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Association between Birth Characteristics and Coronary Disease Risk Factors among Fifth Graders

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Objective To evaluate the associations between selected birth characteristics—prematurity and poor intrauterine growth—and risk factors for coronary artery disease detected among children enrolled in the fifth grade.

Study design Children (n = 3054) with matched birth and fifth grade health screening data on body mass index (BMI), systolic blood pressure, and fasting lipid profiles were analyzed using MANOVA with the following independent variables of weight gain by the fifth grade: BMI percentile, normal or overweight/obese (BMI ≥85th percentile), prematurity, and intrauterine growth (ie, small for gestational age [SGA], appropriate for gestational age [AGA], or large for gestational age [LGA]).

Results LGA status at birth was associated with overweight/obesity later in life. In fifth grade, overweight/obese children had elevated systolic blood pressure and abnormal levels of most fasting serum lipids compared with normal-weight children regardless of birth characteristics. Beyond the effects of BMI percentile, preterm infants had higher levels of triglycerides (TG) than term infants by the fifth grade ($P < .05$). SGA infants who become overweight/obese had higher levels of TGs and very low-density lipoproteins compared with AGA and LGA infants, whether overweight or normal weight ($P < .05$).

Conclusion BMI ≥85th percentile in the fifth grade is associated with abnormalities in most coronary artery risk factors regardless of birth characteristics. Beyond the effects of BMI percentile in the fifth grade, preterm infants had higher TG levels than term infants. SGA infants who were overweight/obese in the fifth grade had higher TG and very low-density lipoprotein levels compared with AGA and LGA infants who were overweight/obese or of normal weight in the fifth grade. *(J Pediatr 2014;164:78-82)*.

Many of the previous analyses examining the associations between birth weight (BW) and subsequent risk factors for coronary artery disease did not include detailed gestational age (GA) assessment.[1] In these studies, lower BW was associated with subsequent findings of coronary artery disease and higher blood pressure (BP) in adults, as well as elevated BP in the pediatric population.[1-4] Relationships between newborn findings and adult disorders have been referred to as the fetal origins of adult disease.[1,5] Several publications have specifically linked these coronary risk outcomes only to those low BW infants who gain excessive weight during childhood or later in life.[4-9]

Lower BW may be related to preterm birth with a normal intrauterine growth pattern, or may be secondary to poor intrauterine growth resulting in a newborn who is small for GA (SGA) at the time of delivery. Many previous analyses relating BW to subsequent outcomes during childhood and adolescence did not include specific GA assessments and thus were unable to clearly delineate whether preterm birth or poor intrauterine growth was responsible for the low BW pattern.[4-9]

In West Virginia, birth data are linked to individual data from coronary artery disease risk factors measured in a fifth grade screening. We undertook an analysis of these matched datasets to determine which early birth factors (ie, prematurity, poor intrauterine growth, or either of these accompanied by excessive weight gain by fifth grade) were associated with coronary disease risk factors.

Methods

The West Virginia Birth Score Project collects data on all newborns delivered in the state within 24 hours of birth, including BW, estimated GA of the newborn, and various maternal risk factors known to be associated with perinatal morbidity and infant mortality[10,11] The project was

AGA	Appropriate for gestational age	LGA	Large for gestational age
BMI	Body mass index	N	Normal
BP	Blood pressure	O	Obese
BW	Birth weight	SBP	Systolic blood pressure
CARDIAC	Coronary Artery Risk Detection in Appalachian Communities	SGA	Small for gestational age
		TC	Total cholesterol
GA	Gestational age	TG	Triglycerides
HDL	High-density lipoprotein	VLDL	Very-low-density lipoprotein
LDL	Low-density lipoprotein		

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initiated in 1985 to facilitate services for neonates deemed at high risk for infant death.[10] The birth score data are collected by health care professionals, tabulated electronically, and merged with the birth certificate data. In the present study, birth score and birth certificate data for children born between 1993 and 1996 were merged with data collected on fifth grade schoolchildren by the Coronary Artery Risk Detection in Appalachian Communities (CARDIAC) Project between 2004 and 2007. The CARDIAC Project measured body mass index (BMI), systolic BP (SBP), and a fasting lipid profile (ie, total cholesterol [TC], high-density lipoprotein [HDL], low-density lipoprotein [LDL], very-low-density lipoprotein [VLDL], and triglycerides [TG]) on all West Virginia fifth graders with informed consent by the parents and assent by the child.[12] All fifth grade children were given the opportunity to participate with no exclusions. This age group was chosen because they are mostly prepubertal, yet old enough to give assent. The CARDIAC Project and this comparative analysis with birth score cohort was approved by the West Virginia University Institutional Review Board for the Protection of Human Subjects and are described in more detail elsewhere.[12,13]

For the purpose of the present analysis, preterm birth was considered birth at <37 completed weeks of gestation, and term birth was considered birth at 37-42 weeks completed gestation. The growth by GA variables were derived using the GA assessment and the BW on Fenton weight graphs.[14] These variables were defined as follows: SGA, weight <10th percentile for each GA; appropriate for GA (AGA), weight 10th-90th percentile for each GA; large for GA (LGA), weight >90th percentile for each GA.

Weight gain by the fifth grade was derived using gestational maturity categories (ie, preterm and term) or growth by GA category (ie, SGA, AGA, and LGA), with BMI percentile determination in the fifth grade. The latter was expressed as normal (N; <85th percentile) or overweight/obese (O; ≥85th percentile). For example, an LGA infant who was overweight in the fifth grade was classified as LGA-O, whereas an LGA infant in a more normal weight category by BMI in the fifth grade was classified as LGA-N.

Anthropometric assessment at the fifth grade included measurement of height to the nearest 0.1 cm using a portable stadiometer (Shorr, Olney, Maryland) and weight to the nearest 0.1 kg using an electronic scale (Seca, Hamburg, Germany). BMI was calculated using the following equation: weight (kg)/height $(cm)^2 \times 10\,000$.[15] BMI percentile was calculated using EpiInfo 7 (Centers for Disease Control and Prevention, Atlanta, Georgia). Seated resting BP was measured in duplicate using a standard sphygmomanometer and an appropriate-sized cuff. School health nurses and health science center students collected the measurements.

SBP percentile was calculated using national norms based on the child's age, sex, and height as established by the National Heart Lung and Blood Institute.[16] For each year of age and each height percentile, the SBP followed an approximately normal distribution. The z score from the standard normal distribution was calculated as follows: $z = (SBP - \text{mean SBP})/SD$ for year of age by sex. The z score was applied to derive the accumulative probability from the standard normal distribution, which is the same as the SBP percentile. The calculations were performed using SAS version 9.1 (SAS Institute, Cary, North Carolina). In the 2004-2007 CARDIAC Project data, the lipid profile samples were collected as overnight fasting venipunctures by trained phlebotomists at the school.

Mother's first name and surname and child's date of birth were used to merge the children's birth data with their fifth grade CARDIAC data. The birth variables BW and GA assessment were matched with BMI, BP, and lipid profile data as measured by the CARDIAC Project screening. Of the 33 658 children screened in the fifth grade, 6507 (5.17%) were matched with their birth records. We analyzed data from 3054 matched subjects with the most complete data. The loss of subjects was related mainly to the absence of serum lipid data. The slight variation in sample size in groups was due to absent data elements.

To assess potential differences in the children's fifth grade anthropomorphic measurements, BP, and fasting lipids based on GA (with term birth as the reference group) and BW (with AGA as the reference group), we conducted a series of MANOVAs to preserve power and reduce the potential for error. Our models used 2 measures of size at birth (term or preterm and SGA, AGA, or LGA) as the independent variables and BMI percentile, SBP percentile, TC, HDL, LDL, log VLDL, and log TG at the fifth grade as the dependent variables. Childhood obesity (based on BMI percentile) was entered into the models first, to assume much of the variance. The remaining independent variables were then entered, to assess the remaining variance impact. VLDL and TG levels were transformed into log functions because of skewed data. A final MANOVA was performed using the weight gain by fifth grade variables (SGA-N, AGA-N, LGA-N, SGA-O, AGA-O, LGA-O, preterm-N, term-N, preterm-O, and term-O), along with BMI percentile, SBP percentile, and TC, HDL, LDL, log VLDL, and log TG values. Analyses were performed with SPSS 18.0 (SPSS, Chicago, Illinois).

Results

A total of 3054 subjects were available for analysis. The study group had a median age of 11 years and was 53.5% female, 95.7% white, and 2.3% African American. BW and GA data for the birth category groups are presented in **Table I**.

There was no difference between the preterm-born and term-born children in fifth grade in any measure except TG level, with significantly higher TG levels in the preterm children ($P < .05$; **Table II**). SGA infants were smaller and LGA children were larger in fifth grade (**Table I**). Growth by GA group (SGA, AGA, LGA) did not predict SBP percentile in fifth grade (**Table I**). There were no differences in fasting lipid profiles across the GA categories.

There was a relationship between weight gain by fifth grade and cardiac risk factors in both normal-weight and obese

Table I. BW, GA, BMI percentile, and SBP percentile data by birth group

Group	Sample size	BW, g	GA, wk	BMI percentile	SBP percentile
Premature	268	2410 (38)	34 (0.1)	73.2 (1.7)	49.5 (2.2)
Term	2773	3440 (9)	39 (0.02)	73 (0.5)	44.1 (0.7)
SGA	239	2518 (27)	39.5 (0.1)	68.2 (1.8)*	41.7 (2.3)
AGA	2552	3353 (9)	39 (0.0)	73 (0.5)*	44.4 (0.7)
LGA	247	4129 (29)	38.5 (0.1)	78 (1.7)*	48.7 (2.2)
Preterm-N	135	2411 (40.7	34 (0.1)	50.5 (1.5)	36.1 (2)*
Term-N	1443	3388 (8.7)	39 (0.0)	52.9 (0.4)	32.8 (0.6)*
Preterm-O	131	2465 (38.8)	34 (0.1)	94.9 (0.2)	53.5 (2.2)
Term-O	1345	3470 (9.1)	39 (0.0)	95.1 (0.1)	52.3 (0.7)
SGA-N	138	2537 (38)	39 (0.2)	48.4 (1.4)	32 (2.9)*
AGA-N	1319	3326 (13)	39 (0.1)	52.4 (0.5)	36.5 (1)*
LGA-N	111	4149 (45)	39 (0.2)	56.6 (1.6)	33.7 (3.3)*
SGA-O	101	2501 (38)	39 (0.2)	95.3 (1.7)	54.9 (3.5)
AGA-O	1233	3381 (14)	39 (0.1)	95 (0.5)	52.9 (1)
LGA-O	141	4096 (41)	38.5 (0.2)	95.9 (1.4)	61 (2.9)
					Preterm-N to Preterm-O, Term-O*
					Term-N to Preterm-O, Term-O*
				SGA to AGA*	SGA-N to SGA-O, AGA-O, LGA-O*
				AGA to LGA*	AGA-N to SGA-O, AGA-O, LGA-O*
				LGA to SGA*	LGA-N to SGA-O, AGA-O, LGA-O*

Data are mean (SE).
*$P < .001$.

children. SBP percentile was significantly higher in children in obese categories compared with those in the normal weight categories (Table I). Almost all obese children had significantly higher TC, LDL, VLDL, and TG levels and lower HDL levels compared with the more normal-weight children (Table II); exceptions were lower TC and LDL levels in the Preterm-N group. The SGA-O group had significantly higher VLDL and TG levels compared with all other groups, including AGA-O and LGA-O, in the fifth grade (Table II).

Discussion

Heart disease, the leading cause of death in the US,[17] begins early in life. In this study, we attempted to define some of the earliest risk factors. In the CARDIAC Project population of fifth grade schoolchildren, obesity was associated with hypertension and lipid profile abnormalities in the present study as well as in other CARDIAC Project–based studies.[12,18] We also found, in agreement with others, that the LGA infants were more likely to be overweight/obese in the fifth grade and thus more likely to have the risk factors for coronary artery disease associated with obesity at that age.[19-22]

This study provides new information on fasting lipid profiles in children and by birth group. Differences were seen in 2 birth groups. First, SGA infants were less likely to be obese/overweight in fifth grade; however, those SGA infants

Table II. Fasting lipid profiles by birth group

Group	TC, mg/dL	HDL, mg/dL	LDL, mg/dL	VLDL, mg/dL	TG, mg/dL
Premature	167.7 (1.8)	50.7 (.7)	96.3 (1.6)	20.7 (.7)	103.9 (3.4)*
Term	166.6 (0.6)	51 (.2)	96.6 (.5)	19 (.2)	95.3 (1.1)
SGA	167.6 (1.9)	50.7 (.8)	97 (1.7)	20 (.7)	100.2 (3.6)
AGA	166.6 (0.6)	51.2 (.2)	96.4 (.5)	19.1 (.2)	96 (1.1)
LGA	165.7 (1.9)	49.9 (.8)	97 (1.7)	18.6 (.7)	93.3 (3.6)
Preterm-N	164.3 (2.3)	54.7 (1)*	94.3 (2.1)‡	15.4 (.5)‡	77.5 (2.6)‡
Term-N	162.5 (.8)†,‡	54.5 (.3)*,‡	92.7 (.7)‡	15.5 (.2)‡	77.6 (1)‡
Preterm-O	171 (2.8)	46.7 (1)	98.3 (2.4)	25.9 (1.5)	129.8 (7.5)
Term-O	170.9 (0.8)	47.5 (.3)	100.7 (.7)	22.9 (.3)	114.6 (1.7)
					Preterm to Term*
	Term-N to preterm-O†	Preterm-N to term-O*	Preterm-N to Preterm-O, Term-O‡	Preterm-N to Preterm-O, Term-O‡	Preterm-N to Preterm-O, Term-O‡
	Term-N to term-O‡	Term-N to term-O‡	Term-N to Preterm-O, Term-O‡	Term-O to Preterm-O, Term-O‡	Term-N to Preterm-O, Term-O‡
		Term-N to preterm-O*			
SGA-N	162.5 (2.5)*	53.9 (1)*	93.8 (2.3)‡	14.9 (0.9)‡	75 (4.4)‡
AGA-N	163.2 (0.8)†,‡	54.6 (0.3)*,‡	92.9 (0.7)‡	15.6 (0.3)‡	78.3 (1.4)‡
LGA-N	157.2 (2.8)‡	52.4 (1)*,†	90.3 (2.5)*,†,‡	14.4 (1)‡	72.1 (5)‡
SGA-O	174.7 (3)	46.4 (1.1)	101.5 (2.6)	26.9 (1)*	134.6 (5.2)*
AGA-O	170.4 (0.8)	47.5 (0.3)	100.1 (0.8)	23 (0.3)	115.1 (1.5)
LGA-O	173.2 (2.5)	47.8 (1)	103.3 (2.4)	22 (0.9)	110.6 (4.4)
	LGA-N to SGA-O, AGA-O, LGA-O‡	SGA-N to AGA-O, LGA-O*	SGA-N to SGA-O, AGA-O, LGA-O‡	SGA-N to SGA-O, AGA-O, LGA-O‡	SGA-N to SGA-O, AGA-O, LGA-O‡
	AGA-N to SGA-O, LGA-O†	AGA-N to AGA-O, LGA-O‡	AGA-N to SGA-O, AGA-O, LGA-O‡	AGA-N to SGA-O, AGA-O, LGA-O‡	AGA-N to SGA-O, AGA-O, LGA-O‡
	SGA-N to SGA-O, AGA-O, LGA-O*	AGA-N to SGA-O*	LGA-N to AGA-O‡		
	AGA-N to AGA-O‡	LGA-N to AGA-O, LGA-O†	LGA-N to SGA-O†	LGA-N to SGA-O, AGA-O, LGA-O‡	LGA-N to SGA-O, AGA-O, LGA-O‡
		LGA-N to SGA-O*	LGA-N to LGA-O*	SGA-O to AGA-O, LGA-O*	SGA-O to AGA-O, LGA-O*

Data are mean (SE).
*$P \leq .05$.
†$P \leq .01$.
‡$P \leq .001$.

who were overweight/obese by fifth grade had significantly higher TG and VLDL levels compared with all other children, including other obese/overweight children. This implies an increased risk for coronary disease in SGA-O children compared with AGA-O and LGA-O children. The significance of elevated VLDL levels in the SGA-O group in relation to coronary disease or other vascular disorders is not well defined, but is thought to be similar to that of elevated TG levels.

At the fifth grade assessment, TG levels were higher in preterm-born children compared with their term-born classmates, although not in the abnormal range. This finding is interesting considering that in the preterm group, the average GA was 34 weeks and the average BW was 2435 g, neither of which is considered particularly low despite the relationship with this higher TG levels. In the fifth grade, SBP percentile was slightly higher in the preterm-born children compared with their term-born classmates despite essentially identical BMI percentiles. These findings, although not statistically significant, are in agreement with previous studies,[1,2] and may ultimately have clinical relevance especially considering the 5% difference in the SBP percentiles.

Limitations of this study include the large number of individuals across multiple sites involved in data measurement in the birth hospitals and the fifth grade screening. The size of the project carries the potential for variation in assessment procedures. Specifically, in the CARDIAC Project, annual training was provided to update staff's knowledge and assessment skills. The validity of the data has not been evaluated. Regarding nonparticipants in the CARDIAC Project and possible selection bias, there was no specific evaluation of the nonparticipants in this study; however, another CARDIAC Project–based study queried randomly chosen parents of participant and nonparticipant children and found that BMI was similar in participants and nonparticipants, but nonparticipants were less likely to have health insurance and a primary care provider.[13]

Our findings have public health implications, supporting the concept that being born at term and AGA is associated with better outcomes both initially and long term. Numerous prenatal conditions can lead to LGA, SGA, or preterm birth. Theoretically, some of these conditions can be influenced during pregnancy to change the infant's birth category. For example, maternal weight control, dietary counseling, and glycemic control may help decrease the incidence of LGA births and thereby reduce the tendency toward obesity later in childhood. SGA births may be the result of various adverse antenatal events, and there are no effective preventive interventions during fetal life except the timing of delivery.[23] However, after birth, emphasis on managing childhood obesity can help both LGA and SGA infants. Support of the mother with breast feeding would help both as it may lessen infant and childhood obesity.[24] Other weight control strategies during childhood may include tracking BMI by the primary care provider and providing diet and exercise counseling for the family.

Preterm birth is sometimes a consequence of planned induction or scheduled cesarean delivery for convenience or an ill-defined fetal condition. Emphasis on delivery only at term rather than at near term should be more strongly considered by obstetricians and families. We need to focus not only on the short-term outcomes that affect infant mortality, but also on the long-term impact on coronary artery disease. ■

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50 Years Ago in *The Journal of Pediatrics*

Poliomyelitis Antibodies in Human Colostrum and Milk

Athreya BH, Coriell LL, Charney J. J Pediatr 1964;64:79-82

Human milk was always thought to have specific factors to protect infants from poliovirus, but it was not until this landmark study that definitive antibodies to the virus were described both in the mother's milk and serum.[1] These investigators sampled the milk and sera of 4 women in the colostrum phase and 4 women on the 13th day postpartum, and identified antipoliovirus antibodies using neutralization assays and micro-immunodiffusion methods. Similar methods of radial immunodiffusion and enzyme-linked immunosorbent assays are still used today to identify antigen-specific antibodies in the milk after viral exposure. More specifically since the article 50 years ago, a functional relevance can be observed. Anti-influenza IgA in human milk can be identified by enzyme-linked immunosorbent assay at a higher concentration with resultant fewer febrile illnesses in infants of women vaccinated with influenza vaccine during pregnancy compared to controls[2]; however, further study is needed to determine the exact mechanisms of human milk immunologic protection against these infectious diseases. New methods in the laboratory, recently described by Lemay et al,[3] can determine pathways involved in the mammary gland by identifying the transcriptome in the milk fat globule. These remarkable findings will not just describe the milk properties but provide the opportunity to design interventional trials on the mother to influence milk production in beneficial ways for the infant.

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