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Is low birth weight associated with adiposity in contemporary U.S. youth? The Exploring Perinatal Outcomes among Children (EPOCH) Study

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Abstract

Little is known about the relationship between low birth weight (BW), as a marker of under-nutrition *in utero*, and childhood body mass index (BMI) and adiposity parameters, including skinfold thickness, abdominal subcutaneous (SAT) and visceral adipose tissues (VAT) and intramyocellular accumulation of lipids (IMCL). The EPOCH Study (Exploring Perinatal Outcomes among Children) explored the association between BW and markers of adiposity in contemporary, multi-ethnic children from Colorado. A total of 442 youth age 6–13 years (50% male, mean age 10.5 years) had anthropometric measurements, abdominal SAT and VAT measured by magnetic resonance imaging and IMCL deposition in the soleus muscle measured by nuclear magnetic resonance spectroscopy. BW and gestational age were ascertained from an electronic perinatal database. A weak positive association between BW and current BMI ($P=0.05$) was seen, independent of demographic, perinatal, socio-economic and current lifestyle factors. When adjusted for current BMI, every one standard deviation decrease in BW (~500 g), was associated with a 8.8 cm² increase in SAT, independent of potential confounders. In conclusion, in a contemporary cohort of youth, BW was positively, but weakly, associated with BMI and inversely, though weakly, associated with SAT, independent of current BMI. There were no significant associations between BW and waist circumference, skinfolds, VAT and IMCL. Our results provide some support to the hypothesis that under-nutrition *in utero*, as reflected by lower BW, is associated with lower overall childhood body size, but an increased propensity for abdominal adiposity, reflected in this young age-group, predominantly as subcutaneous fat.

Introduction

The prevalence of childhood and adolescent obesity has more than doubled in the United States in the past three decades¹ with similar trends observed worldwide.² Childhood obesity frequently persists into adulthood, with up to 80% of obese children becoming obese adults.³ Moreover, overweight and obesity are now present at increasingly younger ages,¹ indicating that risk factors for this condition start operating early in life.

More than two decades ago, Barker proposed that the intrauterine environment and exposures early in life presaged risk for chronic disease in adulthood.⁴ Numerous epidemiological studies have linked *in utero* growth restriction, defined as low birth weight (BW) or thinness at birth, with an increased risk for the metabolic syndrome, insulin resistance, poor glucose tolerance or type 2 diabetes, hypertension and cardiovascular disease later in life.^{4–8} The effects were greatly enhanced by, and sometimes only apparent, in the presence of adult obesity. These findings were linked to poor fetal nutrition during intrauterine life and constitute the basis for the ‘thrifty phenotype’ hypothesis.⁹ On the other hand, high BW has also been associated with greater body size in adolescents¹⁰ and a ‘U-shaped’ relation between BW and risk for type 2 diabetes has been demonstrated among the Pima Indians.¹¹ Thus, it has been suggested that exposures during the intrauterine life resulting in either fetal over-nutrition or under-nutrition, may trigger distinct pathways responsible for an increased risk of obesity later in life.

With a few notable exceptions,^{12,13} the vast majority of studies linking low BW to obesity and related outcomes are based on adults born in the first half of the 20th century.^{14,15} It is unclear whether the ‘thrifty phenotype’ hypothesis is relevant for contemporary U.S. youth, who are likely to be exposed to a much different pre- and postnatal environment than adults born between the two World Wars, or populations experiencing rapid nutritional changes in countries undergoing accelerated Westernization.

In addition, the last few decades have seen an increasing appreciation of fat distribution as an important determinant of morbidity and mortality, with central or abdominal adiposity being now recognized to be more pathological than generalized obesity. Although several epidemiological studies have explored the association between low BW and body mass index (BMI), fat mass (using dual X-ray absorptiometry) and skinfold thickness in adults^{14–16} and children,^{17–19} very few²⁰ have linked objectively measured BW to measures of abdominal fat such as the visceral and subcutaneous abdominal adipose tissue (VAT, SAT). No studies that we are aware of have looked at the associations between BW and measures of ectopic fat deposition, such as intramyocellular accumulation of lipids (IMCL) in youth.

Therefore, the aim of our study was to explore the association between BW and childhood body size (BMI), abdominal adiposity (SAT and VAT) and ectopic fat deposition (IMCL) among children enrolled in the retrospective multi-ethnic cohort study: Exploring Perinatal Outcomes among Children (EPOCH) in Colorado.

Methods

Participants

EPOCH participants included in this report are 6–13-year-old offspring of singleton pregnancies, born at a single hospital in Denver between 1992 and 2002, whose biological mothers were members of the Kaiser Permanente of Colorado Health Plan (KPCO), and were still KPCO members and living in Colorado over the study period (2006–2009), and who were not exposed to maternal diabetes during pregnancy. We excluded participants exposed to maternal diabetes *in utero* since the hypothesized mechanism responsible for their increased obesity risk is over-nutrition, rather than under-nutrition, *in utero*, and we have previously published their adiposity patterns.^{21,22}

Children and their biological mothers were invited for a research visit between 2006 and 2009. The study was approved both by the Colorado Multiple Institutional Review Board and Human Participant Protection Program. All participants provided written informed consent and youth provided written assent.

Perinatal information

The KPCO Perinatal database, an electronic database linking the neonatal and perinatal medical record, was used to collect the relevant data: BW, gestational age and maternal pre-pregnancy BMI. Maternal pre-pregnancy BMI was calculated from the KPCO-measured weight before the last menstrual cycle preceding pregnancy and height collected at the in-person research visit.

Measures of childhood adiposity and fat distribution

Childhood height and weight were measured in light clothing and without shoes. Weight was measured to the nearest 0.1 kg using an electronic scale. Height was measured to the nearest 0.1 cm using a portable stadiometer. BMI was calculated as kg/m^2 . Waist circumference was measured according to the National Health and Nutrition Examination Survey protocol.²³ The subscapular (2 cm along a line running laterally and obliquely downward from the subscapular landmark at a 45° angle) and triceps (the most posterior surface of the arm over the triceps muscle) skinfold thickness was measured in triplicate using Holtain calipers and averaged. Magnetic resonance imaging (MRI) of the abdominal region, performed with a 3T HDx Imager (General Electric, Waukegan, WI, USA), was used to quantify abdominal VAT and SAT. Each study participant was placed supine and a series of T1 weighted coronal images were taken to locate the L4/L5 plane. One axial, 10 mm, T1-weighted image, at the umbilicus or L4/L5 disc space, was analyzed to determine SAT and VAT content. Images were analyzed by a single reader, blinded to exposure status. Soleus muscle IMCL accumulation was assessed by magnetic resonance spectroscopy (MRS). Each subject was positioned to the mid-calf area, using a T1 weighted image as a localizer and homogenous muscle regions were selected for measurement. The spectroscopy acquisition was performed using the PRESS pulse sequence (TR/TE = 2000 ms/100 ms) with the Cr peak at 3.0 ppm used for an internal reference.²⁴ Water suppression was not used so that the IMCL concentration could be scaled to the basis set water peak and therefore normalized. IMCL, although not given in absolute units, can therefore be compared across the subjects studied. Spectra images were analyzed using the LCModel spectroscopy analysis package.

Other measurements

Race/ethnicity was self-reported using 2000 U.S. Census-based questions and categorized as Hispanic, non-Hispanic white (NHW) and non-Hispanic black (NHB). Pubertal development was assessed by child's self-report with a diagrammatic representation of Tanner staging adapted from Marshall and Tanner,²⁵ which was recently showed to be in excellent agreement with physician-assessed Tanner stage.²⁶ Youth were categorized as Tanner <2 (pre-pubertal) and ≥2 (pubertal). Children's total energy intake (calories/day) was assessed using the Block Kid's Food Questionnaire.²⁷ Self-reported key physical activities performed during the previous 3 days were queried using a 3-day physical activity recall questionnaire.²⁸ Results were reported as average number of 30 min blocks of moderate-to-vigorous activity per day. Data on current total household income and maternal level of education were collected through self-administered questionnaire at the time of research visit. All mothers also reported their maternal pre-pregnancy BMI and smoking at any time during pregnancy.

Statistical analysis

Student's *t*-test and χ^2 -test were used to examine the differences in the continuous and categorical variables by gender. The strength of correlation between various measures of adiposity parameters was evaluated by Pearson's correlation coefficient. Simple linear regression was used to assess the relationship between childhood measures of adiposity

(BMI, subscapular and triceps skinfold, SAT, VAT, IMCL) and demographic and current characteristics, in order to identify potential confounders. Multiple linear regression models were built to examine the association of BW (exposure) with measures of offspring adiposity and fat distribution, controlling for potential confounders. Multiple linear regression models were developed for each outcome. Model 1 (base model) was adjusted for demographic factors only (gestational age, current age, sex, race/ethnicity, Tanner stage). Model 2 additionally adjusted for socio-economic factors (maternal education and income), perinatal factors (gestational age and maternal pre-pregnancy BMI) and current lifestyle factors (child's self-reported physical activity and total daily energy intake), to explore the independent, direct effects of BW on current adiposity measures. In Model 3, we assessed the effect of adjustment for current childhood BMI on the relationship between BW and all other adiposity outcomes, to explore whether current childhood body size confounds any possible association between BW and other adiposity measures. An interaction term between BW and current BMI was also added to Model 2 to test whether current child BMI modifies the association between BW and various adiposity measures. To test for potential non-linear associations, a quadratic term for BW was also explored in various models. To examine whether attained BMI modifies the association between abdominal adiposity and BW, a stratified analysis was done to examine the associations between BW and abdominal adiposity separately in normal weight and obese youth. The analyses were performed using SAS 9.2 (SAS Institute Inc., NC, USA) and the level of significance was set to <0.05 .

Results

A total of 442 children, of NHW, NHB and Hispanic ethnicity, not exposed to maternal diabetes *in utero* and had complete MRI data were included in this report. Table 1 shows characteristics of the study population, according to sex. The mean age of participants was 10 years with nearly half of them being males. Girls were born somewhat later (39 weeks *v.* 38.6 weeks, $P=0.01$) and reported consuming less daily calories (1709.0 *v.* 1932.2 kcal/day, $P<0.0001$) than boys. No significant sex differences were evident in terms of age, race/ethnicity, current BMI and pubertal development (Tanner stage).

Table 2 shows the correlations between various measures of adiposity, separately, in boys and girls. Although all the correlations were statistically significant ($P<0.0001$), the correlation between current BMI and VAT were somewhat weaker ($r=0.65, 0.68$) than those between BMI and SAT ($r=0.94, 0.91$) in both boys and girls, respectively. IMCL was only weakly correlated with measures of adiposity.

Table 3 shows the results of multiple regression analyses exploring the relationship between BW and various measures of adiposity. In Model 1 analyses (adjusted for age, sex, race/ethnicity and Tanner stage), BW was positively associated with BMI ($P=0.02$), waist circumference (0.05), triceps ($P=0.006$) and subscapular skinfold thickness ($P=0.02$). On additional adjustment for perinatal (gestational age and pre-pregnant BMI), socio-economic (maternal income and education) and lifestyle factors (current child physical activity and total daily energy intake) in Model 2 an independent, though weak, positive association between BW and current BMI was still present indicating that for every 1 S.D. increase in BW (~500 g), childhood BMI increased by 0.58 kg/m². No other significant associations between BW and adiposity patterns were found in Model 2 analyses. Additional adjustment for maternal smoking during pregnancy had no effect on any estimates. After adjustment for current BMI (Model 3), most associations between BW and adiposity parameters tended to become inverse; however, the only significant inverse association was noted between BW and SAT ($P=0.008$). This model suggests that, for a given body size, for every 1 S.D. decrease in BW (~500 g), there was a 8.8 cm² increase in SAT, independent of perinatal, demographic, socio-economic and lifestyle factors. No associations between low BW

defined as either BW for gestational age z-score < 10th percentile, or BW < 2500 g, and any adiposity outcomes were noted. No U-shaped associations between BW and adiposity measures were observed. We also found no evidence of association between attained height and BW. Finally, no significant interaction between BW and current BMI were noted on adiposity parameters with similar associations being observed in normal weight and obese youth.

Discussion

We show that in a contemporary cohort of healthy youth from Colorado, low BW, as a marker of under-nutrition *in utero*, is not a major determinant of childhood adiposity as assessed by skinfold thickness, visceral fat deposition and ectopic fat accumulation in the muscle. In this retrospective cohort, BW was positively, but weakly, associated with attained BMI. BW was inversely associated with SAT deposition, after adjusting for current BMI. BW has been shown to be positively associated with BMI, whereas negative associations were found with central or total body fat,^{29,30} suggesting that different pathways may be responsible for these associations.³¹ Adjustment for attained BMI helps disentangle overlapping fetal pathways, and helps elucidate the relationships of interest. Our finding of an inverse association of BW with SAT only after adjustment of attained BMI likely reflects an underlying inverse association with overall fat mass, and its major component, abdominal fat. Our results provide some support to the hypothesis that under-nutrition *in utero* is associated with lower overall childhood body size, but an increased propensity for abdominal fat deposition, reflected, in this young age-group, predominantly as subcutaneous fat.

Human epidemiological studies over the last 20 years have provided strong evidence of an association between intrauterine growth restraint, as marked by low BW, and the development of adult metabolic outcomes, including type 2 diabetes.^{32–34} The association has been explained as representing long-term effects of nutritional deprivation *in utero* on fetal growth, development of the endocrine pancreas, and future diabetes risk.³³ Direct evidence that poor maternal nutrition can have detrimental consequences for adult glucose tolerance comes from a study of adults who were *in utero* during the Dutch Famine toward the end of World War II. Offspring of these pregnancies were found to have reduced glucose tolerance, an effect most marked in those who were *in utero* in the last trimester of pregnancy.³⁴ However, an important challenge of the thrifty phenotype hypothesis is that the exact nature, number and timing of intrauterine insults that translate into intrauterine growth restriction in contemporary societies are not known. For example, more recently, smoking in pregnancy, long recognized as a cause of reduced BW, has been shown to increase the amount of type 2 diabetes and overweight/obesity in the offspring,^{35–37} adding to the evidence for adverse consequences of a poor maternal environment, but also highlighting another type of intrauterine exposure with long-term metabolic consequences.

Several epidemiologic studies have linked intrauterine growth restriction with measures of fatness among both children and adults.^{38–40} In particular, this has been with increased visceral adiposity among adults.³⁸ These studies suggest that, *after adjustment for attained BMI*, the lower the BW, the higher the risk of central or visceral adiposity later in life. Limited evidence exists for youth, and most suggest a *relative increase in fat mass*, given an overall smaller body size. In the third National Health and Nutrition Examination Survey (NHANES III, 1988–1994), children with BW below the 10th percentile for gestational age were slightly smaller than their peers, with less lean tissue mass, but no reduction in fat mass, thus having a higher percent body fat.⁴⁰ Gale *et al.*⁴¹ also showed that total body fat was highest in subjects with low BW and high current weight. Among men born in England, after adjustment for current BMI, the mean waist-to-hip ratio increased with decreasing

BW,⁴¹ and in a study of 14–16-year-old girls, a relationship between low BW and increased subscapular-to-triceps skinfold thickness ratio was only seen in overweight girls.⁴² More recently, Dolan *et al.*¹³ showed that among 101 children aged 12–13 years, higher BW was associated with higher total fat mass and percent body fat, whereas lower BW was associated with higher truncal fat mass, adjusted for fat mass.

Our results in one of the largest cohorts of U.S. youth with state-of-art measures of abdominal adiposity, are in general agreement with this body of literature describing a significant, though weak inverse association between BW and abdominal fat deposition in the subcutaneous region, for a given childhood body size. Of note, this association was independent of many potential confounders, both perinatal as well as current, suggesting a direct effect of the intrauterine environment on childhood abdominal subcutaneous fat deposition. The fact that no similar associations were noted with visceral fat may be due to the limited amount of VAT characteristic of this age-group. However, we should also note that no similar associations were observed with waist circumference, skinfold thickness or IMCL. Longitudinal follow-up of this cohort is needed to explore whether these BW – adiposity associations become stronger with age, with increased exposure to a postnatal obesogenic environment, as well as, with transition through puberty and its' associated rise in insulin resistance.⁴³

Our study has several limitations. Almost half of our cohort was pre-pubertal (Tanner stage < 2), thus likely limiting our ability to better explore a plausible biological interaction between a poor intrauterine nutritional environment and an obesogenic postnatal developmental period. The mothers reported relatively high incomes in this cohort of Colorado youth, predominantly of NHW origin, although including a sizeable proportion of Hispanic children (40%). It is possible, even likely, that the intrauterine nutritional environment to which these youth were exposed is very different from that of youth of other racial/ethnic groups in the U.S., or youth from developing countries undergoing rapid transition. Our finding of a weak inverse association between BW and SAT, after adjustment for attained BMI, suggests some effect of the intrauterine environment, but perhaps due to low sample size of very small infants, effects of low BW, *per se*, were not observed. Finally, although our study included state-of-the-art measures of central fat deposition, we do not have measures of total fat mass and fat-free mass to explore the hypothesis of different associations between BW and various body composition compartments. Nevertheless, to our knowledge, our study is the first attempt to explore the relationship between objectively measured BW, as marker of an adverse intrauterine environment, and numerous adiposity outcomes, including MRI-based measures of abdominal fat and ectopic fat deposition in the soleus muscle, among a contemporary, well-characterized cohort of U.S. youth. Our results show a weak association, but suggest future directions for research, such as the longitudinal follow-up of this cohort as it transitions through puberty.

In summary, our study lends some support to the hypothesis that childhood adiposity patterning is programmed *in utero*. The epidemic of childhood obesity is being fueled by both genetic and environmental factors, including specific intrauterine effects. Since the genetic risk cannot be modified, a better understanding of the role of the prenatal environment will contribute substantially to the development of feasible and sustainable strategies directed at preventing future increases in childhood obesity.

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Keywords

BMI	Body mass index
EPOCH	Exploring Perinatal Outcomes among Children
IMCL	intramyocellular accumulation of lipids
SAT	subcutaneous adipose tissue
VAT	visceral adipose tissue

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Table 1

Characteristics of study participants

Variable	Boys (n = 216)	Girls (n = 226)	P-value
Perinatal			
BW (g)	3217 (644)	3142 (494)	0.1
BW z-score	-0.11	-0.13	0.1
Length at birth (cm)	19.2 (1.0)	19.7 (1.5)	0.1
Gestational age (weeks)	38.6 (2.3)	39.0 (1.6)	0.03
Smoking in pregnancy: n (%)	9 (4)	18 (8)	0.09
Maternal education: n (%)			0.5
High school	31 (14)	28 (12)	
Any college	185 (86)	198 (88)	
Total household income: n (%)			0.01
<\$50,000/year	57 (26)	37 (16)	
>\$50,000/year	159 (74)	188 (84)	
Maternal pre-pregnancy BMI	25.6 (6.3)	25.1 (5.9)	0.5
Small for gestational age (%)	28 (13)	28 (12)	0.8
Demographic			
Age (years)	10.6 (1.4)	10.5 (1.2)	0.4
Race/ethnicity: n (%)			0.1
NHW	92 (43)	118 (52)	
Hispanic	104 (48)	87 (39)	
NHB	20 (9)	21 (9)	
Tanner stage: n (%)			0.6
<2	107 (50)	108 (48)	
2	108 (50)	118 (52)	
Physical activity (blocks/day) ^a	4.5 (3.0)	4.1 (2.7)	0.2
Total calories/day	1932 (623)	1709 (489)	<0.0001
% calories from fat/per day	35.8 (4.9)	35.4 (4.8)	0.4
Adiposity			
Weight (kg)	40.9 (14.5)	40.0 (12.9)	0.5
Height (cm)	144.8 (10.8)	144.5 (10.2)	0.7
BMI (kg/m ²)	19.0 (4.7)	18.9 (4.4)	0.6
BMI z-score	0.21 (1.18)	0.27 (1.2)	0.3
Waist circumference (cm)	66.8 (13.0)	64.5 (11.1)	0.04
VAT (cm ²)	21.8 (15.2)	22.8 (17.0)	0.5
SAT (cm ²)	115.1 (116.2)	126.9 (101.7)	0.2
Triceps skinfold (cm)	15.8 (7.9)	16.8 (6.6)	0.1
Subscapular skinfold (cm)	12.3 (8.9)	13.4 (8.1)	0.1
IMCL (mmol/kg muscle wet wt)	2.3 (1.3)	0.3 (1.2)	0.8

BW, birth weight; BMI, body mass index; NHW, non-Hispanic white; NHB, non-Hispanic black; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; IMCL = intramyocellular accumulation of lipids.

^aPhysical activity calculated as average number of 30 min blocks of moderate-to-vigorous activity per day.

All values mean (S.D.) unless otherwise stated.

Table 2

Inter-correlations (Pearson's r) between adiposity variables

	BMI	Waist	VAT	SAT	Subscapular	Triceps	IMCL
Boys							
BMI	1						
Waist	0.95	1					
VAT	0.65	0.68	1				
SAT	0.94	0.94	0.69	1			
Subscapular	0.85	0.85	0.79	0.88	1		
Triceps	0.83	0.81	0.72	0.86	0.88	1	
IMCL	0.39	0.40	0.33	0.38	0.31	0.32	1
Girls							
BMI	1						
Waist	0.91	1					
VAT	0.68	0.71	1				
SAT	0.91	0.93	0.73	1			
Subscapular	0.82	0.80	0.72	0.86	1		
Triceps	0.75	0.72	0.69	0.78	0.85	1	
IMCL	0.54	0.57	0.46	0.57	0.52	0.47	1

BMI, body mass index; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; IMCL, intramyocellular accumulation of lipids.
All *P*-values <0.0001.

Table 3

Association between birth weight (per 1 S.D.) and childhood adiposity parameters

Variable	Model 1		Model 2		Model 3	
	β (95% CI)	P-value	β (95% CI)	P-value	β (95% CI)	P-value
BMI (kg/m ²)	0.60 (0.07, 1.14)	0.02	0.61 (0.02, 1.2)	0.04		
Waist (cm)	1.3 (−0.02, 2.7)	0.05	1.41 (−0.09, 2.9)	0.06	−0.01 (−0.6, 0.6)	0.9
VAT (cm ²)	1.3 (−0.7, 3.4)	0.2	0.7 (−1.2, 2.7)	0.4	−0.6 (−2.1, 0.7)	0.3
SAT (cm ²)	9.3 (−3.6, 22.3)	0.15	4.9 (−9.4, 19.3)	0.5	−8.8 (−15.4, −2.3)	0.008
Triceps skinfold (cm)	1.2 (0.3, 2.1)	0.006	1.0 (−0.02, 2.0)	0.06	0.1 (−0.5, 0.7)	0.7
Subscapular skinfold (cm)	1.22 (0.15, 2.2)	0.02	0.89 (−0.29, 2.0)	0.1	−0.12 (−0.83, 0.58)	0.7
IMCL (mmol/kg muscle wet wt)	0.09 (−0.06, 0.25)	0.2	0.09 (−0.1, 0.2)	0.3	−0.02 (−0.16, 0.21)	0.7

BMI, body mass index; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; IMCL, intramyocellular accumulation of lipids.

Model 1: adjusted for gestational age, current child age, sex, race, Tanner stage.

Model 2: Model 1 + maternal pre-pregnant BMI, maternal smoking, education and income, current child total daily calorie intake and current child physical activity.

Model 3: Model 2 + current child BMI.