Is the Metabolic Syndrome a “Small Baby” Syndrome?: The Bogalusa Heart Study

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Abstract

Background: Metabolic syndrome has been called a “small baby syndrome,” but other analyses suggest that postnatal growth is more important than birthweight, or that large babies are also at risk. The aim of this analysis was to examine whether there was a relationship between both low and high birthweight and metabolic syndrome, using multiple definitions of metabolic syndrome, and to determine whether this relationship varied by body size across the life course.

Methods: Data from the Bogalusa Heart Study, a study of cardiovascular disease in children and young adults, were linked to birth certificate data. Metabolic syndrome was defined by the National Cholesterol Education Program, the International Diabetes Foundation, and the World Health Organization (WHO) definition. Small-for-gestational-age (SGA) was defined as birthweight <10th percentile by sex for gestational age and large-for-gestational-age (LGA) as birthweight >90th percentile. Birthweight-for-gestational-age was also examined as a continuous predictor. Chi-squared tests and logistic regression were used to examine the relationship between birth size and metabolic syndrome.

Results: Higher birthweight-for-gestational-age was associated with a reduced risk of metabolic syndrome, especially by the WHO definition. After adjustment for body mass index (BMI), categorized birthweight was associated with metabolic syndrome, with the protective associations with LGA being stronger than the positive associations with SGA. Among the individual components of metabolic syndrome, higher waist circumference was associated with both SGA and LGA after BMI was controlled for. Effects of SGA and BMI at any age were largely independent rather than interactive.

Conclusions: SGA is associated with some, but not all, components of metabolic syndrome. The relationship between SGA and metabolic syndrome is partially confounded by later BMI.

Introduction

METABOLIC SYNDROME IS A variously defined combination of cardiovascular disease (CVD) risk factors. Generally, it is believed that metabolic syndrome identifies a population subgroup that is at higher risk for CVD events than would be indicated by individual risk factors,¹ although not every study corroborates this.^{2,3} All definitions incorporate raised glucose, low high-density lipoprotein cholesterol (HDL-C), raised triglycerides, higher blood pressure, and some measure of central obesity, whereas others add albumin or albumin:creatinine ratio.¹ Many researchers broaden the definition to general cardiometabolic risk factors.⁴ Risk of CVD generally increases with the number of metabolic syndrome risk factors.¹

Reduced fetal growth has been associated with metabolic syndrome in a number of studies,⁵ to the point that it has been proposed that metabolic syndrome should be called the “small baby syndrome.”⁶ For instance, a study of young adults found that being in the lower tertiles of birthweight was associated with increased risk of metabolic syndrome.⁷ In a group of older men, the occurrence of metabolic syndrome was substantially higher in those born low birthweight (69% vs. 39%, $P=0.11$).⁸ Being overly large at birth has also been associated with metabolic syndrome risk factors, especially in children, in a few studies.^{9,10}

The Barker hypothesis proposes that *in utero* deprivation or impaired growth permanently alters fetal metabolism in such a way as to promote CVD and diabetes. The “thrifty phenotype” hypothesis proposes that impaired nutrient

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supply to the fetus causes the fetus to adapt metabolically to store fuel.¹¹ Effects of insulin resistance seem to be potentiated by obesity,¹² and accelerated postnatal (catch-up) growth raises the risk of complications after low birthweight.¹³ Others have suggested that postnatal growth and adult body mass index (BMI) are more important in explaining any birthweight-metabolic syndrome association¹⁴; at least one study has found that the effects of birthweight on coronary heart disease are limited to those with high adult BMI.¹⁵ One study found that fetal growth was associated with glucose, but childhood weight gain most strongly predicted insulin levels.¹⁶ Catch-up growth may be associated not only with overall weight gain but also with patterns of adiposity and adipose gene expression,^{17,18} which have been shown to be important in development of complications of obesity.¹⁹

Previous work in the Bogalusa Heart Study found that lower birthweight was associated with higher systolic blood pressure, triglycerides, insulin resistance, and low-density lipoprotein-cholesterol (LDL-C), and that the last three associations were stronger in blacks.^{20,21} Frontini et al. found more negative trends in cardiovascular risk factors among children and adolescents born <10th birthweight percentile for gestational age.²² The aims of the current analysis were to examine whether there was a relationship between birthweight and metabolic syndrome as a whole (using multiple definitions of metabolic syndrome) as an adult in an African-American/white cohort and to determine whether this relationship varied by body size.

Materials and Methods

Between 1976 and 1994, six cross-sectional studies of school-aged children were conducted in a semirural, biracial community in Louisiana (The Bogalusa Heart Study). In addition, seven cross-sectional surveys were conducted between 1978 and 2002 with young adults. This design of repeated cross-sectional examinations resulted in serial observations from childhood to young adulthood. Not every participant was eligible or examined in all the surveys, and some participants were added in later surveys who had not participated at baseline. Overall, of the people who participated as a child (ages 4–12), 46% participated as an adolescent (ages 13–18) and 26% participated as adults (age 19+). Of the people who participated as an adolescent, 45% participated as an adult. Criteria for inclusion in this analysis were at least one visit as an adult, data on birthweight, and complete data on metabolic syndrome by at least one definition for at least one visit where they were not pregnant ($N=2078$). Of the participants meeting these criteria, 1470 (70%) had data on childhood BMI (<13 years) and 1917 (92%) had data on adolescent BMI (13–18 years). Birthweight records were obtained from the Office of Vital Statistics in New Orleans in 1991.

Examination

Identical protocols were used by trained examiners across all of the surveys. Subjects were instructed to fast for 12h before screening, and compliance was determined by interview on the morning of examinations. Information on personal health and medication history was obtained by questionnaires. While subjects were wearing a gown, underwear, and socks, height was measured to the nearest 0.1 cm on a standard

board; weight was measured twice to the nearest 0.1 kg using a balance beam metric scale. Waist circumference was measured midway between the rib cage and the superior border of the iliac crest. Anthropometric and blood pressure measurements were made in replicate, and waist circumference was measured in triplicate. Mean values were used in all of the analyses.

Blood pressure measurements were obtained on the right arm of the subject in a relaxed, sitting position. Arm length and circumference were measured to ensure proper cuff size. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded at the first, fourth, and fifth Korotkoff phases using a mercury sphygmomanometer. Blood pressure levels were reported as the mean of six replicate readings, taken by each of two randomly assigned and trained observers. For longitudinal analysis, the fourth phase was used for diastolic pressure for both children and adults, because the fourth phase is more reliably measured in childhood and more predictive of adult hypertension.²³

Laboratory analyses

From 1973 to 1986, cholesterol and triglyceride levels were measured using chemical procedures on a Technicon Autoanalyzer (Technicon Instrument) according to the Laboratory Manual of the Lipid Research Clinics Program.²⁴ These variables were determined by enzymatic procedures on the Abbott VP instrument (Abbott Laboratories) between 1987 and 1996 and on the Hitachi 902 Automatic Analyzer (Roche Diagnostics) afterward. Both chemical and enzymatic procedures met the performance requirements of the Lipid Standardization Program of the Centers for Disease Control and Prevention, which has routinely monitored the precision and accuracy of cholesterol, triglycerides, and HDL-C measurements from the beginning of this study. Measurements on the quality control samples assigned by the agency showed no consistent biases over time within or between surveys. Serum lipoprotein cholesterol levels were analyzed by using a combination of heparin-calcium precipitation and agar-agarose gel electrophoresis.

From 1976 to 1991, plasma glucose was measured by a glucose oxidase method using a Beckman glucose analyzer (Beckman Instruments). Since then, it has been measured enzymatically as part of a multichemistry (SMA20) profile. Plasma immunoreactive insulin levels were measured by a commercial radioimmunoassay kit (Phadebas, Pharmacia Diagnostics). Analysis of lipid and glucose samples was limited to those who reported fasting.

Covariates

Smoking was measured by self-report and defined as both as current smoker/nonsmoker and as a four-level variable: Nonsmokers (never smoker/experimented only), former regular smoker, currently smoke ≤ 15 cigarettes/day, and currently smoke > 15 cigarettes a week.

BMI (weight in kilograms divided by the square of height in meters) was used as a measure of overall adiposity. Three time frames were examined: Childhood (<12 years old), adolescence (12–18 years), and adulthood (>18 years). If a participant had more than one measurement in a given time period, the mean value was used.

Maximum parental education was defined as the highest grade level reached by either parent, reported at any time

point. Annual income was categorized as $\leq \$15,000$; $\$15,001$ – $\$30,000$, $\$30,001$ – $\$45,000$, and $\$45,001$ and higher.

Statistical analyses

The prevalence of metabolic syndrome factors as an adult was calculated using the oldest visit as an adult. Metabolic syndrome and its components were defined using three different definitions. The National Cholesterol Education Program's (NCEP) criteria are: Waist circumference > 102 cm for men and 88 cm for women; HDL-C < 40 mg/dL for men and < 50 mg/dL for women; triglycerides ≥ 150 mg/dL; glucose > 100 mg/dL; and SBP ≥ 130 mmHg and/or DBP ≥ 85 mmHg, with metabolic syndrome defined as any three or more of those.¹ The International Diabetes Federation's (IDF) definition requires central obesity (waist circumference ≥ 94 cm for men, 80 cm for women, or BMI > 30 kg/m²). In addition, at least two of the following are required: Triglycerides ≥ 150 mg/dL or treatment for raised triglycerides; HDL-C < 40 mg/dL for men and < 50 mg/dL for women or treatment for low HDL-C; SBP ≥ 130 mmHg and/or DBP ≥ 85 mmHg or previously diagnosed hypertension; and glucose ≥ 100 mg/dL or type 2 diabetes.²⁵ The World Health Organization (WHO) definition prioritizes insulin resistance, requiring type 2 diabetes, impaired fasting glucose (glucose ≥ 110 mg/dL), or impaired glucose tolerance. In addition, any two of the following are required: SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg or previously diagnosed hypertension; triglycerides ≥ 150 mg/dL; HDL-C < 35 mg/dL for men and < 39 mg/dL for women; BMI > 30 kg/m² or waist-to-hip ratio > 0.9 in men, > 0.85 in women; urinary albumin excretion rate ≥ 20 μ g/min or urinary albumin:creatinine ratio ≥ 30 mg/g.²⁶

Birthweight groups were defined as small-for-gestational age (SGA), $< 10^{\text{th}}$ percentile for sex, and large-for-gestational age (LGA), $> 90^{\text{th}}$ percentile, and compared to an appropriate-for-gestational-age (AGA) group, 10^{th} – 90^{th} percentile, with percentiles calculated from the study population. Birthweight-for-gestational-age (percentile) was also examined as a continuous and quadratic predictor, allowing for a possible U-shaped relationship. Data were also examined excluding preterm births (< 37 weeks gestation); results were similar and so the complete data are presented.

All of the statistical analyses were performed with SAS version 9.2. Proportions meeting the metabolic syndrome criteria were compared by birthweight group using chi-squared statistics and unadjusted odds ratios (OR), and adjusted odds ratios (aOR) were calculated using logistic regression (direct models of the relative risk failed to converge). Three sets of adjusted models were run. The first adjusted for the *a priori* confounders age, race, sex, race*sex, income category, smoking, and parental education. Second, models were adjusted for BMI at the oldest measure. Third, models were adjusted for BMI as a child. Multiple imputation was used to account for missing covariate data; most commonly missing were income and parental education.

For interaction analysis, BMI at latest visit as an adult and as an adolescent was dichotomized, corresponding with previous work¹⁵: BMI ≤ 25 and BMI > 25 . Child BMI was dichotomized at BMI = 20 (BMI = 25 as an adolescent and BMI = 20 as a child both approximately correspond to the 85th percentile in the population.) Interaction on the multiplicative scale was assessed by a product term in the logistic

models. Interaction on the additive scale was assessed by a product term in unadjusted linear risk models; more fully adjusted or detailed models of additive interaction²⁷ failed to converge. Interactions with race and sex were also examined.

All study participants gave informed consent; consent of a parent was obtained for those under 18. Protocols were approved by the Institutional Review Board of the Tulane University Health Sciences Center.

Results

The majority of the study population was female and about two-thirds were white (Table 1). More than one-third currently smoked. The median age for measurement of metabolic syndrome was 31 years.

First, the relationship between birthweight-for-gestational-age and metabolic syndrome was examined. When dichotomized and not adjusted for BMI, SGA and LGA were not associated with metabolic syndrome by the NCEP or WHO

TABLE 1. CHARACTERISTICS OF THE STUDY POPULATION (N=2078)

	N	%
Sex		
Male	918	44.2
Female	1160	55.8
Age at latest visit		
18–24	439	21.1
> 24–30	521	25.1
> 30–35	473	22.8
> 35	645	31.0
Race		
Black	701	33.7
White	1377	66.3
Smoked at oldest visit		
Yes	753	37.3
No	1265	62.7
BMI category		
≤ 20	167	8.1
> 20–25	685	33.0
> 25–30	571	27.5
> 30	652	31.4
Birthweight		
Low birthweight (< 2500 grams)	167	8.0
Not low birthweight	1911	92.0
Gestational age		
Preterm (< 37 weeks)	131	6.3
Full term	1947	93.7
Metabolic syndrome at oldest visit (NCEP definition)		
Yes	310	14.9
No	1767	85.1
Metabolic syndrome at oldest visit (IDF definition)		
Yes	383	18.4
No	1695	81.6
Metabolic syndrome at oldest visit (WHO definition)		
Yes	79	4.7
No	1597	95.3

Some numbers do not add to total due to missing data.

BMI, body mass index; NCEP, National Cholesterol Education Program; IDF, International Diabetes Federation; WHO, World Health Organization.

definitions, and LGA was associated with a reduced risk of metabolic syndrome by the IDF definition (Table 2, unadjusted model and adjusted model 1). After adjustment for BMI, *P* for trend was significant for the NCEP and IDF definitions, but not WHO (Table 2, adjusted model 2). The protective associations with LGA were stronger than the positive associations with SGA. Adjustment for child BMI left similar effect estimates, although not as statistically strong for the IDF definition (Table 2, adjusted model 3). When birthweight-for-gestational-age was continuous, higher birthweight was associated with a lower risk of metabolic syndrome by the WHO definition, regardless of

adjustment, and with metabolic syndrome by all definitions after adjustment for BMI (Table 2, adjusted models 2 and 3).

Those born SGA were more likely to be thin (BMI < 20) as adults (11% vs. 8%) and less likely to be obese (27% vs. 32%; *P* < 0.01 for whole distribution). All of the metabolic syndrome risk factors were strongly positively associated with adult BMI (*P* < 0.01; data not shown²⁸). The individual metabolic syndrome components were examined next (Table 3). Before adjustment for BMI, being born SGA was associated with a reduced risk of meeting the IDF waist circumference criterion and an increased chance of meeting the urinary albumin:creatinine ratio criterion (Table 3, model 1). After

TABLE 2. BIRTHWEIGHT AND METABOLIC SYNDROME IN THE BOGALUSA HEART STUDY

	N	%	P	Unadjusted			Model 1 ^a		
				OR	95% CI	P for trend	OR	95% CI	P for trend
Metabolic syndrome (NCEP)			0.49			0.35			0.19
SGA	27	15%		1.01	(0.66, 1.55)		1.02	(0.65, 1.60)	
LGA	24	12%		0.76	(0.49, 1.19)		0.69	(0.43, 1.08)	
AGA	259	15%		1			1		
Birthweight-for-gestational-age (continuous, per 10 units)				0.986	(0.945, 1.030)	0.53 ^b	0.977	(0.933, 1.023)	0.32
Metabolic syndrome (IDF)			0.27			0.49			0.21
SGA	30	17%		0.87	(0.58, 1.32)		0.91	(0.59, 1.40)	
LGA	29	15%		0.73	(0.48, 1.10)		0.65	(0.42, 0.99)	
AGA	324	16%		1			1		
Birthweight-for-gestational-age (continuous, per 10 units)				0.977	(0.938, 1.016)	0.24	0.962	(0.922, 1.004)	0.08
Metabolic syndrome (WHO)			0.49			0.33			0.33
SGA	9	7%		1.53	(0.74, 3.15)		1.45	(0.67, 3.13)	
LGA	7	4%		0.93	(0.42, 2.07)		0.86	(0.38, 1.94)	
AGA	63	5%		1			1		
Birthweight-for-gestational-age (continuous, per 10 units)				0.922	(0.849, 1.001)	0.05	0.914	(0.838, 0.996)	0.04
				Model 2 ^c			Model 3 ^d		
				OR	95% CI	P for trend	OR	95% CI	P for trend
Metabolic syndrome (NCEP)						0.01			0.01
SGA				1.39	(0.80, 2.41)		1.46	(0.77, 2.74)	
LGA				0.49	(0.28, 0.85)		0.47	(0.24, 0.92)	
AGA				1			1		
Birthweight-for-gestational-age (continuous, per 10 units)				0.931	(0.882, 0.983)	< 0.01	0.902	(0.844, 0.963)	< 0.01
Metabolic syndrome (IDF)						0.01			0.07
SGA				1.17	(0.70, 1.94)		1.09	(0.60, 1.98)	
LGA				0.49	(0.30, 0.81)		0.54	(0.30, 0.97)	
AGA				1			1		
Birthweight-for-gestational-age (continuous, per 10 units)				0.918	(0.874, 0.964)	< 0.01	0.905	(0.852, 0.960)	< 0.01
Metabolic syndrome (WHO)						0.20			0.21
SGA				1.49	(0.61, 3.61)		1.55	(0.53, 4.51)	
LGA				0.68	(0.28, 1.64)		0.57	(0.16, 2.03)	
AGA				1			1		
Birthweight-for-gestational-age (continuous, per 10 units)				0.907	(0.827, 0.994)	0.04	0.870	(0.771, 0.982)	0.02

^aAdjusted for age, race, sex, race*sex, income category, parental education, and smoking.

^b*P* for one-unit change in birthweight-for-gestational-age.

^cAdjusted for above variables plus adult body mass index (BMI).

^dAdjusted for above plus mean child BMI.

OE, odds ratio; CI, 95% confidence interval; NCEP, National Cholesterol Education Program; SGA, small-for-gestational-age, < 10th percentile for gestational age; LGA, large-for-gestational-age, > 90th percentile for gestational age; AGA, appropriate-for-gestational age, 10–90th percentile; IDF, International Diabetes Federation; WHO, World Health Organization.

TABLE 3. BIRTHWEIGHT AND METABOLIC SYNDROME COMPONENTS IN THE BOGALUSA HEART STUDY

	Model 1 ^a			Model 2 ^b			Model 3 ^c		
	OR	95% CI	P	OR	95% CI	P for trend	OR	95% CI	P
Metabolic syndrome (NCEP)									
waist > 102 cm/88 cm			0.11			0.02			0.38
SGA	0.86	(0.60, 1.23)		2.09	(1.04, 4.18)		3.19	(1.46, 7.00)	
LGA	1.25	(0.90, 1.72)		1.80	(0.99, 3.27)		1.74	(0.85, 3.54)	
AGA	1			1			1		
Birthweight-for-gestational-age (per 10 units)	1.055	(1.018, 1.094)	<0.01	1.015	(0.950, 1.085)	0.65	0.964	(0.890, 1.043)	0.36
HDL < 40/ < 50			0.53			0.97			0.74
SGA	0.78	(0.56, 1.09)		0.87	(0.62, 1.23)		0.84	(0.56, 1.25)	
LGA	0.92	(0.68, 1.24)		0.90	(0.65, 1.23)		0.93	(0.64, 1.36)	
AGA	1			1			1		
Birthweight-for-gestational-age (per 10 units)	1.018	(0.985, 1.052)	0.29	1.003	(0.969, 1.038)	0.86	1.008	(0.967, 1.050)	0.72
TG ≥ 150			0.36			0.14			0.28
SGA	0.79	(0.50, 1.24)		0.86	(0.53, 1.39)		0.82	(0.46, 1.45)	
LGA	0.67	(0.45, 0.99)		0.62	(0.41, 0.93)		0.62	(0.38, 1.01)	
AGA	1			1			1		
Birthweight-for-gestational-age (per 10 units)	0.975	(0.935, 1.016)	0.23	0.959	(0.919, 1.001)	0.06	0.950	(0.902, 1.001)	0.06
Glucose > 100			0.51			0.26			0.42
SGA	1.35	(0.78, 2.34)		1.57	(0.87, 2.84)		1.61	(0.82, 3.18)	
LGA	1.06	(0.59, 1.91)		0.98	(0.53, 1.82)		1.14	(0.53, 2.46)	
AGA	1			1			1		
Birthweight-for-gestational-age (per 10 units)	0.970	(0.910, 1.034)	0.35	0.954	(0.893, 1.019)	0.16	0.939	(0.865, 1.019)	0.13
SBP ≥ 130 mmHg or DBP ≥ 85 mmHg			0.62			0.25			0.09
SGA	0.96	(0.62, 1.47)		1.09	(0.70, 1.71)		1.11	(0.64, 1.91)	
LGA	0.82	(0.53, 1.28)		0.76	(0.48, 1.21)		0.54	(0.29, 1.02)	
AGA	1			1			1		
Birthweight-for-gestational-age (per 10 units)	0.952	(0.910, 0.996)	0.03	0.933	(0.890, 0.978)	<0.01	0.876	(0.825, 0.930)	<0.01
Metabolic syndrome (IDF)									
waist > 94 cm/80 cm or BMI > 30			0.02			0.13			0.13
SGA	0.69	(0.49, 0.96)		1.06	(0.55, 2.04)		1.15	(0.54, 2.45)	
LGA	1.19	(0.88, 1.62)		1.89	(1.06, 3.37)		2.24	(1.13, 4.45)	
AGA	1			1			1		
Birthweight-for-gestational-age (per 10 units)	1.046	(1.012, 1.082)	0.01	1.003	(0.941, 1.068)	0.94	1.036	(0.960, 1.119)	0.36
Metabolic syndrome (WHO)									
Waist-to-hip ratio > 0.9/ > 0.85 or BMI > 30			0.24			0.75			0.96
SGA	0.79	(0.55, 1.14)		1.32	(0.68, 2.57)		1.21	(0.55, 2.64)	
LGA	1.06	(0.76, 1.48)		1.11	(0.60, 2.04)		1.19	(0.60, 2.38)	
AGA	1			1			1		
Birthweight-for-gestational-age (per 10 units)	1.040	(1.003, 1.079)	0.03	0.994	(0.932, 1.060)	0.85	0.993	(0.919, 1.074)	0.87
Albumin-to-creatinine ratio ≥ 30 mg/gram			0.04			0.02			0.03
SGA	6.21	(0.94, 41.25)		9.24	(1.26, 67.80)		10.33	(1.09, 98.26)	
LGA									
AGA	1			1			1		
Birthweight-for-gestational-age (per 10 units)	0.645	(0.407, 1.022)	0.06	0.640	(0.400, 1.025)	0.06	0.623	(0.372, 1.045)	0.07

^aAdjusted for age, race, sex, race*sex, income category, and smoking.^bAdjusted for above variables plus adult body mass index (BMI).^cAdjusted for above plus child BMI.

NCEP, National Cholesterol Education Program; OR, odds ratio; CI, 95% confidence interval; SGA, <10th percentile for gestational age; LGA, large-for-gestational age, 90th percentile for gestational age; AGA, appropriate-for-gestational age, 10–90th percentile; HDL, high-density lipoprotein; TG, triglycerides; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WHO, World Health Organization; IDF, International Diabetes Federation.

adult BMI was adjusted for, SGA was associated with a higher risk of high waist circumference by the NCEP definition and high urinary albumin:creatinine ratio (Table 3, model 2). LGA was associated with an increased likelihood of high waist circumference (Table 3, model 2). Because SGA was associated with a reduced risk of obesity as an adult, the relationship with a higher waist circumference appeared only after adjustment for BMI. The IDF definition of high waist circumference also can include higher BMI, and so this association was not seen. Adjustment for child BMI increased the strength of the association between SGA and high waist circumference, but did not affect the size of the association between LGA and high waist circumference (Table 3, model 3). Before adjustment for BMI, continuous higher birthweight-for-gestational age was associated with higher waist circumference and waist-to-hip ratio and lower blood pressure. Adjustment for BMI largely removed the associations with waist circumference, but those with blood pressure remained. There was evidence for a quadratic relationship between birthweight-for-gestational-age and waist circumference (P for quadratic term = 0.01), but no other outcomes, another indication that this factor was related to both the high and low ends of the birthweight spectrum. No interactions were found with gender.

The relationship between BMI at various stages and infant weight was then examined (Table 4). Generally, there was not a multiplicative interaction between high adult BMI and weight as an infant (data not shown). Assessment of additive interaction suggested a negative interaction between LGA and adult BMI in predicting metabolic syndrome (NCEP; $P=0.04$; data not shown) and a positive interaction between SGA and high adult BMI in predicting high glucose levels ($P=0.04$). There was also a positive multiplicative interaction between high childhood BMI and glucose [Table 4; $P=0.04$ for interaction; aOR 2.98 (1.37, 6.46) compared to AGA, low BMI], as well as the suggestion of a negative additive interaction between childhood BMI and LGA for glucose ($P=0.05$), and a positive additive interaction between LGA and waist-to-hip ratio ($P=0.03$). The combination of being born SGA and moving from the lower weight category as a child to the higher weight category as an adult was associated with a higher risk of metabolic syndrome (NCEP; Table 4; aOR 1.47, 1.05–2.06 compared to those born AGA and at a constant BMI category) and higher triglycerides (aOR 1.45, 1.03–2.04). Other analyses did not indicate additive or multiplicative interaction between birthweight and childhood BMI or increased BMI (Table 4), or with adolescent BMI (data not shown).

Conclusions

In this cohort, we find limited support for the idea metabolic syndrome is a “small baby syndrome.” When categorized, SGA was not associated with metabolic syndrome, although after adjustment for BMI, LGA was associated with a reduced risk of metabolic syndrome and the continuous measure did predict metabolic syndrome. Adjustment for childhood BMI had little effect. When adult BMI was adjusted for, an association was seen between SGA and waist circumference. When the interaction was examined, BMI across the life course and SGA did not seem to have a strong synergistic effect. There was some evidence that being born SGA and moving to a higher weight category as an adult

was associated with higher risk. We did not see strong interactions with race. Although blacks were more likely to be born SGA, the effect of SGA or birthweight-for-gestational-age on adult metabolic syndrome was not different in the two races. Previous analysis of this cohort has found that rate of change in metabolic syndrome variables clusters over time and that clustering was greater in blacks than whites,^{21,29} as well as the clear independent effects of BMI and birthweight on adult blood pressure and other metabolic syndrome risk factors.^{30,31}

Some studies have found that the effects of birthweight on coronary heart disease are limited to those with high adult BMI¹⁵ or that fetal growth and adult BMI or weight gain interact.^{32,33} We also found a relationship between BMI and effects of fetal growth. Many children born small remained small, putting them at lower risk for several metabolic syndrome risk factors. On the other end, children born large were more likely to have higher BMIs and/or waist circumference. A Finnish study found some similar contradictory trends: Insulin resistance and type II diabetes were both associated with fetal growth restriction, whereas increased birthweight was associated with reduced blood pressure and increased HDL-C. However, insulin resistance was associated with thinness in childhood but diabetes with higher BMI.³⁴

Some studies have also found adjustment for BMI to explain or strengthen associations between birthweight and metabolic syndrome,^{35,36} although adjustment for current body size is controversial and has been shown to produce artifactual patterns under some circumstances.³⁷ These patterns may be due to patterns of adiposity and adipocyte development associated with both reduced and increased birthweight. Catch-up growth after low birthweight has been associated with patterns of adiposity and adipose gene expression,^{17,18} whereas large-for-dates infants have higher fat cell weight and body fat mass overall and as a percentage of their body weight.³⁸ Rats born macrosomic have high adipose tissue weight postnatally due to higher adipocyte lipoprotein lipase activity and fat storage capacity, not hyperphagia.³⁹

This study provided limited evidence that SGA is associated with metabolic syndrome as a whole. Previous studies have also been somewhat inconsistent on this point. Some have found an association between low birthweight and the whole syndrome,^{5–8} whereas others have found associations with components of the metabolic syndrome, but not the entire set of risk factors.^{35,40} Associations with insulin resistance are probably most consistently found,^{35,41,42} but relationships with blood pressure have also been reported consistently.⁴³

The strengths of this study are the biracial population, longitudinal testing, and standardized protocol. The weaknesses are the lack of a completely prospective cohort and a relatively low number of cases, due to the young age of the cohort. Prevalence of metabolic syndrome in this cohort was about 15% by the NCEP guidelines, reasonable for a sample of this age.⁷ In addition, the interaction analyses lack power, especially for the number of comparisons performed, and the observed significant associations may be due to chance.

In conclusion, we find evidence that birthweight and the entire metabolic syndrome are not directly correlated, with the effect of infant size and adult weight affecting some components positively and some negatively. Future research

TABLE 4. RELATIONSHIP BETWEEN BIRTHWEIGHT, BMI AS A CHILD, AND METABOLIC SYNDROME IN THE BOGALUSA HEART STUDY

	Child BMI						P for interaction
	SGA		AGA		LGA		
	OR ^a	CI	OR	CI	OR	CI	
Metabolic syndrome (NCEP)							0.59
Low BMI	0.91	(0.50, 1.65)	1		0.78	(0.63, 0.97)	
High BMI	2.60	(1.86, 6.97)	1.53	(1.35, 1.74)	3.04	(1.31, 7.09)	
Metabolic syndrome (IDF)							0.85
Low BMI	0.79	(0.44, 1.40)	1		0.81	(0.69, 0.97)	
High BMI	2.43	(1.29, 4.59)	1.40	(1.23, 1.58)	2.57	(1.16, 5.73)	
Metabolic syndrome (WHO)							0.15
Low BMI	1.32	(0.42, 4.15)	1		0.94	(0.64, 1.39)	
High BMI	4.53	(1.75, 11.70)	1.59	(1.25, 2.02)	1.17	(0.14, 9.45)	
HDL < 40/ < 50							0.40
Low BMI	0.78	(0.52, 1.16)	1		0.99	(0.64, 1.39)	
High BMI	1.35	(0.65, 2.39)	1.21	(1.08, 1.35)	1.26	(0.59, 2.69)	
TG ≥ 150							0.34
Low BMI	0.71	(0.39, 1.28)	1		0.81	(0.70, 0.94)	
High BMI	1.34	(0.69, 2.60)	1.11	(0.97, 1.27)	1.92	(0.85, 4.37)	
Glucose > 100							0.04
Low BMI	1.28	(0.64, 2.56)	1		1.12	(0.91, 1.38)	
High BMI	2.98	(1.37, 6.46)	1.31	(1.08, 1.57)	0.65	(0.09, 4.76)	
SBP ≥ 130 mmHg or DBP ≥ 85 mmHg							0.39
Low BMI	0.83	(0.47, 1.45)	1		0.81	(0.67, 0.98)	
High BMI	2.45	(1.28, 4.68)	1.25	(1.09, 1.43)	1.78	(0.66, 4.81)	
Metabolic syndrome (NCEP)							0.11
Constant BMI	0.96	0.52–1.77	1		1.00	0.87–1.14	
Increased BMI	1.47	1.05–2.06	1.28	1.16–1.41	0.64	0.25–1.64	
Metabolic syndrome (IDF)							0.25
Constant BMI	0.84	0.46–1.54	1		0.96	0.84–1.09	
Increased BMI	1.61	1.18–2.21	1.41	1.29–1.54	1.19	0.58–2.44	
Metabolic syndrome (WHO)							0.71
Constant BMI	1.30	0.48–3.54	1		0.97	0.76–1.24	
Increased BMI	1.49	0.84–2.62	1.10	0.91–1.34	1.06	0.24–4.65	
HDL < 40/ < 50							0.82
Constant BMI	0.75	0.49–1.15	1		0.99	0.90–1.08	
Increased BMI	1.16	0.88–1.52	1.20	1.11–1.28	1.47	0.87–2.51	
TG > = 150							0.03
Constant BMI	0.66	0.36–1.23	1		0.98	0.87–1.10	
Increased BMI	1.45	1.03–2.04	1.28	1.18–1.40	0.75	0.37–1.54	
Glucose > 100							0.62
Constant BMI	1.02	0.46–2.23	1		0.99	0.81–1.19	
Increased BMI	1.67	1.14–2.43	1.16	1.01–1.33	2.00	0.81–4.94	
SBP > = 130 mmHg or DBP > = 85 mmHg							0.34
Constant BMI	1.10	0.65–1.86	1		1.04	0.92–1.18	
Increased BMI	1.08	0.76–1.53	1.17	1.06–1.29	0.52	0.20–1.37	

^aAdjusted for age at time of metabolic syndrome measurement, race, sex, race*sex, income, parental education, and smoking.

BMI, body mass index; SGA, < 10th percentile for gestational age; AGA, appropriate-for-gestational age, 10–90th percentile; LGA, large-for-gestational age, 90th percentile for gestational age; OR, odds ratio; CI, 95% confidence interval; NCEP, National Cholesterol Education Program; IDF, International Diabetes Federation; WHO, World Health Organization; HDL, high-density lipoprotein; TG, triglycerides; SBP, systolic blood pressure; DBP, diastolic blood pressure.

should examine the interactions between these risk factors. It is likely the opposite relationships between SGA and adult body size, and between adult body size and metabolic syndrome, contribute to the lack of associations seen in some studies.

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