The Relationship of Maternal Prepregnancy Body Mass Index and Pregnancy Weight Gain to Neurocognitive Function at Age 10 Years among Children Born Extremely Preterm

Elizabeth T. Jensen, MPH, PhD[1], Jelske W. van der Burg, MSc[2], Thomas M. O'Shea, MD, MPH[3], Robert M. Joseph, PhD[4], Elizabeth N. Allred, MS[5,6], Tim Heeren, PhD[7], Alan Leviton, MD[5,6], and Karl C. K. Kuban, MD, SM[8], on behalf of the Extremely Low Gestational Age Newborns Study Investigators*

Objective To assess the association between maternal prepregnancy body mass index and adequacy of pregnancy weight gain in relation to neurocognitive function in school-aged children born extremely preterm.

Study design Study participants were 535 ten-year-old children enrolled previously in the prospective multicenter Extremely Low Gestational Age Newborns cohort study who were products of singleton pregnancies. Soon after delivery, mothers provided information about prepregnancy weight. Prepregnancy body mass index and adequacy of weight gain were characterized based on this information. Children underwent a neurocognitive evaluation at 10 years of age.

Results Maternal prepregnancy obesity was associated with increased odds of a lower score for Differential Ability Scales-II Verbal IQ, for Developmental Neuropsychological Assessment-II measures of processing speed and visual fine motor control, and for Wechsler Individual Achievement Test-III Spelling. Children born to mothers who gained an excessive amount of weight were at increased odds of a low score on the Oral and Written Language Scales Oral Expression assessment. Conversely, children whose mother did not gain an adequate amount of weight were at increased odds of a lower score on the Oral and Written Language Scales Oral Expression and Wechsler Individual Achievement Test-III Word Reading assessments.

Conclusion In this cohort of infants born extremely preterm, maternal obesity was associated with poorer performance on some assessments of neurocognitive function. Our findings are consistent with the observational and experimental literature and suggest that opportunities may exist to mitigate risk through education and behavioral intervention before pregnancy. *(J Pediatr 2017;187:50-7).*

See editorial, p 10

More than one-third of all women of childbearing age in the US are obese (body mass index [BMI] ≥ 30 kg/m^2).[1] The relationship between maternal obesity and neurocognitive function in children has been studied extensively, and a majority of studies associate impaired neurocognitive function with maternal obesity, although conclusions differ as to whether this association arises from a state of obesity before pregnancy, from excess weight gain during pregnancy, or both. Some studies evaluated preschool children,[2-5] at ages when assessments of neurocognitive function are less reliable or stable than at older ages,[6] which is pertinent especially to studies of children born preterm.[7,8]

Children born premature are at increased risk for neurocognitive impairment,[9,10] with the greatest risk occurring among extremely preterm births (<28 weeks' gestation).[11] Although the long-term neurodevelopmental and cognitive outcomes of children born preterm generally are well-described, less is known about antecedents and modifiers of this association. We are not aware of any study that assessed the relationship between the mother's adiposity and her child's neurocognitive function at age 10 years. Identification of such a relationship would

BMI	Body mass index
DAS-II	Differential Ability Scales-II
NEPSY-II	Developmental Neuropsychological Assessment-II
OWLS	Oral and Written Language Scales
WIAT-III	Wechsler Individual Achievement Test-III

From the [1]Department of Epidemiology and Prevention, Wake Forest University Public Health Sciences, Winston-Salem, NC; [2]Department of Health and Life Sciences, Faculty of Earth and Life Sciences, VU University Amsterdam, Amsterdam, The Netherlands; [3]Department of Pediatrics, University of North Carolina School of Medicine, Chapel Hill, NC; [4]Department of Psychology and Neuroanatomy, Boston University; [5]Neuroepidemiology Unit, Department of Neurology, Boston Children's Hospital; [6]Department of Neurology, Harvard Medical School; [7]Department of Biostatistics, Boston University School of Public Health; and [8]Department of Pediatrics, Boston Medical Center, Boston, MA

*List of Extremely Low Gestational Age Newborns Study investigators is available at www.jpeds.com (**Appendix**).

Supported by the National Institute of Neurological Disorders and Stroke (5U01NS040069-05 and 2R01NS040069-06A2) and the National Institute of Child Health and Development (5P30HD018655-28). The authors declare no conflicts of interest.

http://dx.doi.org10.1016/j.jpeds.2017.02.064

strengthen the justification to develop strategies for weight management among women who are planning to conceive and women at risk of having a preterm delivery.

Previously, in a cohort of children born extremely preterm (<28 weeks), the Extremely Low Gestational Age Newborns study, we described an association between maternal prepregnancy obesity and developmental delay at 2 years adjusted age.[12] In the present study, we extend this line of research by evaluating the relationship of both prepregnancy BMI and pregnancy weight gain to neurocognitive and academic outcomes at 10 years of age. We hypothesized that maternal obesity and excessive pregnancy weight gain are associated with less favorable neurocognitive and academic outcomes at school age.

Methods

The Extremely Low Gestational Age Newborns study is a multicenter prospective, observational study of the risk of structural and functional neurologic disorders in infants born extremely preterm.[13] A total of 1506 infants born before the 28th week of gestation were enrolled during the years 2002-2004 and 1200 survived to 2 years, when 1102 returned for a developmental assessment.[14] At age 10 years, 889 (92%) of 966 children who were recruited actively for follow-up (because of the availability of data on inflammation-related proteins in blood samples from their first postnatal month) returned for an assessment of cognitive skills and academic achievement. Of the 889 children, the mothers of 32 did not provide measures necessary for calculating BMI, and an additional 12 did not provide information necessary for calculating adequacy of pregnancy weight gain. Among these 845 children were 535 singletons. We excluded all multiple births. The institutional review boards of all participating institutions approved enrollment and consent procedures for this follow-up study.

After delivery, a trained research nurse interviewed each mother using a structured data collection form and defined procedures for the interview process. Following the mother's discharge, the research nurse reviewed the maternal chart using a second structured data collection form. The medical record was the source of information about events during the mother's and infant's hospitalization. Gestational age estimates were based on a hierarchy of the quality of available information. Most desirable were estimates based on the dates of embryo retrieval or intrauterine insemination or fetal ultrasound before the 14th week (413/535 = 77%). When these were not available, reliance was placed sequentially on a fetal ultrasound at ≥14 weeks (105/535 = 20%), last menstrual period without fetal ultrasound (16/535 = 3%), and gestational age recorded in the log of the neonatal intensive care unit (1/535 = 0/.2%).

Each mother was asked to provide her height and her prepregnancy weight. These were used to calculate her prepregnancy BMI. BMI was characterized as underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), and obese (≥30.0 kg/m^2).[15] Adequacy of pregnancy weight gain at delivery (insufficient, adequate, more than adequate) was characterized by comparing the maternal weight at delivery with the adequacy of weight gain as defined by the Institute of Medicine, based on prepregnancy BMI status (underweight, overweight, or obese, as defined previously) (**Table I**; available at www.jpeds.com).[16]

Participating families were scheduled for a single visit, during which all of the measures reported in the present study were administered. Assessments of both children and their mothers were completed. For mothers, the Kaufman Brief Intelligence Test-2[17] was administered. Assessments of children were completed in 3-4 hours, including breaks. The assessments were selected to provide the most comprehensive information about neurocognitive and academic function in a single testing session. The tests administered were well-validated and provided recently normed standard scores, thus allowing comparison with US population norms. The test measures and outcomes of interest for the children are described briefly to follow.[18]

General Cognitive Ability (IQ)

General cognitive ability (IQ) was assessed with the School-Age Differential Ability Scales-II (DAS-II) Verbal and Nonverbal Reasoning scales.[19]

Language

Expressive and receptive language skills were evaluated with the Oral and Written Language Scales (OWLS), which assess semantic, morphologic, syntactic, and pragmatic production and comprehension of elaborated sentences.[20]

Executive Function

Executive function was assessed with both the DAS-II Working Memory scale[19] and the NEPSY-II (Developmental Neuropsychological Assessment-II).[21] The DAS-II Recall of Digits Backward and Recall of Sequential Order subtests measure verbal working memory, whereas the NEPSY-II Auditory Attention and Response Set measures auditory attention, set switching, and inhibition. NEPSY-II Inhibition Inhibition and Inhibition Switching measure simple inhibition and inhibition in the context of set shifting, respectively, and Animal Sorting measures visual concept formation and set shifting.

Processing Speed, Visual Perception, and Visual-Motor Function

Speed of processing was assessed with the NEPSY-II Inhibition Naming task, which provides a baseline measure of processing speed and has no inhibitory component. Visual perception was assessed with NEPSY-II Arrows and Geometric Puzzles tasks, whereas visual fine motor function was measured with the NEPSY-II Visuomotor Precision task.

Academic Achievement

Wechsler Individual Achievement Test-III (WIAT-III) subtests administered included Word Reading (speed and accuracy of word recognition), Pseudoword Decoding (single-word decoding), Spelling (written spelling of single words), and Numerical Operations (written math calculation skills).[22]

Statistical Analyses

We evaluated 2 generalized null hypotheses. The first is that maternal prepregnancy BMI is not associated with any neurocognitive dysfunction. The second is that adequacy of maternal weight gain during pregnancy is not associated with any neurocognitive dysfunction. We began by assessing the relationship between categories of prepregnancy BMI, as well as of the adequacy of weight gain and maternal demographic and newborn characteristics (**Table II**; available at www.jpeds.com). Next, we examined the proportion of children whose scores were between 1 and 2 SDs below and greater than 2 SDs below the normative mean of each assessment for each prepregnancy BMI category and by adequacy of weight gain (**Table III**).

To allow for the differences in age at the time of the assessment and to facilitate a comparison of our findings with those reported for children presumably born very near term, we calculated z scores based on distributions of values reported for the historical normative samples that are described by the authors of the assessments we used. We created multivariate logistic regression models to estimate the odds of having a score 1 or more SDs below the normative mean of each assessment among the children of women who were underweight, overweight, or obese before pregnancy compared with the children of women who were normal weight. Similarly, we created models that compared the children of women who experienced inadequate or excessive weight gain relative with the children of women who gained an adequate amount of weight during pregnancy.

We calculated unadjusted and adjusted estimates. We used a directed acyclic graph approach to identify a minimally sufficient set of adjustment factors for inclusion in adjustment models.[23] Adjusted models included the possible

Table III. Distribution of neurocognitive assessment scores by maternal prepregnancy BMI and adequacy of pregnancy weight gain (row percent)

Neurocognitive assessment scores	n	Assessment z score	BMI, kg/m²				Pregnancy weight gain*		
			<18.5	18.5 to < 25	25 to < 30	≥30	Inadequate	Adequate	Excessive
IQ									
DAS-II Verbal IQ	101	≤ −2	22	15	18	28	23	14	19
	102	> −2 to ≤ −1	20	18	21	20	19	16	20
DAS-II Nonverbal IQ	84	≤ −2	12	13	19	20	20	10	16
	123	> −2 to ≤ −1	32	22	19	26	24	19	24
Language									
OWLS Listening comprehension	104	≤ −2	12	16	24	27	23	11	22
	149	> −2 to ≤ −1	37	32	27	21	30	31	27
OWLS Oral Expression	104	≤ −2	24	15	20	30	24	13	21
	119	> −2 to ≤ −1	20	24	25	22	24	17	25
Executive function									
DAS-II Working Memory	102	≤ −2	15	15	21	28	21	19	19
	93	> −2 to ≤ −1	27	16	22	14	24	10	17
NEPSY-II Auditory Attention	120	≤ −2	28	20	26	26	26	17	24
	120	> −2 to ≤ −1	30	25	20	21	19	27	24
NEPSY-II Auditory Response set	109	≤ −2	20	18	25	26	23	20	21
	155	> −2 to ≤ −1	33	32	32	25	31	23	32
NEPSY-II Inhibition Inhibition	184	≤ −2	38	30	43	38	40	32	34
	117	> −2 to ≤ −1	18	24	20	24	27	22	21
NEPSY-II Inhibition Switching	149	≤ −2	23	25	32	37	33	21	30
	150	> −2 to ≤ −1	26	30	32	27	33	32	27
NEPSY-II Animal Sorting	169	≤ −2	32	27	31	43	41	30	29
	153	> −2 to ≤ −1	34	31	30	23	22	32	32
Processing speed									
NEPSY-II Inhibition Naming	177	≤ −2	37	30	39	39	40	29	32
	102	> −2 to ≤ −1	17	17	20	24	20	26	17
Visual perception									
NEPSY-II Arrows	145	≤ −2	32	25	27	32	32	25	27
	120	> −2 to ≤ −1	37	22	21	24	18	24	25
NEPSY-II Geometric Puzzles	88	≤ −2	10	17	18	18	19	12	17
	111	> −2 to ≤ −1	24	20	19	23	22	27	19
Fine motor function									
NEPSY-II Visuomotor Precision	119	≤ −2	27	18	21	31	26	19	22
	185	> −2 to ≤ −1	29	36	33	38	30	34	38
Academic achievement									
WIAT-III Word Reading	73	≤ −2	15	12	11	22	18	10	13
	91	> −2 to ≤ −1	17	15	21	18	25	12	16
WIAT-III Pseudoword Decoding	83	≤ −2	12	13	14	26	21	8	16
	94	> −2 to ≤ −1	20	17	20	17	22	19	16
WIAT-III Spelling	60	≤ −2	12	8	11	19	15	8	11
	87	> −2 to ≤ −1	24	12	21	19	19	14	17
WIAT-III Numeric Operations	85	≤ −2	17	13	15	23	23	12	14
	134	> −2 to ≤ −1	34	23	27	26	24	21	27

*Adequacy of weight gain at gestational age of delivery.

confounders of mother's eligibility for government-provided insurance (yes vs no), maternal self-identified race (black vs other or white), and maternal education (≤12 years, >12 to <16 years vs ≥16 years). They also included child sex (male vs female). Women who were overweight or obese before pregnancy were more likely to gain excessive weight during pregnancy. Given this association, there was a potential that prepregnancy BMI could confound the association between pregnancy weight gain and neurocognitive outcomes. Thus, for assessment of the association between adequacy of pregnancy weight gain and each of the outcomes, we additionally adjusted for maternal prepregnancy BMI (<18.5, ≥25 to <30, and ≥30 vs ≥18.5 to <25) in the logistic regression analyses. Finally, as a secondary analysis, we modeled the association for maternal prepregnancy BMI and adequacy of weight gain with each of the outcomes, including adjustment for maternal IQ as determined on the Kaufman Brief Intelligence Test-2.

Results

Of the 535 singletons with follow-up at age 10 years, nearly all participated in the neurocognitive assessments (DAS-II, n = 528; OWLS, n = 516; NEPSY-II, n = 525; WIAT-III, n = 525). Nearly one-half of the infants included were born between 25 and 26 weeks' gestation (48%; n = 255), although 21% (n = 111) were born at 23-24 weeks and 32% (n = 169) were born at 27 weeks (**Table II**). The study population was highly diverse, with 30% (n = 161) of mothers self-identifying as black and 17% (n = 92) <21 years of age at the time of delivery. Nearly one-half (46%; n = 248) of the study population had ≤12 years of education, and 42% (n = 223) received public insurance. One-fourth (26%; n = 140) of the mothers were overweight or obese. Compared with white mothers, a greater proportion of black mothers were identified as overweight or obese before pregnancy (33% for black vs 11% for white). Adequacy of weight gain was similar across racial groups. In general, increasing maternal age was associated with a greater proportion of women with excessive weight gain during pregnancy (60% in ages greater than 35 years vs 41% in women <21 years of age). Although the proportion of women who were overweight or obese was similar across gestational ages at delivery, the proportion of women with excessive weight gain was greater for infants born before the 27th week of gestation (60% for 23-24 weeks vs 51% for 27 weeks) (**Table II**).

Prepregnancy BMI

In unadjusted estimates, children born to underweight mothers appeared to be at an increased odds of a low score ($z \leq -1$) on the WIAT-III spelling assessment. Those born to mothers with a prepregnancy BMI between 25 and <30 appeared to be at increased odds of a low score on the DAS-II Working Memory, the NEPSY-II Inhibition Naming, and the WIAT-III Spelling assessments, whereas those born to mothers whose prepregnancy BMI was ≥30 appeared to be at increased odds of low scores on the DAS-II Verbal IQ, Nonverbal IQ, and Working Memory, the OWLS Oral Expression, the NEPSY-II Inhibition Naming and Visuomotor Precision, and all 4 WIAT-III assessments (**Figure 1**). After adjustment for potential confounders, children of mothers whose prepregnancy BMI was ≥30 were at increased odds of low scores on the DAS-II Verbal IQ, the NEPSY-II Inhibition Naming and Visuomotor Precision assessments, and only the Spelling component of the WIAT-III. Children of mothers whose prepregnancy BMI was <18.5 and those whose mother had a BMI between 25 and <30 were at increased odds of low scores on the WIAT-III Spelling assessment (**Figure 1**). Adjustment for maternal IQ did not substantively change effect estimates observed (data not shown).

Adequacy of Pregnancy Weight Gain

In unadjusted estimates, children whose mother did not gain an adequate amount of weight during pregnancy were at increased odds of a low score on DAS-II Nonverbal IQ, OWLS Oral Expression, DAS-II Working Memory, NEPSY-II Inhibition Inhibition, and 3 of the 4 WIAT-III subtests (Word Reading, Pseudoword Decoding, and Numerical Operations), whereas those whose mother gained what was considered an excessive amount of weight appeared to be at increased odds of a low score on the DAS-II Nonverbal IQ and the OWLS Oral Expression assessments (**Figure 2**, top panel). After adjustment, 3 of the 9 associations seen before adjustment remained significant. Children whose mothers did not gain an adequate amount of weight remained at increased odds of a low score on the OWLS Oral Expression and WIAT-III Word Reading assessments, whereas those whose mothers gained an excessive amount of weight remained at increased odds of a low score on OWLS Oral Expression only (**Figure 2**, bottom panel). Adjustment for maternal IQ did not substantively change effects estimates observed (data not shown).

A limitation of analyzing our exposure and outcome data as categorical variables is loss of statistical power. The rationale for this approach is that we wanted to answer questions related to clinically meaningful categories of exposures and outcomes (rather than each pound of maternal weight, or each point of a child's IQ, NEPSY, or WIAT score). To assess whether a more appropriate approach would be to use continuous variables, we examined scatterplots of several outcomes for which associations were found in categorical analysis. These plots, presented as **Figure 3** (available at www.jpeds.com), suggest that modeling maternal prepregnancy BMI as a continuous variable would not provide additional insight into the relationship of maternal prepregnancy obesity and cognitive outcomes in the child.

Discussion

Our main findings are that even at age 10 years, children born to women who were obese before pregnancy were at increased risk of low scores on the DAS-II Verbal IQ, the NEPSY-II Inhibition Naming, the NEPSY-II Visuomotor Precision, and the WIAT-III Spelling assessments, whereas inadequate weight gain during pregnancy was associated with low scores on the OWLS Oral Expression and WIAT-III Word Reading evaluations. Those children whose mother gained an

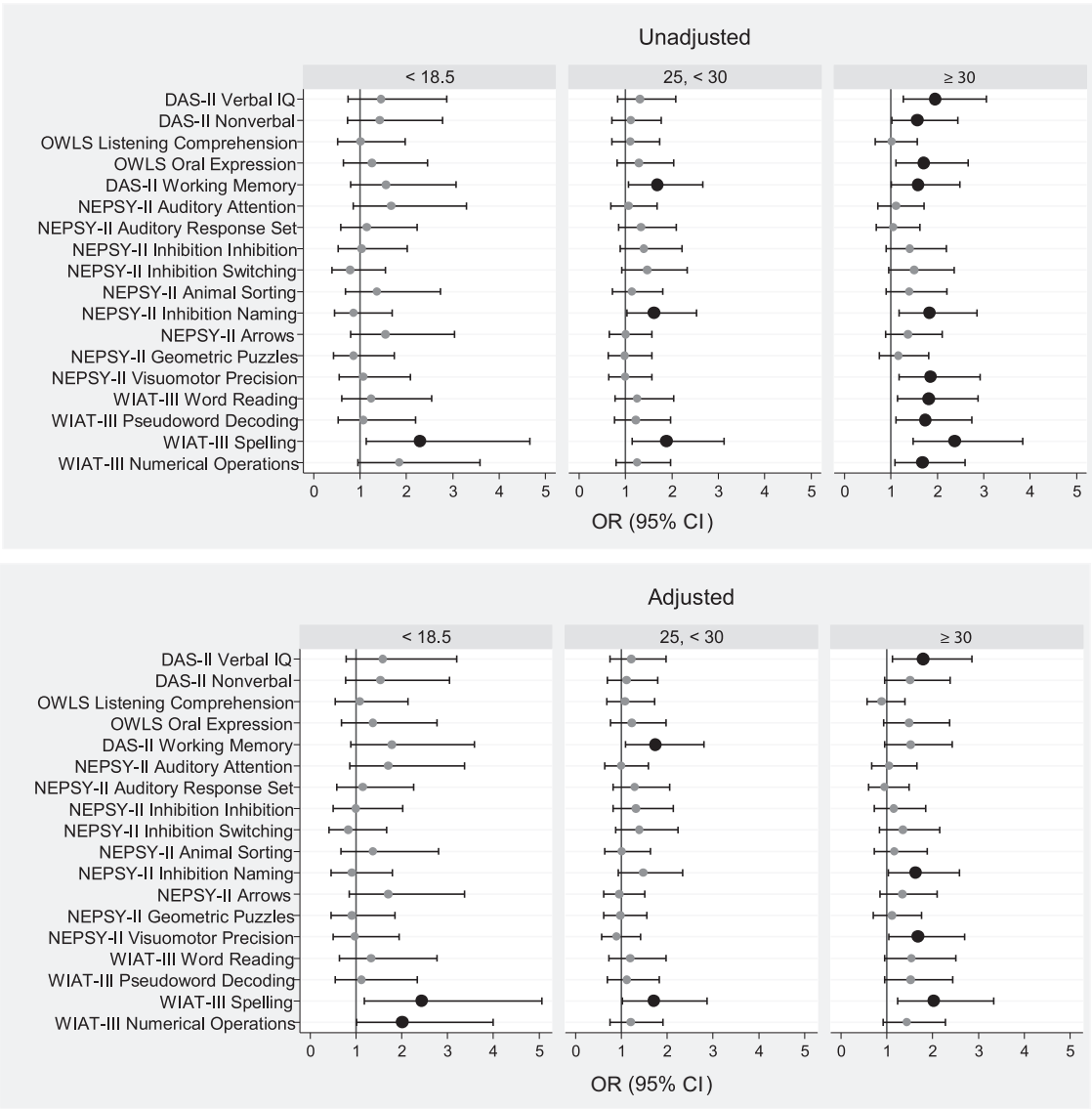

Figure 1. Forest plots of ORs and 95% CIs of a z score ≤ −1 on each DAS-II, OWLS, NEPSY-II, or WIAT-III assessment at age 10 associated with maternal prepregnancy BMI <18.5 (*left*), ≥25, <30 (*middle*), and BMI ≥30 (*right*) relative to BMI 18 to < 25. ORs in the *top panel* are unadjusted, whereas those in the *bottom panel* are adjusted for maternal race, education, and public insurance.

excessive amount of weight gained were at increased risk of low scores on OWLS Oral Expression.

We included multiple neurocognitive and academic achievement assessments that examined a wide breadth of functional skills. This study is novel in that it is limited to infants born extremely preterm. Our study highlights that much of the adverse risk for infants born preterm lies within prepregnancy obesity, as opposed to excessive pregnancy weight gain.

In this sample, once adjustment is made for gestational age, the mortality rate of newborns did not vary by mother's prepregnancy BMI or the relative amount of her weight gain during the pregnancy. Consequently, differential mortality cannot explain our findings.

We evaluated a total of 90 associations (18 assessments for 3 levels of prepregnancy weight and 3 levels of weight gain) that are clearly not independent. With only 7 having statistical significance and our finding of limited internal consistency for non-IQ assessments, we are cautious in drawing inferences. Nonetheless, our finding of an association between maternal obesity and a low Mental Development Index at 2 years,[12] as well as a low nonverbal IQ at 10 years, provides some evidence of consistency over time.

Although our findings cannot be viewed as establishing causality, biologic explanations are plausible. Maternal BMI may contribute to offspring neurocognitive outcomes as a result of alterations in the in utero environment that dysregulate normal fetal brain development[24] or engage mechanisms in the fetus

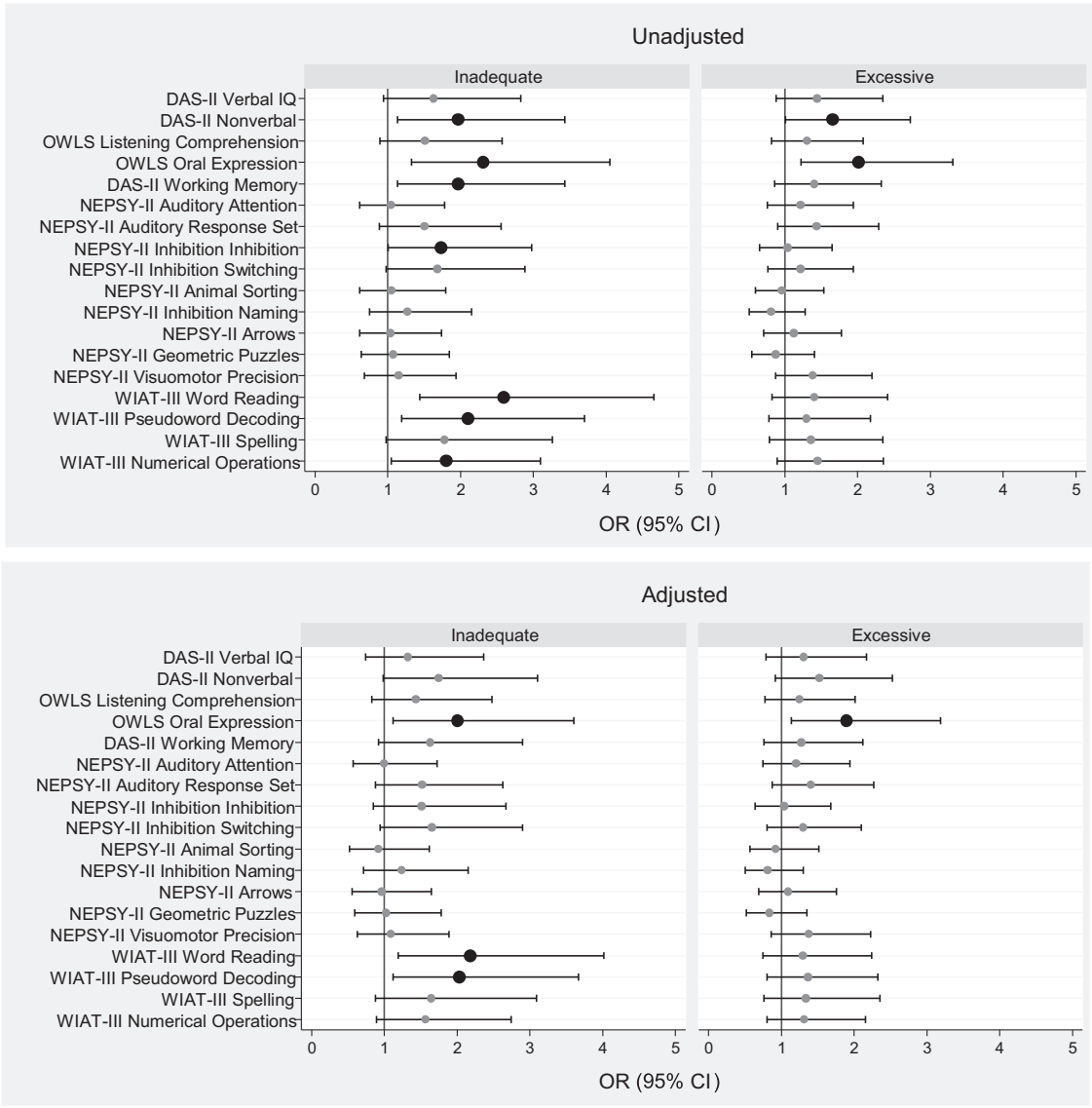

Figure 2. Forest plots of ORs and 95% CIs of a z score ≤ −1 on each DAS-II, OWLS, NEPSY-II, or WIAT-III assessment at age 10 associated with inadequate (*left*) and excessive (*right*) maternal pregnancy weight gain relative to adequate pregnancy weight gain. ORs in the *top panel* are unadjusted, whereas those in the *bottom panel* are adjusted for maternal race, education, public insurance, and prepregnancy BMI.

for adapting to the in utero environment that carry forward into postdelivery life.[25] Epigenetic changes in maternal or paternal germ cells, or in the fetus during a developmentally sensitive period, resulting from environmental perturbations, may alter development.[25-28] We have described consistent associations between early life inflammation and adverse neurodevelopmental outcomes,[29-41] and inflammation has epigenetic effects.[42,43] Maternal obesity is associated with low-grade inflammation in the mother,[44] and also in the offspring,[45-49] and with epigenetic variation that could influence expression of genes involved in immunity.[50-52] Thus, maternal obesity, through epigenetic modifications, might lead to immune dysregulation in the offspring, with adverse influence on brain development.[31,33-41,46-49]

Our finding that maternal prepregnancy obesity is related to neurocognitive impairment at school age in a population born preterm is novel. Evidence that a broad range of deficits in our sample is associated with maternal BMI, including verbal IQ, processing speed, fine motor control, and academic achievement, is consistent with previous findings that children born very preterm in general are at high risk for a wide range of later cognitive difficulties.[53] Our findings suggest that there may be opportunity to mitigate impaired neurocognitive function in children born preterm through behavioral intervention among women with a previous preterm pregnancy who are at risk for a subsequent preterm delivery.

A limitation of many of the studies examining the association between maternal BMI and offspring neurocognitive

outcomes is the potential for residual confounding. As a means of evaluating the potential for residual confounding, some studies also have examined paternal associations.[54,55] Comparing the magnitude of the association between maternal and paternal associations with neurocognitive outcomes provides the opportunity to assess whether associations observed are attributable to an in utero influence or are an artifact of residual confounding. In this study, we were not able to examine associations with paternal BMI; thus, the possibility remains that the associations observed are attributable to residual confounding from familial social factors. Another limitation of the present study is reliance on maternal self-report of weight and height status, increasing not only the possibility of misclassification but also for bias if inaccurate reporting of prepregnancy weight and pregnancy weight gain are associated with the child's neurocognitive function.

This study has a number of strengths. We examined these associations in a population of older children born very preterm. The sample size is sufficiently large to identify modest associations. We used multiple, well-validated assessment instruments for neurocognitive function and identified consistent associations in the areas of achievement and IQ for maternal obesity. Examiners who evaluated neurocognitive and academic outcomes were not aware of children's medical history or mothers' pregnancy history, nor did they have direct information about mother's prepregnancy BMI.

In conclusion, consistent with shorter-term studies of children born at term, 10-year-old children born to women who were obese before pregnancy appear to be at increased risk of neurocognitive and academic achievement impairment. Although pregnancy weight gain is correlated highly with prepregnancy weight status, after adjustment for prepregnancy weight status and other potential confounders, pregnancy weight gain (inadequate or excessive weight gain) generally was not associated with neurocognitive function. We cannot rule out the possibility that the associations observed are attributable to residual confounding. Although we were not able to take into account paternal factors, we were able to account for maternal IQ and estimates substantively were unchanged. This study provides evidence that maternal adiposity status may contribute to neurocognitive function in children born extremely preterm. ■

We acknowledge the contributions of the subjects and their families.

Submitted for publication Oct 11, 2016; last revision received Feb 10, 2017; accepted Feb 23, 2017

Reprint requests: Thomas M. O'Shea, MD, MPH, Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599. E-mail: moshea52@email.unc.edu

References

1. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999-2008. JAMA 2010;303:235-41.
2. Craig WY, Palomaki GE, Neveux LM, Haddow JE. Maternal body mass index during pregnancy and offspring neurocognitive development. Obstet Med 2013;6:20-5.
3. Hinkle SN, Schieve LA, Stein AD, Swan DW, Ramakrishnan U, Sharma AJ. Associations between maternal pre-pregnancy body mass index and child neurodevelopment at 2 years of age. Int J Obes (Lond) 2012;36:1312-9.
4. Krakowiak P, Walker CK, Bremer AA, Baker AS, Ozonoff S, Hansen RL, et al. Maternal metabolic conditions and risk for autism and other neurodevelopmental disorders. Pediatrics 2012;129:e1121-8.
5. Van Lieshout RJ, Schmidt LA, Robinson M, Niccols A, Boyle MH. Maternal pre-pregnancy body mass index and offspring temperament and behavior at 1 and 2 years of age. Child Psychiatry Hum Dev 2013;44:382-90.
6. Lobo MA, Paul DA, Mackley A, Maher J, Galloway JC. Instability of delay classification and determination of early intervention eligibility in the first two years of life. Res Dev Disabil 2014;35:117-26.
7. Janssen AJ, Akkermans RP, Steiner K, de Haes OA, Oostendorp RA, Kollee LA, et al. Unstable longitudinal motor performance in preterm infants from 6 to 24 months on the Bayley Scales of Infant Development—Second edition. Res Dev Disabil 2011;32:1902-9.
8. Lobo MA, Galloway JC. Assessment and stability of early learning abilities in preterm and full-term infants across the first two years of life. Res Dev Disabil 2013;34:1721-30.
9. Stephens BE, Vohr BR. Neurodevelopmental outcome of the premature infant. Pediatr Clin North Am 2009;56:631-46, Table of Contents.
10. Wilson-Costello D, Friedman H, Minich N, Fanaroff AA, Hack M. Improved survival rates with increased neurodevelopmental disability for extremely low birth weight infants in the 1990s. Pediatrics 2005;115:997-1003.
11. Martin JA, Osterman MJ. Preterm births—United States, 2006 and 2010. MMWR Suppl 2013;62(suppl 3):136-8.
12. van der Burg JW, Allred EN, Kuban K, O'Shea TM, Dammann O, Leviton A. Maternal obesity and development of the preterm newborn at 2 years. Acta Paediatr 2015;104:900-3.
13. O'Shea TM, Allred EN, Dammann O, Hirtz D, Kuban KC, Paneth N, et al. The ELGAN study of the brain and related disorders in extremely low gestational age newborns. Early Hum Dev 2009;85:719-25.
14. Helderman JB, O'Shea TM, Kuban KC, Allred EN, Hecht JL, Dammann O, et al. Antenatal antecedents of cognitive impairment at 24 months in extremely low gestational age newborns. Pediatrics 2012;129:494-502.
15. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. JAMA 2014;311:806-14.
16. Institute of Medicine, National Research Council Committee to Reexamine IOM Pregnancy Weight Guidelines. The National Academies Collection: reports funded by National Institutes of Health. In: Rasmussen KM, Yaktine AL, eds. Weight gain during pregnancy: reexamining the guidelines. Washington (DC): National Academies Press (US) National Academy of Sciences; 2009.
17. Kaufman AS, Kaufman NL. Kaufman brief intelligence test - 2 (KBIT-2). San Antonio (TX): Pearson Education; 2004.
18. Joseph RM, O'Shea TM, Allred EN, Heeren T, Hirtz D, Jara H, et al. Neurocognitive and academic outcomes at age 10 years of extremely preterm newborns. Pediatrics 2016;137.
19. Elliott CD. Differential ability scales. 2d ed. San Antonio (TX): The Psychological Corporation; 2007.
20. Carrow-Woolfolk E. OWLS (oral and written language scales) manual : listening comprehension and oral expression. Circle Pines, MN: American Guidance Service; 1995.
21. Korkman M, Kirk U, Kemp S. NEPSY-II: clinical and interpretive manual. San Antonio (TX): The Psychological Corporation.; 2007.
22. Wechsler D. Wechsler Individual Achievement Test-III. San Antonio (TX): Pearson Assessment; 2009.
23. Rothman KJ, Greenland S, Lash TL. Modern epidemiology. 3rd ed. Philadelphia (PA): Wolters Kluwer Health/Lippincott Williams & Wilkins; 2008.
24. Dowling D, McAuliffe FM. The molecular mechanisms of offspring effects from obese pregnancy. Obes Facts 2013;6:134-45.
25. Bale TL. Epigenetic and transgenerational reprogramming of brain development. Nat Rev Neurosci 2015;16:332-44.
26. Cordero P, Li J, Oben JA. Epigenetics of obesity: beyond the genome sequence. Curr Opin Clin Nutr Metab Care 2015;18:361-6.

27. van Dijk SJ, Molloy PL, Varinli H, Morrison JL, Muhlhausler BS. Epigenetics and human obesity. Int J Obes (Lond) 2015;39:85-97.
28. Stel J, Legler J. The role of epigenetics in the latent effects of early life exposure to obesogenic endocrine disrupting chemicals. Endocrinology 2015;156:3466-72.
29. Leviton A, Kuban KC, Allred EN, Fichorova RN, O'Shea TM, Paneth N. Early postnatal blood concentrations of inflammation-related proteins and microcephaly two years later in infants born before the 28th postmenstrual week. Early Hum Dev 2011;87:325-30.
30. O'Shea TM, Joseph RM, Kuban KC, Allred EN, Ware J, Coster T, et al. Elevated blood levels of inflammation-related proteins are associated with an attention problem at age 24 mo in extremely preterm infants. Pediatr Res 2014;75:781-7.
31. Kuban KC, O'Shea TM, Allred EN, Fichorova RN, Heeren T, Paneth N, et al. The breadth and type of systemic inflammation and the risk of adverse neurological outcomes in extremely low gestation newborns. Pediatr Neurol 2015;52:42-8.
32. Kuban KC, O'Shea TM, Allred EN, Paneth N, Hirtz D, Fichorova RN, et al. Systemic inflammation and cerebral palsy risk in extremely preterm infants. J Child Neurol 2014;29:1692-8.
33. Stoll BJ, Hansen NI, Adams-Chapman I, Fanaroff AA, Hintz SR, Vohr B, et al. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. JAMA 2004;292:2357-65.
34. Schlapbach LJ, Aebischer M, Adams M, Natalucci G, Bonhoeffer J, Latzin P, et al. Impact of sepsis on neurodevelopmental outcome in a Swiss National Cohort of extremely premature infants. Pediatrics 2011;128:e348-57.
35. O'Shea TM, Shah B, Allred EN, Fichorova RN, Kuban KC, Dammann O, et al. Inflammation-initiating illnesses, inflammation-related proteins, and cognitive impairment in extremely preterm infants. Brain Behav Immun 2013;29:104-12.
36. Vander Haar E, Gyamfi-Bannerman C. Chorioamnionitis and neurocognitive development at age 2 years. Obstet Gynecol 2016;127:437-41.
37. Martin CR, Dammann O, Allred EN, Patel S, O'Shea TM, Kuban KC, et al. Neurodevelopment of extremely preterm infants who had necrotizing enterocolitis with or without late bacteremia. J Pediatr 2010;157:751-6, e1.
38. Leviton A, Fichorova RN, O'Shea TM, Kuban K, Paneth N, Dammann O, et al. Two-hit model of brain damage in the very preterm newborn: small for gestational age and postnatal systemic inflammation. Pediatr Res 2013;73:362-70.
39. O'Shea TM, Allred EN, Kuban KC, Dammann O, Paneth N, Fichorova R, et al. Elevated concentrations of inflammation-related proteins in postnatal blood predict severe developmental delay at 2 years of age in extremely preterm infants. J Pediatr 2012;160:395-401, e4.
40. Leviton A, Allred EN, Fichorova RN, Kuban KC, Michael O'Shea T, Dammann O. Systemic inflammation on postnatal days 21 and 28 and indicators of brain dysfunction 2 years later among children born before the 28th week of gestation. Early Hum Dev 2016;93:25-32.
41. Rand KM, Austin NC, Inder TE, Bora S, Woodward LJ. Neonatal infection and later neurodevelopmental risk in the very preterm infant. J Pediatr 2016;170:97-104.
42. Pugh SJ, Hutcheon JA, Richardson GA, Brooks MM, Himes KP, Day NL, et al. Gestational weight gain, pre-pregnancy body mass index and offspring attention-deficit hyperactivity disorder symptoms and behaviour at age 10. BJOG 2016;123:2094-103.
43. Claycombe KJ, Brissette CA, Ghribi O. Epigenetics of inflammation, maternal infection, and nutrition. J Nutr 2015;145:1109s-1115s.
44. Madan JC, Davis JM, Craig WY, Collins M, Allan W, Quinn R, et al. Maternal obesity and markers of inflammation in pregnancy. Cytokine 2009;47:61-4.
45. Leibowitz KL, Moore RH, Ahima RS, Stunkard AJ, Stallings VA, Berkowitz RI, et al. Maternal obesity associated with inflammation in their children. World J Pediatr 2012;8:76-9.
46. Nguyen MU, Wallace MJ, Pepe S, Menheniott TR, Moss TJ, Burgner D. Perinatal inflammation: a common factor in the early origins of cardiovascular disease? Clin Sci 2015;129:769-84.
47. Pantham P, Aye IL, Powell TL. Inflammation in maternal obesity and gestational diabetes mellitus. Placenta 2015;36:709-15.
48. Rizzo GS, Sen S. Maternal obesity and immune dysregulation in mother and infant: a review of the evidence. Paediatr Respir Rev 2015;16:251-7.
49. van der Burg JW, Allred EN, McElrath TF, Fichorova RN, Kuban K, O'Shea TM, et al. Is maternal obesity associated with sustained inflammation in extremely low gestational age newborns? Early Hum Dev 2013;89:949-55.
50. Ding Y, Li J, Liu S, Zhang L, Xiao H, Li J, et al. DNA hypomethylation of inflammation-associated genes in adipose tissue of female mice after multigenerational high fat diet feeding. Int J Obes (Lond) 2014;38:198-204.
51. Guenard F, Deshaies Y, Cianflone K, Kral JG, Marceau P, Vohl MC. Differential methylation in glucoregulatory genes of offspring born before vs. after maternal gastrointestinal bypass surgery. Proc Natl Acad Sci USA 2013;110:11439-44.
52. Lesseur C, Armstrong DA, Paquette AG, Li Z, Padbury JF, Marsit CJ. Maternal obesity and gestational diabetes are associated with placental leptin DNA methylation. Am J Obstet Gynecol 2014;211:654, e1-9.
53. Anderson PJ. Neuropsychological outcomes of children born very preterm. Semin Fetal Neonatal Med 2014;19:90-6.
54. Casas M, Chatzi L, Carsin AE, Amiano P, Guxens M, Kogevinas M, et al. Maternal pre-pregnancy overweight and obesity, and child neuropsychological development: two Southern European birth cohort studies. Int J Epidemiol 2013;42:506-17.
55. Gardner RM, Lee BK, Magnusson C, Rai D, Frisell T, Karlsson H, et al. Maternal body mass index during early pregnancy, gestational weight gain, and risk of autism spectrum disorders: results from a Swedish total population and discordant sibling study. Int J Epidemiol 2015;44:870-83.

Appendix

Extremely Low Gestational Age Newborns Study Investigators include:

Baystate Medical Center, Springfield, MA

Bhavesh Shah, MD; Rachana Singh, MD, MS; Anne Smith, PhD; Deborah Klein, BSM, RN; Susan McQuiston, PhD

Boston Medical Center

Julie Rollins, MA; Laurie Douglass, MD

Boston Children's Hospital, Boston, MA

Janice Ware, PhD; Taryn Coster, BA; Brandi Henson, PsyD; Rachel Wilson, PhD; Kirsten McGhee, PhD; Patricia Lee, PhD; Aimee Asgarian, PhD; Anjali Sadhwani, PhD

Tufts Medical Center, Boston, MA

Ellen Perrin, MD; Emily Neger, MA; Kathryn Mattern, BA; Jenifer Walkowiak, PhD; Susan Barron, PhD

University of Massachusetts Medical School, Worcester, MA

Jean Frazier, MD; Lauren Venuti, BA; Beth Powers, RN; Ann Foley, EdM; Brian Dessureau, PhD; Molly Wood, PhD; Jill Damon-Minow, PsyD

Yale University School of Medicine, New Haven, CT

Richard Ehrenkranz, MD; Jennifer Benjamin, MD; Elaine Romano, APRN; Kathy Tsatsanis, PhD; Katarzyna Chawarska, PhD; Sophy Kim, PhD; Susan Dieterich, PhD; Karen Bearrs, PhD

Wake Forest University Baptist Medical Center, Winston-Salem, NC

T. Michael O'Shea, MD, MPH; Nancy Peters, RN; Patricia Brown, RN; Emily Ansusinha, BA; Ellen Waldrep, MA; Jackie Friedman, PhD; Gail Hounshell, PhD; Debbie Allred, PhD

University Health Systems of Eastern Carolina, Greenville, NC

Stephen C. Engelke, MD; Nancy Darden-Saad, BS, RN; Gary Stainback, PhD

North Carolina Children's Hospital, Chapel Hill, NC

Diane Warner, MD, MPH; Janice Wereszczak, MSN; Janice Bernhardt, MS, RN; Joni McKeeman, PhD; Echo Meyer, PhD

Helen DeVos Children's Hospital, Grand Rapids, MI

Steve Pastyrnak, PhD; Wendy Burdo-Hartman, MD; Julie Rathbun, BSW, BSN, RN; Sarah Nota, BS; Teri Crumb, BSN, RN

Sparrow Hospital, Lansing, MI

Madeleine Lenski, MPH; Deborah Weiland, MSN; Megan Lloyd, MA, EdS

University of Chicago Medical Center, Chicago, IL

Scott Hunter, PhD; Michael Msall, MD; Rugile Ramoskaite, BA; Suzanne Wiggins, MA; Krissy Washington, MA; Ryan Martin, MA; Barbara Prendergast, BSN, RN; Megan Scott, PhD

William Beaumont Hospital, Royal Oak, MI

Judith Klarr, MD; Beth Kring, RN; Jennifer DeRidder, RN; Kelly Vogt, PhD

Table I. Relationship between maternal prepregnancy BMI and adequacy of pregnancy weight gain (row percent)

		Pregnancy weight gain*		
BMI values, kg/m^2	n	Inadequate	Adequate	Excessive
<18.5	41	29	34	37
18.5 to < 25	257	19	23	57
25 to < 30	113	23	12	65
≥30	124	39	8	53

*Adequacy of weight gain at gestational age of delivery.

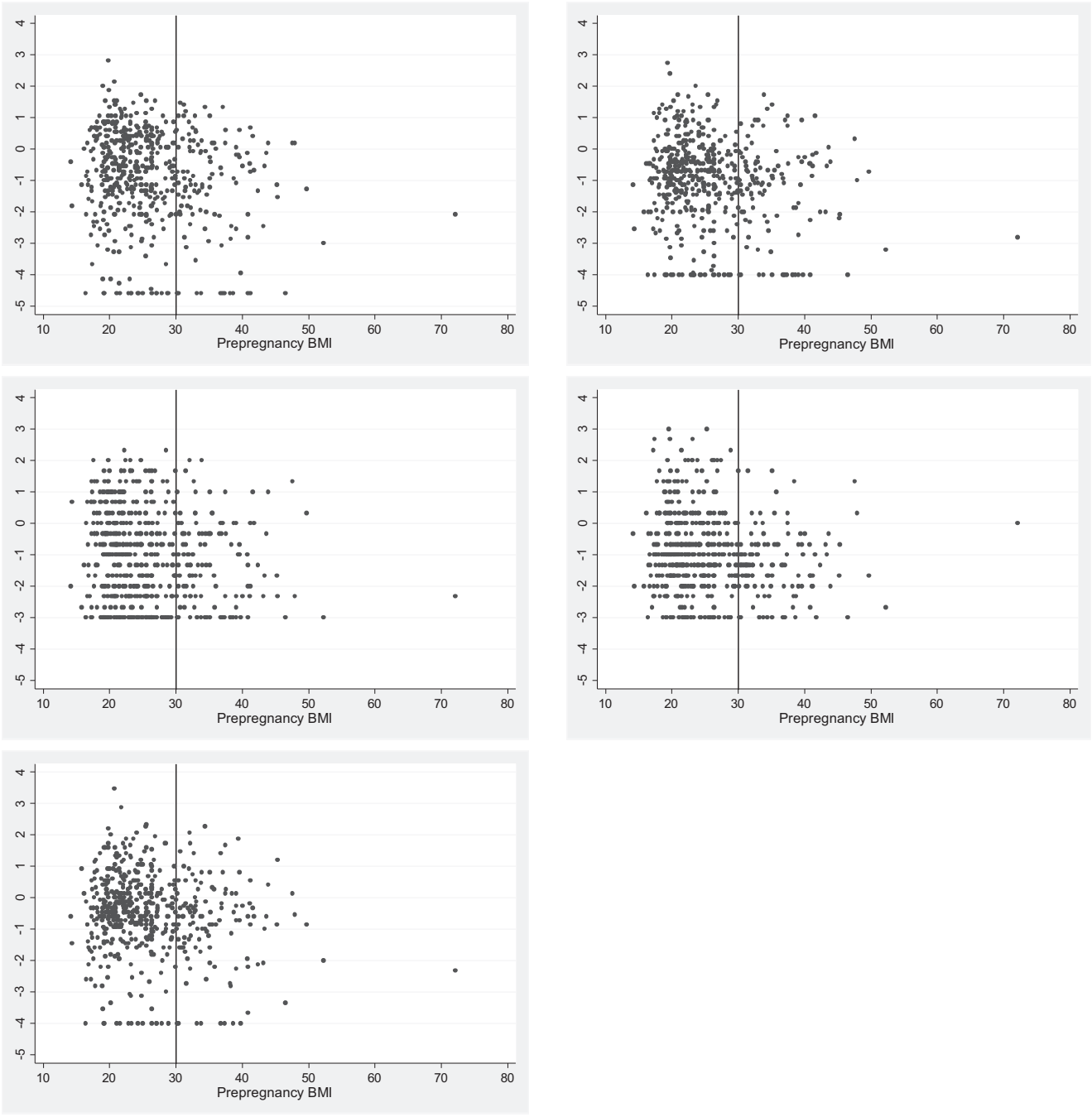

Figure 3. Scatterplots depicting the relationship of maternal prepregnancy BMI to z scores for neurocognitive outcomes. The *vertical line* indicates BMI > 30.

Table II. Study population characteristics (row percent)

Characteristics	n	BMI, kg/m^2				Pregnancy weight gain*		
		< 18.5	18.5 to < 25	25 to < 30	≥30	Inadequate	Adequate	Excessive
Maternal								
Race†								
White	309	10	52	17	21	23	21	56
Black	161	3	44	26	27	26	15	59
Other	63	6	41	30	22	33	16	51
Ethnicity								
Hispanic	57	0	39	28	33	30	21	49
Non-Hispanic	478	9	49	20	22	25	18	57
Age, y								
<21	92	12	57	20	12	35	20	41
21-35	341	8	45	20	27	24	17	59
>35	102	3	50	25	22	20	21	60
Education, y								
≤12	248	11	45	22	22	29	17	64
>12 to < 16	125	4	41	21	34	26	14	60
≥16	162	5	59	20	16	19	23	57
Marital status								
Single	245	11	42	21	25	27	19	54
Married	290	8	83	21	21	24	18	58
Public insurance								
Yes	223	13	40	21	26	28	17	55
No	312	4	54	21	21	23	20	57
Child								
Sex								
Male	284	6	50	20	24	23	18	59
Female	251	10	46	22	23	28	19	53
Gestational age, wk								
23-24	111	5	55	18	23	24	15	60
25-26	255	9	45	23	23	24	18	58
27	169	8	47	21	24	28	20	51
Birth weight, g								
≤750	205	6	49	19	26	28	14	58
751-1000	220	9	45	23	23	23	20	57
>1000	110	8	53	22	17	25	22	53

*Adequacy of weight gain at gestational age of delivery.
†Data missing for the race for 2 mothers.