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Associations Between Maternal Pre-Pregnancy Body Mass Index and Neonatal Neurobehavior in Infants Born Before 30 Weeks Gestation

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Abstract

Objective: To examine the relationship between maternal pre-pregnancy body mass index (BMI) and neonatal neurobehavior in very premature infants.

Study Design: Multi-center prospective observational study of 664 very preterm infants with 227 born to obese mothers. The NICU Network Neurobehavioral Scale (NNS) assessed neurobehavior at NICU discharge.

Results: Elevated BMI combined with infection increased the odds of having the most poorly regulated NNS profile by 1.9 times per BMI SD. Infants born to mothers with elevated BMI in combination with: infection had poorer self-regulation, chorioamnionitis had increased asymmetrical reflexes, diabetes had poorer attention and low SES required more handling.

Conclusion: Maternal pre-pregnancy BMI alone did not affect short-term neonatal neurobehavior in infants born before 30 weeks gestation. Infants born to mothers with elevated pre-pregnancy weight in addition to infections, diabetes, or socioeconomic adversity demonstrated increased risk of having the most poorly regulated NNS profile and deficits in multiple domains.

Keywords

prematurity; neurobehavior; development; outcomes; body mass index; follow-up

Introduction

The worldwide obesity epidemic is a major public health concern and poses additional threats during pregnancy. The rate of pre-pregnancy overweight and obesity has steadily increased over the past 20 years.¹ Elevated pre-pregnancy weight has also been associated with multiple maternal morbidities, including gestational diabetes, pregnancy-induced hypertension², cesarean sections, and labor induction³.

In addition to maternal complications and prematurity, elevated pre-pregnancy weight has been linked to poor neurodevelopmental outcomes in childhood, such as decreased cognitive performance prior to two years of age⁴, behavioral and emotional difficulties between one month of age to adulthood⁵, and attention deficit hyperactivity disorder symptoms in school-aged children⁶. Though a causal pathway has not yet been identified, it has been suggested that these associations may be mediated by increased inflammation^{7,8} and metabolic dysregulation⁹.

A recent study of maternal pre-pregnancy body mass index (BMI) and neurobehavior demonstrated poorer regulation, lower arousal, and higher lethargy in term infants born to mothers with elevated maternal pre-pregnancy weight.¹⁰ To date, there are no published studies addressing maternal pre-pregnancy overweight status or obesity and their association

with neonatal neurobehavior in infants born preterm, especially those born before 30 weeks post-menstrual age (PMA), a group at high risk of developmental impairment^{11, 12}.

Early identification of preterm infants at highest risk for neurodevelopmental difficulties in later childhood presents a challenge. To identify emergent infant neurobehavior, neonatal neurobehavioral assessments such as the NICU Network Neurobehavioral Scale (NNNS) have well documented prognostic value.^{13,14} The NNNS is a validated, comprehensive evaluation developed to assess the at-risk infant.¹⁵ NNNS summary scores are composites of individual items combined to reflect varied aspects of neurologic integrity, behavioral functioning, and stress responses.¹⁶ These 13 summary scores are used to group infants into mutually exclusive categories, or risk profiles.¹⁷ Compared with infants born at term, preterm infants demonstrate altered neurobehavior with atypical NNNS summary scores and profiles.¹⁸

Given that multiple prenatal, perinatal, and post-natal factors have the potential to alter the risk of abnormal neurodevelopment, it is important to acknowledge that interactions between factors may play a crucial role. For example, socioenvironmental resources and adversities influence subsequent neurodevelopment and may be expected to further modify the effects of prenatal exposures.

The goal of this study was to examine the relationship between maternal pre-pregnancy body mass index (BMI) and short-term neurobehavior in infants born <30 weeks PMA. We hypothesized that NNNS summary scores and risk profiles would indicate decreased neurobehavioral regulation in infants born to mothers with elevated pre-pregnancy BMI.

Methods

Design and Study Population

Of 852 infants whose parents were approached for consent, 704 infants were enrolled in NOVI. This study included 664 infants with completed neurobehavioral assessments and medical data. Standard procedures were used to collect data on maternal pre-pregnancy BMI, maternal socioenvironmental and medical risk factors, and infant risk factors. The NNNS was used to assess infant neurobehavior at hospital discharge. This methods section summarizes published methods detailed previously.^{17, 19, 20}

The Neurobehavior and Outcomes in Very Preterm Infants (NOVI) study was designed to evaluate psychosocial characteristics and interactions between pre-pregnancy BMI, gestational diabetes, infection, and hypertension associated with neonatal neurobehavior at NICU discharge. The overarching goal was to identify which infants born <30 weeks PMA are at greatest risk for impaired development based on neurobehavioral dysfunction at NICU discharge. Newborns were recruited from 9 university affiliated neonatal intensive care units (NICUs) participating in the Vermont-Oxford Network (VON) from April 2014 to June 2016. Enrollment and consent procedures were completed in accordance with each of the following center's Institutional Review Board [*Children's Mercy Hospital IRB in Kansas City, MO (IRB00004750)*, *Western Institutional Review Board in Puyallup, WA (WIRB20131387)*, *John F. Wolf Human Subjects Committee in Los Angeles, CA*

(IRB00000389), Spectrum Health Systems, Inc. in Grand Rapids, MI (IRB00009435), Women & Infants Hospital in Providence, RI (IRB00000746), and Wake Forest University Health Sciences in Winston-Salem, NC (IRB00000212)]. Inclusion criteria comprised 1) birth at <30 weeks gestation²¹; 2) maternal ability to read and speak English or Spanish; and 3) residence within 3 hours of the NICU and follow-up clinic. Exclusion criteria included maternal age <18 years, maternal cognitive impairment, infants with major congenital anomalies²², maternal death, or infant death in the NICU.

Parents of eligible infants were invited to participate when survival to discharge was determined to be likely by the attending neonatologist. Study specifics were explained in detail, and informed consent was obtained.

Procedures

Medical Data Collection—Maternal medical variables including pre-pregnancy weight, pregnancy weight change, gestational diabetes, hypertension, infections during pregnancy (urine, bladder, kidney, vaginal, and cervical infections) and chorioamnionitis were abstracted during neonatal hospitalization from medical records. Multisite reliability criteria for medical record review were established by consensus agreement. Structured maternal enrollment interviews were conducted by trained research personnel to assess socioenvironmental characteristics such as race/ethnicity, education, occupation, income, and partner status. Hollingshead socioeconomic status (SES) was calculated based on maternal education and occupation, and low SES in this study included mothers with less than a high school education and those working in unskilled occupations.²³ Information on substance use, anxiety, depression, and the receipt of counseling and/or prescribed medication for these conditions was obtained from both medical records and interviews.

Infant medical characteristics, including gestational age at birth, birthweight, and gestational age at discharge were also abstracted from medical records. Using VON definitions and criteria²⁴, medical records were also reviewed to collect information on neonatal medical complications such as brain injury, retinopathy of prematurity, sepsis, necrotizing enterocolitis, and chronic lung disease.

Neonatal Neurobehavioral Assessments—Neonatal neurobehavior was assessed using the NNNS, a 20–30 minute standardized procedure used to measure active and passive muscle tone, primitive reflexes, and the regulation of attention, movement, arousal, and stress abstinence responses.¹⁵ The NNNS was administered during the week of NICU discharge ± 3 days by certified site examiners trained to reliability using standardized procedures and criteria.²⁵ Examiners were masked to chronological age, PMA at exam, and medical history. Exams were performed prior to a scheduled feeding or care time to maximize alertness, avoid sleep disturbance, and maintain NICU routines. Validated algorithms were used to convert individual items into 13 NNNS summary scores (habituation, attention, handling, regulation, arousal, excitability, lethargy, hypertonia, hypotonia, non-optimal reflexes, asymmetric reflexes, quality of movement, and stress abstinence), where higher scores reflect a higher level of the construct measured.¹⁶ As we previously reported, latent profile analysis of the summary scores grouped infants into

6 mutually exclusive NNNS risk profiles representing the infant's pattern of performance across all summary scores (Fig. 1). Profile 6 infants were the most poorly regulated with decreased attention, self-regulation, and movement quality, hypertonia, and increased stress signs.¹⁷ Infants with this behavior profile demonstrated a dysregulated behavioral pattern associated with early influences of demographic and medical factors.

Statistical Analysis

Pre-pregnancy body mass index (BMI) was computed as reported weight (kg) divided by square of measured height (m). Obesity is defined as BMI ≥ 30 kg/m². Maternal and infant characteristics were examined by maternal obesity using one-way analysis of variance (ANOVA) for continuous measures or chi-square for categorical measures. Significance was accepted at $P < .05$.

Generalized estimating equations (GEEs) accounted for mothers with multiple infants by nesting infants within families. These analyses examined associations between maternal pre-pregnancy BMI and NNNS summary scores and risk profiles, adjusting for site and the following covariates: PMA at birth, PMA at NNNS exam, socioeconomic status, race/ethnicity, gestational diabetes, hypertension, pregnancy weight change, infection during pregnancy, and chorioamnionitis. Low SES, infection during pregnancy, hypertension, gestational diabetes and chorioamnionitis were considered as potential effect modifiers. Pre-pregnancy BMI was analyzed as a continuous variable that was standardized to allow interpretation in the form of change in NNNS scale per standard deviation (SD) increase in BMI. Interactions between pre-pregnancy BMI and the model covariates were examined further when p -values were ≤ 0.10 . The analysis adheres to STROBE guidelines.

Results

A total of 227 infants (34.2%) were born to mothers with pre-pregnancy BMI ≥ 30 kg/m², and 437 infants (65.8%) were born to mothers with pre-pregnancy BMI < 30 kg/m² (Fig. 2). The mean pre-pregnancy BMI for mothers in this sample was 27.9 (SD=7.4).

Between the two BMI groups, there were no differences in maternal age at childbirth, socioeconomic status, prenatal tobacco use, administration of betamethasone or magnesium sulfate, rates of maternal asthma, infection during pregnancy, chorioamnionitis, and pre-pregnancy depression and anxiety. (Table 1). In addition to having increased pre-pregnancy weight change (208.7 vs 136.7 pounds, $P < 0.01$) and increased pre-pregnancy BMI (36.4 vs 23.5, $P < 0.01$), mothers in the obese group were more likely to report being of minority ethnicity (65.3% vs 53.5%, $P < 0.01$), as well as more likely to have hypertension (37.9% vs 21.8%, $P < 0.01$) and gestational diabetes (11.6% vs 3.4%, $P < 0.01$). Though more mothers in the obese group gained weight above Institute of Medicine guidelines (27.6% vs 12.6%, $P < 0.01$), their mean weight gain during pregnancy was lower than that of non-obese mothers (13.7 vs 22.4 pounds, $P < 0.01$). Infant characteristics were similar between the two BMI groups, including PMA at birth, PMA at NNNS exam, birthweight, and multiple gestations.

Maternal pre-pregnancy BMI alone was not found to have a significant association with NNNS risk profiles, or with individual summary scores (Table 2). However, we found

significant interactions for pre-pregnancy BMI in combination with either infections, chorioamnionitis, gestational diabetes, hypertension or low SES on NNNS profiles and varied summary scores. Elevated pre-pregnancy BMI combined with infection during pregnancy increased the odds of infants having the most poorly regulated NNNS profile (Profile 6) by 1.946 times per BMI SD (95% CI: 1.147–3.301, P=0.014) (Table 3). Infants born to mothers with elevated pre-pregnancy BMI and gestational diabetes had decreased attention (−0.376/BMI SD, 95% CI: −0.778, 0.027, P=0.067; Table 4). Those born to mothers with elevated pre-pregnancy BMI and low socioeconomic status were found to have higher handling scores (0.074/BMI SD, 95% CI: 0.017, 0.131, P=0.010) that reflected increased additional handling required to facilitate alertness during the NNNS exam. This combination was also associated with poorer self-regulation (−0.170/BMI SD, 95% CI: −0.352, 0.013), P=0.069; Table 4), which measures the infant’s modulation of attention, arousal, movement, and autonomic responses. Infants born to mothers with elevated pre-pregnancy BMI and chorioamnionitis had increased asymmetrical reflexes (.412/BMI SD, 95% CI: 0.156, 0.668, P=0.002). (Table 4).

Discussion

Our primary aim was to examine the relationship between maternal pre-pregnancy BMI and short-term neurobehavior in very preterm infants. Given, 1) the steady increase in adult overweight and obesity worldwide, 2) emerging research supporting an association between maternal pre-pregnancy BMI and children’s neurodevelopment^{4–6}, and 3) the well-established link between prematurity and neurobehavioral impairment^{13, 14}, these findings could inform the design of effective, targeted antenatal interventions. Unlike many factors associated with perinatal morbidity and mortality not amenable to intervention, pre-pregnancy overweight status or obesity are modifiable risk factors. To this extent, weight control has the potential to affect outcomes found to persist from the perinatal period throughout childhood.

We found that maternal pre-pregnancy BMI alone did not have an effect on short-term neonatal neurobehavior in infants born before 30 weeks gestation. However, very preterm infants born to women with pre-pregnancy obesity combined with gestational diabetes, infection during pregnancy or labor, or socioeconomic adversity were significantly more likely to demonstrate deficits in attention, self-regulation, and handling needs at NICU discharge. These findings identify a high-risk subset of mothers who may benefit from weight control prior to conception, as well as very preterm infants at additional risk of impairment who may benefit from early, targeted intervention. Our findings are in concert with earlier studies reporting prediction from pre-pregnancy BMI to neurodevelopmental deficits in *later* childhood at 10 years of age.^{26, 27} The present study is the first to explore this association at NICU discharge in order to identify the earliest indicators of dysregulated neurobehavior and intervention targets. Further, in this study, we have identified neonatal neurobehavioral characteristics that have also been associated with subsequent neurodevelopmental deficits.^{10, 11} We analyzed NNNS risk profiles in addition to summary scores since pregnancy weight gain strongly predicted membership in a poor neurobehavioral profile in a previous study.²⁸ Our findings indicate that NNNS outcomes

provide a potential basis for early preventive and targeted interventions to facilitate improved self-regulation, attention, and stress responses.

The association between maternal diabetes and poor perinatal outcome including preterm birth²⁹, macrosomia³⁰, congenital malformation³¹, and stillbirth³² has been well established. Prior studies have demonstrated increased risk of poor cognitive development in infants born to mothers with diabetes during pregnancy.^{33, 34} Though the mechanisms by which maternal diabetes is associated with offspring cognitive development are unclear, it has been hypothesized that hyperglycemia and ketoacidosis may lead to neonatal cognitive impairment.³⁵ Maternal pre-pregnancy BMI is a well-known predictor of both maternal diabetes and gestational diabetes.³⁶ Our findings suggest that the combination of elevated pre-pregnancy BMI and maternal diabetes during pregnancy is associated with a higher risk for poor attention on the NNNS than maternal diabetes during pregnancy alone.

It has been hypothesized that maternal pre-pregnancy overweight status and obesity influence offspring neurodevelopment through inflammatory pathways.^{7,8} As a result of increased inflammation, the combination of elevated pre-pregnancy BMI and infection during pregnancy or labor could impact fetal neurodevelopment to a greater degree than either risk factor alone, and lead to abnormal neonatal neurobehavior. In particular, chorioamnionitis has been associated with increased risk of morbidity, including bronchopulmonary dysplasia, severe intraventricular hemorrhage, severe retinopathy of prematurity, and early-onset sepsis in addition to mental delay and cerebral palsy in preterm infants.^{37, 38} Although inflammatory biomarkers were not measured in this study, mediators related to early brain function may provide additional insights in future work. Our findings, however, do suggest that underlying inflammatory processes resulting from the additive effects of maternal pre-pregnancy obesity and infection during pregnancy or labor may be a link to alterations in neurobehavior reflected in the highest risk NNNS profile and to self-regulation, in particular.

The influence of adverse socioeconomic conditions such as poverty and decreased maternal educational attainment and occupational prestige on neurodevelopment has been well documented.^{39–41} In addition to parent-child interactions and stimulation in the home environment, prenatal factors can also impair children's cognitive and emotional development. Low SES in pregnant women increases the risk of premature delivery⁴², which is associated with poor academic performance and childhood mental illness.^{43–45} Low SES is also associated with increased maternal stress, higher rates of infection, and malnutrition during pregnancy.⁴⁶ Our findings indicated that infants born to women with low SES and elevated pre-pregnancy BMI demonstrated increased needs for additional handling support to sustain alertness during the NNNS exam. This is consistent with prior work involving medically and socio-environmentally diverse samples, where low SES has been found to further compromise postnatal neurobehavior as measured by the NNNS¹¹, and to be related to long term behavioral, cognitive, language, and academic problems^{14, 47–49}.

Strengths of this study include its large multi-site sample size. Extensive efforts were made to collect complete and comparative data across all sites through rigorous training and standardized protocols for both recruitment and data collection. All examiners were masked

to infant and maternal histories to reduce bias. Finally, the breadth of data on maternal, infant, and environmental characteristics allowed for more meaningful and integrated assessment of risk factors associated with neonatal neurobehavioral regulation.

It should be noted that due to the observational design of the study, causal inferences cannot be drawn. Because we included outborn infants in children's hospitals to expand the generalizability of our findings, a limitation of the study includes reliance on infant medical records for maternal medical information. Postnatal enrollment of infants expected to survive also resulted in maternal interviews that included retrospective questions regarding prior diagnoses of depression and anxiety and the receipt of counseling and/or prescribed medications for these diagnoses.

In terms of future work suggested by our findings, it would be of interest to examine associations between maternal pre-pregnancy underweight status and infant outcomes. Other studies have suggested that underweight mothers have an increased risk for adverse child outcomes such as low birth weight⁵⁰ and delayed intellectual development⁵¹. Our study population did not include a sufficient number of mothers who were underweight prior to becoming pregnant to allow assessment of this association.

Our findings may inform preconception counseling and identified a category of very preterm infants at additional risk for delayed neurodevelopment. More studies examining the relationship between maternal pre-pregnancy BMI and children's long-term neurodevelopment will be necessary to clarify the implications of our findings. We are currently following this NOVI cohort through early childhood in order to ascertain if the impairments noted at NICU discharge persist and to identify the conditions that contribute to risk and resilience in these most vulnerable infants.

Conclusion

In conclusion, maternal pre-pregnancy weight combined with infection during pregnancy or labor, gestational diabetes, or low SES is associated with specific neonatal neurobehavioral patterns at NICU discharge. Our findings identify prenatal indicators of neurobehavioral risk, and potential areas for early targeted interventions and extended follow-up. Since weight is a modifiable risk factor, improved weight control has the potential to alter both perinatal and long-term outcomes.

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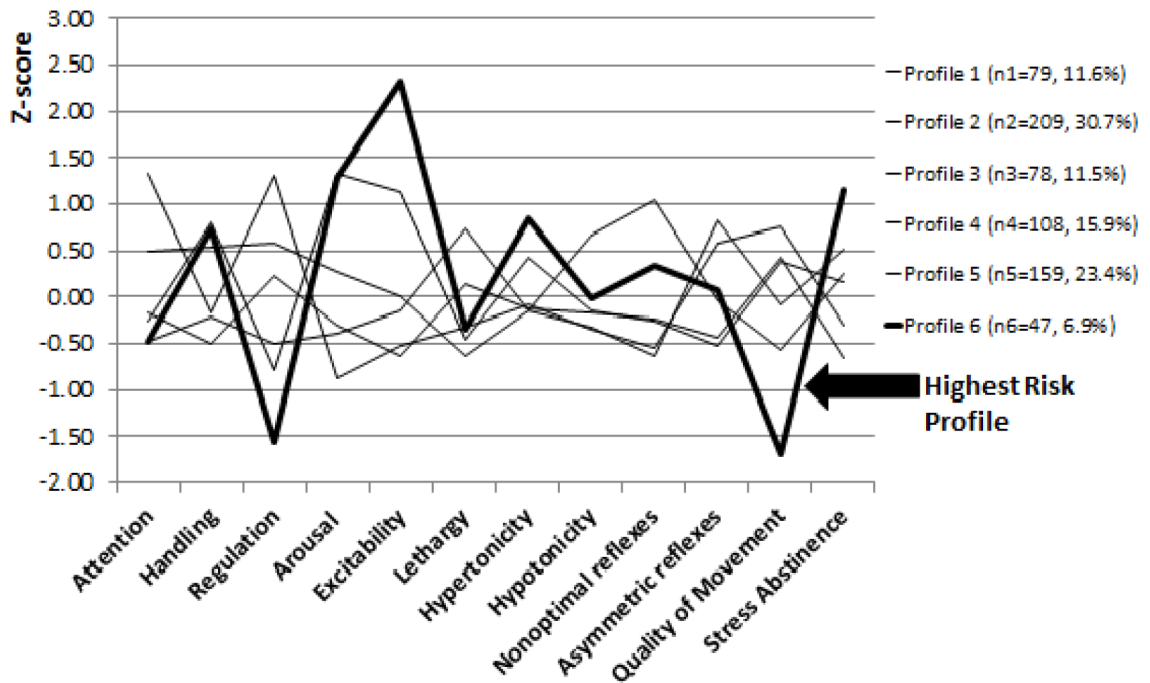


Figure 1. NICU Network Neurobehavioral Scale Risk Profiles
 Adapted from: McGowan EC, Hofheimer JA, O’Shea TM, Carter BS, Helderman J, Neal CR, et al. Sociodemographic and Medical Influences on Neurobehavioral Patterns in Preterm Infants: A Multi-Center Study. *Early Hum Dev.* 2020;142.

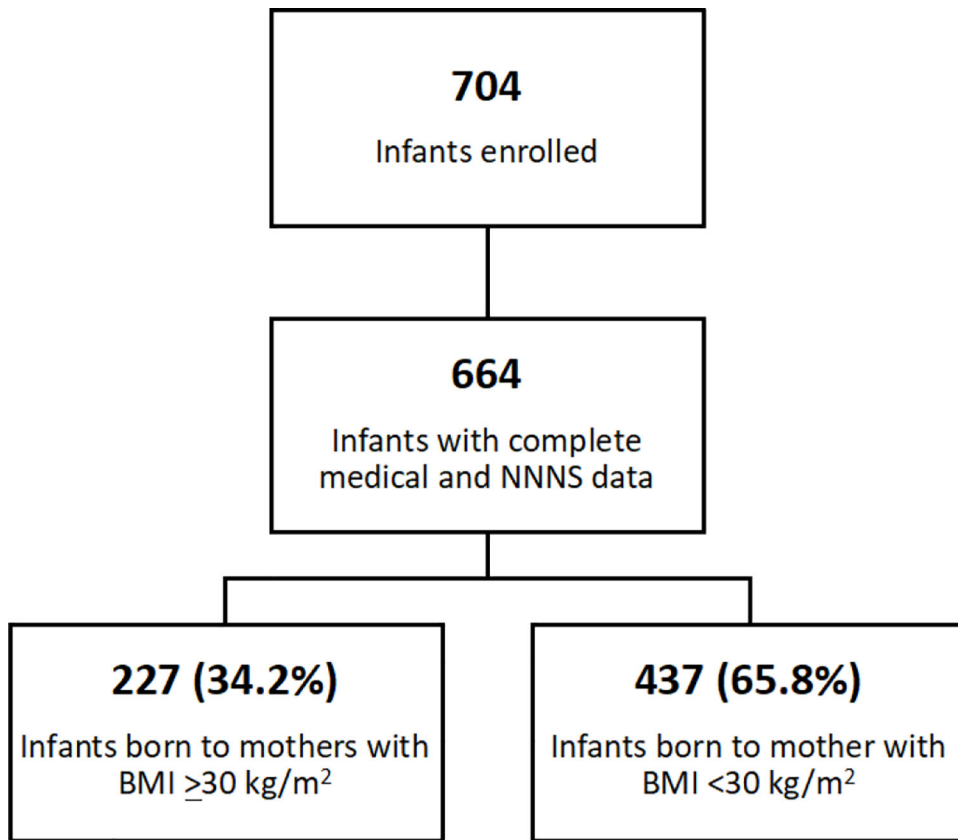


Figure 2.
Flow diagram for identification of study cohort

Table 1.

Maternal and Infant Characteristics

	Maternal Pre-Pregnancy BMI 30 kg/m ²	Maternal Pre-Pregnancy BMI <30 kg/m ²	p-value
Maternal (n=582)	n=199	n=383	
Maternal Age at childbirth (years) (mean, sd)	29.2 (6.2)	28.7 (6.5)	0.36
SES Hollingshead index, neonatal (mean, sd)	33.7 (11.5)	35.8 (13.0)	0.06
Low SES (n, %)	22 (11.1)	34 (8.9)	0.40
Minority race or ethnicity (n, %)	130 (65.3)	205 (53.5)	<0.01
Prenatal tobacco use (n, %)	27 (13.4)	57 (14.5)	0.71
Betamethasone (n, %)	144 (77.0)	264 (73.9)	0.43
Magnesium sulfate (n, %)	126 (64.0)	245 (64.1)	0.97
Pre-pregnancy weight (pounds) (mean, sd)	208.7 (36.8)	136.7 (23.1)	<0.01
Pre-pregnancy BMI (kg/m ²) (mean, sd)	36.4 (5.5)	23.5 (3.4)	<0.01
Pregnancy weight change (pounds) (mean, sd)	13.7 (21.7)	22.4 (14.3)	<0.01
Weight gain above IOM* guidelines (n, %)	55 (27.6)	48 (12.6)	<0.01
Maternal asthma (n, %)	18 (9.1)	26 (6.8)	0.32
Infection during pregnancy (n, %)	21 (10.6)	39 (10.2)	0.88
Chorioamnionitis (n, %)	38 (19.3)	69 (18.1)	0.73
Pre-pregnancy depression dx (n, %)	48 (24.5)	75 (19.7)	0.19
Pre-pregnancy anxiety dx (n, %)	46 (23.5)	86 (22.6)	0.82
Maternal hypertension, chronic or pregnancy-induced (n, %)	75 (37.9)	83 (21.8)	<0.01
Gestational diabetes (n, %)	23 (11.6)	13 (3.4)	<0.01
Infant (n=664)	(n=227)	(n=437)	p-value
PMA at birth (weeks) (mean, sd)	27.1 (1.9)	27.0 (1.9)	0.96
Birthweight (grams) (mean, sd)	949 (267)	953 (283)	0.89
PMA at NNNS Exam (weeks) (mean, sd)	39.2 (3.2)	39.3 (3.5)	0.63
Multiple gestation (n, %)	55 (24.3)	120 (27.5)	0.38

Table 2. Associations between pre-pregnancy BMI and NNNS summary scores and profiles

NNNS Summary Scale	Pre-pregnancy BMI			
	Adjusted Mean *	B	95% CI	P
ATTENTION	5.56	-0.043	-0.166, 0.081	0.499
HANDLING	0.39	0.016	-0.006, 0.038	0.154
QUALITY OF MOVEMENT	4.46	0.032	-0.019, 0.084	0.218
SELF-REGULATION	5.55	-0.006	-0.062, 0.051	0.848
NON-OPTIMAL REFLEXES	5.58	0.078	-0.083, 0.239	0.344
STRESS ABSTINENCE	0.13	0.002	-0.003, 0.007	0.505
AROUSAL	3.72	0.038	-0.016, 0.093	0.163
EXCITABILITY	2.54	0.042	-0.119, 0.202	0.609
LETHARGY	4.54	0.013	-0.156, 0.181	0.884
	Adjusted OR *			
HYPERTONICITY	0.93	-0.073	-0.228, 0.082	0.353
HYPOTONICITY	0.83	-0.188	-0.399, 0.023	0.080
ASYMMETRICAL REFLEXES	0.98	-0.023	-0.124, 0.079	0.662
NNNS Dysregulated Profile	0.99	-0.009	0.739, 1.329	0.950

* Model adjusted for site, PMA at NNNS exam, PMA at birth, maternal minority race or ethnicity, gestational diabetes, maternal hypertension, pregnancy weight change, low SES, infection during pregnancy, and chorioamnionitis

Table 3.Multivariable model for pre-pregnancy BMI and NNNS poorly regulated profile (Profile 6)¹

Effect modifier ²	Pre-pregnancy BMI			per SD Pre-pregnancy BMI		
	B	SE	P	aOR ²	95% CI OR	
Low SES						
Yes	0.149	0.591	0.800	1.161	0.365	3.695
No	-0.045	0.176	0.798	0.956	0.677	1.350
Pregnancy infection ³						
Yes	0.670	0.2697	0.014	1.946	1.147	3.301
No	-0.075	0.1645	0.650	0.928	0.672	1.281

¹Model adjusted for site, PMA at NNNS exam, PMA at birth, maternal minority race or ethnicity, gestational diabetes, maternal hypertension, pregnancy weight change, low SES, infection during pregnancy, and chorioamnionitis

²Follow up analyses on gestational diabetes, hypertension, chorioamnionitis were not completed due to few cases with these conditions and a poorly regulated profile

³Infections include urinary tract, bladder, kidney, vaginal, and cervical

Table 4.

Multivariable models for pre-pregnancy BMI and NNNS summary scores¹

NNNS Summary Scale	Effect modifier	Interaction with Pre-Pregnancy BMI		Pre-pregnancy BMI stratified estimates		
		Wald χ^2	P	B	95% CI	P
ATTENTION						
Low SES		2.393	0.122			
Yes				0.167	-0.175, 0.509	0.340
No				-0.072	-0.200, 0.057	0.277
Gestational diabetes		3.493	0.062			
Yes				-0.376	-0.778, 0.027	0.067
No				-0.013	-0.142, 0.116	0.848
Hypertension		0.374	0.541			
Yes				0.031	-0.193, 0.255	0.785
No				-0.046	-0.188, 0.097	0.529
Pregnancy infection ²		0.404	0.525			
Yes				-0.007	-0.345, 0.330	0.966
No				-0.057	-0.190, 0.075	0.397
Chorioamnionitis		0.177	0.674			
Yes				0.023	-0.233, 0.279	0.862
No				-0.045	-0.182, 0.093	0.524
HANDLING						
Low SES		2.631	0.105			
Yes				0.074	0.017, 0.131	0.010
No				0.012	-0.012, 0.036	0.313
Gestational diabetes		0.003	0.955			
Yes				-0.001	-0.071, 0.069	0.977
No				0.016	-0.008, 0.039	0.190
Hypertension		1.271	0.260			
Yes				0.001	-0.040, 0.042	0.970
No				0.022	-0.004, 0.047	0.092

NNNS Summary Scale	Effect modifier	Interaction with Pre-Pregnancy BMI			Pre-pregnancy BMI stratified estimates		
		Wald χ^2	P	B	95% CI	P	
	Pregnancy infection	0.154	0.695				
	Yes			0.031	-0.036, 0.098	0.365	
	No			0.015	-0.009, 0.038	0.225	
	Chorioamnionitis	0.229	0.632				
	Yes			0.034	-0.009, 0.076	0.118	
	No			0.012	-0.014, 0.037	0.367	
SELF-REGULATION							
	Low SES	0.081	0.776				
	Yes			0.036	-0.198, 0.269	0.764	
	No			-0.013	-0.071, 0.045	0.657	
	Gestational diabetes	0.401	0.527				
	Yes			-0.088	-0.256, 0.081	0.308	
	No			0.003	-0.056, 0.062	0.912	
	Hypertension	1.298	0.255				
	Yes			0.059	-0.050, 0.168	0.291	
	No			-0.022	-0.086, 0.042	0.497	
	Pregnancy infection	4.714	0.030				
	Yes			-0.170	-0.352, 0.013	0.069	
	No			0.013	-0.047, 0.072	0.677	
	Chorioamnionitis	0.157	0.692				
	Yes			0.027	-0.118, 0.173	0.712	
	No			-0.005	-0.066, 0.055	0.860	
ASYMMETRICAL REFLEXES							
	Low SES	0.219	0.64				
	Yes			0.046	-0.271, 0.363	0.776	
	No			-0.047	-0.145, 0.052	0.355	
	Gestational diabetes	0.848	0.357				
	Yes			0.177	-0.290, 0.645	0.457	
	No			-0.060	-0.160, 0.040	0.243	

NNNS Summary Scale	Effect modifier	Interaction with Pre-Pregnancy BMI				Pre-pregnancy BMI stratified estimates			
		Wald χ^2	P	B	95% CI	P	B	95% CI	P
Hypertension	Yes	0.345	0.557	-0.082	-0.247, 0.082	0.325	-0.044	-0.162, 0.074	0.466
	No								
Pregnancy infection	Yes	0.189	0.664	-0.063	-0.287, 0.162	0.585	-0.047	-0.150, 0.057	0.378
	No								
Chorioamnionitis	Yes	11.51	P<0.001	0.412	0.156, 0.668	0.002	-0.086	-0.196, 0.023	0.122
	No								

¹Model adjusted for site, PMA at NNNS exam, PMA at birth, maternal minority race or ethnicity, gestational diabetes, maternal hypertension, pregnancy weight change, low SES, infection during pregnancy, and chorioamnionitis

²Infections include urinary tract, bladder, kidney, vaginal, and cervical