Thoracic Aortic Intima-Media Thickness in Preschool Children Born Small for Gestational Age

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Objective To assess thoracic aortic intima-media thickness (aIMT) as a marker of thoracic aortic remodeling in children born small for gestational age (SGA).

Study design We assessed thoracic aIMT, carotid intima-media thickness (cIMT), and pulse wave velocity (PWV) in 239 patients (117 SGA; 122 appropriate for gestational age controls) age 6-8 years. Each SGA participant was matched 1:1 based on sex, gestational age, and birth date. Thoracic aIMT was determined by 2-dimensional transthoracic echocardiography.

Results SGA children showed a significant increase in both aIMT (0.89 mm [0.12] vs 0.79 mm [0.11], $P < .001$) and cIMT (.50 mm [0.05] vs 0.49 mm [0.04], $P < .001$) compared with appropriate for gestational age controls, but the magnitude of the difference in aIMT was greater than that in cIMT (standardized difference of the means: +84% vs +27%). aIMT was linearly correlated with aortic arch PWV as measured by echocardiography ($r = 0.211$, $P < .001$) but not with carotid-femoral PWV ($r = 0.113$, $P = .111$). Born SGA was independently associated with increased aIMT after controlling for perinatal, anthropometric, and biochemical determinants in linear regression models.

Conclusions SGA children exhibit increased thoracic aIMT and aortic arch PWV in early childhood that may suggest the presence of structural changes in the thoracic aorta wall architecture. Measurement of ascending aIMT by transthoracic echocardiography is feasible and reproducible and may be a useful marker of vascular disease. *(J Pediatr 2019;208:81-8)*.

Cardiovascular disease is the leading cause of morbidity and mortality in developed countries.[1] Current recommendations for primary prevention are based on a healthy lifestyle and early management of classical cardiovascular risk factors. After the first observations of Barker,[2] numerous studies have shown an association between unfavorable fetal or early life environment with an increased risk of metabolic disease, chronic kidney disease, and cardiovascular disease later in life. This is described in the concept of Developmental Origins of Health and Disease.[3] The association of unfavorable fetal and perinatal environment, reduced fetal growth rate, and small body size at birth with disease risk later in life may reflect the long-term consequences of fetal adaptive responses.[4] The underlying mechanisms of this programing and their timing have not been completely elucidated. However, epigenetic mechanisms (DNA-methylation, histone acetylation, etc) can be activated by environment cues and subsequently modulate tissue-specific gene expression, resulting in metabolic, hormonal, and vascular structure changes.[3,5]

Experimental animal models have demonstrated aberrant architecture of the thoracic aortic wall in growth-restricted subjects with media thickening (increased collagen accumulation and vascular smooth muscle cell hypertrophy) and stiffening of the aortic wall (reduced relative elastin content).[6,7] These changes are similar to those seen in physiological arteriosclerosis; therefore, early vascular aging (EVA) is now considered to be one of the most important underlying pathways of cardiovascular fetal programing.[8]

AGA	Appropriate for gestational age
aIMT	Aortic IMT
BMI	Body mass index
BSA	Body surface area
cIMT	Carotid IMT
EVA	Early vascular aging
FGR	Fetal growth restriction
ICC	Interclass correlation coefficient
IMT	Intima-media thickness
PWV	Pulse wave velocity
SGA	Small for gestational age

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Arterial intima-media thickness (IMT) is a known marker of subclinical vascular damage in both adults and children. Carotid IMT (cIMT) and aortic IMT (aIMT) have been studied in children to evaluate cardiovascular risk in different clinical situations. Moreover, some neonatal studies have shown increased abdominal aIMT in patients born small for gestational age (SGA) at perinatal stages.[9]

Thoracic aortic intima-media thickening could represent a fetal adaptive process in the media layer that may differ from abdominal aIMT increase, which is regarded as a surrogate marker of arterial atherosclerosis. We hypothesized that children born SGA as consequence of altered fetal environment may have aberrant thoracic aorta wall modifications that are already detectable at 6-8 years old.

Methods

This study included children age 6-8 years between January 2014 and January 2015. All children were born at the same tertiary hospital in northern Spain. Children born SGA, which was defined as a birth weight under the 10th percentile for gestational age, were matched 1 to 1 with healthy controls born with appropriate for gestational age (AGA) weight (birth weight ≥10th to <90th percentile) according to sex, gestational age (±6 days), and birth date (±3 months). Exclusion criteria included twin pregnancy, suspected or confirmed congenital infection, renal or cardiac disease, conditions known to be associated with an increased IMT, any congenital disorder associated with intrauterine or extrauterine growth restriction, and lack of parental informed consent.

Information on demographic characteristics, maternal reproductive history, and obstetric and perinatal data was obtained from the medical records of the children and mothers and by means of an initial interview prior to initiation of the study protocol.

All children underwent a complete physical examination, and anthropometric measures (height, weight, body mass index [BMI], skinfold thickness [tricipital and subscapular]), and body circumferences (arm, hip, and waist) were evaluated. A standard transthoracic echocardiogram and routine blood and urine laboratory tests were performed to evaluate health status and confirm the absence of exclusion criteria. For each neonatal and anthropometric measure, the percentile and/or SD were calculated using local growth charts. Blood pressure was measured 3 times in the right upper arm using a sphygmomanometer with the appropriate cuff size after a 10-minute resting period in the supine position.[10] Office blood pressure status was defined as normal (<90th percentile for sex, age, and height), normal-high (90th-95th percentile for sex, age, and height), and hypertension (>95th percentile for sex, age, and height).[11]

Carotid, thoracic aorta, and pulse wave velocity (PWV) assessments were performed by a pediatric cardiologist who was unaware of the clinical characteristics of the subjects. Vascular ultrasound and echocardiography were performed using a Vivid I ultrasound machine (General Electrics, Haifa, Israel) with simultaneous electrocardiographic recording in a quiet environment and at a stable temperature. Still images and videos were obtained according to a predefined protocol and digitally stored and analyzed offline using EchoPac software (GE Vingmed Ultrasound AS, Horten, Norway). Carotid-femoral PWV was measured using the SphygmoCor device (AtCor Medical, Sydney, Australia).

Carotid arteries were assessed using a 12-MHz linear array probe. Patients were placed in the supine position with the neck extended and rotated 45°. Three measurements of artery diameters at end-systole and end-diastole were obtained from a transverse view of the carotid artery using M mode. cIMT was measured in a longitudinal view according to previously published recommendations.[12] Briefly, 3 segments of each carotid artery were imaged: the internal carotid artery at 10 mm from the carotid bifurcation, at the carotid bulb, and the common carotid at 10 mm from the carotid bifurcation. Images were captured when near and far wall margins were clearly seen to ensure perpendicular insonation of the vessel wall. Three end-diastolic frames were selected and analyzed for mean and maximum cIMT using an automatic tracing software. Measurements from each segment of both carotid arteries were pooled and averaged.

Aortic diameters were measured at systole and end-diastole using M mode at 2 cm from the aortic valve in a long parasternal view with a 3- to 6-MHz phased array probe. aIMT was measured at the same point in B mode with a standard magnification (2 × 2 cm) using an 8-MHz microconvex probe. Three measurements of maximum and mean aIMT were obtained at the far wall of the aorta at end-diastole using the same approach and software as for the cIMT measurement (**Figure 1**; available at www.jpeds.com).

Carotid-femoral PWV was measured using the validated SphygmoCor device (AtCor Medical, Sydney, Australia) according to current recommendations.[12] Three measurements were obtained from each subject and averaged.

Aortic arch PWV was measured using a Doppler method previously described.[13,14] Briefly, the aortic arch length from the aortic annulus to the isthmus was measured in a long-axis view of the aorta from the suprasternal notch. Time from the electric systole (as assessed by the onset of QRS in a simultaneous electrocardiogram tracing) to the beginning of the aortic systolic Doppler flow signal (mechanical systole) was measured both at the aortic annulus and at the isthmus. The pulse wave transit time of the Doppler flow signal from the aortic valve to the isthmus was calculated. Then, the aortic arch length was divided by the pulse wave transit time to obtain aortic arch PWV. Three measurements were averaged in each subject.

Data are expressed as the mean (SD) and number (percentage). Comparisons between study groups were performed using the Student *t* test for independent samples or Mann-Whitney U and χ^2 tests where appropriate. Based on previous studies measuring abdominal aIMT in neonates[15,16] and an exploratory pediatric study of thoracic aortic aIMT by our group (unpublished data), the sample size was calculated

to allow observation of a difference of 0.05 mm in maximum aIMT between the study groups. Conservatively, a SD of 0.11 (at the top range of published data), was chosen for the calculation. With a power of 0.9 and α risk of 0.05, a minimum of 102 subjects per study group would be required. We estimated a minimum of 246 subjects in anticipation of a 20% rate of potential losses and missing data. In addition, our estimated sample size provided a statistical power >0.8 in the planned subgroup analyses.

cIMT and aIMT measurements were indexed by body surface area (BSA), BMI, and vessel (carotid and aortic) diameter to account for differences in body size. Standardized differences in vascular measurements between SGA and AGA children were calculated as the difference in means divided by the pooled SD. This method allowed an assessment of the magnitude of the differences between cIMT and aIMT. The linear correlation of carotid-femoral and aortic arch PWV with IMT was evaluated by Pearson correlation coefficients. Carotid-femoral and aortic arch PWVs were compared between children in the first and fourth quartiles of the whole-cohort IMT distribution. The distribution of aIMT (indexed by BSA) according to birth weight z score sextiles was assessed by box plots and the Jonckheere trend test. Several multivariate linear regression models were used to assess whether the study group (SGA vs AGA) was independently associated with the maximum aIMT. The covariates for linear regression were selected according to a review of relevant literature and were grouped in 4 different models. An additional fifth model was fitted including all covariates in our sample that had a P value less than 0.2 in the univariate analysis.

Intraobserver variability was determined for maximum and mean aIMT by intraclass correlation coefficients (ICCs) from 3 measurements from 50 randomly selected subjects. Interobserver variability was determined by ICC and Bland-Altman plots from the average value of 3 maximum and mean aIMT measurements performed by 2 independent raters in 30 randomly selected subjects.

All tests were 2-sided, and a P value of $< .05$ was considered statistically significant. SPSS v 22 (SPSS Inc, Chicago, Illinois) was used for the analysis.

Written informed consent was obtained from parents or legal guardians. All procedures were performed in accordance with the guidelines of the Helsinki Declaration on Human Experimentation. The study protocol was approved by the Institutional Review Board.

Results

Of the 250 previously recruited children, 239 (117 SGA cases and 122 AGA controls) were included in the study. Eleven children were excluded for several reasons: twin gestation (n = 4), cardiac disease (n = 4), nephrologic disease (n = 1), spastic tetraparesis causing postnatal growth restriction (n = 1), and lack of prenatal information (n = 1). None of the children in the study had past history of diabetes, hypercholesterolemia, or other conditions associated with a higher risk of increased aIMT.

The clinical characteristics of the study groups are summarized in **Table I**. Mothers of children born SGA were shorter, had less gestational weight gain, and were more frequently smokers and nulliparous than mothers of children born AGA. There was a slight difference in maternal academic status, with a greater number of mothers with university degrees in the AGA group.

At the time of the study, children born AGA continued to be larger (weight, height, and BSA) than children born SGA, but there were no statistically significant differences in anthropometric measurements indicating body fatness (BMI, triceps fold thickness, and hip/waist ratio). Unadjusted systolic, diastolic, and pulse pressure was not different between groups. After adjustments based on height, children born SGA had higher systolic blood pressure than children born AGA (103.3 vs 100.8 mm Hg; mean difference of 2.49 mm Hg; 95% CI 0.21-4.76). No differences were found between study groups in blood and urine biochemical parameters.

The carotid and aortic diameters and IMT measurements are presented in **Table II**. Both the aortic and carotid diameters were significantly smaller in the SGA group, indicating smaller vessels, than in the AGA group.

The maximum and mean aIMT was significantly greater in the SGA group than in the AGA group, including both the absolute values (maximum aIMT: 0.89 [0.12] mm vs 0.79 [0.11] mm [$P < .001$]; mean aIMT: 0.81 [0.12] mm vs 0.71 [0.10] mm [$P < .001$]) and values indexed to vessel diameter, BSA, and BMI. Unlike aortic measurements, the maximum cIMT (0.50 [0.05] mm vs 0.49 [0.04] mm [$P = .033$]) but not the mean cIMT (0.43 [0.03] mm vs 0.42 [0.04] mm [$P = .159$]) was greater in the SGA group than in the AGA group. Nevertheless, both measurements achieved statistically significant differences after indexation by vessel diameter and body size. The magnitude of differences, as assessed by standardized differences of the means, in aIMT measurements (range: +77% to +104%) was greater than that in cIMT measurements (range: +19% to +65%).

By analyzing the distribution of aIMT in the whole cohort, we observed that children born SGA were overrepresented in the highest percentiles (90-95th percentile and >95th percentile), whereas most children with an aIMT below the 50th percentile of the cohort were born AGA (**Figure 2**). In addition, we assessed the relationship between aIMT indexed by BSA and birth weight z scores grouped in sextiles. We observed an inverse linear trend with the highest aIMT values in children with the lowest birth weights (Jonckheere trend test $P < .001$) (**Figure 3**). Both the carotid-femoral and aortic arch PWVs were significantly higher in the SGA group than in the AGA group, but the magnitude of the difference in aortic arch pulse wave velocity (standardized difference of the means + 131% vs +46%) was greater than that in the carotid-femoral PWV. There was a linear correlation between aIMT and aortic arch PWV (maximum aIMT,

Table I. Clinical characteristics of SGA and AGA groups

Children characteristics	SGA	AGA	P
Sex (male)	57/117 (48.7%)	60/122 (49.2%)	.943
Age (y)	7.07 (0.82)	7.15 (0.81)	.478
Weight (kg)	24.11 (5)	26.67 (5.1)	<.001
Weight (z)	0.06 (0.8)	0.54 (0.83)	<.001
Height (cm)	120 (7.6)	124.4 (7.1)	<.001
Height (z)	−0.12 (0.79)	0.46 (0.76)	<.001
BMI (kg/m^2)	16.58 (2.1)	17.1 (2.2)	.066
BMI (z)	0.09 (0.87)	0.30 (0.91)	.070
Overweight (BMI >85th percentile)	14 (12%)	25 (20.5%)	.075
BSA (m^2)	0.89 (0.11)	0.95 (0.11)	<.001
Tricipital fold (cm)	10.7 (3.5)	11.4 (3.7)	.163
Tricipital fold (z)	−0.01 (1.05)	0.17 (1.11)	.173
Waist (cm)	56.5 (5.0)	58.5 (4.9)	.002
Waist (z)	0.12 (0.95)	0.51 (0.88)	.002
Hip (cm)	62.3 (5.7)	64.5 (5.9)	.004
Hip (z)	−0.26 (1.02)	0.1 (0.96)	.005
Waist/hip ratio	0.90 (0.04)	0.90 (0.04)	.877
Office BP status			
Office SBP (mm Hg)	102.9 (8.6)	101.1 (8.2)	.098
Office DBP (mm Hg)	61.9 (6.2)	60.8 (6.6)	.204
Office PP (mm Hg)	40.9 (7.1)	40.2 (7.5)	.485
Heart rate (bpm)	85.3 (10.7)	84 (11)	.379
Normal BP (<90th percentile)	85 (72.6%)	99 (81.1%)	
Normal-high BP (90-95th percentile)	17 (14.5%)	13 (10.7%)	.287
High BP (>95th percentile)	15 (12.8%)	10 (8.2%)	
Blood and urine analysis			
Glucose (mg/dL)	84.9 (6)	83.7 (6)	.168
Insulin (μU/mL)	7.1 (3.5)	7.3 (4.1)	.698
HOMA	1.49 (0.81)	1.51 (0.9)	.871
HbA1c (%)	5.42 (0.29)	5.44 (0.27)	.725
Uric acid (mg/dL)	3.82 (0.75)	3.66 (0.74)	.144
Cholesterol (mg/dL)	165.7 (26.1)	169.1 (27.3)	.381
Triglycerides (mg/dL)	52 (19.3)	54.4 (19)	.384
LDL-cholesterol (mg/dL)	89.8 (25.7)	90.8 (24.9)	.783
HDL-cholesterol (mg/dL)	64.5 (14.4)	67.5 (13.1)	.183
Ferritin (ng/mL)	45.2 (22.5)	43.9 (20)	.690
Urine albumin/creatinine (mg/g)	8.7 (7.4)	10 (20.1)	.541
Maternal characteristics	**SGA (n = 117)**	**AGA (n = 122)**	**P**
Maternal age (y)	32.47 (4.7)	32.48 (4.6)	.993
Maternal height (cm)	161.13 (5.8)	163.3 (6)	.005
Pregestation weight (kg)	59.58 (10.6)	61.59 (13.1)	.221
Gestational weight gain (kg)	10.45 (4.9)	12.09 (4.8)	.010
Maternal ethnicity (non-Caucasian)	6/116 (5.2%)	4/122 (3.3%)	.475
Maternal smoking	37/113 (32,7%)	22/122 (18%)	.013
Number of cigarettes per d	8.5 (7)	5.3 (4)	.066
Maternal academic degree (University)	41/117 (35%)	60/122 (49.2%)	.027
Maternal number of siblings	2 (0.8)	2.3 (0.8)	.020
Nulliparous	74/117 (63.2%)	48/122 (39.3%)	<.001
Newborn characteristics	**SGA**	**AGA**	**P**
Gestational age (wk)	38.39 (1.6)	38.34 (1.6)	.799
Birth weight (g)	2389 (298)	3356 (391)	<.001
Birth weight (z)	−1.8 (0.51)	0.73 (0.77)	<.001
Birth length (cm)	46.76 (2.2)	50.03 (2.0)	<.001
Birth length (z)	−1.34 (0.95)	0.57 (1.05)	<.001
Head perimeter	32.82 (1.5)	34.96 (1.7)	<.001
Head perimeter (z)	−1.38 (1.2)	0.81 (1.5)	<.001

BP, blood pressure; *DBP*, diastolic blood pressure; *HbA1c*, hemoglobin A1c; *HDL*, high-density lipoprotein; *HOMA*, homeostatic model assessment; *LDL*, low-density; *PP*, pulse pressure; *SBP*, systolic blood pressure.

r = 0.211, $P < .001$; mean aIMT: r = 0.226, $P < .001$) but not between aIMT and carotid-femoral PWV (maximum aIMT r = 0.113, $P = .111$; mean aIMT r = 0.124, $P = .056$). Neither the maximum nor mean cIMT was linearly correlated with PWV. Children with a maximum aIMT above the 75th percentile of the cohort had higher aortic arch PWV than children with a maximum aIMT below the 25th percentile (4.4 [1.14] vs 3.7 [1.01] m/second, $P = .001$). This difference was not observed for the carotid-femoral PWV (3.9 [0.35] vs 3.8 [0.4] m/second, $P = .395$).

Finally, being born SGA (vs AGA) was independently associated with increased aIMT based on the multivariate linear

Table II. Vascular assessment

	SGA (n = 117)	AGA (n = 122)	Difference in means (95% CI)	*P*	St. diff. (%)
PWVs					
Carotid-femoral PWV (m/s)	3.97 (0.42)	3.78 (0.40)	0.19 (0.09, 0.3)	<.001	+46%
Aortic arch PWV (m/s)	4.8 (1.08)	3.49 (0.98)	1.31 (1.05, 1.5)	<.001	+131%
Aortic measurements					
Aortic diameter, mm (systole)	18.93 (1.8)	20.2 (1.7)	−1.28 (−1.74,−0.83)	<.001	−72%
Aortic diameter, mm (diastole)	16.6 (1.6)	17.3 (1.5)	−0.74 (−1.14, −0.34)	<.001	−46%
aIMT max, mm	0.89 (0.12)	0.79 (0.11)	0.1 (0.07, 0.12)	<.001	+84%
aIMT max/aortic diast. Diameter	0.054 (0.00)	0.046 (0.00)	0.008 (0.006, 0.01)	<.001	+93%
aIMT max/BSA, mm/m^2	1.01 (0.18)	0.84 (0.15)	0.17 (0.13, 0.22)	<.001	+101%
aIMT max/BMI	0.054 (0.00)	0.047 (0.00)	0.008 (0.005, 0.01)	<.001	+77%
aIMT mean	0.81 (0.12)	0.71 (0.10)	0.09 (0.07, 0.12)	<.001	+81%
aIMT mean/aortic diast. Diameter	0.049 (0.00)	0.041 (0.00)	0.007 (0.005, 0.01)	<.001	+94%
aIMT mean/BSA, mm/m^2	0.92 (0.17)	0.75 (0.13)	0.16 (0.12, 0.20)	<.001	+104%
aIMT mean/BMI	0.049 (0.01)	0.042 (0.00)	0.007 (0.006, 0.01)	<.001	+79%
Carotid measurements					
Carotid diameter, mm (systole)	6.72 (0.58)	6.97 (0.87)	−0.25 (−0.44, −0.06)	.010	−51%
Carotid diameter, mm (diastole)	5.69 (0.55)	5.92 (0.80)	−0.22 (−0.4, −0.05)	.012	−48%
cIMT max, mm	0.50 (0.05)	0.49 (0.04)	0.013 (0.001, 0.026)	.033	+27%
cIMT max/carotid diast. diameter	0.090 (0.01)	0.0836 (0.01)	0.006 (0.003, 0.009)	<.001	+57%
cIMT max/BSA, mm/m^2	0.57 (0.09)	0.53 (0.07)	0.054 (0.033, 0.076)	<.001	+65%
cIMT max/BMI	0.031 (0.00)	0.029 (0.00)	0.002 (0.0006, 0.003)	.004	+38%
cIMT mean, mm	0.43 (0.03)	0.42 (0.04)	0.007 (−0.003, 0.017)	.159	+19%
cIMT mean/carotid diast. Diameter	0.076 (0.00)	0.072 (0.00)	0.005 (0.002, 0.007)	<.001	+52%
cIMT mean/BSA, mm/m^2	0.49 (0.07)	0.45 (0.06)	0.041 (0.025, 0.06)	<.001	+63%
cIMT mean/BMI	0.026 (0.00)	0.025 (0.00)	0.001 (0.0003, 0.002)	.011	+33%

St. diff., standardized differences of the means.

regression analysis, with consistent results across the different models accounting for perinatal, anthropometric, and blood and urine laboratory test determinants (**Table III**; available at www.jpeds.com).

Measurement of aIMT at the ascending thoracic aorta with transthoracic echocardiography showed very good to excellent intra- and interobserver agreement. In the intraobserver analysis, the ICC was 0.918 (95% CI 0.869-0.951) for the maximum aIMT and 0.921 (95% CI 0.873-0.952) for the mean aIMT. In the interobserver analysis, the ICC between the 2 observers was 0.894 (95% CI 0.778-0.950) for the maximum aIMT and 0.945 (95% CI 0.885-0.974) for the mean aIMT. Bland-Altman plots showed that the disparity between observers was consistent across the range of measurements (**Figure 4**; available at www.jpeds.com).

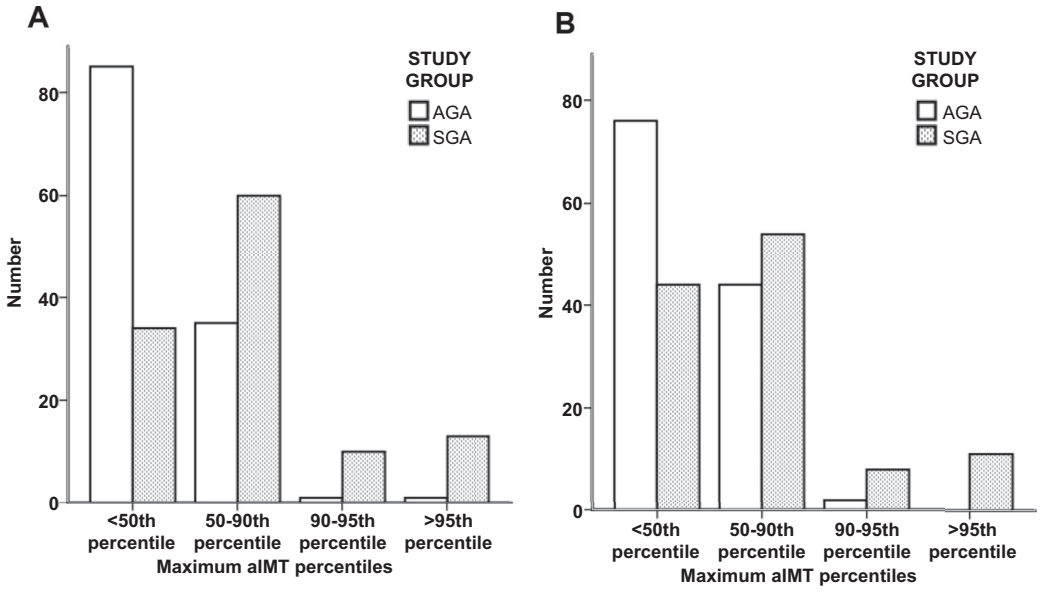

Figure 2. Number of AGA vs SGA subjects according to aIMT percentile. **A,** maximum aIMT sample. **B,** mean aIMT sample.

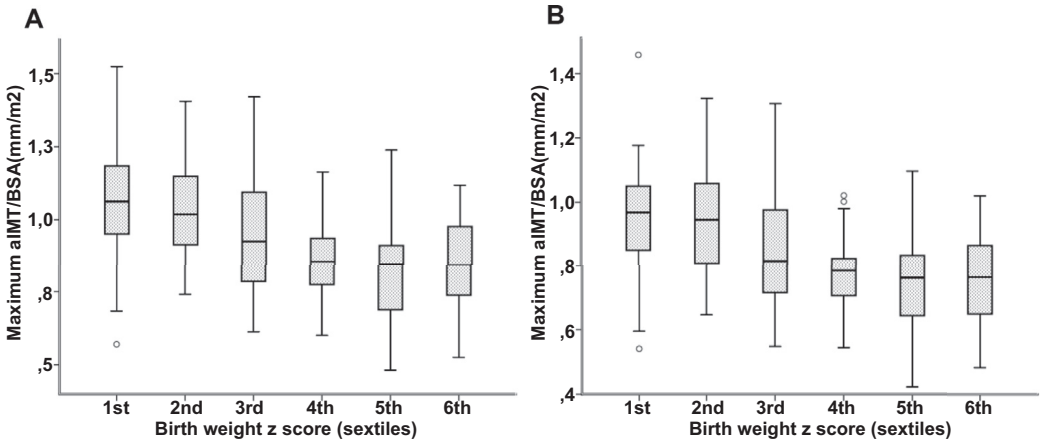

Figure 3. Values of aIMT indexed by BSA for each sextile of the birth weight z score. **A,** maximum aIMT measurements. **B,** mean aIMT measurements.

Discussion

In the last 2 decades, some studies have presented the EVA syndrome as one of the pathologic pathways linking impaired fetal growth with adult cardiovascular disease.[8] Several animal models have shown aberrant remodeling of the thoracic aortic wall in fetuses under nutritional restriction.[6,7] In our study, we evaluated the ascending thoracic aIMT in SGA and AGA children age 6-8 years. We showed increased thoracic aortic intima-media wall thickness in children born SGA that was not explained by differences in body size.

Previous pediatric studies have demonstrated an association between aIMT and known risk factors of atherosclerosis, such as type 1 diabetes,[17] hypercholesterolemia,[18,19] obesity,[20] and smoking exposure.[21] Chronic diseases with increased risk of cardiovascular disease have also been studied, and greater aIMT has been observed in children with inflammatory bowel disease[22] and chronic rheumatic diseases[23] and children born preterm.[24,25]

Neonatal studies have assessed aIMT in fetal growth restriction (FGR) or SGA patients, showing increased aIMT compared with healthy newborns.[9,15,16,26,27] However, Gomez-Roig et al showed increased aIMT in neonates with demonstrated FGR by fetal Doppler ultrasound but not in neonates born SGA.[28]

Several other studies have evaluated aIMT in children born SGA after the neonatal period. Trevisanuto et al investigated aIMT in preschoolers born SGA, and no statistically significant differences were observed.[29] This discrepancy with our study findings may be explained by the small sample size and lack of statistical power in the aforementioned study. In addition, the authors measured aIMT at the abdominal aorta, which makes the comparison with our study results difficult. Cosmi et al[30] showed increased mean abdominal aIMT in 18-month-old children with FGR, and recently, Cruz-Lemini et al noted persistent cardiovascular remodeling, including increased mean and maximum aIMT, in a prospective cohort study of SGA children at 6 months of life.[31] Last, the sequence of prenatal growth restraint followed by postnatal catch-up was also shown to be associated with greater abdominal aIMT in SGA children age 3-6 years.[32]

Previous studies have suggested that aIMT may be a more discriminating measure of cardiovascular risk than cIMT in childhood.[15,16] In our study, children born SGA had increased IMT both at the carotid artery and thoracic aorta. By using standardized differences of the means, we were able to assess the magnitude of these differences. We found that intima-media thickening was greater at the thoracic aorta than at the carotid artery. This may indicate that aIMT can be an earlier marker of vascular disease in children born SGA.

In all previous studies, aIMT was assessed in the distal abdominal aorta (far wall), as autopsy studies have found that this area is most likely to contain early atherosclerotic lesions (fatty streaks) in subjects younger than 20 years old and that these lesions progress most rapidly to raised lesions.[33] Nevertheless, we decided to assess the thoracic aorta for different reasons. EVA syndrome has been postulated as an important underlying mechanism of cardiovascular fetal programing,[8] and vascular aging is known to exhibit a heterogeneous distribution among central and peripheral arteries.[34] Ascending aorta stiffening represents one of the major determinants of both central blood pressure and left ventricular load. Aberrant remodeling of the thoracic aortic wall has been shown in FGR animal models.[6,7] Furthermore, in adults, thoracic aIMT measurements by transesophageal echocardiography have been widely used to assess the risk of coronary artery disease.[35] Moreover, assessment of thoracic aIMT has several advantages supporting its clinical implementation. In addition to having fewer technical requirements (standard echocardiography), assessment of thoracic aIMT does not possess the limitations (adiposity and fasting time) described for the assessment of abdominal aIMT. Our results demonstrate that assessment of thoracic

aIMT in children age 6-8 years who were born SGA or AGA is feasible. The intraobserver and interobserver variability demonstrates the adequate reproducibility of aIMT measurements at this localization.

Whether the increase in thoracic aIMT represents intima thickening (atherosclerosis), media thickening (vascular hypertrophy/arteriosclerosis), or both remains unknown. Our study shows significant differences in aIMT between SGA and AGA children, but we failed to find any significant associations between aIMT and body fatness, metabolic biomarkers, or blood pressure, all of which are classic determinants of cIMT and abdominal aIMT in adolescents and adults. This may suggest that the observed thoracic aorta thickening is an expression of programed vascular remodeling that tracks into childhood rather than a biomarker of early atherosclerotic changes. Recent experimental evidence has shown increased aortic stiffness in offspring and adults born after chronic placental insufficiency as a consequence of altered media layer composition, which likely originated in utero. Only the most severely hypoxic fetuses show markedly increased intima thickness compared with controls.[7] In our study, carotid-femoral PWV, an indicator of global arterial stiffness, was slightly higher in SGA than in AGA children. However, this measurement did not correlate with aIMT. Conversely, we showed greater differences in the aortic arch PWV, which was positively correlated with aIMT. This suggests that the increase in thoracic aIMT may be related to altered media layer composition rather than intima thickening. The association between increased ascending aIMT with decreased ascending aorta elasticity in children born SGA may help explain the well-known association between low birth weight and arterial hypertension.[36] Whether thoracic aIMT can be used as a biomarker for risk stratification among children born SGA needs to be further investigated in large prospective studies. Future investigations should also evaluate whether the increased aIMT observed in our study cohort persists into adulthood.

Several limitations of our study were identified. The presence of preterm children within the cohort, albeit at a low percentage, may negatively influence the generalizability of our results. On the other hand, the lack of obstetric information makes it impossible to determine how many SGA children were affected by FGR, as determined by fetal vascular Doppler examination. Comparison with other studies is further limited by the methods and lack of normative aIMT data. Use of automated analysis software may reduce some of these measurement discrepancies in the reports.

Our study showed increased thoracic aIMT in preschool children born SGA. The assessment of thoracic aIMT by transthoracic echocardiography is accurate and reproducible, which may facilitate its implementation in clinical practice. Therefore, thoracic aIMT may be a promising marker of aortic remodeling and arterial stiffness in children born SGA. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

References

1. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med 2005;352:1685-95.
2. Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ. Weight in infancy and death from ischaemic heart disease. Lancet 1989;2:577-80.
3. Wadhwa PD, Buss C, Entringer S, Swanson JM. Developmental origins of health and disease: brief history of the approach and current focus on epigenetic mechanisms. Semin Reprod Med 2009;27:358-68.
4. Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. N Engl J Med 2008;359:61-73.
5. Alexander BT, Dasinger JH, Intapad S. Fetal programming and cardiovascular pathology. Compr Physiol 2015;5:997-1025.
6. Thompson JA, Gros R, Richardson BS, Piorkowska K, Regnault TRH. Central stiffening in adulthood linked to aberrant aortic remodeling under suboptimal intrauterine conditions. AJP Regul Integr Comp Physiol 2011;301:R1731-7.
7. Thompson JA, Richardson BS, Gagnon R, Regnault TRH. Chronic intrauterine hypoxia interferes with aortic development in the late gestation ovine fetus: Aortic development in the hypoxic ovine fetus. J Physiol 2011;589:3319-32.
8. Nilsson PM, Lurbe E, Lauren S. The early life origins of vascular ageing and cardiovascular risk: the EVA syndrome. J Hypertens 2008;26:1049-57.
9. Stergiotou I, Crispi F, Valenzuela Alcaraz B, Cruz Lemini M, Bijnens B, Gratacos E. Aortic and carotid intima-media thickness in term small-for-gestational-age newborns and relationship with prenatal signs of severity. Ultrasound Obstet Gynecol 2014;43:625-31.
10. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. 2007 guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiolgy (ESC). J Hypertens 2007;25:1105-87.
11. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 2004;114(2 Suppl 4th Report):555-76.
12. Urbina EM, Williams RV, Alpert BS, Collins RT, Daniels SR, Hayman L, et al. Noninvasive assessment of subclinical atherosclerosis in children and adolescents: recommendations for standard assessment for clinical research: a scientific statement from the American Heart Association. Hypertension 2009;54:919-50.
13. Sandor GG, Hishitani T, Petty RE, Potts MT, Desouza A, Desouza E, et al. A novel Doppler echocardiographic method of measuring the biophysical properties of the aorta in pediatric patients. J Am Soc Echocardiogr 2003;16:745-50.
14. Styczynski G, Rdzanek A, Pietrasik A, Kochman J, Huczek Z, Sobieraj P, et al. Echocardiographic assessment of aortic pulse-wave velocity: validation against invasive pressure measurements. J Am Soc Echocardiogr 2016;29:1109-16.
15. Skilton MR, Evans N, Griffiths KA, Harmer JA, Celermajer DS. Aortic wall thickness in newborns with intrauterine growth restriction. The Lancet 2005;365:1484-6.

16. Sehgal A, Doctor T, Menahem S. Cardiac function and arterial biophysical properties in small for gestational age infants: postnatal manifestations of fetal programming. J Pediatr 2013;163:1296-300.
17. Harrington J, Peña AS, Gent R, Hirte C, Couper J. Aortic intima media thickness is an early marker of atherosclerosis in children with type 1 diabetes mellitus. J Pediatr 2010;156:237-41.
18. Dawson JD, Sonka M, Blecha MB, Lin W, Davis PH. Risk factors associated with aortic and carotid intimal-medial thickness in adolescents and young adults: the Muscatine Offspring Study. J Am Coll Cardiol 2009;53:2273-9.
19. Järvisalo MJ, Jartti L, Näntö-Salonen K, Irjala K, Rönnemaa T, Hartiala JJ, et al. Increased aortic intima-media thickness. Circulation 2001;104:2943-7.
20. Yücel O, Cevik H, Kinik ST, Tokel K, Aka S, Dinc F. Abdominal aorta intima media thickness in obese children. J Pediatr Endocrinol Metab 2013;26:735-41.
21. Kallio K, Jokinen E, Saarinen M, Hämäläinen M, Volanen I, Kaitosaari T, et al. Arterial intima-media thickness, endothelial function, and apolipoproteins in adolescents frequently exposed to tobacco smoke. Circ Cardiovasc Qual Outcomes 2010;3:196-203.
22. Aloi M, Tromba L, Rizzo V, D'Arcangelo G, Dilillo A, Blasi S, et al. Aortic intima-media thickness as an early marker of atherosclerosis in children with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2015;61:41-6.
23. Del Giudice E, Dilillo A, Tromba L, La Torre G, Blasi S, Conti F, et al. Aortic, carotid intima-media thickness and flow-mediated dilation as markers of early atherosclerosis in a cohort of pediatric patients with rheumatic diseases. Clin Rheumatol 2018;37:1675-82.
24. Shimizu T, Fujii T, Iwasaki J, Nakano Y, Sakurai M, Miura F, et al. Abdominal aortic intima-media thickness in preschool children born preterm. Pediatr Cardiol 2014;35:121-5.
25. Schubert U, Müller M, Abdul-Khaliq H, Norman M, Bonamy A-KE. Relative intima-media thickening after preterm birth. Acta Paediatr 2013;102:965-9.
26. Akazawa Y, Hachiya A, Yamazaki S, Kawasaki Y, Nakamura C, Tekeuchi Y, et al. Cardiovascular remodeling and dysfunction across a range of growth restriction severity in small for gestational age infants—implications for fetal programming. Circ J 2016;80:2212-20.
27. Miyamoto K, Tsuboi T, Suzumura H, Arisaka O. Relationship between aortic intima-media thickening, serum IGF-I and low-density lipoprotein particle diameter in newborns with intrauterine growth restriction. Clin Pediatr Endocrinol 2009;18:55-64.
28. Gomez-Roig MD, Mazarico E, Valladares E, Guirado L, Fernandez-Arias M, Vela A. Aortic intima-media thickness and aortic diameter in small for gestational age and growth restricted fetuses. PLoS One 2015;10:e0126842.
29. Trevisanuto D, Avezzù F, Cavallin F, Doglioni N, Marzolo M, Verlato F, Zanardo V. Arterial wall thickness and blood pressure in children who were born small for gestational age: correlation with umbilical cord high-sensitivity C-reactive protein. Arch Dis Child 2010;95:31-4.
30. Cosmi E, Visentin S, Fanelli T, Mautone AJ, Zanardo V. Aortic intima media thickness in fetuses and children with intrauterine growth restriction. Obstet Gynecol 2009;114:1109-14.
31. Cruz-Lemini M, Crispi F, Valenzuela-Alcaraz B, Figueras F, Sitges M, Bijnens B, et al. Fetal cardiovascular remodeling persists at 6 months in infants with intrauterine growth restriction. Ultrasound Obstet Gynecol 2016;48:349-56.
32. Sebastiani G, Díaz M, Bassols J, Aragonés G, López-Bermejo A, De Zegher F, et al. The sequence of prenatal growth restraint and post-natal catch-up growth leads to a thicker intima-media and more pre-peritoneal and hepatic fat by age 3-6 years. Pediatr Obes 2016;11:251-7.
33. McGill HC, McMahan CA, Herderick EE, Malcom GT, Tracy RE, Strong JP. Origin of atherosclerosis in childhood and adolescence. Am J Clin Nutr 2000;72:1307s-15s.
34. Van der Heijden-Spek JJ, Staessen JA, Fagard RH, Hoeks AP, Boudier HA, Van Bortel LM. Effect of age on brachial artery wall properties differs from the aorta and is gender dependent: a population study. Hypertension 2000;35:637-42.
35. Rohani M, Jogestrand T, Ekberg M, van der Linden J, Källner G, Jussila R, et al. Interrelation between the extent of atherosclerosis in the thoracic aorta, carotid intima-media thickness and the extent of coronary artery disease. Atherosclerosis 2005;179:311-6.
36. Law CM, Shiell AW, Newsome CA, Syddall HE, Shinebourne EA, Fayers PM, et al. Fetal, infant, and childhood grown and adult blood pressure: a longitudinal study from birth to 22 years of age. Circulation 2002;105:1088-92.

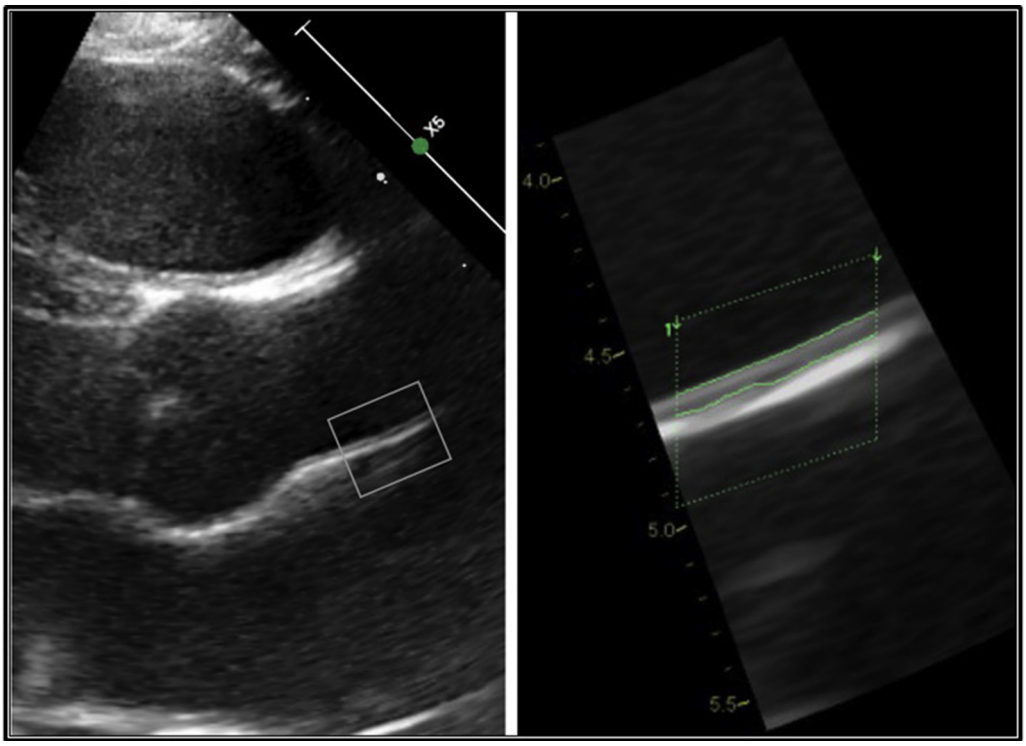

Figure 1. aIMT measurement.

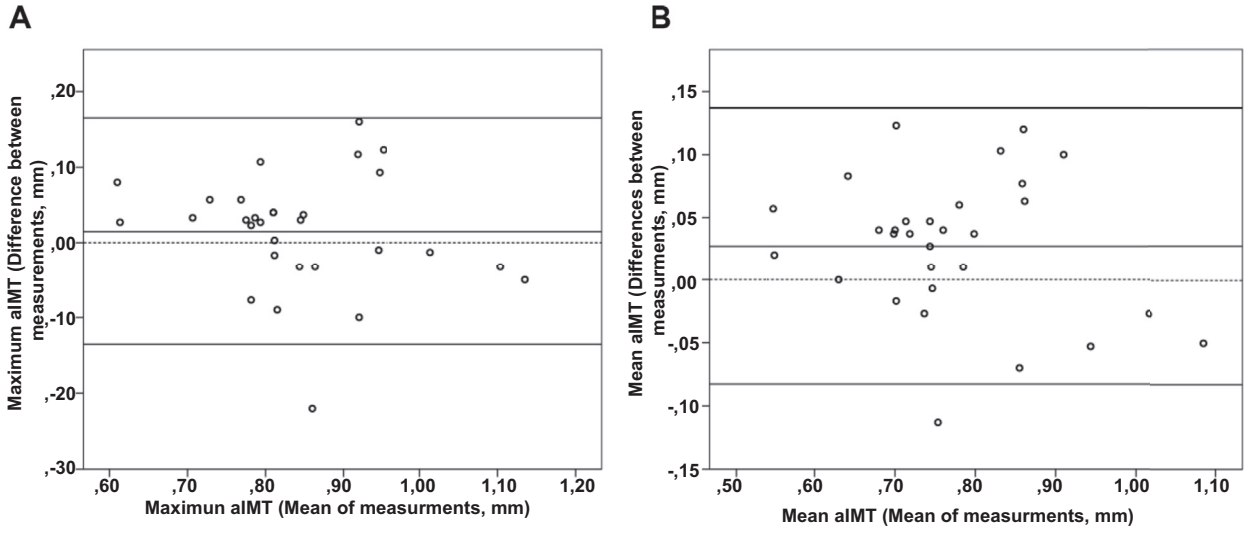

Figure 4. Bland-Altman plots. **A,** maximum aIMT measurements. **B,** mean aIMT measurements.

Table III. Association between SGA (vs AGA) children and aIMT by multivariate linear regression analysis

	Multivariate	
	B Coefficient (95% CI)	*P* value
Model 1		
SGA (vs AGA)	0.100 (0.071, 0.129)	<.001
Sex (male)	0.057 (0.027, 0.086)	<.001
Age (y)	0.08 (−0.10, 0.026)	.403
Model 2 (perinatal determinants)		
SGA (vs AGA)	0.105 (0.072, 0.138)	<.001
Sex (male)	0.063 (0.033, 0.092)	<.001
Age (y)	0.009 (−0.009, 0.028)	.318
Preterm	−0.019 (−0.064, 0.25)	.392
Breast feeding	0.003 (−0.003, 0.009)	.299.
Maternal age	0.004 (0, 0.007)	.027
Maternal height	0.003 (0, 0.005)	.042
Gestational weight gain	0.002 (−0.001, 0.004)	.067
Maternal university studies	−0.031 (−0.062, −0.01)	.046
Smoking	0.023 (−0.14, 0.061)	.224
Nulliparity	0 (−0.032, 0.033)	.983
Model 3 (anthropometric, measurements)		
SGA (vs AGA)	0.098 (0.067, 0.13)	<.001
Sex (male)	0.059 (0.027, 0.092)	<.001
Age (y)	0.001 (−0.029, 0.03)	.954
BMI (z score)	−0.028 (−0.058, 0.003)	.073
BSA (m^2)	0.079 (−0.18, 0.338)	.598
SBP (mm Hg)	0 (−0.002, 0.0021)	.853
Heart rate (bpm)	0 (−0.02, 0.02)	.919
Tricipital fold (z score)	0.009 (−0.012, 0.030)	.381
Waist/hip ratio	0.14 (−0.217, 0.498)	.441
Model 4* (analysis)		
SGA (vs AGA)	0.096 (0.062, 0.131)	<.001
Sex (male)	0.078 (0.041, 0.114)	<.001
Age (y)	0.018 (−0.004, 0.059)	.109
Glucose	−0.003 (−0.008, 0.003)	.380
Insulin	−0.008 (−0.067, 0.051)	.794
HOMA	0.028 (−0.25, 0.306)	.892
HbA1c	0.008 (−0.056, 0.073)	.797
Uric acid	−0.007 (−0.032, 0.018)	.575
Triglycerides	0 (−0.002, 0.001)	.398
LDL-cholesterol	0 (0, 0.001)	.205
HDL-cholesterol	0 (−0.001, 0.002)	.660
Urine albumin/creatinine	0 (0, 0.001)	.811
Model 5 (statistical model)†		
SGA	0.097 (0.067, 0.126)	<.001
Sex (male)	0.063 (0.034, 0.092)	<.001
Mother age (y)	0.004 (0.001, 0.007)	.016
Gestational weight gain (kg)	0.003 (0.001, 0.006)	.030
Mother university academic degree	−0.033 (−0.063, −0.007)	.029

HbA1c, hemoglobin A1C; *HDL*, high-density lipoprotein; *HOMA*, homeostatic model assessment; *LDL*, low-density; *PP*, pulse pressure; *SBP*, systolic blood pressure.

*Model 4 was obtained from 200 subjects with complete data from blood and urine analysis (97 in the SGA group and 103 in the AGA group).

†Regression model based on 200 subjects with complete data from blood and urine test (97 subjects in the SGA group and 103 subjects in the AGA group). Variables considered in the model (entry criteria *P* value of < .2 in univariate analysis): birth weight, birth length, sex, BSA, BMI, tricipital fold, waist/hip ratio, HOMA index, insulin levels, serum triglycerides, mother's age, mother's height, smoking during gestation, mother's academic level (university), and exclusive breast feeding (months).