Growth, Obesity, and Cardiac Structures in Early Childhood
The Generation R Study

Layla L. de Jonge, Lennie van Osch-Gevers, Sten P. Willemsen, Eric A.P. Steegers, Albert Hofman, Willem A. Helbing, Vincent W.V. Jaddoe

Abstract—Cardiac structural adaptations in response to physical growth and obesity in older children have been identified and might have long-term consequences. We examined the associations of growth and obesity with cardiac structures during the first 2 years of life. In a population-based prospective cohort study among 974 children, left atrial diameter, left ventricular diastolic diameter, left ventricular mass, aortic root diameter, and fractional shortening were repeatedly measured by ultrasound at the ages of 1.5, 6, and 24 months. Height, weight, and subcutaneous fat mass were measured at the same visits, and blood pressure was measured at the age of 24 months. Height, weight, body mass index, and body surface area were positively associated with all of the cardiac structures during the first 2 years of life. At the age of 24 months, as compared with normal weight children, obese children had a greater left ventricular mass (1.04 SD score [95% CI: 0.20 to 1.89]) and a higher fractional shortening (0.91 SD score [95% CI: 0.02 to 1.80]). Nonsignificant tendencies were found for left atrial diameter, left ventricular diastolic diameter, and aortic root diameter. Our results suggest that normal variation in growth affects cardiac structures in early life. Overweight and obese children show cardiac adaptations already at the age of 2 years. Further studies are needed to assess whether these structural adaptations influence the risk of cardiovascular disease in later life. (Hypertension. 2011;57:934-940.) ● Online Data Supplement

Key Words: echocardiography ■ anthropometrics ■ cardiac development ■ obesity

In childhood and adolescence, cardiac dimensions are closely related to physical growth.1,2 Previous studies have shown associations of height, weight, body mass index (BMI), and body surface area (BSA) with cardiac size in children and adolescents.3–6 Body composition, especially lean body mass, has also been recognized as an important determinant of cardiac parameters in children.4,5,7,8 Because of the increasing prevalence of obesity in children, much attention has been focused on the influence of obesity on cardiovascular structure and function.4,5,9–11 In school-age children and adolescents, both overweight and obesity are associated with structural cardiac changes, such as an increase in left atrial diameter, left ventricular dimensions and mass and an elevated blood pressure, as compared with normal weight individuals.5,6,12 Recent studies have also shown preclinical alterations in the aortic elastic properties in obese children.13

Because cardiac structures track from childhood to adulthood, early cardiac structural adaptations in response to physical growth might have consequences in later life. Therefore, we assessed in a population-based cohort study among 974 children the associations among growth characteristics, obesity, and left cardiac structures during the first 2 years of life.

Methods

Design and Study Population
The study was embedded in the Generation R Study, a population-based, prospective cohort study from fetal life onward.14 This cohort includes mothers, fathers, and their children of different ethnicities living in Rotterdam and has been described in detail previously.14 Mothers were enrolled between 2001 and 2005, and all of the children were born between April 2002 and January 2006. Enrollment was aimed at early pregnancy (gestational age: <18 weeks) at the routine fetal ultrasound examination in pregnancy but was allowed until birth of the child. More detailed assessments of fetal and postnatal growth and development were conducted in a random subgroup of 1098 Dutch children (see the online Data Supplement at http://hyper.ahajournals.org for Figure S1). The study has been approved by the Erasmus Medical Center Medical Ethics Committee. Written informed consent was obtained from all of the parents of participants. The present analysis was limited to singleton live births (N=1071). None of these children had congenital heart disease. Detailed information on anthropometrics and body composition was available in 994 children. In 974 children, ≥1 echocardiographic measurement was performed during the first 2 years of life.

Child Anthropometrics, Body Composition, and Blood Pressure
Information about child anthropometrics was obtained by measurements at the research center at the ages of 1.5, 6, and 24 months.

Hypertension is available at http://hyper.ahajournals.org DOI: 10.1161/HYPERTENSIONAHA.110.163303
Length was measured in supine position to the nearest 0.1 cm by a neonanometer (Holtaim Limited) at the ages of 1.5 and 6 months, and height was measured in upright position at the age of 24 months. Weight was measured in naked infants to the nearest gram by using an electronic scale (SECA). BMI (in kilograms per meter squared) and BSA (in meter squared) were calculated.\textsuperscript{15} For child BMI, we obtained age adjusted SDS scores (SDSs) using Dutch reference growth curves (Growth Analyzer 3.0, Dutch Growth Research Foundation, Rotterdam, The Netherlands). Children were categorized as normal weight (SDS BMI: <1.0), overweight (SDS BMI: 1.0 to 2.29), or obese (SDS BMI: ≥2.30) at the age of 24 months, as defined by Cole et al.\textsuperscript{16} Subcutaneous fat mass was measured as biceps, triceps, and suprailiacal and subscapular skinfold thicknesses using a standard skinfold caliper (SlimGuide, Creative Health Products) as described previously.\textsuperscript{17} Total subcutaneous fat mass was measured as the sum of biceps and triceps skinfold thickness (peripheral subcutaneous fat mass) and suprailiacal and subscapular skinfold thickness (central subcutaneous fat mass). At 24 months of age, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured to the nearest millimeter of mercury at the left upper arm by using an automatic sphygmomanometer (Vital Signs Monitor CAS 740; CAS Medical Systems, Inc, Branford, CT).\textsuperscript{18} The mean of 2 consecutive measurements was used in the analyses. Blood pressure measurements were successfully performed in 70% of the children. In 215 children, blood pressure was measured only once because of crying and oppositional behavior.

### Cardiac Outcomes

2D M-mode and Doppler echocardiographic measurements were performed using ATL-Philips Model HDI 5000 (Seattle, WA) equipment at the ages of 1.5, 6, and 24 months. In total, 86% of the measurements were performed by a single echocardiographer. The other measurements were performed by 2 other echocardiographers. The echocardiographers were supervised by a pediatric cardiologist. Echocardiographic measurements were successfully performed in 90%, 92%, and 85% of the children examined at 1.5, 6, and 24 months. Missing echocardiograms were mainly attributed to crying or unavailability of equipment or echocardiographer. Left atrial diameter, aortic root diameter, interventricular end-diastolic septal thickness, left ventricular end-diastolic diameter as a measure of left ventricular end-diastolic volume, left ventricular end-diastolic posterior wall thickness, and shortening fraction were measured, and left ventricular mass was calculated as described previously.\textsuperscript{19}

### Covariates

Gestational age was established by fetal ultrasounds.\textsuperscript{20} Date of birth, infant sex, and birth weight were obtained from midwife and hospital registries. Information on maternal age, prepregnancy weight, parity, and smoking habits during pregnancy was obtained by questionnaire. Maternal height was measured without shoes and heavy clothing in the first trimester of pregnancy. Socioeconomic status was defined as highest completed education according to the classification of Statistics Netherlands.\textsuperscript{21} Information about breastfeeding was collected by postnatal questionnaires and medical charts.

### Statistical Methods

Associations of child anthropometrics with repeatedly measured cardiac structures and fractional shortening at 1.5, 6, and 24 months of age were first assessed using regression analysis for repeated measures using the Proc Mixed module of SAS. To compare effect estimates for the associations of child anthropometrics and body composition with cardiac structures at different ages, all of the measurements were converted to SDSs. The best-fitting models were constructed, and the models can be written as follows: cardiac outcome = $\beta_0 + \beta_1 \times$anthropometric measurement $+ \beta_2 \times$child age $+ \beta_3 \times$anthropometric measurement $\times$child age $+$terms for additional variables.

In these models, "$\beta_0 + \beta_1 \times$anthropometric measurement" reflects the intercept, "$\beta_2 \times$child age" reflects the slope of change in SDSs of cardiac structures and fractional shortening per week. The term "$\beta_3 \times$anthropometric measurement $\times$child age" reflects the difference in change in SDSs of cardiac structures and fractional shortening per week with increasing anthropometrics.

Subsequently, we performed multiple linear regression models to study the associations of blood pressure with cardiac structures at the age of 24 months, and the change in anthropometrics and body composition in the time period of 1.5 months to 24 months with cardiac structures at the age of 24 months, and with the change in cardiac structures in the time period of 1.5 to 24 months. We used the same models to assess the differences in cardiac structures and fractional shortening among normal weight, overweight, and obese children. The category of normal weight children was taken as the referent. All of the analyses were adjusted for child sex, gestational age, birth weight, breastfeeding status, and maternal height, weight, parity, educational level, and smoking habits during pregnancy. Multiple linear regression models were additionally adjusted for child age at measurement and analyses with growth rates, because determinants were additionally adjusted for time between measurements. For all of the analyses, missing values were imputed with the mean for continuous variables or with an additional category for categorical variables.

Statistical analyses were performed using the SAS version 9.2 (SAS for Windows Version 9.2; SAS Institute, Cary, NC), including the Proc Mixed module for unbalanced repeated measurements and the Statistical Package of Social Sciences version 17.0 for Windows (SPSS Inc, Chicago, IL).

### Results

#### Subject Characteristics

Maternal and child characteristics are shown in Table 1. The overall median gestational age was 40.3 weeks (95% range: 35.8 to 42.4 weeks), with a mean birth weight of 3510 g (SD: 543 g). Descriptives of all of the cardiac measurements are given in the online Data Supplement (see http://hyper.ahajournals.org for Table S1). Overall, boys had a larger aortic root diameter and left ventricular mass at all ages. Of the 701 children who underwent successful echocardiographic examinations at the age of 24 months, 53 were overweight (8.0%), and 5 were obese (0.7%).

#### Normal Growth Variation and Cardiac Structures

Table 2 presents regression coefficients of the associations of child anthropometrics and body composition with the repeatedly measured left cardiac structures and fractional shortening until the age of 24 months. Height, weight, BMI, and BSA were positively associated with left ventricular diastolic diameter and left ventricular mass (all $P$ values <0.05) at all ages and with aortic root diameter at the age of 6 and 24 months. For left atrial diameter, child anthropometrics also showed a positive tendency. At the age of 1.5 months, total subcutaneous fat mass was associated with left atrial diameter, and both total and central subcutaneous fat mass were associated with fractional shortening. At older ages, no consistent associations were observed between subcutaneous fat mass and cardiac structures. No association with SBP or DBP measured at 24 months with any of the cardiac structures or fractional shortening was found.

Table 3 shows that gains in height, weight, and BSA between the ages of 1.5 and 24 months were positively associated with left atrial diameter, aortic root diameter, left ventricular mass, and left ventricular diastolic diameter at the age of 24 months. The increase in BSA was the strongest...
determinant, with 0.17 SDS (95% CI: 0.07 to 0.27), 0.33 SDS (95% CI: 0.24 to 0.42), 0.35 SDS (95% CI: 0.25 to 0.44), and 0.26 SDS (95% CI: 0.16 to 0.35) change in left atrial diameter, left ventricular diastolic diameter, left ventricular mass, and aortic root diameter, respectively, per SDS change in BSA. A higher weight gain and increase in BSA tended to be associated with cardiac growth, particularly with left ventricular mass, whereas height gain between 1.5 and 24 months showed a strong association with aortic root diameter growth rate (Table S2). The effect estimates for the associations between growth characteristics and cardiac structures at 24 months were not materially affected by adjustment for blood pressure (data not shown).

Overweight, Obesity, and Cardiac Structures

The Figure shows the differences of left cardiac structures and fractional shortening among normal weight, overweight, and obese children. As compared with normal weight children, left ventricular mass was significantly greater in both overweight (0.44 SDS [95% CI: 0.17 to 0.71]) and obese (1.04 SDS [95% CI: 0.20 to 1.89]) children. Nonsignificant tendencies were found for left atrial diameter, left ventricular diastolic diameter, and aortic root diameter. The cardiac contractility indicated by fractional shortening was similar in normal and overweight children and was higher in obese children (0.91 SDS [95% CI: 0.02 to 1.80]). SBP and DBP did not differ among the normal weight, overweight, and obese children.

Discussion

In this population-based prospective cohort study, observed positive associations of weight, height, BMI, and BSA with left atrial diameter, aortic root diameter, left ventricular diastolic diameter, and left ventricular mass during the first 2 years of life. Furthermore, this study provides evidence that overweight and obesity already in early childhood exert an influence on the cardiac size.

Strengths and Limitations

A major strength of this study was its prospective design in a large cohort of children. Because of the repeated measurements, we were able to investigate the effect of early growth rates on the left cardiac structures. A limitation might be that information on left cardiac structures was missing in 10%, 8%, and 15% of the children measured at the ages of 1.5, 6, and 24 months, respectively. Blood pressure measurements were successfully obtained in only 70% of the children. Missing echocardiographic or blood pressure measurements could lead to both selection bias and loss of power. Our results would be biased if the associations among anthropometrics, blood pressure, and cardiac structures and function differ between those included and not included in the study. This seems unlikely but cannot be excluded. Although we adjusted the regression models for several potential confounders, residual confounding might be an issue, as in any observational study. No information was available about dietary patterns, except for breastfeeding status. However, other components of child diet may influence the relationship of anthropometric measures and cardiac structures.
Growth and Cardiac Structures

In children and adolescents, cardiac growth is influenced by physical growth, including body size and body composition. Results from the Bogalusa Heart Study showed that body fat percentage is associated with left ventricular mass, independent of body mass index (BMI) and other anthropometric factors. This association is consistent across BMI quartiles. Various studies have observed that body fat percentage is a determinant of cardiac size and growth during adolescence, and that the association between body fat and left ventricular mass is independent of BMI and other anthropometric factors. Results from the Muscatine Study indicated that body fat free mass as a determinant of cardiac size and growth during adolescence is also closely related to cardiac size in childhood and adolescence. The same study demonstrated that there is a positive association between left ventricular mass in childhood and adolescence across BMI quartiles. Various studies have observed that body composition measured by skinfold thickness, bioelectric impedance, or dual energy X-ray absorptiometry was also closely related to cardiac size. Results from the Bogalusa Heart Study showed that body fat percentage is a determinant of cardiac size and growth during adolescence, and that the association between body fat and left ventricular mass is independent of BMI and other anthropometric factors. Results from the Muscatine Study indicated that body fat free mass as a determinant of cardiac size and growth during adolescence is also closely related to cardiac size. Results from the Bogalusa Heart Study showed that body fat percentage is a determinant of cardiac size and growth during adolescence, and that the association between body fat and left ventricular mass is independent of BMI and other anthropometric factors. Results from the Muscatine Study indicated that body fat free mass as a determinant of cardiac size and growth during adolescence is also closely related to cardiac size.
adolescence, and another study among children supported the findings that lean tissue mass was a strong predictor in the youth. In our study, we observed no consistent associations of subcutaneous fat mass measures with cardiac structures during the first 2 years of life. These results seem to be in contrast to the associations of BMI with left cardiac structures. BMI represents both fat-free mass and fat mass though, and lean body mass might also be elevated in obese individuals. Our results are in line with the hypothesis that the demands of lean body mass are the primary determinants of left ventricular mass in children.

In normal and hypertensive children, SBP and left ventricular mass are shown to be positively associated across a wide range of blood pressure values. Sorof et al observed left ventricular hypertrophy in 27% of adolescents with systolic hypertension and that patients with left ventricular hypertrophy had a greater BMI than those without hypertrophy. These observations suggest that left ventricular hypo-

Table 3. Associations of Child Growth Between the Ages of 1.5 Months and 24 Months With Left Cardiac Structures and Fractional Shortening at 24 Months of Age

<table>
<thead>
<tr>
<th>Change in Child Anthropometrics and Body Composition</th>
<th>Left Atrial Diameter (SD=2.44 mm)</th>
<th>Left Ventricular Diastolic Diameter (SD=2.37 mm)</th>
<th>Left Ventricular Mass (SD=5.56 g)</th>
<th>Aortic Root Diameter (SD=1.45 mm)</th>
<th>Fractional Shortening (SD=4.57%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (SD=3.07 cm)</td>
<td>0.13 (0.02 to 0.23)*</td>
<td>0.30 (0.21 to 0.40)†</td>
<td>0.22 (0.12 to 0.32)†</td>
<td>0.20 (0.11 to 0.30)†</td>
<td>−0.02 (−0.13 to 0.09)</td>
</tr>
<tr>
<td>Weight (SD=1290 g)</td>
<td>0.17 (0.07 to 0.26)†</td>
<td>0.27 (0.19 to 0.36)†</td>
<td>0.31 (0.23 to 0.40)†</td>
<td>0.23 (0.14 to 0.31)†</td>
<td>0.04 (−0.06 to 0.13)</td>
</tr>
<tr>
<td>BMI (SD=1.67 kg/m²)</td>
<td>0.06 (−0.03 to 0.15)</td>
<td>0.08 (−0.01 to 0.17)‡</td>
<td>0.19 (0.10 to 0.28)‡</td>
<td>0.08 (0.00 to 0.17)‡</td>
<td>0.04 (−0.06 to 0.13)</td>
</tr>
<tr>
<td>BSA (SD=0.03 m²)</td>
<td>0.17 (0.07 to 0.27)†</td>
<td>0.33 (0.24 to 0.42)†</td>
<td>0.35 (0.25 to 0.44)†</td>
<td>0.26 (0.16 to 0.35)†</td>
<td>0.01 (−0.09 to 0.12)</td>
</tr>
</tbody>
</table>

Subcutaneous fat mass

<table>
<thead>
<tr>
<th>Subcutaneous fat mass</th>
<th>Total (SD=9.00 mm)</th>
<th>−0.07 (−0.16 to 0.02)</th>
<th>−0.08 (−0.17 to 0.00)</th>
<th>0.00 (−0.09 to 0.09)</th>
<th>0.05 (−0.03 to 0.13)</th>
<th>−0.03 (−0.12 to 0.07)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central (SD=4.26 mm)</td>
<td>−0.06 (−0.15 to 0.03)</td>
<td>−0.07 (−0.16 to 0.01)</td>
<td>0.02 (−0.07 to 0.11)</td>
<td>0.09 (0.01 to 0.18)*</td>
<td>−0.02 (−0.11 to 0.08)</td>
<td>−0.02 (−0.11 to 0.08)</td>
</tr>
<tr>
<td>Peripheral (SD=5.80 mm)</td>
<td>−0.05 (−0.14 to 0.04)</td>
<td>−0.09 (−0.17 to −0.01)*</td>
<td>−0.02 (−0.11 to 0.06)</td>
<td>−0.01 (−0.09 to 0.08)</td>
<td>−0.03 (−0.12 to 0.06)</td>
<td>−0.02 (−0.11 to 0.08)</td>
</tr>
</tbody>
</table>

Values are regression coefficients (95% CI) and reflect the change in SDS of left cardiac structure and fractional shortening per change in SDS of increase in child anthropometrics and body composition. Models are adjusted for child sex, gestational age, birth weight, breastfeeding status, age at 24-month visit, time between moments of measurement, and maternal height and weight at intake, parity, educational level, and smoking habits during pregnancy.

*P<0.05.
†P<0.01.

Figure. Left cardiac structures and fractional shortening in normal, overweight, and obese children at 24 months of age. The Figure presents the difference in cardiac structure SDS between overweight and obese children, as compared with the reference group (normal weight). Adjustments were made for child sex, gestational age, birth weight, breastfeeding status, age at visit, and maternal height and weight at intake, parity, educational level, and smoking habits during pregnancy.
trophy can occur early in the course of hypertension in young individuals and that the combination of obesity and hypertension enhances the risk for adverse cardiovascular outcomes. However, in our study, there was no difference in SBP or DBP among the normal weight, overweight, and obese children, and the effect estimates for the associations between growth characteristics and cardiac structures were not materially affected by adjustment for blood pressure.

**Obesity and Cardiac Structures**

The recognition of obesity as an important determinant of cardiac remodeling has led to increased interest in the influence of overweight and obesity on early cardiovascular development. In the Strong Heart Study among adolescents aged 14 to 20 years, both overweight and obese participants had a greater left ventricular diameter and mass than normal weight adolescents. Di Salvo et al demonstrated that obesity, in the absence of hypertension, was associated with a significant reduction in systolic myocardial deformation properties in childhood, involving both the right and left ventricles. In our cohort, we showed that overweight and obesity exert a significant influence on left cardiac structures already in early childhood. Severe obesity is also associated with arterial wall stiffness and endothelial dysfunction in children. Obese children have a larger abdominal aortic diameter and increased aortic stiffness compared with normal weight children, suggesting that preclinical changes in the aortic elastic properties are already early detectable. The present study showed a nonsignificant tendency toward a larger aortic root diameter in overweight and obese children.

**Mechanisms**

The associations of obesity with cardiac structures in childhood may be explained by various interrelated hemodynamic, metabolic, neurohormonal, and genetic mechanisms. In adulthood, obesity-related hypertension creates a continuous pressure overload, inducing concentric left ventricular hypertrophy. Elevated blood pressure and an increase in left ventricular mass have been described previously in obese children. In our study, the associations between growth and cardiac structures were not explained by blood pressure. In normotensive patients, obesity is related to an elevated cardiac output and chronic volume overload, leading to an eccentric left ventricular hypertrophy. These changes are most likely attributed to the increased metabolic demand of the higher lean and fat masses in obesity, which might establish an effect already in early childhood. Another possible pathway that links obesity with cardiovascular remodeling is through its association with insulin resistance and hyperinsulinemia. Studies in children found significant partial correlations of insulin with left ventricular mass and percentage of fat, suggesting that insulin may mediate the relation of fatness to cardiac structures. In addition, obesity is related to a stimulated sympathetic outflow and inappropriately activated renin-angiotensin system. These neurohormonal mechanisms may induce hemodynamic changes such as peripheral vasoconstriction and volume retention. Finally, the influence of body size and obesity on left cardiac structures might be explained by a common genetic mechanism that modulates both somatic and cardiac growth. The mechanisms that are associated with cardiac remodeling in childhood and adulthood remain subject to further investigation.

**Perspectives**

Cardiac structural adaptations in response to physical growth and obesity might have consequences in later life. This study demonstrated that physical growth is an important determinant of cardiac development in infancy and early childhood. Furthermore, the results of this study indicate that obesity is not only a risk factor for cardiovascular disease in later life but also affects cardiac development as early as the age of 2 years. Our results suggest that left cardiac size and function in adulthood have at least part of their origin in infancy and early childhood. Further studies are needed to investigate the possible influence of early cardiac growth and adaptations on the risk of cardiovascular disease in later life.

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**Acknowledgments**

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**Disclosures**

None.
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Short title: Child growth, obesity and cardiac structures

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Number of tables: 2
Number of figures: 1
Table S1. Cardiac Structures and Fractional Shortening at the Ages of 1.5, 6 and 24 Months

<table>
<thead>
<tr>
<th>Echocardiographic measurements</th>
<th>Boys</th>
<th>Girls</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.5 Months</strong></td>
<td>(N=402)</td>
<td>(N=376)</td>
<td></td>
</tr>
<tr>
<td>Left atrial diameter (mm)</td>
<td>17.0 (1.9)</td>
<td>16.6 (1.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Left ventricular diastolic diameter (mm)</td>
<td>22.5 (1.8)</td>
<td>21.5 (1.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Left ventricular mass (g)</td>
<td>15.2 (3.1)</td>
<td>13.8 (2.8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Aortic root (mm)</td>
<td>12.0 (1.2)</td>
<td>11.5 (1.1)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fractional shortening (%)</td>
<td>35.4 (4.8)</td>
<td>35.4 (5.1)</td>
<td>0.92</td>
</tr>
<tr>
<td><strong>6 Months</strong></td>
<td>(N=420)</td>
<td>(N=381)</td>
<td></td>
</tr>
<tr>
<td>Left atrial diameter (mm)</td>
<td>18.0 (1.9)</td>
<td>17.9 (1.8)</td>
<td>0.59</td>
</tr>
<tr>
<td>Left ventricular diastolic diameter (mm)</td>
<td>25.6 (1.8)</td>
<td>24.7 (1.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Left ventricular mass (g)</td>
<td>20.3 (4.1)</td>
<td>18.4 (3.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Aortic root (mm)</td>
<td>13.9 (1.2)</td>
<td>13.4 (1.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fractional shortening (%)</td>
<td>37.2 (4.6)</td>
<td>37.1 (4.8)</td>
<td>0.72</td>
</tr>
<tr>
<td><strong>24 Months</strong></td>
<td>(N=358)</td>
<td>(N=343)</td>
<td></td>
</tr>
<tr>
<td>Left atrial diameter (mm)</td>
<td>20.7 (2.5)</td>
<td>20.5 (2.4)</td>
<td>0.23</td>
</tr>
<tr>
<td>Left ventricular diastolic diameter (mm)</td>
<td>31.9 (2.4)</td>
<td>30.9 (2.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Left ventricular mass (g)</td>
<td>32.5 (5.7)</td>
<td>30.0 (5.1)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Aortic root (mm)</td>
<td>16.7 (1.4)</td>
<td>16.0 (1.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fractional shortening (%)</td>
<td>35.4 (4.6)</td>
<td>35.4 (4.6)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Values represent means (SD). Differences between boys and girls were compared using independent samples t test.
Table S2. Associations of Child Growth Characteristics with Cardiac Growth from 1.5 Months to 24 Months of Age

<table>
<thead>
<tr>
<th>Change in child anthropometrics and body composition</th>
<th>Increase in left atrial diameter (SD=2.88 mm)</th>
<th>Increase in left ventricular diameter (SD=2.45 mm)</th>
<th>Increase in left ventricular mass (SD=5.35 g)</th>
<th>Increase in aortic root diameter (SD=1.44 mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in height (SD=3.07 cm)</td>
<td>0.05 (-0.06, 0.16)</td>
<td>0.28 (0.17, 0.40)†</td>
<td>0.23 (0.10, 0.35)†</td>
<td>0.25 (0.14, 0.35)†</td>
</tr>
<tr>
<td>Increase in weight (SD=1290 g)</td>
<td>0.10 (0.00, 0.20)</td>
<td>0.19 (0.09, 0.30)†</td>
<td>0.29 (0.19, 0.39)†</td>
<td>0.22 (0.12, 0.32)†</td>
</tr>
<tr>
<td>Increase in BMI (SD=1.67 kg/m²)</td>
<td>0.08 (-0.02, 0.18)</td>
<td>0.07 (-0.03, 0.18)</td>
<td>0.24 (0.13, 0.34)†</td>
<td>0.08 (-0.02, 0.18)</td>
</tr>
<tr>
<td>Increase in BSA (SD=0.03 m²)</td>
<td>0.09 (-0.01, 0.20)</td>
<td>0.24 (0.13, 0.35)†</td>
<td>0.33 (0.22, 0.44)†</td>
<td>0.26 (0.15, 0.36)†</td>
</tr>
</tbody>
</table>

Increase in subcutaneous fat mass

| Total (SD=9.00 mm)                                   | 0.02 (-0.07, 0.12)                          | -0.13 (-0.23, -0.03)*                           | 0.04 (-0.07, 0.14)                           | 0.01 (-0.08, 0.11)                           |
| Central (SD=4.26 mm)                                | -0.01 (-0.11, 0.09)                         | -0.14 (-0.24, -0.04)†                           | 0.04 (-0.07, 0.15)                           | 0.08 (-0.02, 0.18)                           |
| Peripheral (SD=5.80 mm)                             | 0.06 (-0.04, 0.15)                          | -0.09 (-0.19, 0.00)                             | 0.04 (-0.06, 0.14)                           | -0.04 (-0.14, 0.05)                          |

Values are regression coefficients (95% CI) and reflect the change in SDS of increase in left cardiac structure per change in SDS of increase in child anthropometrics and body composition. Models are adjusted for child gender, gestational age, birth weight,
breastfeeding status, age at 24 months visit, time between moments of measurement, and maternal height and weight at intake, parity, educational level and smoking habits during pregnancy. * $P<0.05$ † $P<0.01$
Focus Cohort postnatal participation  
\( N=1,098 \)

Singleton live births  
\( N=1,071 \)

Data on child anthropometrics or body composition available  
\( N=994 \)

Data on cardiovascular structures available  
\( N=974 \)

Participation in 6 weeks visit:  
\( N=861 \)  
Cardiac ultrasounds:  
\( N=778 \) (90%)

Participation in 6 months visit:  
\( N=867 \)  
Cardiac ultrasounds:  
\( N=801 \) (92%)

Participation in 24 months visit:  
\( N=821 \)  
Cardiac ultrasounds:  
\( N=701 \) (85%)