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Fetal and infant growth patterns and left and right ventricular measures in childhood assessed by cardiac MRI

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Abstract

Objectives: Early life is critical for cardiac development. We examined the associations of longitudinal fetal and childhood growth patterns with childhood right and left ventricular structures measured by cardiac magnetic resonance imaging.

Methods: In a population-based prospective cohort study among 2827 children, we measured growth at 20 and 30 weeks of pregnancy, at birth, 0.5, 1, 2, 6 and 10 years. At 10 years, we measured right ventricular end-diastolic volume, left ventricular end-diastolic volume, left ventricular mass and left ventricular mass-to-volume ratio by cardiac magnetic resonance imaging.

Results: Small size for gestational age at birth was associated with smaller right and left ventricular end-diastolic volume relative to current body surface area, but with larger left ventricular mass-to-volume ratio ($P < 0.05$). Children in the upper 25% of right and left ventricular end-diastolic volume and left ventricular mass at age 10 years were larger at birth and became taller and leaner in childhood ($P < 0.05$). In contrast, children in the lower 25% of right and left ventricular end-diastolic volume and left ventricular mass were smaller at birth and became shorter and heavier in childhood ($P < 0.05$). Both fetal and childhood growth were independently of each other associated with childhood right and left ventricular end-diastolic volume and left ventricular mass.

Conclusion: Children who are larger at birth and grow taller and leaner in childhood have larger hearts relative to body surface area. Small size at birth children, who grow shorter and heavier in childhood, have relatively smaller hearts with larger left ventricular mass-to-volume ratio. Both fetal and childhood growth are important for the development of cardiac dimensions.

Keywords

Epidemiology, paediatric, growth, cardiac structure, left ventricular mass

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Introduction

Fetal exposure to an adverse environment leads to cardiovascular adaptations, which predispose individuals to disease in later life.^{1,2} Evidence suggests that early-life growth patterns directly affect cardiac structure and up studies have shown that individuals with a lower weight in infancy have a higher left ventricular mass (LVM) in adulthood, an independent risk factor for mortality.³ Recent studies have shown that children with fetal growth restriction have more globular, shorter ventricles and cardiac dysfunction.⁵ Similar changes were observed in preterm born young adults.⁶ A major limitation of previous studies is that no

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information is available on right ventricular measures, while the right ventricle is dominant in fetal life.⁷ Cardiac magnetic resonance imaging (cMRI) is a more precise method to assess cardiac measures than echocardiography and enables imaging of both left and right ventricular dimensions.⁸ A previous cMRI study in adolescents showed that preterm birth was associated with changes in cardiac geometry, which were more pronounced in the right than in the left ventricle.⁹ Although these previous studies strongly suggest that early life is important for the programming of cardiac structure, function and disease in later life, it remains unknown which period in fetal life or infancy is critical.

We examined in a population-based prospective cohort study among 2827 children the associations of fetal and infant growth with cardiac measures assessed by cMRI in children aged 10 years. Cardiac measures included right ventricular end-diastolic volume (RVEDV), right ventricular ejection fraction (RVEF), left ventricular end-diastolic volume (LVEDV), left ventricular ejection fraction (LVEF), LVM and left ventricular mass-to-volume ratio (LMVR). We hypothesised that both gestational age at birth, and fetal and childhood growth across their full spectrum are associated with right and left cardiac adaptations, independent of current body size. Analyses were focused on longitudinal growth patterns and the identification of critical growth periods.

Methods

Design and study population

This study was embedded in the Generation R Study, a population-based, prospective cohort study from fetal life onwards in Rotterdam, The Netherlands.¹⁰ The response rate at birth was 61% (2002–2006).¹⁰ Fetal and childhood growth were repeatedly assessed by ultrasound and physical examinations until the age of 10 years. Good quality cMRI was obtained in 2827 children (see Supplementary Figure 1). Written informed consent was obtained from all parents of participants. The study has been approved by the local medical ethics committee.

Fetal and childhood growth measurements

As previously described, fetal ultrasound examinations were carried out in each trimester of pregnancy.¹¹ Second trimester (median 20.5 weeks, 95% range 18.6–23.4) and third trimester (median 30.4 weeks, 95% range 28.4–33.1) fetal head circumference, abdominal circumference and femur length as proxy for fetal length were measured to the nearest millimetre using

standardised ultrasound procedures.¹² Estimated fetal weight was calculated using the Hadlock formula.¹³ Gestational age adjusted standard deviation scores (SDS) for all fetal growth characteristics were constructed based on reference growth curves.^{11,12} At birth, information on infant sex, date of birth and weight was obtained from community midwife and hospital registries. We created gestational age and sex-adjusted birth length and weight SDS by using Growth Analyzer 3.5 (Dutch Growth Research Foundation, Rotterdam, The Netherlands) based on north European reference standards.¹⁴ We defined small or large size for gestational age as being less than 10th or over 90th sex-specific percentile for weight. Preterm birth was defined as birth at less than 37 weeks of gestation.

Infant length and weight were measured at the community health centres using standardised procedures at the median ages of 6.2 months (95% range 5.2–8.3), 11.1 months (95% range 10.1–15.5) and 24.8 months (95% range 23.4–28.1). Sex and age-adjusted SDS were obtained using Dutch reference growth curves.¹⁵

At the median ages of 5.9 years (95% range 5.7–7.3) and 9.9 years (95% range 9.5–11.8), we measured child height and weight without shoes and heavy clothing, and calculated body mass index (BMI) and body surface area (BSA) using the Haycock formula.¹⁶

Cardiac magnetic resonance imaging

We performed cMRI using a wide-bore GE Discovery MR 750 3T scanner (General Electric, Milwaukee, MI, USA), as described in more detail in Supplementary Methods file 1. Briefly, we acquired localiser images, followed by ECG gated breath-held scans lasting less than 10 seconds per breath-hold. A short-axis steady-state free precession (SSFP) cine stack was then obtained with basal slice alignment and covering the ventricles with contiguous 8 mm thick slices over several end-expiration breath-holds. The scans were stored on a digital archive for post-processing.

Off-line image analyses for right and left ventricular measures on the short-axis cine stack was performed by Precision Image Analysis (Kirkland, WA, USA) using Medis QMASS software (Medis, Leiden, The Netherlands). The guidelines of the Society for Cardiovascular Magnetic Resonance were followed to contour right and left ventricular short-axis endocardial and left ventricular epicardial borders semi-automatically.¹⁷ Papillary muscle was included in the ventricular cavity. Cardiac measurements included RVEDV, RVEF, LVEDV, LVEF and LVM. We calculated LMVR as LVM/LVEDV.

Covariates

Information about education, household income, height and parity was collected by questionnaires and medical charts. Infant ethnicity was classified by the countries of birth of the parents and was categorised as Dutch or non-Dutch.¹⁰ The largest non-Dutch ethnicities are: European, Turkish, Moroccan, Surinamese, Cape Verdian and Dutch Antilles. Child systolic and diastolic blood pressure was measured on the right brachial artery, using the validated automatic sphygmomanometer Accutorr Plus (Datascope Corporation, Fairfield, NJ, USA). Child blood pressure and anthropometric measurements preceded the cMRI visit by 1.1 months (95% range 0–2.8 months).

Statistical analysis

We constructed BSA adjusted SDS for the cardiac measures using generalized additive models for location, size and shape (GAMLSS) in R, version 3.2.0 (R Core Team, Vienna, Austria). This enables flexible modelling, taking into account the distribution of the outcome variable.¹⁸ As LMVR is a ratio we did not create a BSA-adjusted SDS, but standardised this measure as (observed value mean)/standard deviation. Similarly, we created SDS for all growth measures to enable comparison of effect estimates. First, we used linear regression models to assess the associations of birth characteristics (gestational age, weight and gestational age-adjusted size at birth), both continuously and in clinical categories, with cardiac measures (RVEDV, RVEF, LVEDV, LVEF, LVM, LMVR). Second, we compared longitudinal fetal and childhood growth patterns between different quartiles of the cardiac measures. For these analyses, we used repeated measurement regression models, which take into account the correlation between repeated growth measurements of the same participant.¹⁹ Finally, we performed conditional regression analyses to identify independent critical growth periods associated with cardiac measures. Conditional regression analyses take into account the correlations between growth measures at different ages. This allows simultaneous inclusion of all growth measures in a regression model to assess the most critical periods of growth.²⁰ All models were adjusted for relevant covariates, selected on the basis of their associations with the outcomes of interest based on previous studies and change in effect estimate greater than 10%. Maternal BMI, blood pressure, smoking during pregnancy or gestational hypertensive disorders did not change the effect estimates and were therefore not included in the final models. We did not observe significant statistical interaction terms with

child sex or ethnicity. Missing data of covariates and anthropometric measures for conditional analyses were imputed using multiple imputations in five created datasets and analysed together.²¹ We performed repeated analyses using SAS software version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA),¹⁹ all other analyses were performed using the Statistical Package for the Social Sciences version 21.0 for Windows (IBM Corp., Armonk, NY, USA).

Results

Study participant characteristics

Maternal and child characteristics are shown in Supplementary Table 1. Non-response analysis is shown in Supplementary Table 2. Correlation coefficients between growth and cardiac measures are given in Supplementary Table 3.

Birth outcomes and cardiac measures at school age

Table 1 shows that preterm birth was associated with higher LVEF in childhood than term birth (difference 0.25 SDS, 95% confidence interval (CI) 0.07, 0.43), but not with other cardiac measures. A 1 SDS higher birth weight was associated with higher RVEDV (0.09 SDS, 95% CI 0.06, 0.13) and LVEDV (0.10 SDS, 95% CI 0.06, 0.13), relative to current body size. Birth weight adjusted for gestational age was also associated with lower LMVR (−0.06 SDS, 95% CI −0.10, −0.02). Supplementary Table 4 shows that additional adjusting for lean body mass percentage did not change the main results.

Longitudinal fetal and infant growth patterns and cardiac measures at school age

Figure 1 shows the results of the longitudinal growth analyses. As compared with children in the 25–75% range of RVEDV and LVEDV, those in the upper 25% had higher fetal length and weight growth, whereas those in the lower 25% had lower fetal length and weight. In childhood the children in the upper 25% for RVEDV and LVEDV had normal height and slightly lower weight growth, whereas children in the lower 25% had lower childhood height growth and higher weight gain (Figure 1(a) and (b)). Children in the highest quartile of LVM had higher height and lower weight gain in childhood (Figure 1(c)). Children in the highest LMVR had higher weight gain (Figure 1(d)). No differences in fetal and infant growth patterns were observed for RVEF and LVEF (Figure 1(e) and (f)).

Table 1. Birth characteristics and ventricular outcomes at the age of 10 years (N = 2827).

Birth characteristics	N	Difference in cardiac measures standard deviation scores (95% confidence interval)							
		Right ventricular end-diastolic volume	Right ventricular ejection fraction	Left ventricular end-diastolic volume	Left ventricular ejection fraction	Left ventricular mass	Left ventricular mass-to-volume ratio		
Gestational age									
<37.0 weeks	126	-0.08 (-0.24, 0.07)	0.04 (-0.14, 0.22)	-0.16 (-0.31, 0.00)	0.25 (0.07, 0.43)**	-0.08 (-0.24, 0.08)	0.05 (-0.13, 0.23)		
37.0–41.9 weeks	2500	Reference	Reference	Reference	Reference	Reference	Reference		
≥42 weeks	201	-0.01 (-0.14, 0.12)	-0.05 (-0.19, 0.10)	-0.08 (-0.20, 0.05)	0.00 (-0.15, 0.14)	0.00 (-0.13, 0.12)	0.06 (-0.09, 0.20)		
Trend	2827	-0.01 (-0.04, 0.03)	0.00 (-0.04, 0.03)	0.01 (-0.03, 0.04)	-0.05 (-0.09, -0.01)*	0.01 (-0.02, 0.04)	0.01 (-0.03, 0.05)		
Birth weight									
<2000 g	28	-0.01 (-0.33, 0.32)	0.00 (-0.37, 0.37)	-0.16 (-0.49, 0.16)	0.41 (0.03, 0.78)*	-0.33 (-0.66, -0.00)*	-0.25 (-0.62, 0.12)		
2000–2499 g	88	-0.06 (-0.25, 0.13)	0.11 (-0.11, 0.33)	-0.08 (-0.27, 0.11)	0.16 (-0.06, 0.38)	0.06 (-0.13, 0.25)	0.12 (-0.10, 0.34)		
2500–2999 g	401	-0.02 (-0.12, 0.08)	-0.08 (-0.20, 0.04)	-0.09 (-0.19, 0.01)	-0.04 (-0.16, 0.08)	0.03 (-0.08, 0.13)	0.10 (-0.02, 0.22)		
3000–3499 g	959	Reference	Reference	Reference	Reference	Reference	Reference		
3500–3999 g	922	0.13 (0.05, 0.21)**	0.02 (-0.08, 0.11)	0.12 (0.04, 0.20)**	0.00 (-0.10, 0.09)	0.00 (-0.08, 0.08)	-0.09 (-0.18, 0.00)		
4000–4499 g	351	0.20 (0.09, 0.31)**	-0.10 (-0.23, 0.02)	0.17 (0.06, 0.28)**	-0.10 (-0.22, 0.03)	0.10 (-0.01, 0.21)	0.00 (-0.13, 0.12)		
≥4500 g	75	0.44 (0.24, 0.65)**	-0.02 (-0.26, 0.22)	0.31 (0.11, 0.52)**	0.16 (-0.08, 0.40)	0.13 (-0.08, 0.34)	-0.09 (-0.33, 0.14)		
Trend	2827	0.09 (0.06, 0.13)**	-0.03 (-0.07, 0.01)	0.10 (0.06, 0.13)**	-0.05 (-0.09, -0.01)*	0.02 (-0.01, 0.06)	-0.05 (-0.08, 0.01)		
Birth weight for gestational age									
Small	255	-0.14 (-0.26, -0.03)**	0.00 (-0.13, 0.13)	-0.18 (-0.29, -0.06)**	-0.03 (-0.16, 0.10)	0.04 (-0.08, 0.15)	0.16 (0.03, 0.29)*		
Normal	2274	Reference	Reference	Reference	Reference	Reference	Reference		
Large	298	0.22 (0.11, 0.32)**	-0.02 (-0.15, 0.09)	0.18 (0.07, 0.28)**	0.01 (-0.11, 0.14)	0.12 (0.01, 0.22)*	0.01 (-0.12, 0.13)		
Trend	2827	0.11 (0.08, 0.14)**	-0.03 (-0.07, 0.11)	0.11 (0.08, 0.14)**	-0.02 (-0.06, 0.02)	0.02 (-0.01, 0.05)	-0.06 (-0.10, -0.02)**		

Values are regression coefficients (95% confidence interval) and reflect the change in standard deviation (SDS) of each cardiac measure for each birth weight or gestational age group, compared with the reference group. Trend estimates represent the effect estimates for the continuous associations per SDS change in birth characteristic. We used body surface-adjusted standard deviation scores, except for left ventricular mass-to-volume ratio. Models are adjusted for maternal height, parity, educational level, income level, child's sex, ethnicity, current age and time difference between BSA measurement and MRI.

* $P < 0.05$; ** $P < 0.01$. Models additionally adjusted for childhood lean body mass percentage are shown in Supplementary Table 4.

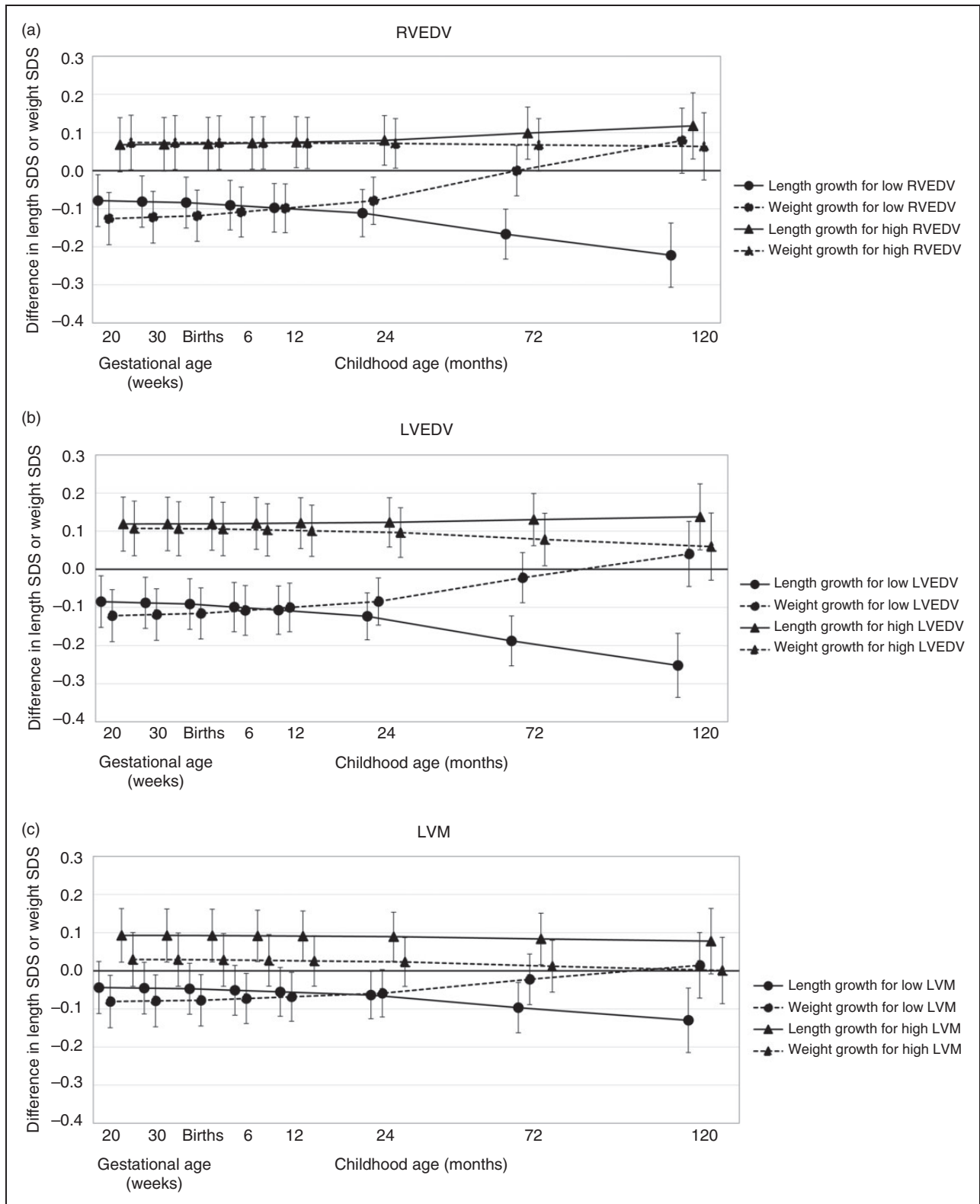


Figure 1. Fetal and childhood growth patterns and cardiac structure and function measures ($N = 2827$). Figures show results of repeated measurement regression models. Each point shows the difference in length or weight ($\pm 95\%$ confidence interval), from children in the lowest or highest 25% of the cardiac measure, compared with the children in the middle 25–75%. A parallel line indicates growth rates comparable with the reference group, while an increase or decrease of the slope indicates lower or higher growth rates. 1a: right ventricular end-diastolic volume; 1b: left ventricular end-diastolic volume; 1c: left ventricular mass; 1d: left ventricular mass-to-volume ratio; 1e: right ventricular ejection fraction; 1f: left ventricular ejection fraction. SDS: standard deviation score; RVEDV: right ventricular end-diastolic volume; RVEF: right ventricular ejection fraction; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVM: left ventricular mass; LMVR: left ventricular mass-to-volume ratio.

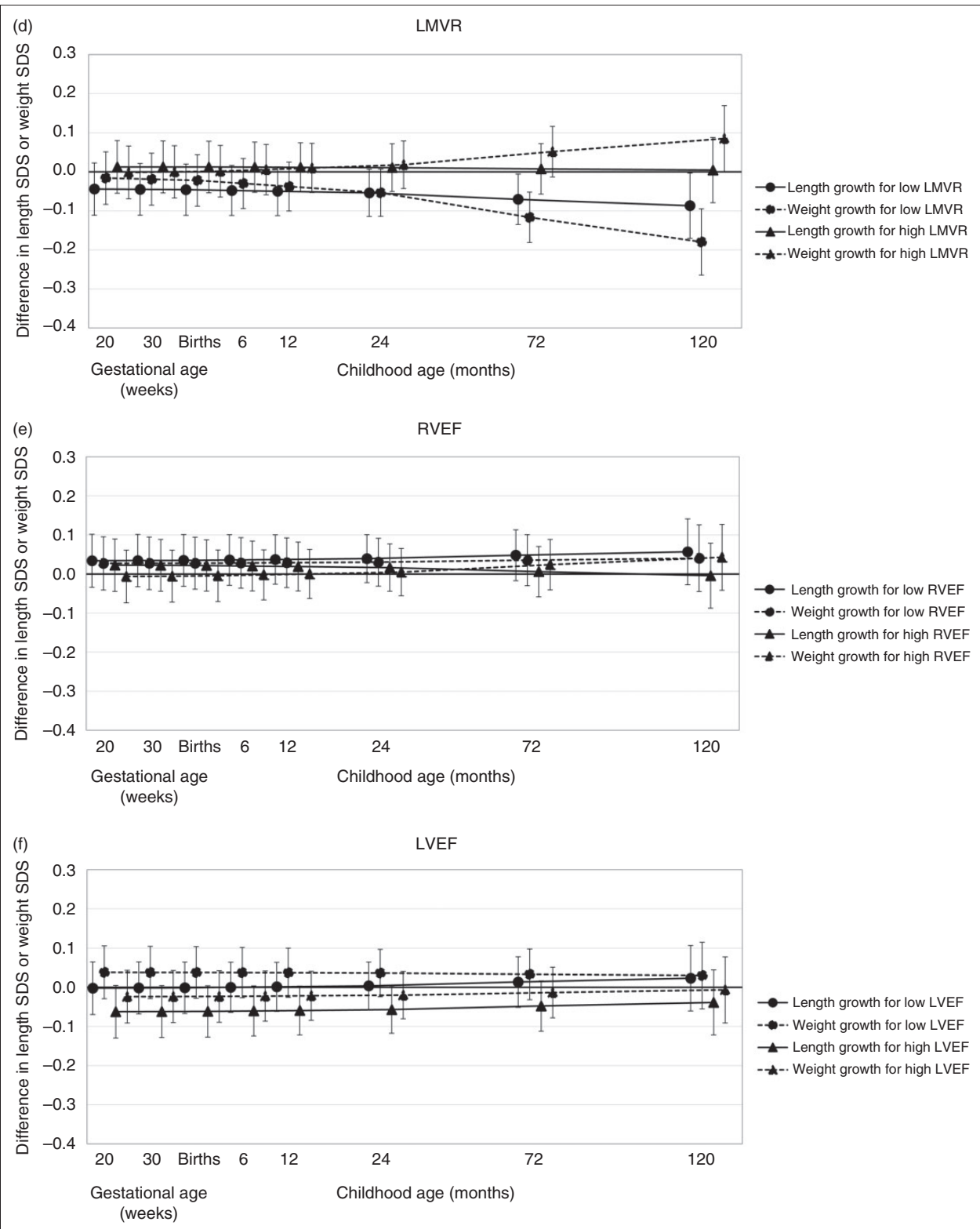


Figure I. Continued.

Early life critical periods and cardiac measures at school age

Figure 2(a) and (b) shows that fetal length and weight growth from 20 weeks' gestational age until birth was positively associated with RVEDV and LVEDV, independent from growth in other periods, or from current childhood body size ($P < 0.05$). The highest effect estimate was observed for height gain from 24 months to 6 years. Higher weight and BMI gain from 6 to 10 years was associated with lower RVEDV and LVEDV. Height gain between 24 months and 6 years was associated with higher LVM relative to current body size, while higher weight and BMI gain between 6 and 10 years was associated with lower LVM at the age of 10 years (Figure 2(c)). Weight gain between 24 months and 6 years was associated with higher LMVR, while weight gain in late pregnancy was associated with lower LMVR (Figure 2(d)). We did not observe independent associations of fetal or infant growth with RVEF or LVEF at school age (Figure 2(e) and (f)).

Discussion

In this population-based prospective cohort study, we observed that higher birth weight for gestational age was associated with higher RVEDV and LVEDV, and with lower LMVR. Longitudinal growth analyses suggest that children who are larger at birth and grow to be taller and leaner in childhood have larger hearts relative to their body size, whereas children who are smaller at birth and who are shorter and heavier in childhood have smaller hearts with a larger LMVR. Both fetal and childhood growth seem to be independently related to cardiac dimensions in childhood.

Interpretation of main findings

Adults who were born preterm or with low birth weight are at increased cardiovascular risk later in life, especially when followed by increased childhood weight gain.² In an adverse fetal environment, fetal blood flow and cardiac adaptations may lead to better short-term survival.¹ However, previous studies suggest that a mismatch reflected by a restricted fetal environment followed by an affluent postnatal environment leads to an increased risk of cardiovascular disease.²² Animal and human studies show that fetal growth restriction affects the maturation and sarcomere structure of cardiomyocytes, and causes changes in fetal haemodynamics leading to cardiac pressure and volume overload.^{23–25} These changes might affect cardiac structure and shape around the time of birth and the development of the heart in later life.^{23,25} During childhood, the heart grows in accordance with

the haemodynamic demands of a growing body.⁴ A study in adolescents observed that both birthweight and current body size were independently of each other associated with LVM, but infant growth was not.⁴ In the current study, we examined the associations of fetal, infant and childhood growth with right and left cardiac structure and function, independent of current body size and aimed to identify critical periods of growth.

Previous studies in young adults have shown that those who were born preterm had higher right ventricular mass and LVM, but lower RVEDV and LVEDV than term-born adults.^{6,9} The changes were greater in the right ventricle.⁹ In our study, we did not find associations of gestational age with cardiac structure. In our study, preterm birth averaged at 34.4 weeks' gestational age, compared with 30.3 weeks in the previous studies.^{6,9} The effects of preterm birth on cardiac structure in later life might only be present in extreme prematurity, or changes might become detectable after childhood when the heart has been exposed to more and longer periods of physical stress. Next to preterm birth, fetal growth restriction may affect cardiac development.²⁵ A study in 11-year-old children with fetal growth restriction showed shorter and more global ventricles than in children with normal fetal growth.²⁵ The Young Finns Study in 784 young adults showed a slightly larger left ventricular diameter in the adults who were born small for gestational age, but no differences in LVEDV, RVEDV or LVM.²⁶ We observed smaller ventricular volumes and mass in children who were born small for gestational age. Direct comparison with the two previous studies is difficult because they used echocardiography. Also, the indexing methods to account for current body size were different.^{25,26} Altogether, preterm birth and weight at birth might influence cardiac size and cardiac shape in later life. These changes in cardiac size and shape could also relate to subclinical cardiac dysfunction and ultimately to cardiac disease risk in later life.²⁵

We have previously observed that higher weight in fetal life, but not infant weight, were independently associated with higher LVM at the age of 6 years.²⁷ One study in 418 adolescents observed that both birth weight and current size were associated with LVM, independently of each other.⁴ We observed that children with larger ventricular volumes and mass are taller and heavier from fetal life onwards until childhood. In addition, we observed that children with relatively smaller ventricular volumes had lower height gain and higher weight gain than children with normal sized hearts in childhood, relative to current body size. Children with higher LMVR had higher weight gain in childhood than children with lower LMVR. This is in line with previous studies that show cardiac

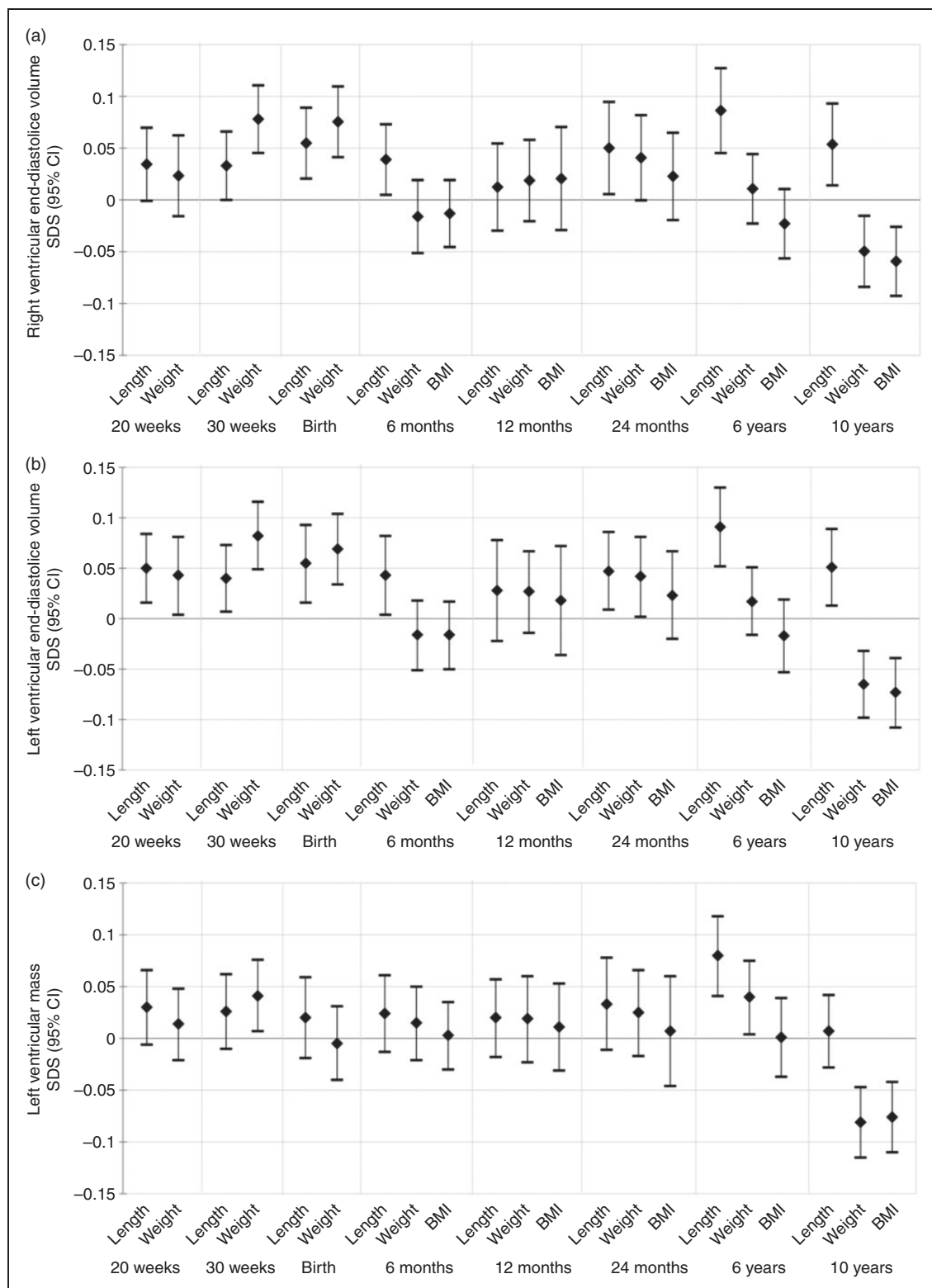


Figure 2. Associations of fetal and childhood growth measures with childhood cardiac measures from conditional analyses ($N = 2827$). Conditional growth models for length, weight, and BMI to cardiac structure at 10 years. Each point shows the strength of association ($\pm 95\%$ CI) for the period of growth from the preceding point and represents a difference from normal population growth over that period. 2a: right ventricular end-diastolic volume; 2b: left ventricular end-diastolic volume; 2c: left ventricular mass; 2d: left ventricular mass-to-volume ratio; 2e: right ventricular ejection fraction; 2f: left ventricular ejection fraction. BMI: body mass index; CI: confidence interval.

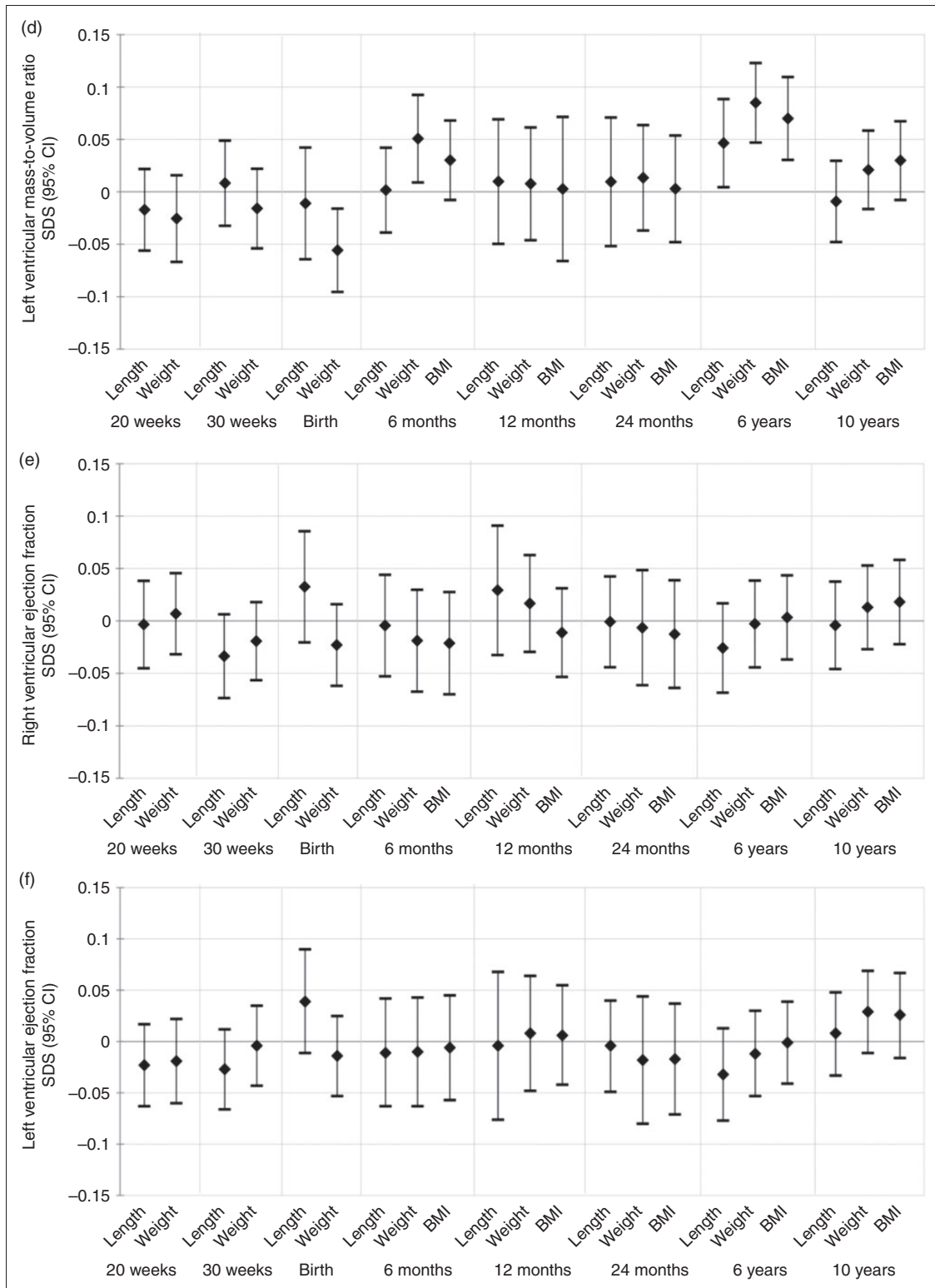


Figure 2. Continued.

remodelling in obese children.²⁸ The higher LMVR we observed could be the first sign of concentric remodeling, known to be associated with cardiac disease in adulthood.²⁹

We used conditional regression analyses to identify critical periods of growth. Both fetal and childhood growth, but not infant growth, were associated with cardiac dimensions. Our findings suggest that fetal

and childhood growth patterns influence cardiac structure at school age. We previously observed moderate tracking of cardiac measures between infancy and childhood, which became stronger later in childhood.³⁰ This tracking also continues until late adolescence and possibly into adulthood.³¹ However, it is unclear how the observed cardiac adaptations in childhood relate to adult cardiac disease. In adults, cardiac remodelling resulting in left ventricular hypertrophy is associated with cardiac disease.²⁹ Obesity in childhood is associated with left ventricular hypertrophy in later adulthood.³² However, the larger cardiac dimensions we observed in taller and leaner children might not be a sign of pathological adaptation, but of physiological adaptation. This adaptive remodelling can also be observed in preadolescent athletes.³³ We observed that a growth pattern with higher childhood weight gain was associated not only with lower RVEDV, LVEDV and LVM, but also with higher LMVR. This might be a first sign of adverse cardiac remodelling, leading to increased cardiac risk later in life. Further research is necessary to examine childhood right and left cardiac growth and remodelling and relate these to cardiac disease.

Methodological considerations

The main strengths of this study are its population-based prospective design, and the large number of fetal and child growth measurements and cardiac imaging available. The population is representative of the general Dutch population, but one should be careful when generalising our results to other countries or ethnicities. Repeated measurements allowed us to examine growth patterns and to identify critical periods of growth. By using cMRI, we were able to study the right ventricle.⁸ Some limitations need to be discussed. Of all children, 72% attended the MRI centre and 69% of those had good quality cMRI. This loss to follow-up could lead to bias if the associations of growth with cardiac measures differ between those included and not included in the analyses (Supplementary Table 2). However, we deem this unlikely. We used a 3T MRI because this was available and used in our other population-based studies. Use of this scanner could have affected image quality and maybe led to missing data because of artifacts in some scans, we consider it unlikely that this has affected the associations between growth and cardiac measures.³⁴ We standardised our measures on BSA to account for current body size. However, height and weight were measured 1.1 months before MRI. The calculated BSA might underestimate the actual BSA at time of cMRI. We adjusted all our analyses for the time difference,

but this measurement error could lead to attenuation of the effect estimates we observed. We did not observe statistical interaction between growth measures and sex. The BSA standardised measures possibly already took into account differences in body size between boys and girls. It is also possible that although boys and girls have different cardiac measures, the associations between growth and cardiac measures do not differ. Despite the fact that we adjusted for a significant number of confounders, residual confounding might be of concern, as in any observational study. In childhood, cardiac mass and size is mainly determined by lean body mass, and not by blood pressure.³⁵ This is in line with our observations, the results did not change after adding childhood blood pressure to our models (results not shown). We do not have detailed information on exercise and fitness levels, which might also influence body composition and cardiac measures.

Conclusion

Size for gestational age is related to right and left cardiac measures in mid-childhood. Relative to current body size, children who are larger at birth and grow to be taller and leaner in childhood have larger hearts, whereas children who are smaller at birth and who are shorter and heavier in childhood have smaller hearts but a larger LMVR. Both fetal and childhood growth are critical for the development of cardiac dimensions. How these differences in cardiac structure in childhood relate to adult cardiovascular disease needs to be investigated further.

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Author contribution

ES and VWVJ contributed to the concept of the work. LT, RG and VWVJ designed this study, collected data or carried out the initial analyses and interpretation of data, or drafted the initial manuscript. RvdG, WAH and AvdL designed the data collection instruments. AAR contributed to data interpretation. All authors critically reviewed and revised the manuscript for important intellectual content and approve the final manuscript as submitted and agree to be accountable for all aspects of the work.

Declaration of conflicting interests

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