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EPIDEMIOLOGY/GENETICS

Obesity

Impact of Early-Life Weight Status on Cognitive Abilities in Children

Nan Li [1], *Kimberly Yolton* [2], *Bruce P. Lanphear* [3], *Aimin Chen* [4], *Heidi J. Kalkwarf* [5], *and Joseph M. Braun* [1]

Objective: Whether obesity is associated with childhood cognition is unknown. Given the sensitivity of the developing brain to environmental factors, this study examined whether early-life weight status was associated with children's cognition.

Methods: Using data from mother–child pairs enrolled in the Health Outcomes and Measures of the Environment (HOME) Study (2003–2006), children's early-life weight status was assessed using weight-for-length/height standard deviation (SD) scores. A battery of neuropsychological tests was administered to assess cognition, executive function, and visual-spatial abilities at ages 5 and 8 years. Using linear mixed models, associations between early-life weight status and cognition were estimated.

Results: Among 233 children, 167 were lean (≤1 SD) and 48 were nonlean (>1 SD). After covariate adjustment, the results suggest that full-scale intelligence quotient scores decreased with a 1-unit increase in weight-for-height SD score ($\beta = -1.4$, 95% CI: –3.0 to 0.1). For individual component scores, with a 1-unit increase in weight-for-height SD score, perceptual reasoning ($\beta = -1.7$, 95% CI: –3.3 to 0.0) and working memory (β: –2.4, CI: –4.4 to –0.4) scores decreased. Weight status was generally not associated with other cognition measures.

Conclusions: Within this cohort of typically developing children, early-life weight status was inversely associated with children's perceptual reasoning and working memory scores and possibly with full-scale intelligent quotient scores.

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Introduction

Childhood obesity is an important public health issue (1). The global prevalence of childhood overweight and obesity has increased substantially since the 1990s, and approximately 60 million children are expected to have obesity in 2020 (2). In the United States, approximately 32% of children and adolescents had overweight including 17% with obesity, according to the 2009-2010 National Health and Nutrition Examination Survey (3). Young children with excess adiposity are more susceptible to overweight or obesity in later childhood (4) and at increased risk for adverse health consequences and obesity in adulthood (5).

Obesity is associated with lower cognition in adults; these associations may be mediated by proinflammatory cytokines, leptin, and C-reactive protein (6,7). In addition, obesity-induced dysregulation of appetite hormones, such as ghrelin and glucagon-like peptide 1 (GLP-1), may have detrimental effects on cognition because these hormones act in multiple brain regions that are relevant to cognitive abilities (7-10). In rodents, both obesity and high-fat diets can adversely affect hippocampal-dependent learning (11,12).

The association between obesity and cognition in children is less well understood. Previous studies examining childhood weight status and cognition using cross-sectional designs were not able to specify the directionality of this relationship (13,14). Results from prospective studies are inconsistent, possibly because of discrepancies in age and weight distribution, assessment of weight status or cognitive abilities, and confounder adjustment (15-21). Furthermore, only two studies examined the impact of early-life obesity on childhood cognition; however, both studies focused on early growth (15,16). Given that cognition develops rapidly in the first few years of life, it is important to investigate whether weight

[1] Department of Epidemiology, Brown University, Providence, Rhode Island, USA. Correspondence: Joseph M. Braun (joseph_braun_1@brown.edu)
[2] Department of Pediatrics, Division of General and Community Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA [3] Child and Family Research Institute, BC Children's Hospital and the Faculty of Health Sciences, Simon Fraser University, Burnaby, British Columbia, Canada
[4] Division of Epidemiology, Department of Environmental Health, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA [5] Department of Pediatrics, Division of Gastroenterology, Hepatology and Nutrition, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA.

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status in early life has an impact on cognitive function in children during this critical period of neurodevelopment (22).

To address these gaps in the current literature, we investigated whether weight status in the first 2 years of life was associated with an array of cognitive abilities in school-age children using data from a prospective cohort study. Our analysis was guided by the hypothesis that adipose tissue produces adipocytokines or inflammatory molecules that may adversely affect children's neurodevelopment.

Methods

Study participants

We used data from mother–child pairs participating in the Health Outcomes and Measures of the Environment (HOME) Study, a longitudinal cohort that enrolled pregnant women in the Cincinnati, Ohio, metropolitan area from 2003 to 2006 and conducted follow-up visits with children through age 8 years. Inclusion criteria and recruitment for the HOME Study have been described previously (23). Of 1,263 eligible women, 468 (37%) enrolled in our study. The current analysis was restricted to 233 children who had early-life weight and length/height measurements, covariates, and at least one measurement of cognitive abilities at age 5 or 8 years.

The HOME Study protocols were approved by the institutional review boards at Cincinnati Children's Hospital Medical Center and cooperating delivery hospitals. All mothers provided written informed consent for themselves and their children.

Early-life weight status measures

Study staff measured weight and length/height when children were ages 1 and 2 years. We used an infant scale to measure weight at age 1 year and a pediatric scale at age 2 years (ScaleTronix Inc., White Plains, New York). We measured length with a length board at age 1 year and standing height with a stadiometer at age 2 years. All measures were done in triplicate and the average was used.

According to World Health Organization (WHO) guidelines, weight-for-length/height z score (WHZ) should be used to assess weight status for children under age 5 years, with WHZ $>$ 2 standard deviations (SD) considered overweight and WHZ $>$ 3 SD considered obesity (24). We calculated WHZ using WHO sex-specific standard data (25). Because only a small number of children in this study had WHZ $>$ 2 SD (n = 18), the threshold for overweight or obesity, we grouped children into two categories: lean ($\leq$1 SD) and nonlean ($>$1 SD). We used WHZ at 2 years to determine children's weight status for 85% of children (n = 199), while WHZ at age 1 year was used for 15% (n = 34) of children with no weight and height data collected at 2 years (we used the phrase "early life" to represent ages 1-2 years). We calculated Pearson correlation coefficients to examine the correlation of WHZ at different ages, including 1 month, 1 year, 2 years, 3 years, and 4 years. We focused on weight at age 1 to 2 years rather than other ages or WHZ trajectories because our primary interest was in the impact of adiposity in the first 2 years of life, a period of development when cognition develops rapidly (22).

Cognitive outcomes

Trained examiners assessed several domains of children's cognitive abilities at ages 5 and 8 years using valid and reliable neuropsychological instruments that have been used extensively in epidemiological studies. These included tests of general cognitive abilities, attention, impulsivity, working memory, and reference memory.

We administered the Wechsler Preschool and Primary Scale of Intelligence-III (WPPSI-III) and Wechsler Intelligence Scale for Children-IV (WISC-IV) (The Psychological Corporation, San Antonio, Texas) at ages 5 and 8 years, respectively (26,27). Both Wechsler instruments measure children's overall intellectual abilities (Full-Scale Intelligence Quotient [FSIQ]), verbal abilities (Verbal IQ, WPPSI-III; Verbal Comprehension Index [VCI], WISC-IV), perceptual reasoning and organization skills (Performance IQ, WPPSI-III; Perceptual Reasoning Index [PRI], WISC-IV), and speed of mental and graphomotor processing (Processing Speed Quotient, WPPSI-III; Processing Speed Index [PSI], WISC-IV). Additionally, digit span and letter-number sequencing (Working Memory Index [WMI]) was measured using the WISC-IV. Standardized scores on these tests have mean = 100 and SD = 15, and lower scores indicate lower cognitive abilities.

We administered the Conners' Kiddie Continuous Performance Test and Conners' Continuous Performance Test-II (K-CPT/CPT-II) at ages 5 and 8 years, respectively (28,29). These two computerized tasks assess children's attention, impulsivity, and executive control. During the test, children were told to press the space bar on a computer whenever they saw any picture except for the "soccer ball" picture (K-CPT) or any letter except for the letter "X" (CPT-II). Both CPTs generate T-scores for the following measures: commission error, which measures response inhibition (i.e., hitting space bar when the nontarget stimulus is presented); omission error, which assesses sustained attention (i.e., failing to hit space bar when a target stimulus is presented); and hit reaction time (RT), which measures speed of processing and responding. Tau is an ex-Gaussian indicator of RT, and higher values of tau indicate instances of longer RT in the RT stream. Higher T-scores on the K-CPT/CPT-II tests indicate poorer performance.

Finally, we administered the virtual Morris water maze (VMWM), a computerized version of the rodent Morris water maze, to test children's learning and spatial reference memory at age 8 years (30). Children were instructed to find an escape platform as quickly as possible in a virtual pool using a joystick. Children first completed four practice trials in which the platform was visible in a room with no visual cues. Subsequently, children completed four blocks of four trials with visual landmarks on the walls and the platform hidden in a fixed location. Performance was measured by the average latency to find the platform and distance from the start location to the platform across the four blocks. Children also completed a 30-second probe trial in the same room with the platform removed; performance was measured by the percentage of time spent in the correct quadrant, which assesses children's visual-spatial reference memory.

Covariate assessment

We used directed acyclic graphs to identify potential confounders in our exposure-outcome association (Supporting Information Figure S1) (31). Maternal age, education, marital status, length of breastfeeding, child's race, and interest in playing video games were assessed using questionnaires administered by trained interviewers. Child's sex and birth weight were abstracted from hospital medical charts. We calculated maternal BMI using weight and height measurements collected at the 16-week prenatal clinic visit. We measured mothers' FSIQ using the Wechsler Abbreviated Scale of Intelligence (32). We assessed

TABLE 1 Descriptive statistics of weight-for-height *z* score at ages 1 or 2 years and full-scale intelligence quotient (IQ) scores at ages 5 or 8 years in the HOME Study ($N = 233$)

	Weight-for-height *z* score ($N = 233$)		5-year full-scale IQ ($n = 191$)		8-year full-scale IQ ($n = 204$)	
	n	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)
Child sex						
Male	105	0.5 (1.1)	84	101 (15)	90	103 (15)
Female	128	0.5 (1.1)	107	104 (15)	114	102 (16)
Child race						
Non-Hispanic white	141	0.5 (1.0)	117	108 (13)	123	108 (12)
Non-Hispanic black	75	0.5 (1.2)	60	91 (13)	68	91 (15)
Other	17	0.5 (1.2)	14	105 (12)	13	110 (16)
Child birth weight						
Small for gestational age (<10%)	23	−0.2 (1.0)	19	96 (16)	21	96 (18)
Appropriate for gestational age	177	0.4 (1.0)	144	103 (15)	155	103 (16)
Large for gestational age (>90%)	33	1.5 (1.0)	28	102 (14)	28	103 (13)
Breastfeeding duration						
0 month	42	0.5 (1.3)	33	95 (16)	38	96 (17)
>0-6 months	88	0.4 (1.1)	67	101 (16)	76	101 (16)
>6 months	103	0.5 (1.0)	91	106 (14)	90	107 (14)
Maternal age at delivery (y)						
18-25	52	0.4 (1.2)	40	93 (14)	48	94 (16)
>25-35	148	0.5 (1.0)	122	104 (15)	126	104 (15)
>35	33	0.4 (1.1)	29	110 (14)	30	110 (13)
Annual household income						
>$80,000	60	0.4 (0.8)	49	112 (11)	53	112 (12)
$40,000-$80,000	83	0.6 (1.1)	75	105 (13)	70	105 (13)
<$40,000	90	0.4 (1.2)	67	93 (15)	81	94 (16)
Maternal education						
≥College graduate	116	0.5 (0.9)	96	110 (12)	98	110 (12)
Tech school/some college	66	0.2 (1.1)	56	98 (14)	58	101 (14)
≤High school graduate	51	0.7 (1.4)	39	90 (14)	48	90 (16)
Marital status						
Married	154	0.5 (1.0)	131	107 (13)	132	108 (13)
Unmarried	79	0.5 (1.2)	60	92 (14)	72	93 (16)
Gestational smoking status						
Unexposed (<0.015 ng/mL)	77	0.4 (1.0)	64	107 (13)	65	107 (13)
Secondhand smoke (<3.0 ng/mL)	133	0.5 (1.1)	113	100 (15)	118	101 (16)
Active smoking (>3.0 ng/mL)	23	0.7 (1.3)	14	97 (21)	21	96 (17)
Maternal BMI (kg/m^2)						
< 25 (lean)	93	0.2 (1.0)	73	105 (16)	80	104 (16)
25-30 (overweight)	79	0.5 (1.0)	65	104 (14)	72	105 (14)
>30 (obesity)	61	0.9 (1.3)	53	97 (15)	52	97 (16)
Maternal full-scale IQ						
First tercile 58-99	78	0.4 (1.3)	63	92 (14)	71	92 (15)
Second tercile > 99-114	80	0.3 (0.9)	64	106 (15)	67	107 (13)
Third tercile > 114	75	0.7 (1.0)	64	109 (12)	66	109 (14)

prenatal tobacco smoke exposure by measuring the concentration of cotinine (a sensitive and specific biomarker of secondhand and active tobacco smoke exposure) in maternal serum samples collected at 16 and 26 weeks of pregnancy (33). We used the mean of the $\log_{10}$-transformed serum cotinine concentrations in our analyses.

Statistical analyses

We analyzed the association between early-life WHZ and cognitive abilities (measured repeatedly at ages 5 and 8 years) using linear mixed models. Outcomes of FSIQ score, each IQ component score, commission T-score, omission T-score, RT T-score, and $\log_e$-transformed

TABLE 2 Unadjusted and adjusted difference or relative risk in children's cognitive abilities by 1-unit change in early life weight-for-height *z* score[a]

	n	Unadjusted difference or relative risk (95% CI)	*P*	Adjusted difference or relative risk (95% CI)[b]	*P*
WPPSI-III/WISC-IV full-scale IQ	233	−0.7 (−2.4 to 1.0)	0.41	−1.4 (−3.0 to 0.1)	0.07
WPPSI-III/WISC-IV verbal	233	−0.7 (−2.4 to 0.9)	0.39	−0.8 (−2.2 to 0.7)	0.30
WPPSI-III/WISC-IV perceptual reasoning	233	−0.3 (−2.0 to 1.3)	0.70	**−1.7 (−3.3 to 0.0)**	**0.047**
WPPSI-III/WISC-IV processing speed	224	−0.3 (−1.7 to 1.2)	0.74	−0.6 (−2.4 to 1.2)	0.51
WISC-IV working memory	204	−1.3 (−3.2 to 0.5)	0.16	**−2.4 (−4.4 to −0.4)**	**0.02**
VMWM latency (s)	185	0.2 (−1.0 to 1.5)	0.84	0.4 (−1.0 to 1.8)	0.60
VMWM distance (pool units)	185	−0.6 (−1.9 to 0.6)	0.49	−0.3 (−1.7 to 1.1)	0.69
VMWM time in correct quadrant	185	1.0 (0.9 to 1.2)	0.99	1.0 (0.8 to 1.2)	0.66
K-CPT/CPT-II commissions T-score	225	0.3 (−0.6 to 1.2)	0.53	0.4 (−0.6 to 1.4)	0.46
K-CPT/CPT-II omissions T-score	225	0.0 (−1.8 to 1.8)	0.99	1.2 (−0.8 to 3.2)	0.25
K-CPT/CPT-II reaction time T-score	225	1.1 (−0.2 to 2.4)	0.10	1.1 (−0.2 to 2.5)	0.10
K-CPT/CPT-II tau	188	1.0 (0.97 to 1.1)	0.55	1.0 (0.98 to 1.1)	0.16

[a]Relative risks calculated for VMWM time spent in correct quadrant (0 vs > 0) and K-CPT/CPT-II tau; differences calculated for other outcomes.
[b]Adjusted for continuous variables maternal age, BMI, IQ, child's birth weight, age at outcome measurement, and maternal serum cotinine concentration (mean of $\log_{10}$-transformed cotinine concentrations during 16 and 26 weeks of pregnancy) and for categorical variables maternal education (high school graduate or less, tech school or some college, college graduate or above), marital status (married, unmarried), length of breastfeeding (0 month, ≤ 6 months, > 6 months), child's sex (male, female), and race (non-Hispanic white, non-Hispanic black, other). Interest in playing video games (a lot, some, a little) was adjusted for in models with VMWM outcomes.
IQ, intelligence quotient; CPT-II: Conner's Continuous Performance Task-II; K-CPT: Kiddie Conner's Continuous Performance Task; VMWM: virtual Morris water maze; WISC-IV: Wechsler Intelligence Scales for Children-IV; WPPSI-III: Wechsler Preschool and Primary Scale of Intelligence-III.

tau were modeled separately. We used a multivariable linear regression model to analyze the association with WMI because it was measured only at age 8 years. We analyzed the association of early-life WHZ with VMWM latency and distance using linear mixed models because the hidden platform trials included four repeated trials in each block. We modeled the percentage of time in the correct quadrant in the probe trial as a binary variable (0%, > 0%) using a Poisson regression model because 25% of children did not spend any time in the correct quadrant.

For each outcome, we modeled WHZ as a continuous and binary (lean, nonlean) variable. In addition, we examined the shape of the association between continuous WHZ and cognition using three-knot restricted cubic polynomial splines (34). We adjusted for maternal age, education, marital status, BMI, maternal serum cotinine concentrations, maternal FSIQ, length of breastfeeding, child's sex, race, birth weight, and age at outcome measurement in the multivariable models. We additionally adjusted for interest in playing video games in models with VMWM outcomes.

Because prior studies have observed that the association between adiposity and cognition is stronger in males, we conducted secondary analyses in which we included WHZ × sex interaction terms to determine whether associations between WHZ (either in continuous or binary form) and cognitive abilities were modified by child sex (17,18). $P < 0.2$ for interaction term was considered to indicate the association varied by sex. We also conducted secondary analyses examining IQ subtests when the associations between WHZ and individual IQ components were significant and the IQ subtests were comparable across WPPSI-III and WISC-IV. In a sensitivity analysis, we examined the association between WHO BMI-for-age *z* scores (BMIZ) and children's cognition because prior studies have used BMI instead of weight-for-height to assess adiposity. We considered BMIZ ≤ 1 SD as lean and BMIZ > 1 SD as nonlean. We conducted all statistical analyses using SAS version 9.4 (SAS Institute, Cary, North Carolina).

Results

Among the 233 children who were included in our analyses, 167 (71%) were lean and 66 (29%) were nonlean. The Pearson correlation coefficient between the 1-year and 2-year WHZ was $r = 0.8$ (Supporting Information Table S1). On average, children who were large for gestational age at birth or children whose mothers were less educated (high school education or less), had obesity (BMI > 30 kg/m^2), had higher FSIQ scores, or actively smoked during pregnancy had higher WHZ. On average, children's FSIQ scores were lower if they were non-Hispanic black, small for gestational age, not breastfed, or born to a mother who was 18 to 25 years old at delivery, was unmarried, had obesity (BMI > 30 kg/m^2), was less educated (high school education or less), actively smoked during pregnancy, had lower FSIQ, or had lower household income (Table 1).

IQ and its associated components were measured among 233 children with a total of 395 repeated measurements at ages 5 and 8 years. After adjusting for covariates, with a 1-unit increase in WHZ, we observed decreases in FSIQ ($\beta = -1.4$, 95% CI: −3.0 to 0.1), PRI, and WMI scores, wherein the associations for PRI ($\beta = -1.7$, 95% CI: −3.3 to 0.0) and WMI ($\beta = -2.4$, 95% CI: −4.4 to −0.4) were statistically significant (Table 2). We observed linear associations of WHZ with FSIQ, VCI, PRI, and WMI scores (all nonlinearity $P \geq 0.20$; Figure 1 and Supporting Information Figure S2). There was some evidence of a nonlinear association between WHZ and PSI scores, wherein PSI scores increased and reached a peak at WHZ of ∼0.5 SD and then decreased with increasing WHZ (nonlinearity $P = 0.05$). When WHZ

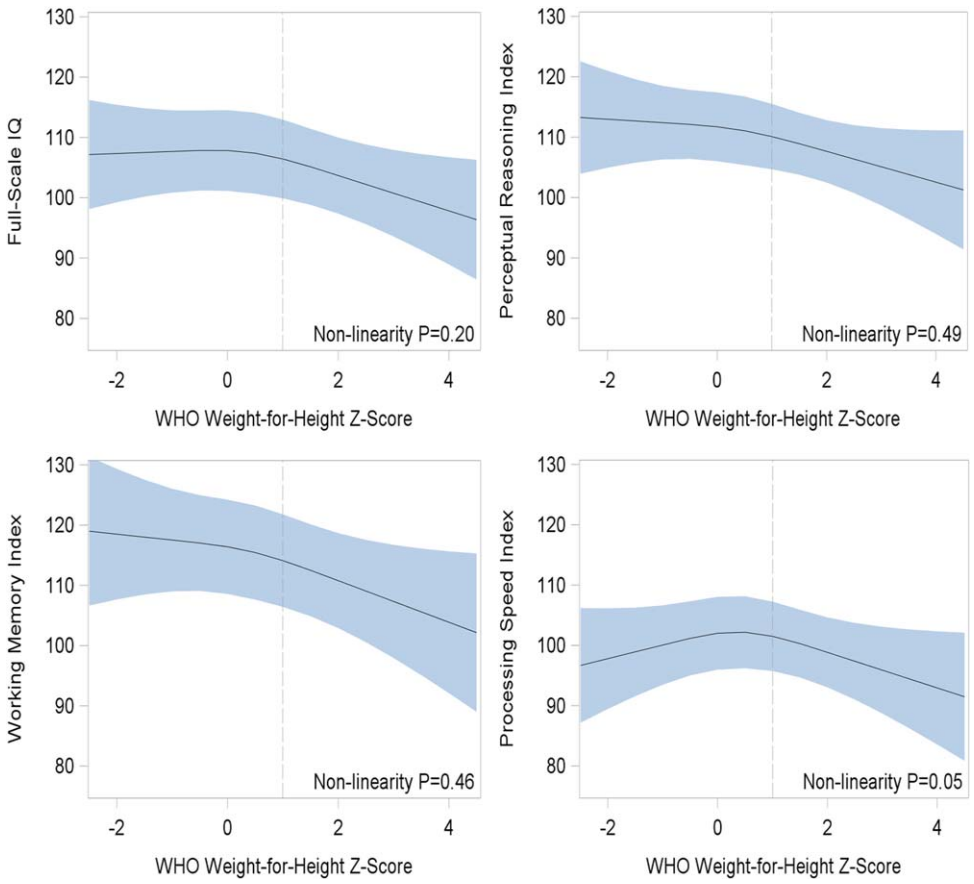

Figure 1 Adjusted restricted cubic polynomial spline of weight-for-height *z* scores and children's full-scale IQ, perceptual reasoning index, working memory index, and processing speed index at 5 or 8 years of age. Adjusted for continuous variables maternal age, BMI, IQ, child's birth weight, age at outcome measurement, and maternal cotinine concentration (mean of $\log_{10}$-transformed cotinine concentrations during 16 and 26 weeks of pregnancy) and for categorical variables maternal education (high school graduate or less, tech school or some college, college graduate or above), marital status (married, unmarried), length of breastfeeding (0 month, ≤ 6 months, > 6 months), child's sex (male, female), and race (non-Hispanic white, non-Hispanic black, other). [Color figure can be viewed at wileyonlinelibrary.com]

was modeled as a binary variable, children who were nonlean had lower FSIQ scores compared with lean children ($\beta = -4.3$, 95% CI: -8.4 to -0.2; Supporting Information Table S2). For individual component scores, children who were nonlean had lower working memory ($\beta = -7.7$, 95% CI: -12 to -3.0) scores than lean children. Children who were nonlean also had lower scores of perceptual reasoning and processing speed compared with lean children; however, these associations were not statistically significant.

The K-CPT/CPT-II was administered to 225 children, with a total of 340 repeated measurements at ages 5 and 8 years. The RT T-score increased with a 1-unit increase in WHZ ($\beta = 1.1$, CI $= -0.2$ to 2.5), and the RT T-score was higher among nonlean children compared with lean children ($\beta = 3.6$, CI $= 0.7$ to 6.6). RT T-score increased monotonically with WHZ (nonlinearity $P = 0.70$; Figure 2). WHZ was not associated with commission or omission T-scores or tau.

Visual-spatial abilities were measured among 185 children at age 8 years. Latency (seconds) and distance (pool units) to find the hidden platform were not associated with weight status (Table 2 and Supporting Information Table S2). In the probe trial, the portion of children who found the correct quadrant was not associated with weight status.

Generally, the association between WHZ and cognitive abilities did not differ by child sex. However, WHZ (modeled as either continuous or binary variable) was inversely associated with WMI scores and VMWM distance among boys (sex $\times$ WHZ $P < 0.05$) but not girls (Supporting Information Tables S3 and S4). Other WHZ-cognition associations were consistent across boys and girls. When we examined the associations with IQ subtests, a 1-unit increase in early-life WHZ was inversely associated with block design ($\beta = -0.4$, 95% CI: -0.7 to -0.1) but was not associated with other PRI subtests (Supporting Information Table S5). Results from sensitivity analyses using WHO BMIZ were similar to our main findings (Supporting Information Table S6).

Discussion

In the present study, we investigated the associations between early-life weight status and children's cognitive abilities in a longitudinal cohort of children from Cincinnati, Ohio. Our findings suggest that

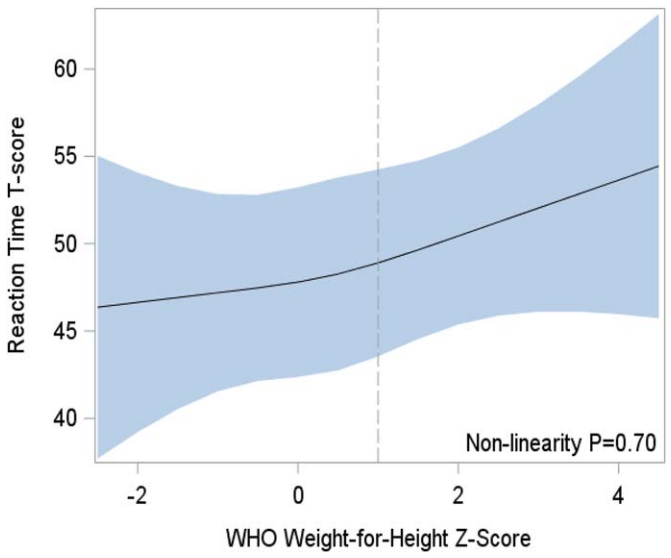

Figure 2 Adjusted restricted cubic polynomial spline of weight-for-height *z* scores and children's hit reaction time T-score at 5 or 8 years of age. Adjusted for continuous variables maternal age, BMI, IQ, child's birth weight, age at outcome measurement, and maternal cotinine concentration (mean of $\log_{10}$-transformed cotinine concentrations during 16 and 26 weeks of pregnancy) and for categorical variables maternal education (high school graduate or less, tech school or some college, college graduate or above), marital status (married, unmarried), length of breastfeeding (0 month, $\leq$6 months, $>$6 months), child's sex (male, female), and race (non-Hispanic white, non-Hispanic black, other). [Color figure can be viewed at wileyonlinelibrary.com]

early-life WHZ may be inversely associated with FSIQ, PRI, and WMI scores after adjusting for potential confounders. Early-life WHZ was also suggestively associated with higher RT T-scores on the K-CPT/CPT-II. Other measures of cognitive abilities were not associated with early-life WHZ.

Prospective studies examining the association between weight status and cognitive abilities in children have yielded inconsistent results (15-21). Two studies examined the impact of early-life weight status on cognitive abilities; however, both studies focused on change in BMI or weight over the first few years of life (15,16). In a study of Finnish children, both small and large body size was associated with decreased visual-motor integration at age 56 months (15). This inverted U-shape relationship is similar to the pattern we observed when examining WHZ and children's PSI, a measure of visual perception and organization, as well as motor skills. In a large population-based study of British children, rapid weight gain between birth and age 25 months (defined as an increase of $>$ 0.67 in the SD score of weight) was not associated with cognitive abilities at ages 49 months or 8 years, measured using the WPPSI and WISC-III, respectively (16). Unlike our study, this British study focused on weight gain in the first 2 years of life, without accounting for children's height and obesity status. This could result in misclassification of early-life adiposity because children with constant overweight/obesity during the first 2 years may not be considered as having rapid growth; in contrast, lean children who grew but did not develop overweight or obesity were still classified as having rapid growth.

Other prospective studies have examined the impact of obesity in childhood on global measures of cognition, with varied results (17-21). Consistent with one of our findings, two studies reported that obesity at ages 3 to 5 years was associated with lower cognitive abilities in boys only at ages 5 or 8 to 12 years (17,18). In contrast, two other studies reported that children with underweight had lower cognitive abilities (19,20). Very few children were underweight in our study, and thus we were not able to precisely examine this association. Finally, a study of Dutch children did not observe associations between BMI at age 4 years and cognitive abilities at age 7 years, assessed using the Kaufman Assessment Battery for Children (21). However, this study had a small number of children with overweight (n = 18), limiting the statistical power. In sum, discrepancies in the findings above may be explained by differences in the age of exposure and outcome measurements, measures of weight status, weight status distribution of the study population, different lengths of follow-up, measures of cognitive abilities, and adjustment for confounding factors (15-21).

Executive function is a set of self-regulatory cognitive processes that aid in managing thoughts, emotions, and goal-directed behaviors. It includes domains such as inhibitory control, working memory, reward sensitivity, and attention (14). Executive function is associated with academic success in children and is critical for physical health and success throughout life (35). Previous studies have reported a consistent inverse association between obesity and executive function in children; however, most studies have been cross-sectional in design, and thus the directionality of the association cannot be determined (14). Some have speculated that children with lower executive function have lower self-regulation of caloric intake and physical activity, which ultimately leads to overweight or obesity, whereas others have argued that obesity may decrease executive function through the action of adipocytokines or inflammatory molecules (7,14,36). Moreover, some have proposed a bidirectional relation wherein low executive function promotes excess adiposity and excess adiposity exacerbates executive function decrements (36).

Our results suggest that nonlean children had higher RT T-scores (indicating lower speed of processing and responding) compared with lean children. Some cross-sectional studies included in a systematic review by Reinert et al. have reported shorter RT and more commission errors among children with higher BMI (14). While the reasons for the inconsistency with our own results is unclear, it is possible that the shorter RT in those studies may reflect high impulsivity, which may have led to overconsumption of food and higher BMI. Given the cross-sectional nature of prior studies, it is not possible to delineate the temporal relation between BMI and these executive functions. In contrast, the longitudinal design of our study ensured that we could determine the directionality of the relationship (from adiposity to executive function) and ensure that it was not influenced by bidirectionality, because weight status was measured years prior to executive function assessment and at an age when eating behavior was more affected by parental influence than children's self-regulation (37). A population-based study in Germany investigated the 1-year longitudinal associations and found that BMI was not associated with executive function (38). However, the 1-year follow-up time might be too short to allow overweight-associated pathophysiological processes to affect executive function, and they did not adjust for mothers' BMI in the analysis. The CPT tests utilized in our study assess only the attention and inhibitory control aspects of executive functioning; therefore, additional longitudinal studies with repeated and comprehensive measures of executive function are needed.

In our study, weight status in general was not associated with visual-spatial abilities measured by VMWM, except that weight-for-height may be inversely associated with distance in the VMWM hidden platform trials among boys (Supporting Information Tables S3-S4). We found that early-life WHZ was inversely associated with performance on a block design test, a PRI subtest that also measures visual-spatial organization. Consistent with our findings, BMI was inversely associated with block design test performance among school-aged US children and adolescents in a cross-sectional study (13). Some other studies have examined the relationship between obesity and visual-spatial abilities in children. In a UK cohort study, obesity at age 3 years was associated with worse visual-spatial skills at age 5 years in boys (18). A randomized controlled trial conducted among school-aged Danish children found that visual-spatial construction skills were improved after obesity intervention among children with overweight or obesity, indicating that obesity may play a detrimental role in visual-spatial abilities (39). The underlying mechanisms for these sex-specific effects are unclear. Sex hormones or psychosocial factors may partly explain the differences. Given the sparsity of the current literature, additional prospective studies are needed to confirm these findings and examine whether the associations differ by sex.

There are several biological mechanisms by which early-life adiposity could affect neurodevelopment. Adipose tissue produces pro-inflammatory cytokines that activate inflammatory pathways in children and adults (7). Systematic inflammation may affect multiple brain regions relevant to cognitive abilities and has been shown to adversely affect spatial learning and memory in rodents (7). In addition, the dysregulation of appetite-regulating hormones among children with excess adiposity may adversely affect cognition (7). Ghrelin, a hunger hormone, can cross the blood–brain barrier and activate hippocampal regions to improve memory in rodents (9). GLP-1, which promotes satiety, also acts on multiple brain regions that are involved in cognitive abilities, such as the hypothalamus and the prefrontal cortex (8). In rodents, deficiencies in ghrelin and GLP-1 have caused deficits in learning and memory (7,10).

Our study had some limitations. This study had limited statistical power to detect small effects and precisely estimate associations, especially for children with overweight/obesity, because of our modest sample size. Thus, we were not able to examine children with obesity and overweight separately. However, by using different categories of weight status, we were able to examine the group of children who were at the high end of the normal WHZ range (>1 SD) compared with lean children (≤ 1 SD), which brings attention to this group of children who are at risk of overweight or obesity later in childhood and adolescence (40). Furthermore, while WHZ at age 2 years was used in most children as an exposure, WHZ at age 1 year was used in some children when 2-year data were not available. However, 2-year WHZ was highly correlated with 1-year, 3-year, and 4-year WHZ in this study, which reduced the possibility of exposure misclassification. The correlation pattern (and the one observed for repeated BMI *z* scores; Supporting Information Table S7) indicates that 2-year WHZ tends to predict weight status in childhood, which is consistent with previous findings (4). Another limitation is that we did not use direct measurement of adiposity, such as dual energy X-ray absorptiometry, which can provide a more accurate assessment of body composition (41). However, given that young children may not be cooperative for this measurement, WHZ is a more practical measurement of excess weight in early childhood and is endorsed by WHO to assess body composition for children under 5 years. Finally, we made several comparisons, and it is possible that some of our results may be chance findings. However, adjusting for multiple comparisons may undeservedly reduce statistical power (42), and the general pattern of our results suggests an inverse association between early-life adiposity and cognitive abilities.

Our study had several strengths. Our prospective data enabled us to investigate whether weight status in the critical period of brain development—the first 2 years of life—impacts cognitive abilities in childhood. Compared with prior cross-sectional studies examining the association between childhood weight status and cognition, the prospective design helped us determine the directionality of the association. Furthermore, we repeatedly administered valid and reliable neuropsychological tests to assess an array of cognitive abilities. In addition, weight and length/height were measured by trained study staff rather than self-reported by parents, which provided more accurate measurements and reduced potential exposure misclassification. Finally, we collected detailed information on covariates in this study, which enabled us to adjust for multiple potential confounding factors including sociodemographic factors, perinatal factors, and maternal IQ.

Conclusion

Excess early-life weight-for-height may be inversely associated with full-scale IQ, perceptual reasoning scores, and working memory scores (boys only) and suggestively associated with longer reaction time among school-aged children. Future prospective cohort studies should confirm these findings and investigate whether early-life weight-for-height is associated with school performance, attention-deficit/hyperactivity disorder diagnosis, learning disabilities, or special education service use. O

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