

Chapter 2

Fetal Origins of Variables Related to Cardio-Metabolic Risk

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Abstract Low birth weight for gestational age, regardless of socio-economic background and geographical location, is considered a risk factor for chronic diseases such as cardiovascular disease and type 2 diabetes mellitus in later life. This overview focuses on the racial (black–white) divergence in birth weight and adverse effects of low birth weight on aspects of cardio-metabolic risk involving anthropometric, hemodynamic, metabolic and inflammatory variables during growth periods of childhood, adolescence, and adulthood along with pulsatile behavior of the vasculature in adulthood noted in the Bogalusa Heart Study cohort. Several putative mechanisms linking these adverse relationships are discussed, thereby providing a rationale for primordial prevention.

Keywords Arterial stiffness • Cardio-metabolic risk • CV risk factor • Fetal growth • Inflammatory marker • Low birth weight • Racial difference

2.1 Introduction

Low birth weight for gestational age is considered to be an indicator of metabolic imprinting and developmental plasticity associated with a compromised intrauterine growth and development [1–5]. Developmental plasticity reflects gene expression mediated in part by epigenetic processes in response to environmental factors and subsequent risk of diseases [6]. Studies world-wide, regardless of socio-economic background, have linked low birth weight to increased risk of developing insulin resistance, dyslipidemia, hypertension, coronary heart disease, and type 2 diabetes [7–10], although some investigators question this relationship [11, 12]. This chapter highlights the effect of low birth weight on aspects of cardio-metabolic risk noted in the Bogalusa Heart Study biracial (black–white) cohort [13–22].

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2.2 Racial (Black–White) Difference

Birth weight of children born to Bogalusa residents between January, 1974 and June, 1975 were examined by race. Of these children, 100% blacks and 97.5% whites participated in the study [13]. As illustrated in Fig. 2.1, white children at birth when compared to black children consistently weighed more. Ninety percent of white newborns weighed between 2353 g (5th percentile) and 4186 g (95th percentile); whereas for black newborns the corresponding values were 1962 g and 3989 g, respectively. This black–white contrast in birth weight for gestational age was also seen in later studies, including our own [15, 18, 23, 24].

The effect that socio-economic and genetic factors may have on the birth weight of these two racial groups were indirectly assessed by comparing the birth weight data by race of children born in Bogalusa public vs private hospitals. The racial make-up of children born at the state hospital was 66% black and 34% white; at the private hospital, 19% black and 81% white. At both hospitals, white neonates weighed significantly more than their black counterparts, although in both races those born at the private hospital weighed significantly more than those born at the public hospital. Further, mean birth weight of blacks born at the private hospital was almost identical to the mean birth weight of whites born at the public hospital. Taken together, these findings indicate that both socio-economic and genetic factors influence the weight at birth.

2.3 Relation to Anthropometric, Metabolic, and Hemodynamic Variables

Earlier studies have linked low birth weight to adverse levels of cardiovascular risk factor variables in childhood and adolescence [25–29]. However, information is scant on data linking low birth weight to longitudinal trends of adiposity, blood pressure, lipids, and glucose homeostasis variables (glucose, insulin, and insulin

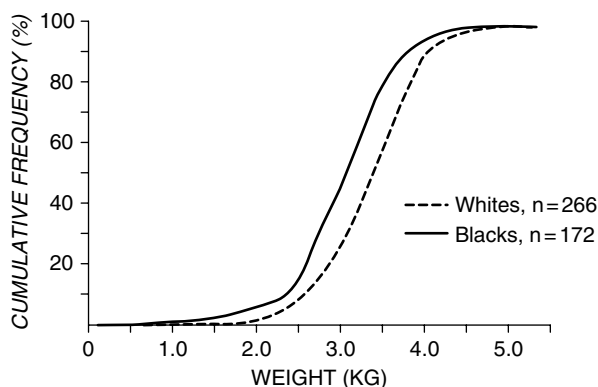


Fig. 2.1 Cumulative frequency distributions for weight at birth of black and white Bogalusa newborns: the Bogalusa Heart Study. [13]

Table 2.1 Levels (mean±SD) of risk variables during childhood and adolescence by birth weight: the Bogalusa Heart Study. [14]

Variable	Childhood (4–11 years)		Adolescence (12–18 years)	
	Low birth weight	Control	Low birth weight	Control
BMI (kg/m ²)	16.7±2.6	17.5±2.9	21.6±5.2	22.7±5.0
Subsc. skinfold (mm)	8.2±5.1	8.3±6.4	15.9±10.0	16.0±10.7
Syst. BP (mm Hg)	96.4±9.0	98.6±8.1	108.8±9.1	105.2±8.7
Diast. BP (mm Hg)	57.2±10.2	58.7±7.9	66.1±8.0	66.4±7.4
Triglycerides (mg/dL)	62.6±23.2	52.8±20.3	87.1±29.0	83.2±35.3
HDL cholesterol (mg/dL)	44.3±22.6*	54.7±17.4	49.9±12.8	51.2±11.5
LDL cholesterol (mg/dL)	76.0±35.4*	68.6±37.6	99.5±24.7	98.4±24.3
Glucose (mg/dL)	79.7±8.1	80.9±9.7	85.4±8.2**	81.6±7.4
Insulin (μU/mL)	8.5±5.7	7.4±4.6	14.8±7.5	13.2±8.6
HOMA-IR	1.7±1.2	1.6±1.0	3.0±2.4	2.7±2.0

Difference between groups (adjusted for age, race, and gender), *p=0.05; **p=0.02
HOMA-IR homeostasis model assessment index of insulin resistance

resistance index) measured simultaneously and serially during the developmental periods of childhood and adolescence. The Bogalusa Heart Study subjects followed from childhood to adolescence by repeated surveys were categorized into singleton and full term low birth weight (below the gestation age- and race-specific 10th percentile) and control (between the gestation age- and race-specific 50th and 75th percentiles) groups [14]. As shown in Table 2.1, low birth weight vs control group had significantly lower mean high-density lipoprotein (HDL) cholesterol and higher low-density lipoprotein (LDL) cholesterol during childhood (ages 4–11 years); higher glucose during adolescence (ages 12–18 years). In addition, yearly rates of change from childhood to adolescence in systolic blood pressure, LDL cholesterol, and glucose were faster, and body mass index (BMI) slower among the low birth weight group. In a multivariate analysis of the serial data, presented in Table 2.2, the

Table 2.2 Independent association of low birth weight with longitudinal trends of systolic blood pressure, triglycerides and glucose from childhood to adolescence. [14]

Independent variables retained	Syst. BP		Triglycerides		Glucose	
	β [†]	p-value	β	p-value	β	p-value
Birth weight (low vs control)	3.84	0.02	48.6	0.08	15.20	0.07
Gender (male vs female)	–	–	–	–	4.31	<0.001
Age	0.39	0.40	12.21	0.01	6.60	<0.001
Age ²	0.06	0.002	–0.44	0.04	–0.31	<0.001
Insulin	0.11	0.03	1.16	<0.001	0.22	0.02
BMI	0.34	<0.001	–	–	–	–
Birth weight×age	0.45	0.004	12.71	0.03	0.10	0.07
Birth weight×age ²	–	–	0.55	0.02	2.65	0.10

[†] GEE regression coefficient. The model included birth weight (low vs control) along with age, age², race, and gender, and their interaction with birth weight; and risk variable as applicable

independent adverse effects of low birth weight on the longitudinal trends of systolic blood pressure, triglycerides, and glucose were discernable in the study cohort, regardless of race and sex. An analysis of the data set using the World Health Organization criteria for low birth weight (<2500 g) gave essentially the same results. Of note, observed adverse trends associated with low birth weight group vs control group were influenced by age in that the difference became greater in magnitude as the children got older. Earlier studies have found such strong associations with increasing age [30]. Further, although the rate of yearly increase in BMI, which also includes muscle mass, was significantly lower in low birth weight group, the rate of increase in subscapular skinfold, a measure of truncal fat, remained similar to that of the control group. This suggests a gaining of truncal fat, in relative term, over muscle mass in the low birth weight group.

In terms of hemodynamic variables, additional studies on the developmental trends from childhood to mid-adulthood indicated that birth weight was independently inversely associated with systolic blood pressure as well as diastolic blood pressure and pulse pressure [17]. The interaction of birth weight with BMI was negative for all these three hemodynamic variables, but the trend was significant only for systolic blood pressure. Figure 2.2 illustrates the relation between birth weight and later systolic blood pressure (at age ≥ 35 years) within each tertile of adult BMI. That adjustment for later BMI strengthens this association indicates BMI as a negative confounder as originally proposed by Gillman [31]. Importantly, the magnitude of the birth weight–systolic blood pressure relationship was significantly amplified with increasing age from pre-adolescence to mid-adulthood, regardless of adjustment for current BMI and race [18]. These findings are consistent with previous reports [30, 32]. Further, in this cohort, low birth weight was significantly associated with increased within-individual blood pressure variability assessed in terms of standard deviations of six serial blood pressure measurements from childhood to adulthood. In a multivariate model adjusted for race, sex and average age and blood pressure from childhood to adulthood, 1 kg of lower birth weight was associated with

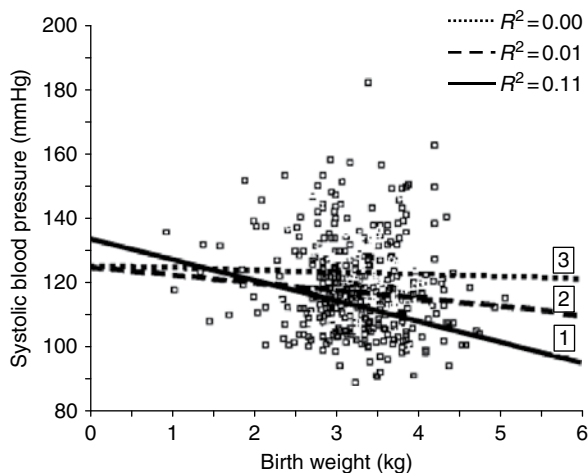


Fig. 2.2 The interaction of birth weight with body mass index (BMI) on systolic blood pressure at age ≥ 35 years. BMI: 1 lowest tertile, 2 middle tertile, 3 highest tertile: the Bogalusa Heart Study. [15]

0.43 mm Hg increase in standard deviation of systolic blood pressure ($p=0.023$); 0.55 mm Hg of diastolic blood pressure ($p=0.002$). These observations suggest that the fetal programming and the increasing burden with age of unhealthy lifestyle behaviors affect the development of adult hypertension in a synergistic manner.

It is well established that genetics play a major role in determining both blood pressure levels and birth weight [33, 34]. Candidate genes and chromosomal regions have been identified for birth weight [35–37]. The genetic influence of β -adrenergic receptor gene polymorphisms ($\beta 2$ -AR Arg 16 Gly and $\beta 3$ -AR Trp 64 Arg), important modulators of fetal growth, sympathetic nervous system, hemodynamic status, obesity, and insulin sensitivity [38–41], on the inverse relation of birth weight to longitudinal changes in blood pressure has been found in the Bogalusa cohort, aged 21–47 years [19]. Blacks showed significantly lower birth weight and frequencies of $\beta 2$ -AR Gly 16 and $\beta 3$ -AR Trp 64 alleles and higher blood pressure levels and age-related trends than whites. Importantly, the strength of the birth weight—blood pressure association, measured as regression coefficients, was significantly modulated by the combination of $\beta 2$ -AR and $\beta 3$ -AR genotypes for systolic blood pressure ($p=0.042$ for interaction) and diastolic blood pressure ($p=0.039$ for interaction) age-related trend, with blacks and whites showing a similar trend in the interaction. Further, low birth weight was adversely related to longitudinal changes in BMI from childhood to adulthood depending on fat mass and obesity risk associated (FTO) genotype in the Bogalusa cohort [42]. These findings underscore the role of genetic factors in the fetal origins of hypertension later in life.

2.4 Relation to Inflammation

It is well recognized that cardio-metabolic syndrome and related CV diseases and type 2 diabetes all share inflammation as a common pathologic trait [43–45]. Further, a few studies have linked low birth weight for gestational age to increases in systemic inflammation as depicted by C-reactive protein [46, 47]. The influence of low birth weight on the white blood cell (WBC) count, a widely used biomarker of systemic inflammation [48, 49], during different growth periods of childhood (ages 4–11 years), adolescence (ages 12–17 years), and adulthood (ages 18–38 years) was examined in the Bogalusa cohort [20]. As illustrated in Fig. 2.3, the WBC count significantly decreased with increasing quartiles of birth weight in children and adults of both races. This inverse relationship was independent of age, race, sex, BMI, and smoking status. Adolescents, regardless of race, showed no such significant trend in this relationship. Because the pubertal period of growth and maturation is characterized by marked changes in fat mass and distribution along with insulin sensitivity [50–52], known strong correlates of inflammation [44, 48], it is likely that low birth weight may not be a strong enough proxy for prenatal factors influencing the WBC count during adolescence. These observations by showing inverse association between birth weight WBC count provide further rationale for linking fetal growth retardation to CV diseases and type 2 diabetes, and implicating an impact of inflammation.

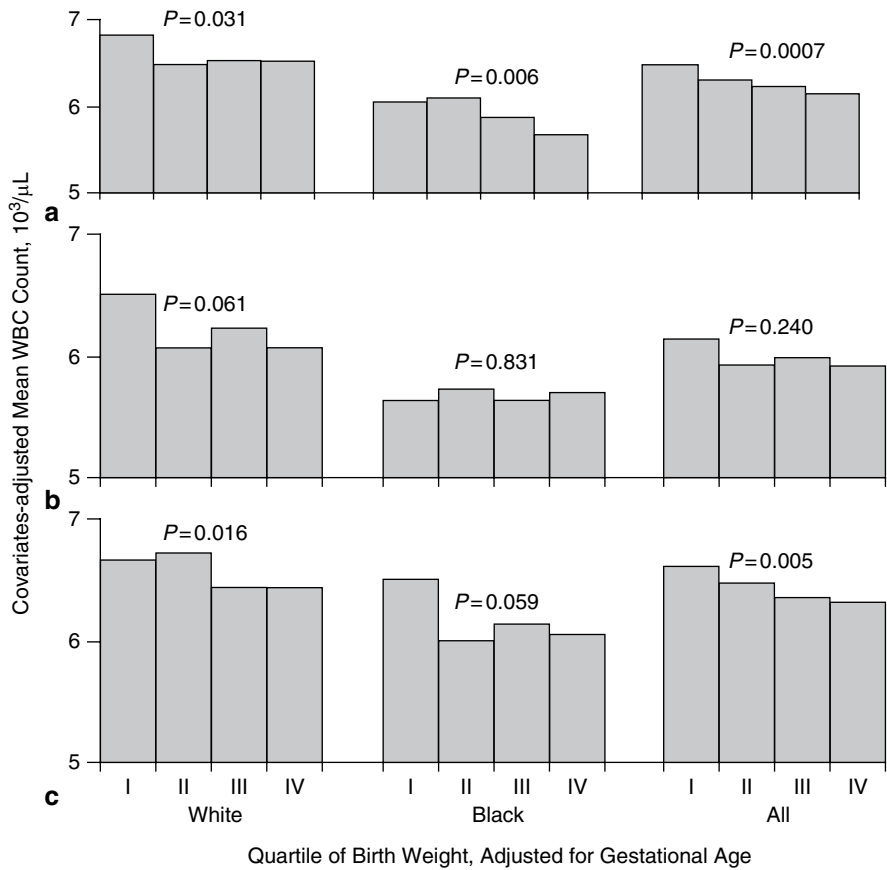
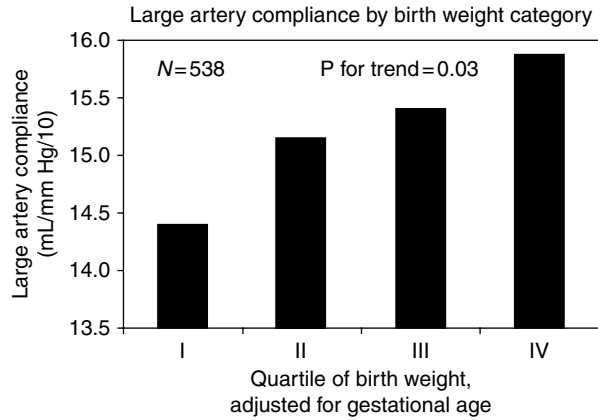


Fig. 2.3 Covariate-adjusted mean values of white blood cell (WBC) count by race- and sex-specific quartiles of gestational age-adjusted birth weight. Quartiles *I* and *IV* represent the lowest and highest birth weights, respectively, in children (**a**), adolescents (**b**), and adults (**c**). Covariates included age, sex, race (total sample), body mass index, and smoking status (adolescents and adults). The Bogalusa Heart Study. [20]

2.5 Relation to Arterial Stiffness

Recent studies have shown that alterations in the pulsatile behavior of the vasculature may be a sensitive marker to detect vascular dysfunction related to CV risk factors and mortality [53–55]. Therefore, studies of arterial compliance in terms of pulsatile behavior can help determine the role of birth weight in relation to CV risk. This aspect was examined in the Bogalusa cohort of asymptomatic younger adults aged 18–44 years [21]. Subjects were categorized into low (below the race–sex specific 10th percentile) and normal (between the race–sex specific 10th and 90th

Fig. 2.4 Covariates-adjusted mean values of large artery compliance by race–sex specific gestational age-adjusted birth weight. Quartile *I* represents lowest birth weight; *IV* highest birth weight. Covariates included race, sex, and age. The observations show the relation of low birth weight and loss of vascular compliance and early vascular stiffness. The Bogalusa Heart Study. [21]



percentiles) birth weight groups. Pulsatile arterial function was assessed in terms of large artery compliance and small artery compliance. A modified Windkessel model of the circulation was used to quantify changes in arterial waveform morphology in terms of large artery (capacitive) compliance, representative of the aorta and major branches, and small artery (oscillatory) compliance, representative of the distal part of the circulation including the arteriolar bed, and systemic vascular resistance [56]. Low vs normal birth weight group had significantly lower large artery compliance. Further, in the total sample, after adjusting for gestational age, race and sex, the large artery compliance increased significantly across quartiles of increasing birth weight specific for race, sex, and gestational age (Fig. 2.4). This relationship was independent of race, sex, and adulthood age, BMI, body surface area, systolic blood pressure, diastolic blood pressure, pulse rate, triglycerides/HDL cholesterol ratio, insulin resistance index and smoking status. No such adverse independent effect of low birth weight was noted with respect to small artery compliance and systemic vascular resistance.

The observed positive association between birth weight and large artery compliance is consistent with earlier studies [57–60], except Atherosclerosis Risk in Young Adults study in somewhat older subjects [61]. The lack of association between birth weight and small artery compliance may be due to the fact that the association between birth weight and compliance was found to be stronger in elastic arteries than the small muscular arteries [57, 62]. Further, birth weight was also inversely and independently related to both systolic blood pressure and brachial-ankle pulse wave velocity, another marker of arterial stiffness related to elastic properties of aorta and its larger branches, measured at younger to mid-adulthood in the Bogalusa cohort [22]. Because arterial stiffness is both a cause and result of hypertension [63, 64], increased arterial stiffness may be a link between the inverse association between birth weight and blood pressure later in life, also to developing systolic hypertension and increasing pulse pressure. These findings, regardless of underlying mechanisms, highlight the adverse CV risk associated with low birth weight.

2.6 Mechanisms

Several putative mechanisms link low birth weight to the adverse cardio-metabolic risk profile [65]. It has been suggested that insulin resistance may be one mechanism by which intrauterine events may program disease risk [66]. Under-nutrition in utero is known to cause permanent impairment in growth, structure, and function of, among others, muscle [66, 67], fat [68], endocrine pancreas [69, 70], liver [71], renal nephrons [72, 73], sympathetic nervous system [74], glucocorticoid hormones [75], hypothalamic–pituitary–adrenal axis [76] and vasculature [77] due to adaptive programming, resulting in adverse profiles of cardio-metabolic risk factor variables and related disorders later in life [7, 9, 65]. Of interest, since there is little muscle cell replication after birth [78], low birth weight individuals under a nutritionally rich environment later in life will develop a disproportionately high fat mass and related state of chronic low grade inflammation induced by adipose tissue cells including monocytes [65, 79]. With respect to large artery compliance, it has been proposed that impairment of synthesis of elastin and changes in collagen along with endothelial dysfunction in large arteries during the period of intrauterine growth retardation in low birth weight babies result in permanent changes in mechanical properties of these vessels [80, 81]. In addition, structural adaptations in the large artery wall occur in response to alterations in Doppler blood flow velocity waveforms under conditions of intrauterine growth retardations [61].

2.7 Conclusion

Low birth weight, albeit a crude surrogate marker for fetal growth and maturation, is a potential early risk factor for the emergence of anthropometric, metabolic and hemodynamic disorders and related diseases [2, 65]. In terms of public health, the importance of primordial prevention is obvious. As stated by Barker and colleagues [2, 7], primary prevention lies in protecting fetal development. This entails providing comprehensive prenatal care services, taking into account differences in the prevalence of low birth weight babies among racial groups in the general population.

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Berenson, G.S. (Ed.)

2011, XIII, 210 p., Hardcover

ISBN: 978-94-007-1450-2