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Early neurodevelopment in the offspring of women enrolled in a randomized controlled trial assessing the effectiveness of a nutrition + exercise intervention on the cognitive development of 12-month-olds

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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 Development* third edition (BSID-III) as the outcome measure. We also examined if maternal factors (prepregnancy BMI, gestational weight gain (GWG)) moderated associations. Expressive language (MD = 9.62, 95% CI = (9.05–10.18), $p = 0.03$, $\eta^2p = 0.07$) and general adaptive composite (GAC) scores (MD = 103.97, 95% CI = (100.31–107.63), $p = 0.04$, $\eta^2p = 0.06$) 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 behavior 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.

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]

The developmental origins of health and disease (DOHaD) hypothesis posits that prenatal and early postnatal exposures can alter the physiology of an organism and increase the risk of disease across the lifespan.[4] The process by which these alterations result from exposure to intrauterine conditions (including poor maternal nutrition and/or physical inactivity) has been referred to as prenatal programming.[5] Therefore, intervening on these exposures through maternal lifestyle interventions could represent effective early approaches to improving offspring cognition.

Prenatal nutrients provide the building blocks for neuronal proliferation, patterning and function, and neurotransmitter metabolism in the brain.[6] Research from observational studies of maternal nutritional status has long supported a link between maternal nutrient deficiencies and reduced cognitive functioning in offspring.[7–9] 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]

The synergistic effects of nutrients are thought to be crucial for the development of the brain's structure, size, function, and the neural circuits that underlie cognitive development.[14] While many nutrients play a role in brain development, nutrients such as folate, iron, and omega-3 fatty acids are required for neural tube formation, myelination, and synaptic function, respectively.[15] Imbalances in these nutrients can result in fewer synaptic connections between brain regions underlying cognition such as the prefrontal-cortex (PFC) and hippocampus.[16] Other nutrients such as choline and protein may influence gene expression and alter the DNA methylation of genes implicated in development of cognitive brain structures.[17] Lastly, good overall maternal diet quality has been linked to reductions in inflammation, oxidative stress, and gestational diabetes mellitus (GDM), all of which have been independently linked to adverse fetal brain development.[14] Therefore, since nutrients work in a synergistic manner to benefit the fetus,[18–20] 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.[21] 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.[21–23] 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.[24] Lastly, in two small RCTs, pregnant persons who exercised during pregnancy had infants with higher heart rate variability,[25] and infants with superior auditory memory at 8–12 days of age compared to nonexercising women.[26] These studies suggest that maternal exercise may benefit fetal brain development. Potential mechanisms underlying these findings may include alterations in the development and maintenance of the placenta and improved blood, oxygen, and nutrient delivery to the fetal brain for optimal development and function.[21] Maternal exercise may also lead to increased levels of neurotrophic factors such as BDNF in the fetal brain (specifically the hippocampus). BDNF has been associated with increased neurogenesis (formation of new neurons) and improved cognitive outcomes.[26] 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

This study was an extension of the original BHIP RCT[27] 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[29] more than UPC alone (control group). Given that opportunities to assess the neurodevelopment of the offspring of women who have participated in combined nutrition+exercise interventions are very rare, and since research supports the independent impact of nutrition and exercise interventions on offspring neurodevelopment, we assessed cognition in a subset of participants enrolled in the original RCT at 12 months of age. 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 prepregnancy 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#12469) 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 center using block sizes of two, four, and six at random using the online Research Electronic Data Capture (REDCap) randomization system and was stratified by study site and BMI category as detailed previously.[27] The study was open-label with blinded endpoints due to the nature of the intervention,[27] 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.

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 Fig. 1); 74 participants were eligible and agreed to participate at 12 months of age. The study took place at McMaster University.[27–28]

Inclusion Criteria: Healthy pregnant persons > 18 years old with singleton pregnancies, prepregnancy 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.

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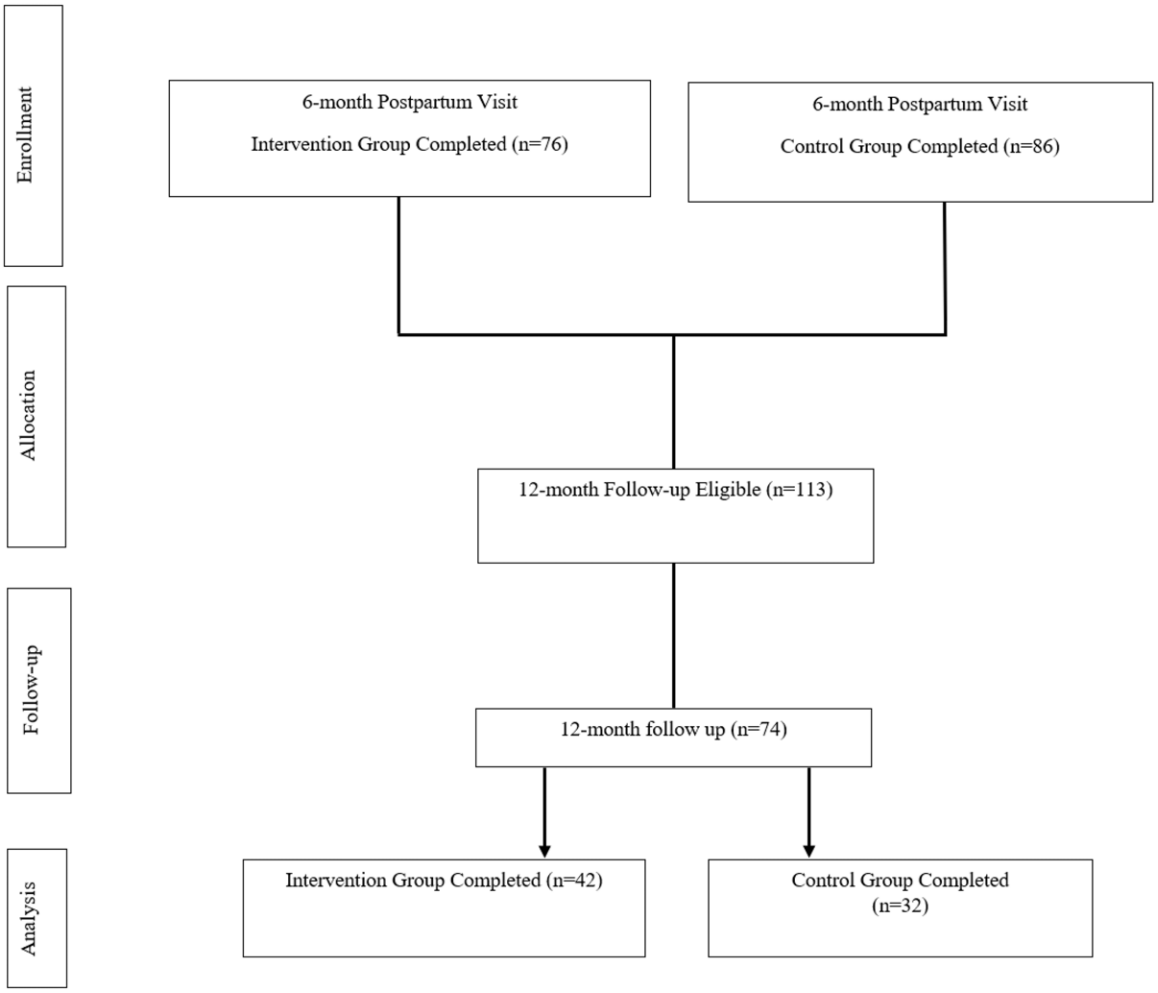

Figure 1. Flow of participants through the BHIP trial.

Exclusion Criteria: Contraindications to exercise, significant heart, kidney, or liver disease, refusal to consume dairy products, preexisting diabetes mellitus, smoking, or a baseline score ≥ 12 on the Edinburgh Postnatal Depression Scale (EPDS) at recruitment. Inclusion and exclusion criteria for this study extension are identical to the original trial.

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 comprises an individualized nutrition plan with a high-protein intake (~25% of energy needs) primarily provided by dairy products. Nutrition consumption was individualized to each participants energy requirements as calculated by the Dietary Reference Intake report[30] and revised as necessary throughout pregnancy. Participants visited the study site biweekly to receive their 4–5 servings of dairy products (i.e., fresh low-fat milk, cottage cheese, Greek yogurt, etc . . .) and see the study nutritionist, who provided them with strategies to reach their nutritional goals. Dairy products of preference were provided to participants to ensure consumption of the recommended quantity of dairy products. The study nutritionist also provided participants with recipes to incorporate their daily nutritional needs as means to improve adherence to the dietary component of the intervention.

The exercise component of the intervention consisted of a controlled walking program with the study nutritionist, 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. Participants maintained 10,000 steps per day using a pedometer and exercise logs to track their progress each day. Participants wear and track their step counts weekly using a pedometer, as well as walk with research staff in order to increase motivation and adherence to the intervention. These exercise guidelines are based on the Physical Activity Readiness Medical Examination (PARmed-X) for Pregnancy.[31]

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.[27]

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.[32]

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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.[33] 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, preacademic, 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,[34] 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 and therefore ensuring fair comparisons.. Scaled scores range from 1 to 19, with a mean of 10 and standard deviation of 3.[33] However, GAC scores are only reported as composite scores, and these scores range from 40 to 160, with a mean of 100 and standard deviation of 15.[33]

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 (prepregnancy 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 stratified by participant BMI category in each model. All analyses were conducted using SPSS Statistics 23.

Results

Participant recruitment, eligibility, and randomization (which occurred at baseline (12-17 weeks gestation)) criteria in Figure 1 are detailed in the manuscript outlining the original BHIP RCT.[28] The characteristics of the BHIP 12-month subsample (intervention = 42, control = 32) involved in the present study are presented in Table 1. Baseline mean maternal age_{years} (intervention = 31.0, control = 31.8) and mean prepregnancy BMI (intervention = 25.0, control = 25.1) 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 mean birthweight (3587.8 vs. 3560.8 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.

It is important to note that although data on maternal compliance to the intervention are relatively limited, we found that the 10,000-step goal was achieved by 15% of mothers in the second trimester and 5% of mothers in the third trimester. However, step count was statistically significantly higher in the intervention group compared to the control group in the second trimester ($p = 0.004$, $n^2p = 0.25$) but not the third trimester ($p = 0.282$, $n^2p = 0.12$). Protein intake was statistically significantly higher in the intervention group compared to the control group in the second ($p < 0.001$, $n^2p = 0.40$) and third ($p < 0.001$, $n^2p = 0.40$) trimesters, and overall diet quality (assessed using a short form food frequency questionnaire (FFQ)- PrimeScreen) was also better in the intervention group than the control group in the second ($p < 0.001$, $n^2p = 0.38$) and third ($p = 0.002$, $n^2p = 0.29$) trimesters.

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, $p = 0.03$, $\eta^2p = 0.07$) and GAC ($M = 103.97$, 95% CI=(100.31–107.63), $p = 0.04$, $\eta^2p = 0.06$) scales compared to infants in the control group. There were no statistically significant sex differences for the cognitive (t (df) = 69, $p = 0.57$), receptive language (t (df) = 69, $p = 0.46$), expressive language (t (df) = 61, $p = 0.16$), fine motor (t (df) = 68, $p = 0.17$), gross motor (t (df) = 68, $p = 0.69$), social-emotional (t (df) = 63, $p = 0.31$), and GAC (t (df) = 66, $p = 0.29$) outcomes.

A one-way ANCOVA found no evidence for moderating effects of prepregnancy 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.[35] 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.[36] In terms of the impact of pregnancy exercise, one observational study

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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) (M, SD)	31.0 (3.1)	31.8 (3.4)	0.31
Gestational age at randomization (wk) (M, SD)	13.1 (1.5)	12.7 (1.4)	0.24
Maternal education level *n* (%) Education above Bachelor's degree	37 (88.0)	26 (81.0)	0.72
Maternal EPDS depression score ≥ 12 (at 6 months) *n* (%)	0 (0.0)	1 (3.0)	0.33
Prepregnancy BMI (kg/m^2) (M, SD)	25.0 (4.6)	25.1 (4.3)	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			0.72
Yes	5 (12.0)	4 (13.0)	
No	31 (74.0)	18 (56.0)	
Nulliparous n (%)	21 (50.0)	17 (53.0)	0.71
Infant characteristics			
Birthweight (g) (M, SD)	3587.8 (433.1)	3560.8 (409.4)	0.79
Breastfeeding 6 months			0.64
Exclusive	35 (83.0)	24 (74.0)	
Mixed	4 (10.0)	4 (13.0)	
Formula	3 (7.0)	4 (13.0)	

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

suggested that exercise during pregnancy was associated with higher language scores at 15 months of age in a sample of British children.24 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.[23] Nonhuman 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.[26] 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.[37] 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.[38]

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,[39] while adaptive behavior refers to skills (conceptual, social, and practical) that affect the ways individuals meet their personal and environmental needs.[40] However, both of these domains of the BSID-III are heavily

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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

dependent on frontal lobe development and functioning,[41] and sub-optimal maternal nutrition has been linked to structural abnormalities in brain regions such as the frontal lobe.[42] 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.[43] Nonhuman 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.[44] 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.[44] 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.[21] 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 and increase neurotrophic factor expression in various brain regions.[26]

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.[12] 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.[8] 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 prepregnancy 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.[45]

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-center 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.[33] 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, limited data on maternal compliance to the intervention were reported. 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, this intervention had medium-sized effects on expressive language and adaptive functioning. These subtle improvements in cognitive and adaptive functioning observed at 12 months of age could contribute to greater improvements at later stages of development. From a developmental cascade perspective, the impact of diet and exercise on brain development may not be static, but viewed as a precursor of future adaptive functioning. In other words, in addition to early observed benefits in cognitive and adaptive functioning, prenatal diet+exercise could initiate a cascade of adaptive events that unfold across time, manifesting in multiple, diverse benefits in functional outcomes. Therefore, 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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Competing interests. None.

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