest to include measures that examine maternal outcomes during pregnancy and the postpartum period to better understand the underlying mechanisms of these results. Since diet and exercise can be modified to fit the lifestyle and health of everyone, this intervention can be tailored and applied to various populations to observe the effects on offspring neurodevelopment.

It may also be beneficial for future RCTs to use additional physiological and neurophysiological measures to identify underlying mechanism involved in offspring cognitive and ER improvements. For example, using salivary tests to measure cortisol and oxytocin levels in women and offspring can provide us with insight on whether improvements in maternal mood outcomes are primarily responsible for improved ER outcomes in offspring or if the intervention had a direct impact on offspring brain development. Additionally, the use of neurophysiological measures such as functional near infrared spectroscopy (fNIRS) can result in determining brain activation of specific cortical areas that may be responsible for the changes we observe. Since studies in the DOHaD field have proposed epigenetic modifications as a potential mechanism underlying the DOHaD hypothesis, it may also be interesting to collect blood samples (DNA and RNA) from women in order to examine epigenetic changes that may have resulted in improvements in offspring cognition and ER, and further improve our mechanistic understanding of these results. Furthermore, this intervention only included step count as a measure of exercise adherence. Future studies can include additional measures of exercise, so data on participants who engage in physical activity aside from walking can be collected as well. Additionally, in order to determine who this intervention may benefit most, or what factors may affect the outcomes of this intervention, examining mediating or moderating factors such as child diet, pre-pregnancy BMI, maternal complications, or the HOME environment using sub-group analyses may be needed.

Another recommendation for future RCTs is to include longer follow-up times in order to test the stability of cognitive and ER changes in offspring. Longer follow-up periods can provide us with insight on the developmental trajectories of cognitive and ER development and factors that may facilitate in stability or instability of these results.

Next Steps in Clinical Research: Recommendations

Nutrient intake and exercise intensity should be modified throughout pregnancy based on fetal needs (Most et al., 2019). Examining the effects of this intervention introduced at different times during pregnancy might be beneficial in observing if there are further improvements to offspring development or if results are consistent. Additionally, since research has suggested that longer interventions may yield lower adherence rates (Ivers et al., 2020), it may be of interest to examine the effects of this intervention in a shorter duration to possibly increase adherence rates, and reduce cost and resources needed for such interventions. However, if this intervention is most successful over a longer duration of time, it is important to incorporate additional strategies to improve adherence. For example, including an individualized exercise program (such as our individualized dietary component) may be beneficial as experts can create an exercise plan that participants enjoy and are more likely to follow (as compared to only walking). Additionally, providing bi-weekly video or phone calls to participants to review their exercise logs and provide suggestions for improvement has been suggested to improve adherence in the literature (Room et al., 2017). Lastly, involving a partner, family member, or friend as a source of motivation and accountability for participants may also improve adherence rates. In terms of the dietary component of the intervention, this includes most of the recommended strategies to improve adherence that has been examined in the literature. However, one additional recommendation may be to provide other sources of protein (i.e., non-dairy products) to offer additional options.

Additional adherence strategies that may benefit both components of the intervention include providing participants with an educational brochure prior to the start of the intervention which highlights the specific advantages of a combined diet and exercise intervention (i.e., improvements in the development and size of the placenta). It may be more motivational to participants if they knew the specific potential advantages of this intervention on their fetus's neurodevelopment (as opposed to being told a healthy diet and exercise regimen is important during pregnancy). Second, providing a smaller incentive multiple times throughout the intervention as opposed to one incentive at the end of the intervention may be more motivating to participants to adhere to the intervention. Lastly, studies have suggested that daily or weekly text-reminders have significantly improved adherence rates as participants are consistently being reminded of their goals and the importance to their fetus (Fenerty et al., 2012). However, since the results of this intervention are not generalizable currently, these suggestions are preliminary in nature, and should be considered once larger RCTs with more diverse populations are conducted.

Conclusion

Cognitive and ER development in infancy and early childhood depends primarily on prenatal and early postnatal environmental conditions. The DOHaD hypothesis posits that adverse prenatal conditions can affect the function and structure of key physiological systems and increase the risk of psychopathology. The studies in this thesis highlight the importance of modifiable risk factors introduced during the prenatal period, and their benefits on fetal and child development. Given the promise of these findings, larger RCTs using more diverse samples are needed to determine if their application in public health settings is a sound investment. Since investment in early intervention programs have resulted in impressive returns, intervening on modifiable risk factors during pregnancy may be the best chance of preventing or reducing psychiatric disorders in offspring, and the burden these problems have on Canadian families and the health care system.

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Appendix

Chapter 2: Maternal pregnancy diet, postnatal home environment and executive function and behavior in 3- to 4-y-olds (Study 1)

Supplementary Table 1

Table 1: Statistical variance of all variables included in the fully adjusted model for each study outcome

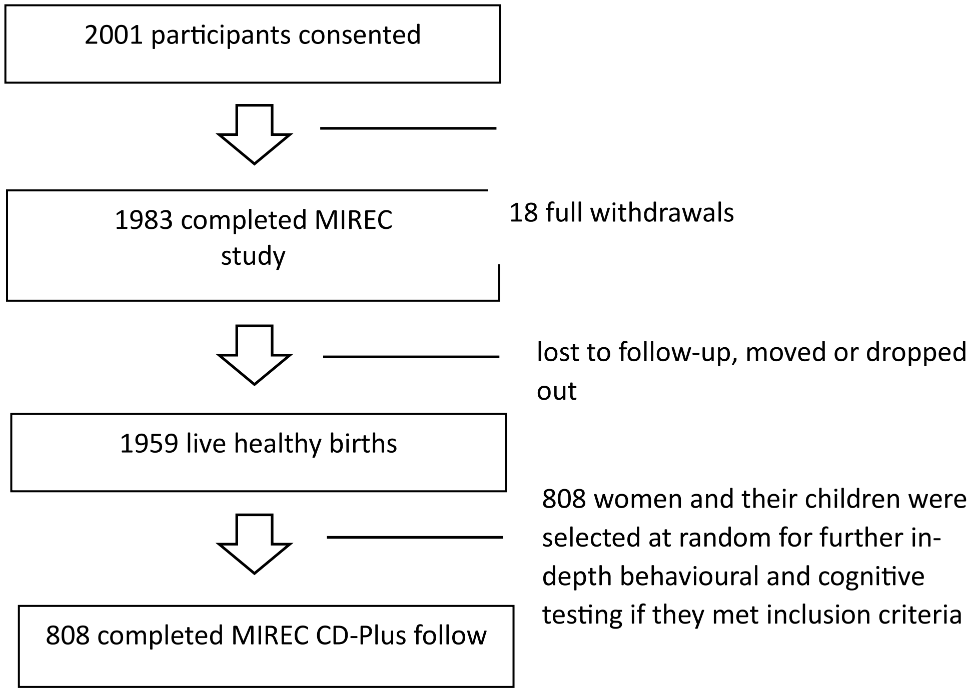
BRIEF-P	**Standardized β**	***P***
Working Memory Scale		
Home Total Score	-0.16	0.013
Total Diet Score	0.11	0.084
Maternal Education	-0.05	0.464
Maternal Postpartum Depression	0.16	0.012
Maternal Pre-Pregnancy BMI	0.01	0.883
Maternal Pregnancy Smoking	-0.01	0.850
DietxHome	0.20	0.001
Planning Scale		
Home Total Score	-0.11	0.140
Total Diet Score	0.13	0.054
Maternal Education	-0.08	0.257
Maternal Postpartum Depression	0.15	0.022
Maternal Pre-Pregnancy BMI	0.06	0.376
Maternal Pregnancy Smoking	-0.07	0.297
DietxHome	0.06	0.007
BASC-2		
Adaptability Composite		
Home Total Score	0.17	0.008
Total Diet Score	0.07	0.277
Maternal Education	0.01	0.972
Maternal Postpartum Depression	-0.17	0.008
Maternal Pre-Pregnancy BMI	0.09	0.154
Maternal Pregnancy Smoking	0.13	0.039
DietxHome	-0.13	0.032

BASC-2, Behavioral Assessment of Children- 2nd Edition

BMI, Body mass index

BRIEF-P, Behavior Rating Inventory of Executive Function- Preschool version

Supplemental figure 1: MIREC CD-Plus participant flow chart

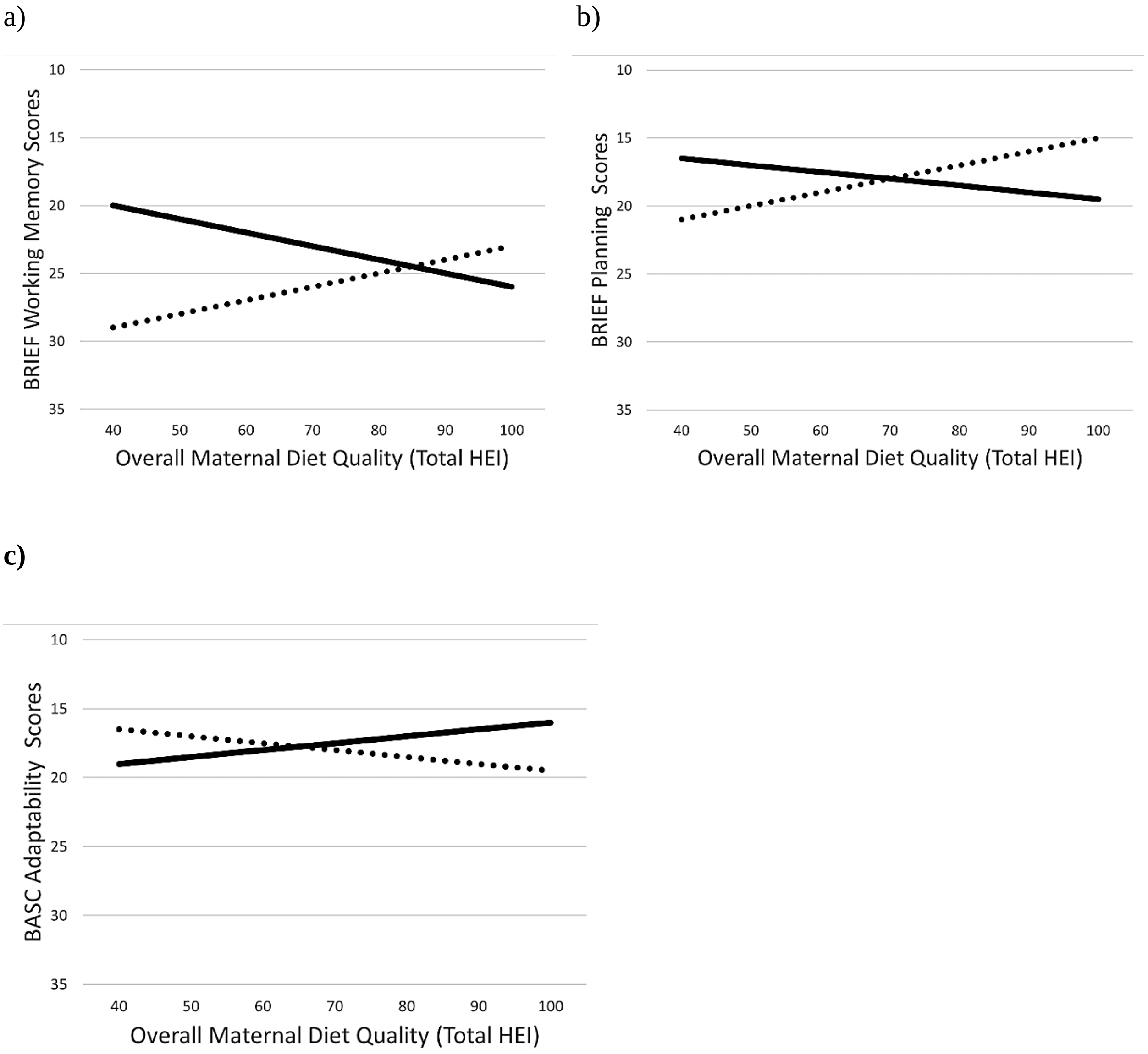


The above flow chart was adapted from the following MIREC publication:

Arbuckle TE, Fraser WD, Fisher M, Davis K, Liang CL, Lupien N, Bastien S, Velez MP, von Dadelszen P, Hemmings DG, Wang J et al. Cohort profile: the maternal-infant research on environmental chemicals research platform. Paediatr Perinat Epidemiol. 2013;27(4):415-25

Supplementary figure 2:

Figure 2: Line graphs for the association between maternal diet quality during pregnancy and working memory, planning scores of the BRIEF-P, and adaptability scores of the BASC-2 in better or poorer home environments[1]



[1]= Home environment was dichotomized at the median for graphing and interpretation purposes

━ Better home environment

⋯ Poorer home environment

BASC, Behavioral Assessment Scale for Children (2nd Edition)

BRIEF, Behavior Rating Inventory of Executive Function (Preschool version)

HEI, Healthy Eating Index

Chapter 3: Early Neurodevelopment in the Offspring of Women Enrolled in a Randomized Controlled Trial Assessing the Effectiveness of a Nutrition + Exercise Intervention for Optimizing Gestational Weight Gain During Pregnancy (Study 2)

Supplementary Table S1:

Table 1: Measures of the influence of pre-pregnancy BMI, GWG and maternal complications during pregnancy on BSID-III measures for the intervention group by ANCOVA

Source	SS	df	MS	F	Sig	η²p	Observed power
Cognition							
BMI	0.19	1	0.19	0.07	0.79	0.00	0.06
GWG	2.06	1	2.06	0.78	0.38	0.02	0.14
Complications	0.05	1	0.05	0.02	0.89	0.00	0.05
Treatment	0.32	1	0.32	0.12	0.73	0.00	0.06
Error	128.55	49	2.62				
Receptive Language							
BMI	6.32	1	6.32	0.76	0.39	0.02	0.14
GWG	0.57	1	0.57	0.07	0.80	0.00	0.06
Complications	5.71	1	5.71	0.68	0.41	0.01	0.13
Treatment	3.86	1	3.86	0.46	0.50	0.00	0.10
Error	410.37	49	8.38				
Expressive Language							
BMI	1.88	1	1.88	0.56	0.46	0.00	0.11
GWG	1.16	1	1.16	0.34	0.56	0.01	0.09
Complications	0.14	1	0.14	0.05	0.84	0.00	0.06
Treatment	9.92	1	9.92	2.91	0.09	0.06	0.39
Error	170.81	50	3.42				
Fine Motor							
BMI	0.23	1	0.23	0.07	0.79	0.00	0.06
GWG	4.41	1	4.41	1.31	0.26	0.03	0.20
Complications	0.61	1	0.61	0.18	0.67	0.00	0.07
Treatment	1.38	1	1.38	0.41	0.52	0.01	0.10
Error	161.11	48	3.36				
Gross Motor							
BMI	10.00	1	10.00	1.50	0.23	0.03	0.22
GWG	11.75	1	11.75	1.76	0.19	0.04	0.25
Complications	2.33	1	2.33	0.35	0.56	0.01	0.09
Treatment	10.13	1	10.13	1.52	0.23	0.03	0.23
Error	293.96	44	6.68				

Social Emotional							
BMI	0.57	1	0.57	0.17	0.69	0.00	0.07
GWG	0.00	1	0.00	0.00	0.99	0.00	0.05
Complications	0.01	1	0.01	0.00	0.95	0.00	0.05
Treatment	7.02	1	7.02	2.02	0.16	0.04	0.29
Error	163.13	47	3.47				
GAC							
BMI	40.88	1	40.88	0.56	0.46	0.01	0.11
GWG	72.72	1	72.72	1.00	0.32	0.02	0.17
Complications	15.22	1	15.22	0.21	0.65	0.01	0.07
Treatment	268.61	1	268.61	3.70	0.07	0.07	0.47
Error	3338.71	46	72.58				

BMI, Body mass index; GWG, Gestational weight gain; BSID-III, Bayley's Scale of Infant and Toddler Development- 3rd Edition; ANCOVA, analysis of covariance

Chapter 4: Preliminary Findings of Emotion Regulation in 12-Month Old Infants of Mothers Enrolled in a Randomized Controlled Trial Assessing a Nutrition + Exercise Intervention (Study 3)

Supplementary table 1:

Table 1: Correlations between HRV metrics and IBQ-R short form factors

		HF-HRV	HR	RMSSD	SDNN	SURG.	NEG.	REG.
HF-HRV	Pearson Correlation	1	-.519*	.888**	.875**	.369	.134	.184
	Sig. (2-tailed)		.033	<.001	<.001	.194	.647	.529
	N	17	17	17	17	14	14	14
HR	Pearson Correlation	-.519*	1	-.466	-.550*	-.250	.269	-.439
	Sig. (2-tailed)	.033		.060	.022	.389	.353	.116
	N	17	17	17	17	14	14	14
RMSSD	Pearson Correlation	.888**	-.466	1	.923**	.262	-.128	.165
	Sig. (2-tailed)	<.001	.060		<.001	.366	.662	.574
	N	17	17	17	17	14	14	14
SDNN	Pearson Correlation	.875**	-.550*	.923**	1	.039	.040	.058
	Sig. (2-tailed)	<.001	.022	<.001		.894	.892	.843
	N	17	17	17	17	14	14	14

SURG; Surgency/extraversion; NEG, Negative affectivity; REG, Regulation/orienting; HF-HRV; High frequency heart rate variability; HR, Hear rate; RMSSD, Root mean square of successive differences; SDNN; Standard deviation of N-N intervals

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).