ORIGINAL ARTICLE

The effect of feto-maternal size and childhood growth on left ventricular mass and arterial stiffness in Afro-Caribbean children

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We hypothesized that maternal size, fetal size and childhood growth are associated with childhood blood pressure, left ventricular mass (LVM) and arterial stiffness. The Vulnerable Windows Cohort is a longitudinal study of 569 mothers and their offspring. Anthropometry was measured on each child at birth, at 6 weeks, once in 3 months upto 2 years and then every 6 months. Blood pressure and body composition were assessed in 185 children (age 11.5 years) and echocardiography performed. LVM was not associated with maternal size after adjustment for child's weight. LVM was significantly associated with faster growth in childhood and with current weight, fat mass and lean mass. Systolic blood pressure was not related to maternal, fetal or

newborn anthropometry, but was positively associated with infant and childhood growth, as well as current body size and fat mass. The pulse pressure/stroke volume ratio (an index of arterial stiffness) was inversely associated with maternal size, placental volume at 20 weeks, fetal size at 35 weeks and childhood growth even after adjustment for current weight. In conclusion, LVM in childhood is positively associated with maternal height, child's current size and rate of growth. Arterial stiffness is inversely related to maternal, fetal and placental size as well as growth throughout childhood.

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Introduction

Myocardial hypertrophy, most frequently due to hypertension in adults, is associated with several risk factors that operate at different times across the life course. These include the intrauterine changes in cardiovascular mechanics that redistribute blood flow from body to brain in the presence of fetal growth retardation.^{1–6} In later life, left ventricular hypertrophy is a strong predictor of stroke, heart failure and coronary artery disease.⁷

Growth in infancy and childhood also appear to modulate the risk of hypertension, stroke and coronary artery disease, and thus might relate to left ventricular hypertrophy.^{8,9} Left ventricular hypertrophy is causally related to mechanical loading whether characterized by blood pressure, wave

mechanics or indices of arterial stiffness, such as arterial pulse wave velocity and compliance.^{10,11} However, arterial stiffness has also been shown to be an independent risk factor for fatal and non-fatal cardiovascular events both in patients with hypertension and in the general population.^{12–14}

The risk of coronary artery disease, stroke and other vascular pathology is reportedly increased in the offspring of mothers who were undernourished while they were pregnant.¹⁵ As preclinical markers, such as left ventricular hypertrophy and arterial stiffness,¹³ are such powerful predictors of future vascular pathology, we hypothesized that maternal, fetal, placental, newborn size as well as growth in infancy and childhood would be associated with left ventricular mass (LVM) or its determinants, blood pressure and pulse pressure/stroke volume ratio, an index of arterial stiffness.

Methods

Subjects and study design

As previously described,¹⁶ 712 women attending the antenatal clinic at the University Hospital of the

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West Indies, Kingston, Jamaica, were invited to participate in a prospective study of intrauterine growth, and risk factors for chronic cardiovascular disease in later life. Inclusion criteria were the following: women who were aged between 15 and 40 years, were 7–10 weeks pregnant (which was confirmed by a 14-week ultrasound) and without systemic illnesses (for example, pre-eclampsia and diabetes) or genetic abnormality (for example, sickle cell disease). Only 17 (3.5%) of the mothers smoked. The 712 women yielded 569 babies to the cohort: 82 had pregnancy losses; 56 withdrew for reasons such as work constraints and migration; and five sets of twins were excluded. This study is confined to the 185 children who accepted an invitation to have echocardiographic measurements. The Ethics Committee of the University of the West Indies approved the study, and each mother gave written informed consent.

Measurements

Maternal and feto-placental anthropometry. Using a standardized protocol,¹⁶ maternal weight was measured to the nearest 0.01 kg and height was measured to the nearest 0.1 cm. Abdominal ultrasound was performed using a linear probe (ATL Ultramark IV, Advanced Technology Labs, Bothell, WA, USA) at 14, 17, 20, 25, 30 and 35 weeks of gestation. Fetal head and abdominal circumferences were measured in triplicate at all six visits, and the average for each visit was used. Placental volume was measured sonographically at 14, 17 and 20 weeks.¹⁶ The long axis of the placenta was identified and a continuous recording of the image of the placenta orthogonal to the axis was carried out. This axis was divided into six sections of equal length; the five interior cross-sectional areas were measured and integrated to estimate placental volume.

Offspring anthropometry and blood pressure

Birth weight, crown-heel length, head circumference and placental weight were measured within 24 h of delivery. We measured anthropometry at 6 weeks, once in 3 months up to 2 years and then every 6 months. Blood pressure was measured every 6 months from the age of 1 year using a mercury sphygmomanometer (Baumanometer, Copiague, NY, USA). Two readings were taken with the child in the seated position and the average used. Inter- and intra-observer variabilities were measured every 3 months, followed by training/recertification for any observer whose scores were not acceptable.

Assessment of pubertal stage was performed every 6 months starting at age 8 years. Girls were asked at each clinic visit whether they had started their menses and, if so, at what age. Pubic hair and breast development were measured according to the method of Marshall and Tanner.^{17,18} Testicular

volume was measured with a Prader orchidometre, with volumes ranging from 1 to 25 ml.

Body composition at mean age 11.5 years was measured using single frequency bioelectrical impedance analyzer (50 KHz model 101Q RJL Systems, Clinton Twp, MI, USA) in the supine position. The mean of two measurements was used in the calculations. Lean mass and fat mass were estimated from the manufacturer's equations.

Two-dimensional transthoracic echocardiography

Cardiac structure and function was assessed using transthoracic echocardiography at age 11.5 ± 1.3 years using ATL Ultramark 7 (Advanced Technology Labs) and Philips iE33 phased-array echocardiogram machines. Parasternal views were obtained with optimal orientation to maximize left ventricular internal dimensions; and apical views obtained to evaluate optimal trans-mitral and trans-aortic Doppler signals. Left ventricular internal dimensions and wall thicknesses were measured from the M-mode left ventricular recordings at end-diastole, according to the American Society of Echocardiography recommendations.¹⁹ When optimal orientation of M-mode left ventricular recordings were not obtained, linear left ventricular measurements were taken from the two-dimensional images, using the leading-edge convention. These linear measurements were then used to determine LVM, geometry and systolic function. Doppler measurements were used to assess left ventricular diastolic function. Together with the participant's blood pressure and heart rate, ventricular linear measurements were used to estimate participant systemic haemodynamics.

We used the pulse pressure/stroke volume ratio as a measure of arterial stiffness.^{20,21} This surrogate of arterial stiffness is easy to measure and is based on a Windkessel model of the arterial tree. It is highly correlated ($r=0.85$) with the ratio of the diastolic-decay time constant (τ) of the arterial system and the peripheral resistance¹⁴ and has been shown to predict cardiovascular events both in hypertensive patients¹² and in the general population²¹. The pulse pressure/stroke volume ratio is calculated by dividing the brachial pulse pressure (that is, brachial systolic minus diastolic blood pressure) as measured by mercury sphygmomanometer by the left ventricular stroke volume (that is, end-diastolic minus end-systolic volume) as determined from linear echocardiographic left ventricular measurements.

Statistical analyses

Body mass index (BMI) was calculated as weight in kg divided by the square of the height in metres. Growth (that is, gains in weight, height and BMI) was measured in three time intervals: birth to 6 months; 6 months to 2 years; and 2 years to age 11 years. Growth was defined as the amount by which

the size at the end of a time interval exceeded that which would have been predicted by linear regression using the measurements available at the beginning of the interval.¹⁴ Such measures are uncorrelated by construction. Simple differences in z-score do not have this property, as a large difference may result from either a low value at the beginning of the interval or a high one at the end.²²

Multiple regression analyses were used to examine the relationships among maternal, placental, fetal and neonatal measurements with LVM, systolic blood pressure and pulse pressure to stroke volume ratio in the 185 children. Variables were log transformed to normality. We used outcomes and predictors in standardized form. We evaluated for interactions by sex to see if the regression coefficients were similar in boys and girls, so we used product terms of sex with anthropometric variables. We always adjusted risk factors for age at the clinic visit. A *P*-value <0.05 was considered statistically significant. SPSS 15.0 for Windows (Chicago, IL, USA) was used for the statistical analyses.

Results

The 185 subjects studied were similar to the other members of the cohort in maternal age, height, weight and BMI. At birth, they were not different in crown-heel length, head circumference, placental weight or gestational age at delivery, but were 120 g heavier (*P* = 0.02).

Mean values for maternal, placental, fetal and newborn measurements as well as childhood anthropometry and cardiovascular measurements are shown in Table 1. As expected, the boys were larger until age 11 years, at which stage more girls had started their pubertal growth spurt and had a higher BMI, fat mass and percent body fat. The median age at reaching Tanner stage 3 for pubic hair development was 11.1 years in girls and 12.8 years in boys.

Table 2 shows the associations of LVM, systolic blood pressure and pulse pressure/stroke volume with maternal, placental, fetal and newborn size. Table 3 describes the associations of these outcomes with infant and childhood growth. Table 4 shows the associations of the outcomes with various measures of current size after adjustment for sex and current age. We describe the outcomes in sequence.

LVM

LVM was positively associated with maternal height measured in the first trimester (Table 2). The relationship of LVM with maternal height was however lost after adjustment for child's weight. LVM was also related to growth in childhood, that is, gains in height, weight and BMI that were greater than predicted (Table 3 Figure 1a). LVM was

Table 1 Maternal, placental, fetal, birth, infant and childhood measurements

	Boys (n = 86)		Girls (n = 99)	
	Mean	s.d.	Mean	s.d.
<i>Maternal measurements (first trimester)</i>				
Age (years)	27.0	5.7	26.3	5.1
Height (cm)	163.5	5.9	163.0	5.9
Weight (kg)	66.7	12.8	65.6	13.4
Pregnancy weight gain (kg per 4 weeks)	1.3	0.6	1.4	0.7
<i>Placental measurements</i>				
14 week volume (ml)	128	59	114	58
17 week volume (ml)	250	75	242	80
20 week volume (ml)	373	82	364	89
Weight at delivery (g)	601	147	566	115
<i>Fetal abdominal circumference (mm)</i>				
14 week	87.2	11.9	85.0	13.5
25 week	209.1	12.7	205.3	16.2
35 week	319.2	16.5	311.7	18.7
<i>Birth measurements</i>				
Weight (g)	3278	502	3123	474
Length (cm)	49.9	2.9	49.3	3.0
Head circumference (cm)	32.9	2.1	32.4	2.3
Gestational age (days)	274.4	12.2	274.6	13.0
<i>Size at age 6 months</i>				
Weight (kg)	8.2	0.9	7.7	0.9
Height (cm)	67.7	2.1	66.3	2.1
<i>Size at age 2 years</i>				
Weight (kg)	12.3	1.3	11.8	1.5
Height (cm)	87.2	2.9	87.0	2.8
<i>Size at age 11 years</i>				
Weight (kg)	37.6	7.7	42.0	8.9
Height (cm)	146.4	6.0	150.1	6.5
<i>Clinic measurements</i>				
Age (years)	10.9	0.9	11.0	1.0
Height (cm)	149.3	9.0	152.2	10.1
Weight (kg)	41.5	9.8	46.1	12.9
Body mass index (kg m ⁻²)	18.5	3.3	19.7	4.3
Waist circumference (cm)	66.6	7.5	68.7	9.5
Lean mass (kg)	30.4	6.4	29.9	6.6
Fat mass (kg)	11.1	6.7	16.2	8.5
Fat percentage (%)	25.4	10.2	33.4	9.7
<i>Cardiac measurements at age 11 years</i>				
Left ventricular mass (g)	85.1	22.0	85.3	23.2
Systolic blood pressure (mm Hg)	100.1	6.2	99.5	5.1
Diastolic blood pressure (mm Hg)	53.0	4.0	51.4	3.1
Stroke volume (ml)	50.5	11.2	50.3	11.4
Pulse pressure per stroke volume (mm Hg ml ⁻¹)	0.98	0.27	1.01	0.26

strongly correlated with all anthropometric and body composition measurements (Table 4), most strongly with current weight. As boys and girls had progressed to varying degrees through puberty, we adjusted for pubertal stage. Again, after adjustment for current weight, pubertal stage made no contribution to LVM (data not shown). Expressing LVM as the LVM index (LVM/height^{2.7}) did not alter these relationships.

Table 2 Regression coefficients between maternal, placental, fetal and birth measurements of 185 Jamaican children and their left ventricular mass (LVM), systolic blood pressure (SBP), pulse pressure/stroke volume (PPSV)

	Adjusted for age and sex			Adjusted for age, sex and weight ^b		
	LVM	SBP	PPSV	LVM	SBP	PPSV
<i>Maternal measurements</i>						
Age at booking	0.082	-0.036	-0.037	0.073	-0.047	-0.029
Height	0.181 ^a	0.056	-0.168 ^a	0.126	0.017	-0.134
Weight at booking	0.126	-0.003	-0.201 ^a	0.074	-0.040	-0.174 ^a
Body mass index at booking	0.070	-0.022	-0.154 ^a	0.032	-0.048	-0.135
Pregnancy weight gain	0.073	0.093	-0.060	0.071	0.091	-0.057
Socioeconomic status	0.042	0.011	0.053	0.068	0.023	0.043
<i>Placental measurements</i>						
14-week volume	-0.010	-0.069	-0.137	-0.033	-0.083	-0.130
17-week volume	-0.014	-0.148	-0.129	0.001	-0.144	-0.141
20-week volume	0.093	-0.080	-0.208 ^a	0.083	-0.093	-0.204 ^a
Weight at delivery	0.040	0.037	-0.088	0.020	0.025	-0.078
<i>Fetal measurements</i>						
14 week: abdominal circulation	-0.029	0.051	0.084	0.023	0.083	0.058
Femoral length	-0.043	0.076	0.096	-0.002	0.104	0.075
Head circulation	-0.090	-0.051	-0.037	-0.040	-0.020	-0.070
25 week: abdominal circulation	0.035	0.010	-0.072	0.097	0.042	-0.016
Femoral length	-0.001	-0.002	-0.058	0.033	0.017	-0.078
Head circulation	0.015	-0.037	-0.053	0.075	-0.006	-0.086
35 week: abdominal circulation	-0.048	0.010	-0.073	-0.025	-0.029	-0.215 ^a
Femoral length	-0.011	-0.076	-0.211 ^a	-0.020	-0.083	-0.213 ^a
Head circulation	0.010	-0.097	-0.218 ^a	0.070	-0.069	-0.258 ^a
<i>Birth measurements</i>						
Weight	0.032	-0.016	-0.124	0.001	-0.036	-0.109
Length	-0.047	-0.142	-0.092	-0.053	-0.148	-0.094
Body mass index	0.079	0.078	-0.060	0.050	0.060	-0.042
Head circumference	-0.009	-0.075	-0.103	-0.029	-0.088	-0.096
Gestation at delivery	0.013	-0.029	-0.069	0.002	-0.036	-0.064

Variables are in standardized form. Each cell corresponds to a different regression analysis.

^aCorresponds to $P < 0.05$.

^bWeight refers to child's current weight.

Systolic blood pressure

Systolic blood pressure was not significantly related to any maternal, fetal or newborn anthropometric measurement (Table 2). However, it was positively correlated with gains in height, weight and BMI after age 6 months till age 11 years (Table 3 and Figure 1b). Systolic blood pressure was also directly related to the child's weight, BMI, waist circumference and fat mass (Table 4). After adjusting for current weight, pubertal stage did not account for any of the variance in systolic blood pressure (data not shown).

Pulse pressure/stroke volume ratio

Pulse pressure/stroke volume ratio was inversely associated with maternal height, weight and BMI during the first trimester. It was also negatively associated with the placental volume measured at 20 weeks, and fetal femoral length and head circumference measured at 35 weeks gestation (Table 2). These associations remained relatively similar after adjustment for child current weight and

maternal size (data not shown). The ratio was inversely related to childhood growth, especially after age 2 years (Table 3 and Figure 1c), as well as current weight and body composition (Table 4). After adjustment for current weight, the association of pubertal stage with the pulse pressure/stroke volume ratio was not significant (data not shown).

Discussion

This longitudinal cohort study provides additional evidence for the developmental programming of preclinical markers of cardiovascular disease in a cohort of Afro-Jamaican children followed from intrauterine life through to mean age 11.5 years. LVM was not independently associated with maternal or fetal markers of early development, but rather was determined by child's weight. However, arterial stiffness, which is a major predictor of left ventricular concentric hypertrophy in adults,^{12,20,21,23} was strongly related to small size in mother, placenta and fetus as well as slower growth throughout

Table 3 Regression coefficients between the size at birth and childhood growth of 185 Jamaican children and their cardiovascular measurements after adjustment for sex and current age

Measurement of size and growth	Left ventricular mass	Systolic blood pressure	Pulse pressure/stroke volume
Height			
Size at birth	-0.025	-0.134	-0.117
Growth: 0–6 months	0.187 ^a	0.132	-0.213 ^a
Growth: 6 months–2 years	0.209 ^a	0.281 ^b	-0.093
Growth: 2–11 years	0.244 ^b	0.108	-0.186 ^a
Weight			
Size at birth	0.041	0.005	-0.132
Growth: 0–6 months	0.144 ^a	0.094	-0.132
Growth: 6 months–2 years	0.229 ^b	0.305 ^b	-0.095
Growth: 2–11 years	0.392 ^b	0.198 ^a	-0.211 ^a
Body mass index			
Size at birth	0.076	0.097	-0.056
Growth: 0–6 months	0.137 ^a	0.044	-0.069
Growth: 6 months–2 years	0.125	0.170 ^a	-0.016
Growth: 2–11 years	0.371 ^b	0.240 ^a	-0.168 ^a

All variables are in standardized form.

^aCorresponds to $P < 0.05$.^bCorresponds to $P < 0.001$.**Table 4** Regression coefficients between measurements of current size of 185 Jamaican children and their cardiovascular measurements after adjustment for sex and current age

	Left ventricular mass	Systolic blood pressure	Pulse pressure/stroke volume
Weight	0.421 ^a	0.256 ^a	-0.239 ^a
Height	0.201 ^a	0.092	-0.230 ^a
Body mass index	0.404 ^a	0.261 ^a	-0.170 ^a
Body surface area	0.396 ^a	0.229	-0.263 ^a
Height ^{2.7}	0.201 ^a	0.081	-0.228 ^a
Lean mass	0.231 ^a	0.173	-0.245 ^a
Waist circumference	0.387 ^a	0.255 ^a	-0.164
Fat mass	0.422 ^a	0.233 ^a	-0.155
Percentage fat	0.345 ^a	0.167	-0.070

All variables are in standardized form.

^aCorresponds to $P < 0.01$.

childhood. The associations with placental and fetal factors remained significant even after adjustment for maternal size.

Birth size is correlated with LVM at age 1 year,²⁴ but this effect seems to be attenuated by age 2 years.²⁵ Intrauterine growth retardation has been associated with increased LVM in childhood, but some of this effect may be confounded by prematurity itself.²⁶ In Dutch children maternal weight gain in late pregnancy, but not maternal size, was related to LVM in infancy.² We found that by late childhood, LVM was not dependent on birth size, but was dependent on the current size of the child, and these data are consistent with that of other

Figure 1 Regression coefficients and their 95% confidence intervals (CIs) of (a) left ventricular mass (LVM), (b) systolic blood pressure and (c) pulse pressure/stroke volume on height, weight and body mass index (BMI) of 185 Jamaican children at age 11 years in relation to size in childhood. Analyses are adjusted for sex. Variables are analysed in standardized units.

investigators.^{25,27} The effect of maternal size on LVM in their children was mediated by child's attained weight, and accelerated growth during infancy and

childhood was associated with greater LVM. Some of our findings are comparable with those of Kumaran *et al*.²⁸ In their study of middle-aged Indians, there was no relation between birth size and blood pressure, arterial compliance or LVM. Decreased maternal size and pelvic diameter were however associated with decreased arterial compliance, as derived from non-invasive optical measurement of pulse wave velocity.

Although current size correlates with LVM, it is not clear if fat mass or lean mass may be the driver of ventricular growth. Both appear to be determinants in American children, but lean mass has a stronger effect.^{29,30} However, the size of the regression coefficients in our data suggest that fat mass has a larger effect in our cohort of Jamaican children.

Our data are consistent with other investigators who found that children with intrauterine growth retardation or who were born small for gestational age have abnormal arterial stiffness even if their blood pressure is normal.^{31,32} Current size also has a major role, as arterial stiffness in children is increased by adiposity³³ and in the presence of features of the metabolic syndrome.^{34,35} In fact, ethnic differences in arterial stiffness are mostly explained by differences in adiposity,^{36,37} which itself may have early life origins³⁸.

A developmental contribution to cardiovascular structure and function has been proposed and potential mechanisms mooted.^{2,39–43} Intrauterine undernutrition may cause hypercortisolaemia, which can cause accelerated cardiac ontogeny, tipping the balance to cardiac fibrosis, and in turn giving rise to cardiac dysfunction.³⁹ In addition, early pressure loading of cardiac myocytes may lead to fewer but larger myocytes.⁴⁰ Large artery elasticity is dependent on elastin, which is laid down *in utero* and during infancy. Intrauterine undernutrition causes shunting of blood flow from the trunk to the brain, and reduces elastin deposition in the large arteries of the trunk and legs, making these vessels less compliant and facilitating the development of hypertension in adult life.^{41,42} Also, upregulation of matrix metalloproteinases-2 and -9 increases arterial stiffness by degrading elastic fibre, as well as inhibiting angiogenesis by generating angiostatin in diabetic persons.⁴³ It is possible that inhibited fetal growth could also lead to similar effects. In support, children with lower birth weights also have smaller coronary artery, aortic root and left ventricular outflow tract diameters, and these changes in association with a greater predisposition to hypertension would increase the risk for coronary heart disease.⁴⁴ The additional effect of rapid postnatal growth on ventricular mass would be of prognostic significance as LVM appears to track over time;^{45,46} these effects would be expected to persist into later life.⁴⁷

Unfortunately, we do not have concurrent dietary and physical activity data for this cohort, both of which can influence arterial stiffness. High-dietary

fat intake is associated with rapid postnatal growth and increased arterial stiffness.⁴⁸ Arterial stiffness in children can be reversed by a regular physical activity programme, which also delays arterial wall remodelling.^{49,50} The combination of diet and cardiorespiratory fitness may be even more useful.⁵¹

The strengths of our study include its prospective, longitudinal design and the standardized manner in which the measurements were performed. One limitation however is that arterial stiffness was measured at clinic only. Echocardiographic pulse pressure/stroke volume index is however recognized as a good surrogate for arterial stiffness estimated using other more direct techniques, such as tonometry.^{20,52,53} This measure is more than adequate to rank subjects.

In this study, therefore, LVM in childhood is positively associated with maternal height, child's current size and child's rate of growth. Arterial stiffness, a marker of the future risk of left ventricular hypertrophy, is inversely related to maternal, fetal and placental size as well as growth throughout childhood. As the capacity to respond to vascular challenges in adulthood is dependent upon cardiovascular development during childhood, one avenue of prevention might focus on this developmental period.

What is known about topic

- Growth *in utero*, infancy and childhood may influence the risk of hypertension and atherosclerotic disease.
- It is unclear if maternal factors and offspring growth are related to preclinical markers of atherosclerotic disease, such as left ventricular mass and arterial stiffness.

What this study adds

- Maternal size, through its influence on child's weight, is positively related to left ventricular mass in children.
 - Arterial stiffness is inversely related to maternal, fetal and placental size as well as growth throughout childhood.
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Conflict of interest

The authors declare no conflict of interest.

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