Published in final edited form as:

Early Hum Dev. 2019 May ; 132: 24–29. doi:10.1016/j.earlhumdev.2019.03.018.

Proportionality at birth and left ventricular hypertrophy in healthy adolescents

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Abstract

Background: Perinatal growth has important implications for cardiac development. Low birth weight is associated with cardiovascular (CV) events and mortality, and animal studies have shown that fetal growth restriction is associated with cardiac remodeling in the perinatal period leading to a permanent loss of cardiomyocyte endowment and compensatory hypertrophy.

Aims: To determine associations of birthweight (BW) and multiple proportionality indexes (body mass index (BMI); weight/length² and Ponderal index (PI); weight/length³) at birth on one hand, with left ventricular (LV) structure and function during adolescence.

Subjects: 379 healthy adolescents aged 14–18 years in Augusta, Georgia.

Outcome measures: LV structure and function parameters, including intraventricular septal thickness in diastole (IVSd), LV internal dimension in diastole (LVIDd), LV internal diameter in systole (LVIDs), LV posterior wall thickness in diastole (LVPWd), relative wall thickness (RWT), midwall fractional shortening (MFS), and ejection fraction, were assessed by echocardiography.

Results: When associations of birthweight, birth BMI, and birth PI with LV structure and function parameters were separately evaluated with linear regression adjusting for age, sex, race, Tanner stage, socioeconomic status, and physical activity, significant positive associations of BW with LVIDd ($P = 0.004$), birth BMI with LV mass index ($P = 0.01$), and birth PI with IVSd ($P = 0.02$), LVPWd ($P = 0.03$), and LV mass index ($P = 0.002$) were identified. When LV structure and function parameters were compared across PI tertiles, a significant U-shaped trend for LV mass index ($P_{\text{quadratic}} = 0.04$) was identified.

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Declarations of interest
None.

Conclusions: Our adolescent data suggest that proportionality at birth may identify associations between perinatal growth and cardiac remodeling independent of birthweight alone.

Keywords

Ponderal index; Birth size; Birth weight; Body mass index; Left ventricular hypertrophy; Cardiac development; Heart failure; Intrauterine growth restriction

1. Introduction

A growing body of evidence supports the paradigm that perinatal and early life growth are linked to cardiovascular disease risk later in life. Perturbations in nutrient availability and utilization during critical developmental stages have profound effects on insulin signaling, adipose tissue deposition and growth, and vascular integrity and responsiveness, which result in altered weight gain *in utero*. In particular, the cardiovascular system seems to be disproportionately affected by perinatal growth. More specifically, early studies suggested that all-cause cardiovascular mortality associated inversely with birth weight for both men and women [1,2].

Early development and maturation of the cardiovascular system may contribute to the increased susceptibility of the heart and blood vessels to poor fetal growth. Animal models have demonstrated that cardiac mass is largely determined at birth, and the number of proliferating cardiomyocytes quickly diminishes over the first months postnatally [3,4]. This limited capacity to regenerate new cardiomyocytes forces the heart to enlarge through cardiomyocyte hypertrophy rather than hyperplasia in response to physiologic increases in systemic vascular resistance as infants grow. It was recently shown that poor fetal growth suppresses cardiomyocyte proliferation and promotes early cardiomyocyte apoptosis leading to decreased cardiomyocyte number and cardiomyocyte hypertrophy in adulthood [3]. Similarly, human cohort studies have identified an association of intrauterine growth restriction (IUGR) with cardiac remodeling in childhood [5,6]. Coupled with the loss of cardiomyocyte number associated with aging, perturbations in fetal growth and cardiomyocyte maturation may underscore the strong predisposition to cardiovascular mortality in low birth weight infants.

Interpreting linkage studies between early life growth and late-onset cardiovascular disease is challenging due to the nature of defining fetal and/or neonatal growth. At any given age, a wide variation exists among fetuses and infants in stature, body composition, and the timing and tempo of rate of growth. In this regard, birth weight has long served as a rudimentary end point of perinatal growth and the focus of linkage studies demonstrating the effects of fetal growth on adult-onset diseases. However, birth weight represents a single measurement and does not account for *in utero* growth trajectory. Proportionality indexes that include length, such as body mass index (BMI) or ponderal index (PI), more accurately reflect fetal growth trajectory and differentiate fetuses who are constitutionally small for gestational age from fetuses who fail to reach their *in utero* growth potential [7]. Unfortunately, studies linking proportionality at birth to cardiac structural and functional abnormalities later in life are limited, particularly in adolescents.

The objective of this study was to determine associations between birth weight, birth BMI, and birth PI (birth weight/birth length³) and subclinical parameters of left ventricular (LV) structure and function in a healthy adolescent population living in the southeastern U.S. We hypothesized that proportionality at birth would reveal associations between fetal growth and cardiac structure and function that are not identified by birth weight alone.

2. Methods

2.1. Participants

The participants in this study were 379 adolescents who were recruited from local high schools in the Augusta, Georgia area. Inclusion criteria for the study were white/Caucasian or black/African-American race and age 14–18 years. Adolescents were excluded if they were taking medications or had any medical conditions that could affect growth, maturation, physical activity, nutritional status, or metabolism. Informed consent and assent were obtained from all parents and adolescents, respectively. The Institutional Review Board at Augusta University approved the study.

2.2. Anthropometry, pubertal stage, socioeconomic status, physical activity, and body composition

The original data on birth weight and height were obtained by parental recall, and these measurements were used to calculate BMI (defined as the birth weight (g) divided by birth length (cm) to the second power (g/cm^2) and PI (defined as the birth weight (g) divided by birth length (cm) to the third power (g/cm^3)). Body weight and height during the study visit in adolescence were measured and used to calculate sex- and age-specific body mass index (BMI) percentiles from CDC growth charts for body weight classification: not overweight (< 85th percentile), overweight (85–94.99th percentile), and obese (> 95th percentile) [8]. Pubertal maturation stage (or Tanner stage) was measured with a 5-stage scale, ranging from I (pre-pubertal) to V (fully mature), as described by Tanner [9]. Participants reported their pubertal stage by comparing their own physical development with the 5 stages in standard sets of diagrams. Socioeconomic status was assessed with the Hollingshead 4-factor index of social class, which combines educational attainment and occupational prestige for the number of working parents in the child's family [11]. Scores ranged from 11 to 51, with greater scores indicating greater theoretical socioeconomic status. The mean daily minutes spent in moderate and vigorous physical activity was assessed by the use of MTI Actigraph monitors (model 7164; MTI Health, Fort Walton Beach, Florida), uniaxial accelerometers that measure vertical acceleration and deceleration. Participants wore the monitor for 7 days and returned the monitor 1 week later. Daily movement counts were converted to average minutes per day spent in moderate (3–6 metabolic equivalents) and vigorous (> 6 metabolic equivalents) physical activity by the software accompanying the device.

2.3. Left ventricular structure and function

LV structure and function parameters were assessed by two-dimensionally directed M-mode echocardiography (Hewlett-Packard Sonos 1500, Hewlett-Packard, Andover, MA) by experienced sonographers using a standard institutional protocol in the Georgia Prevention Institute's Echocardiography Laboratory [12]. Measurements of LV structure included the

following variables: LV mass index, relative wall thickness, inter-ventricular septal wall thickness in diastole (SWTd), LV posterior wall thickness in diastole (PWTd), LV internal diameter in diastole (LVIDd), LV internal diameter in systole (LVIDs), end-diastolic volume (EDV), and end-systolic volume (ESV). LV mass index and RWT were our primary outcome variables for LV structure. SWTd, PWTd, LVIDd, and LVIDs were measured by American Society of Echocardiography guidelines [13]. LV mass was calculated by using the following equation [14]: $LV\ mass = 0.08 \times (1.04[(LVIDd + PWTd + SWTd)^3 - (LVIDd)^3] + 0.6\ g$. To minimize the effects of differences in body size of children and adolescents, it is necessary to adjust LV mass relative to body size [15]. Hence, LV mass was indexed to body height raised to the power of 2.7 (LV mass index), as recommended by De Simone and colleagues [16]. LV hypertrophy was defined as LV mass index > 95th percentile for age and gender [17]. Relative wall thickness was calculated using the equation: relative wall thickness = $2 \times PWTd/LVIDd$. The LV volumes, EDV and ESV, were estimated from end-diastolic and end-systolic dimensions, respectively [18].

Measurements of LV systolic function included the following variables: endocardial fractional shortening (EFS), midwall fractional shortening (MFS), and ejection fraction. MFS and ejection fraction were our primary outcome variables for LV function. EFS, defined as $((LVIDd - LVIDs)/LVIDd) \times 100$, was calculated according to Lutas et al. [19]. MFS was calculated using the following equation reported by de Simone and colleagues [20]:

$$\text{Midwall fractional shortening} = \frac{([LVIDd + SWTd/2 + PWTd/2] - [LVIDs + Hs/2])}{(LVIDd + SWTd/2 + PWTd/2) \times 100}.$$

In the equation above, Hs/2 is the LV inner shell myocardial thickness at end systole, taking into account the epicardial migration of midwall during systole in a spherical model.

Ejection fraction was calculated by using the following equation: ejection fraction = $((EDV - ESV)/EDV) \times 100$.

2.4. Statistical analyses

We examined the relationship between birthweight, birth BMI, and birth PI and LV structure and function variables using linear regression. The models were adjusted for age, sex, race, Tanner stage, socioeconomic status, and moderate/vigorous activity. We further examined the ponderal index–cardiac structure and function association by comparing the LV structure and systolic function variables across tertile groups of PI. Ponderal index values reported within each group are medians (range). Group differences for age, Tanner stage, BMI percentile, socioeconomic status and physical activity variables were determined by ANOVA. Descriptive statistics for raw variables are presented as mean $\pm$ SD if not stated otherwise. The proportions of male and female and black and white participants were compared between groups by using χ^2 test goodness of fit. For comparison of the dependent variables, an *F* test was performed to test the assumption of homogeneity of regression slopes for the interactions between the independent variable (*i.e.*, PI tertile groups) and the covariates (age, sex, race, Tanner stage, physical activity, and socioeconomic status). These covariates have been shown to associate with cardiac indices of mass and body composition

[21–23]. Because there were no interactions, linear and nonlinear ANCOVA with polynomial contrast was used to compare the primary dependent variables across PI tertiles after adjusting for covariates. Besides linear trends, this method also examines quadratic (U-shaped) trends [24]. The linear contrast compares the lowest with the highest PI tertile category, and the quadratic compares both middle with the highest and the lowest PI tertile categories together [25]. Adjusted means are reported as mean $\pm$ SD. All the analyses were conducted with SPSS software (version 22.0; IBM), and significance was set at P -value < 0.05 .

3. Results

The sample was composed of 379 adolescents aged 14–18 years (50% female, 36% black). Participant characteristics are described in Table 1. Table 2 reports the association of birth size and left ventricular structure and function parameters using linear regression after adjusting for age, sex, race, Tanner stage, physical activity, and socioeconomic status. There was a significant positive association of birthweight with LVIDd ($P = 0.004$). Birth BMI and birth PI were both positively associated with LV mass index ($P = 0.01$, $P = 0.002$). Additionally, birth PI was positively associated with IVSD ($P = 0.02$) and LVPWd ($P = 0.03$).

Table 3 reports measurements of left ventricular (LV) structure and function parameters across tertiles of PI adjusting for age, sex, race, Tanner stage, physical activity, and socioeconomic status. Results of the polynomial trend analysis revealed a significant U-shaped trend across tertiles of PI for LV mass index ($P_{quadratic} = 0.04$). There were no differences in IVSD, LVIDd, LVIDs, LVPWd, RWT, MFS, or ejection fraction (all P_{linear} and $P_{quadratic} > 0.05$). Participant characteristics by PI tertile are described in Table 3. There was no significant difference between groups in age. However, a polynomial trend analysis showed a significant positive quadratic effect between adolescent BMI percentile and PI ($P = 0.02$). In addition, results of the χ^2 analysis revealed significant differences in sex and racial distributions across tertiles of PI (both $P < 0.01$).

4. Discussion

To the best of our knowledge, this is the first study to link proportionality at birth with cardiac structure and function in a healthy adolescent population. Unique, positive associations between birth BMI and PI and cardiac indices were identified, including strong associations with LV mass, that were not reflected when accounting for birthweight alone. In fact, most relationships between birth size and measured cardiac parameters increased with greater inclusion of proportionality. For example, when evaluating LV mass index, birth weight had the weakest association ($P = 0.11$) and birth PI had the strongest association ($P = 0.002$). In order to understand these relationships in greater detail and examine the impact of proportionality at birth on cardiac structure and function, which may be masked by high birth weight in linear models, LV structure and function parameters across tertiles of birth PI were compared. By segregating subjects into tertiles, a U-shaped relationship between PI and LV mass index in adolescents independent of potential confounding factors such as age, sex, race, Tanner stage, physical activity and socioeconomic status was identified. Thus, both

low and high PI are associated with increased left ventricular mass, an intermediate risk factor for multiple cardiovascular diseases and mortality. These findings suggest that perturbations in fetal growth significantly alter cardiac development and may have a permanent and negative impact on heart function and cardiovascular health in adulthood.

The *in utero* environment is uniquely designed to support fetal growth and organogenesis. Unlike most organs, cardiac development in humans is largely complete at birth with little post-natal cardiomyocyte accumulation, which is thought to be due to a rapid decline in the number of proliferating mononuclear cardiomyocytes after birth [4]. In fact, ^{14}C dating of human cardiomyocytes suggests that < 1% of cardiomyocytes are mononucleated at birth, and this number decreases significantly with age [26]. Therefore, the fetal heart is particularly susceptible to alterations in available nutrients and/or oxygen to support physiologic growth and development, and there is little capacity for repair or “catch-up” growth even if sufficient substrate becomes available. Animal models have largely supported this paradigm. Fetal sheep models of placental insufficiency consistently demonstrate a proportional reduction in cardiac mass in growth restricted lambs; however, these models have suggested that either a primary reduction in mononuclear cardiomyocytes or a failure to undergo maturation to a binucleated cell are likely responsible for the reduction in cardiac mass [27,28]. Similar observations have been made in precocious developers, like guinea pigs, that closely mimic human gestation. Fetal hearts isolated from growth-restricted guinea pigs are proportionately small compared to controls, but exhibit a significant reduction in cardiomyocyte number without alteration in the number of mononuclear cells [3]. However, during the final maturation phases of cardiac development, growth-restricted guinea pig hearts consistently demonstrate a high number of proliferative cardiomyocytes in the fetal and early post-natal phase relative to control hearts, but the total number of cardiomyocytes in growth restricted hearts continues to lag behind controls suggesting that cardiomyocyte expansion is impaired. This lack of postnatal cardiomyocyte expansion and maturation begets a reduction in cardiomyocyte number, with compensatory hypertrophy in adult guinea pig hearts.

Human studies support the early impact of nutrition on the developing heart. Biomarkers of cardiac dysfunction, including troponin and B-type natriuretic peptide, are elevated in the cord blood of growth-restricted neonates with early evidence of systolic dysfunction and a globular appearance to the ventricles noted on echocardiography [29–32]. In the most severe forms of fetal growth restriction, stroke volume is reduced with compensatory increases in heart rate to maintain adequate cardiac output [5]. Cardiac remodeling appears to persist into late childhood with evidence of impaired ventricular relaxation and reduced longitudinal motion noted in children 8–12 years old with a history of fetal growth restriction [6]. More subtle differences may persist into adulthood with slight increases in heart size, primarily restricted to the atria, and modest reductions in stroke volume noted in a recent report from the “Cardiovascular Disease in Young Finns” study [33]. However, most of these epidemiologic studies, including the Young Finns study, rely on birth weight as a solitary indicator of fetal growth and use terminology such as “small for gestational age” SGA to indicate fetal growth restriction. The major limitations of such designations is that 1) SGA reflects a single point in fetal growth and does not reflect trajectory; 2) SGA is variably defined as < 3rd, 5th, or 10th percentile; and 3) fetuses with constitutional growth that

follows these low percentile curves may not carry the same risk profile as fetuses with *in utero* growth failure [34]. For these reasons, emerging interest in proportionality indexes that include length to reflect body composition have shed considerable light on the relationship between *in utero* and postnatal growth and long-term cardiometabolic risks. Recently, Roy et al. demonstrated that BMI > 85th percentile at birth and 2 months yielded a higher positive predictive value for overweight and obese designations at 2 years when compared to weight-for-age or weight-for-length [7]. Similarly, PI at birth more accurately predicted lean body mass, lean-to-fat mass ratio, and visceral fat content than birth weight or length alone in a large study of 6000 male and female adolescents [35].

While cross-sectional and prospective studies have yielded considerable evidence of the relationship between weight-for-age and other indexes at birth and later obesity or metabolic syndrome, the relationship between fetal growth and body composition and later heart disease is not well explored. Here, evidence is provided that low PI is associated with increased LV mass index in health adolescents after correcting for several covariates. LV mass index is strongly and positively associated with hypertension, heart failure, intima-media ratio, renal disease, and metabolic syndrome [36–40]. In this regard, the finding that LV mass indexed to body surface area demonstrates a U-shaped relationship in cohorts allocated by PI at birth may in part underlie the strong association between fetal growth restriction and cardiovascular diseases including hypertension, heart failure, coronary disease, and stroke as well as metabolic syndrome [41–43]. PI increases linearly during the third trimester when fetuses experience substantial mass accumulation, which outpaces gains in length. Large cross-sectional studies have confirmed the direct relationship between PI and gestational age [44,45]. In this study, median PI in the lowest tertile was > 3 standard deviations below the mean PI for male and female neonates at term birth and represents a value below the 3rd percentile for 35–40 weeks gestation [45]. While data was not collected on gestational age, it is reasonable to infer that the lowest tertile in this study represents a population with a high incidence of fetal growth restriction. Further, the U-shaped relationship between PI at birth and BMI percentile in adolescents at study entry supports this hypothesis since fetal growth restriction is associated with increased risk for later obesity.

We acknowledge limitations of this study. As data was not collected on gestational age or perinatal comorbidities, the effect of prematurity and/or perinatal illness cannot be excluded, which may modify the association between PI and LV mass index. Gestational age associates inversely with risk for hypertension in adulthood, and this association is independent of birth weight [46]. Similar risk associations have been noted for insulin resistance and visceral adiposity, but have not been demonstrated for primary heart disease [47]. Thus, while it cannot be excluded that premature infants may be over-represented in the lowest PI tertile, gestational age has not previously been shown to associate with LV dysfunction, cardiac hypertrophy, or adult-onset heart failure. Additionally, birth weight and length were determined by parental recall which may be inaccurate. However, previous studies have shown high reliability of parental recall of birthweight [48,49].

Another important limitation is the over-representation of African American and female adolescents in Tertile 1. Since the late 1990s, the incidence of infants born small for

gestational age is rising and appears to disproportionately affect the offspring of African American mothers. Over 5% of term African American infants have a birth weight below 2500 g compared to just over 2.5% of term Caucasian infants [50]. Additionally, intrauterine growth restriction and prematurity are more common complications of pregnancy in African American women than in Caucasian women [51]. Conversely, 4.3% of African American infants have a birthweight > 4000 g compared to 9.7% of Caucasian infants suggesting that African American infants are over-represented in normal and low birth weight categories in the United States (Martin NVS 2018). These differences in early life body composition coupled with the increased prevalence of obesity in African American adolescents may overestimate the relationship between PI and LV mass index in our cohort despite accounting for race as a co-variable in our analysis [52]. Interestingly, LV mass index is generally lower in females than age-matched males, and this relationship is consistent across age and race [53].

In conclusion, this data suggests that birth size impacts cardiac structure in adolescence and proportionality indexes may provide greater insight than birthweight alone. The current study shows both low and high PI extremes are associated with a subclinical marker of LV hypertrophy. Further research is needed to probe whether these perturbations in fetal growth negatively impact cardiac development in childhood and presumably a greater risk of CVD events in adulthood.

Financial support

Supported by grants from the National Institutes of Health (N.L.W., B.K.S.) American Heart Association (N.K.P., B.K.S.): Department of Defense (B.K.S.) Department of Pediatrics, Augusta University, Augusta, GA, USA (A.A.S., B.K.S.)

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Table 1Descriptive characteristics in 379 adolescents aged 14–18 years.^a

Age (y)	16.0 ± 1.1
Females (%)	49.9
Blacks (%)	35.6
Tanner stage (1–5)	4.5 ± 0.6
BMI percentile	59.8 ± 28.1
BMI percentile category (%)	
Not overweight	77.6
Overweight	10.3
Obese	12.7
Moderate/vigorous PA (min/d)	45.4 ± 31.4
Socioeconomic status	42 ± 12.1

Abbreviations: BMI, body mass index; PA, physical activity.

^aValues are mean ± SD or %.

Table 2

Association between birthweight, BMI, or PI and left ventricular structure and function parameters in 14–18 year old adolescents.^a

<i>n</i> = 379	B	<i>P</i> -value
IVSD (cm)		
BW	0.08	0.09
BMI	0.09	0.07
PI	0.12	0.02
LVIDD (cm)		
BW	0.12	0.004
BMI	0.07	0.18
PI	0.02	0.64
LVIDS (cm)		
BW	0.07	0.16
BMI	0.006	0.92
PI	−0.003	0.96
LVPWD (cm)		
BW	0.08	0.07
BMI	0.10	0.06
PI	0.11	0.03
RWT (cm)		
BW	−0.002	0.96
BMI	0.05	0.43
PI	0.09	0.14
LV mass index (g/m ²)		
BW	0.08	0.11
BMI	0.15	0.01
PI	0.17	0.002
MFS (%)		
BW	0.02	0.64
BMI	0.02	0.71
PI	−0.03	0.68
MFS ratio		
BW	0.02	0.69
BMI	0.02	0.78
PI	−0.04	0.54
Ejection fraction (%)		
BW	0.04	0.48
BMI	0.06	0.33
PI	0.04	0.50

Abbreviations: IVSD, intraventricular septal thickness in diastole; LVIDD, left ventricular internal dimension in diastole; LVIDS, left ventricular internal diameter in systole; LVPWD, left ventricular posterior wall thickness in diastole; RWT, relative wall thickness; MFS, midwall fractional shortening.

^aThe model was adjusted for age, sex, race, Tanner stage, socioeconomic status, and moderate/vigorous activity.

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Table 3

Left ventricular structure and function across tertiles of PI in 14–18 year old adolescents.^{a–d}

	Ponderal index ²			P_{linear}	$P_{\text{quadratic}}$
	Tertile 1 2.0 g/cm ³ (0.8–2.3 g/cm ³)	Tertile 2 2.4 g/cm ³ (2.2–2.6 g/cm ³)	Tertile 3 2.8 g/cm ³ (2.5–4.9 g/cm ³)		
<i>n</i>	123	134	129		
Age (y) ^e	16.1 ± 1.1	15.9 ± 1.2	16.0 ± 1.2	0.21	
Females (%) ^f	60.8	52.3	41.7	<0.01	
Blacks (%) ^f	59.3	44.2	33.2	<0.01	
BMI percentile ^e	62.0 ± 27.5	58.7 ± 28.8	66.9 ± 27.5	0.02	
IVSD (cm)	0.79 (0.77, 0.81)	0.81 (0.79, 0.82)	0.81 (0.79, 0.83)	0.33	0.88
LVIDD (cm)	4.91 (4.84, 4.97)	4.85 (4.79, 4.91)	4.90 (4.84, 4.96)	0.91	0.29
LVIDS (cm)	2.57 (2.50, 2.64)	2.55 (2.49, 2.61)	2.61 (2.55, 2.67)	0.35	0.35
LVPWD (cm)	0.80 (0.78, 0.82)	0.81 (0.79, 0.83)	0.81 (0.79, 0.83)	0.60	0.94
RWT (cm)	0.33 (0.32, 0.34)	0.34 (0.33, 0.34)	0.33 (0.32, 0.34)	0.73	0.39
LV mass index (g/m ²)	32.2 (31.0, 33.4)	31.1 (30.0, 32.3)	33.2 (32.0, 34.4)	0.32	0.04
MFS (%)	24.0 (23.5, 24.5)	23.8 (23.4, 24.2)	23.8 (23.4, 24.3)	0.38	0.60
MFS ratio	132.3 (129.9, 134.7)	131.3 (129.1, 133.6)	131.4 (129.1, 133.7)	0.54	0.61
Ejection fraction (%)	0.78 (0.77, 0.79)	0.78 (0.77, 0.79)	0.78 (0.77, 0.79)	0.28	0.85

Abbreviations: IVSD, intraventricular septal thickness in diastole; LVIDD, left ventricular internal dimension in diastole; LVIDS, left ventricular internal diameter in systole; LVPWD, left ventricular posterior wall thickness in diastole; RWT, relative wall thickness; MFS, midwall fractional shortening; BMI, body mass index.

^aValues are means and 95% CI.

^bValues are median (range) of Ponderal index in a given tertile.

^cAdjustment for age, sex, race, Tanner stage, socioeconomic status, and moderate/vigorous activity.

^d P_{linear} and $P_{\text{quadratic}}$ refer to P -values obtained from the ANCOVA for linear and quadratic terms, respectively.

^e P -values comparing differences between tertile groups of ponderal index were calculated with ANOVA.

^fTest of significance between groups were based on χ^2 test.