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Differences in cardiac geometry in relation to body size among neonates with abnormal prenatal growth and body size at birth

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2020-12

Olander , R F W , Sundholm , J K M , Ojala , T H , Andersson , S & Sarkola , T 2020 , ' Differences in cardiac geometry in relation to body size among neonates with abnormal prenatal growth and body size at birth ' , Ultrasound in Obstetrics & Gynecology , vol. 56 , no. 6 , pp. 864-871 . https://doi.org/10.1002/uog.21972

http://hdl.handle.net/10138/338123
https://doi.org/10.1002/uog.21972

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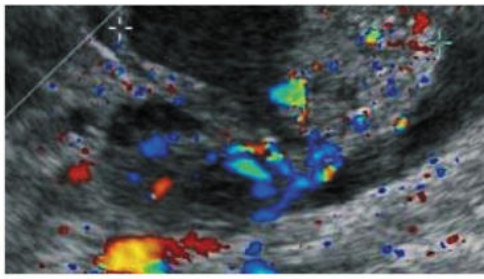

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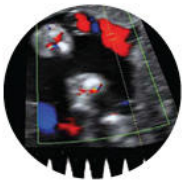

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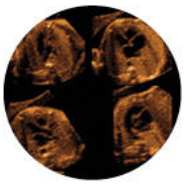

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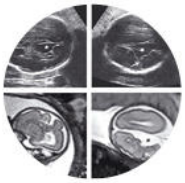

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Differences in cardiac geometry in relation to body size among fetuses with abnormal fetal growth and body size at birth

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Key words: fetal, Neonatal, abnormal intra-uterine growth, small for gestational age, large for gestational age, echocardiography

Short title: Cardiac geometry and body size in fetal growth

CONTRIBUTION

What are the novel findings of this work?

The study shows differences among cardiac dimensions relations with overall body size among foetuses with abnormal foetal growth and body size at birth.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/uog.21972

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What are the clinical implications of this work?

Left ventricular outflow tract size is underestimated in large for gestational age newborns when adjusting for body surface area (and body weight) due to influence of adiposity.

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ABSTRACT

Objectives:

Both excessive and restricted foetal growth is associated with changes in cardiac geometry and function at birth. There are significant issues when indexing cardiac parameters for body size in the neonate stage. The aim of our study was to determine to what extent cardiac geometry is dependent on body size in term and preterm neonates with restricted or excessive foetal growth and how this is affected by adiposity.

Methods:

We compared the cardiac geometry and function with body morphometrics in 174 infants born between 31 and 42 weeks of gestation, divided into three groups: 1) Small for gestational age (SGA, weight < -2 SD, n=39), 2) large for gestational age (LGA, weight >+2 SD, n=45), and appropriate for gestational age controls (AGA, weight between -2SD and +2SD, n=90).

Results:

Body size was reflected in cardiac dimensions with differences in dimensions disappearing between the SGA and AGA groups when indexed for body surface area (BSA) or thoracic circumference. The same was true for the atrial and ventricular areas of the LGA group. However, inflow- and outflow areas did not follow this trend as indexing with BSA was related with adiposity related diminished dimensions among LGA compared with AGA and SGA. Adiposity was positively associated with left ventricular mass.

We found no evidence of altered systolic function among the groups. However, the SGA group showed an increased right-ventricle fractional area change, possibly reflecting differences in the systolic function of

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the right ventricle. We found evidence of altered diastolic function among the groups, with the MVE/MVE'-ratio increased in the LGA group, while decreased in the SGA.

Conclusions:

Cardiac geometry is explained by body size in both term and preterm AGA and SGA infants. However, the nature of the relationship between body size and cardiac dimensions may be influenced by adiposity in LGA infants leading to underestimates of inflow and outflow dimensions when adjusted with BSA. Adjustments with thoracic circumference provide similar results as BSA.

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Introduction

Aberration in foetal size during gestation and longitudinal deviations in foetal growth are commonly related to the impact of maternal or gestational disease on placental function and transfer of nutrients and oxygen. Maternal cardiovascular disease, such as poorly controlled hypertension or preeclampsia, and pregestational diabetes are commonly associated with abnormal foetal growth.

Previous studies have demonstrated that foetal growth restriction is related to changes in cardiac geometry and function. Restricted growth is associated with a more globular structure of the left and the right ventricle *in utero* [1-2] and during infancy [3]. Restricted growth is also associated with other changes in cardiac geometry and function [4-5].

Historically cardiomegaly, severe hypertrophy and left ventricular outflow obstruction were observed in the setting of maternal pregestational diabetes [6-7]. Structural changes, such as increased septal and posterior wall thickness, can still be seen in infants of diabetic mothers postnatally [8]. Adiposity has also been associated with changes in heart structure – with especially low body fat index being related to thicker septal and ventricular walls [9].

Assessing the impact of gestation on the growth of the foetus is key when differentiating the effect of prenatal and postnatal factors on the cardiovascular phenotype [10]. The definitions of abnormal foetal growth vary, and though body surface area (BSA) is the recommended method for adjusting cardiac geometry for body size in the child [11] there is lack of consensus concerning how geometry should be adjusted in the preterm or term newborn period [12]. For instance, left ventricle volume has been suggested to best follow $BSA^{1.50}$ [13] or $BSA^{1.38}$ [14], and the use of neonatal z-scores based on a normal birth weight or BSA range might not be appropriate for neonates with abnormal body size at birth.

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The aim of our study was to determine to what extent cardiac geometry is dependent on body size in preterm and term neonates with restricted or excessive foetal growth and how geometry is affected by adiposity. We have previously reported on the important relations between regional foetal body size and peripheral arterial morphology in the same study population [15].

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Methods

Subjects

This is a cross-sectional study including 174 Caucasian neonates recruited at the Helsinki University Hospital between November 2011 and January 2014. The neonates were born at weeks 31-42 and recruited within days (5-184 h) from birth. To be included in the study, the infants had to be healthy at birth with no medication. Patients with any major cardiovascular anomalies, chromosomal anomalies or other diseases, abnormalities or syndromes were excluded. Minor cardiac abnormalities of no clinical significance, such as a very small muscular ventricular septal defect, mild pulmonary stenosis or small patent foramen ovale or small ductus arteriosus were included.

The neonates were recruited into three groups: 1) Small for gestational age (SGA) with a birth weight less than -2 standard deviations (SD) (n=39), 2) large for gestational age (LGA) (n=45) with a birth weight more than +2 SD, and controls, appropriate for gestational age (AGA) (n=90) with birth weights between -2SD and +2SD). SD's for gestational age were based on national Finnish foetal growth curves [16]. Study groups are illustrated in figure 1.

Hospital charts and registries were retrospectively assessed for maternal and gestational data, with maternal height and weight being obtained from data recorded before pregnancy. Maternal diabetes was classified according to the White classification [17]. Preeclampsia was defined as hypertension (>140 mm Hg systolic or >90 mm Hg diastolic blood pressure on repeat visits, with onset after week 20) together with >0.3 g of protein in a 24-hour urine sample.

Anthropometrics and clinical parameters

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The length, head circumference and body weight of the infants were recorded at birth to the closest unit of millimeter and gram. These measurements were performed using the Seca 717 set of scales, equipped with the Seca 231 measuring rod. The thoracic circumference (TC) was measured at the level of processus xiphoideus and the circumference of the thigh at the midpoint between the medial aspect of the knee and the junction between the thigh and torso. BSA was calculated from body weight and length using the Haycock formula [18].

Cardiac geometry

The subjects were examined by one investigator (TS) with transthoracic echocardiography, using the Vivid 7 ultrasound system (GE Medical Systems, Horten, Norway) equipped with the 7 MHz 7S-transducer. Measurements were made offline from B-mode images by one observer (RO) from standard apical, parasternal and suprasternal short and long-axis views, using the Excelera (R3.3L1) workstation. Measurements were made in accordance with the American Society of Echocardiography guidelines [19-20]. The thickness of the septal and left ventricle posterior wall, as well as the lumen dimensions, were measured in the parasternal short axis view in end-diastole. Left ventricle mass was calculated with Deveraux' formula:

$$Left\ ventricle\ mass\ (g)$$
$$= 0.8\{1.04[([Ventricle\ diastolic\ dimension\ +\ Septal\ wall\ thickness$$
$$+\ Posterior\ wall\ thickness]^3\ -\ Ventricle\ diastolic\ dimension^3)]\}\ +\ 0.6$$

Base to apex lengths and the basal diameters of both ventricles were measured in end-diastole, and atrial areas measured at maximum in systole from the apical four and two chamber views. Basal sphericity index was defined as ventricle length divided by basal diameter, and mid-cavity sphericity index as ventricle

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length divided by ventricle short axis diameter at mitral valve leaflet tips, both in end-diastole. The volume of the ventricle was calculated according to the biplane area/length-method using the following formula:

$$Left\ ventricular\ volume\ (ml) = \frac{0.85 * A_1 * A_2}{L}$$

, where A_1 is the left ventricular diastolic area in the apical four-chamber view, A_2 is the diastolic area in the apical two-chamber view, and L is the length of the ventricle in the apical four-chamber view.

Right ventricle mid-cavity sphericity index was defined as ventricle length divided by the mid-cavity dimension in end-diastole. The diameters of the aortic valve and pulmonary valves were obtained from the parasternal long axis view and the diameter of the aortic isthmus from the suprasternal long axis view. The cardiac phase was monitored throughout the echocardiographic examination with ECG.

Observer variability was assessed by determining the coefficient of variation for the measurements, measured for 10 patients.

Cardiac function

Cardiac function was measured for both the left ventricle and the right ventricle. Left ventricle ejection fraction was determined using the Simpson bi-plane method. Mitral valve pulsed-wave and tissue Doppler E- and E'-waves (MVE and lateral MVE', respectively) were determined from the apical view. The right ventricle systolic function was assessed by measuring the right ventricle fractional area change.

Blood pressure

The oscillometric measurement of systolic and diastolic blood pressure from the right brachial artery and in the supine position was assessed with neonate sized cuffs using the Philips IntelliVue P70 monitoring

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unit. Three measurements were recorded at rest. The pulse pressure was calculated from the mean of these measurements.

Data analysis

The aim of the data analysis was to compare cardiac dimensions between the SGA, LGA groups and the AGA (control) group, adjusting the cardiac dimension for body size, and to assess the potential impact of infant adiposity and maternal disease. Distributions were assessed for outliers using histograms and analysed for normality using the Shapiro-Wilk test. SGA and LGA groups with normal distributions were compared with AGA using one-way analysis of variance (ANOVA), with a post-hoc Tukey's test. Not normally distributed groups were compared using Kruskal-Wallis test with a post-hoc Dunn's test. The distribution of categorical variables was assessed by using Pearson's Chi-Square test. The results of the Dunn's test and Pearson's Chi-Square test were Bonferroni corrected. This analysis was done both for background variables (table 1) and those cardiac parameters that were not indexed for body size (table 3).

Issues of allometry

To compare neonatal study groups of different body sizes we initially explored indexing the cardiac dimensions for TC and BSA raised to different exponents in the AGA control group, after which we performed simple linear regression analyses with the transformed body size parameter as the independent and indexed cardiac parameter as the dependent variable. The aim of the regression analyses was to assess residual association in the AGA group indicated by a low coefficient of determination (R^2). The indexing method with the lowest residual association was then chosen to index the cardiac parameters. The indexed cardiac variables were then compared similarly to the background and non-indexed parameters, shown in table 2.

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Role of adiposity and background parameters

The cardiac parameters where then further analysed with simple regression analysis in relation to infant adiposity using thigh circumference divided by head circumference as a surrogate marker for adiposity (table 4), as thigh circumference has been shown to be associated with adiposity in neonates [21]. Those parameters that varied significantly among groups, when properly indexed, were further assessed with analysis of co-variance (ANCOVA), with adiposity (thigh to head circumference -ratio), patent ductus arteriosus, age at examination, mode of delivery, preeclampsia, pregestational diabetes, maternal BMI and sex entered as covariates. Data was analysed using SPSS version 23.

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Results

Maternal and neonatal background characteristics

The background characteristics are displayed in table 1. Pregestational diabetes was more prevalent in the LGA group, and preeclampsia was found predominantly in the SGA group. Maternal disease of clinically milder forms was also found in the AGA subgroup. No statistically significant difference in patency of the ductus arteriosus was observed between groups. Maternal weight and body mass index (BMI) were higher in the LGA group while both height and weight tended to be lower in the SGA group. The thigh to head circumference -ratio was highest in the LGA group and lowest in the SGA group, reflecting the level of adiposity and leanness. Neonatal body size and anthropometric parameters reflected inclusion criteria for the study groups with a statistically non-significant difference in sex distribution. Systolic BP was highest among LGA. Gestational age and age at examination did not vary among the groups. The ratio of caesarean sections was higher for both SGA and LGA.

For the blood pressure measurements, the 95% limits of agreement of the parallel measurements were ±6 mmHg around the mean for systolic blood pressure and ±7 mmHg for diastolic blood pressure with CVs of 4.5% and 8.7%, respectively.

Issues of allometry

In these analyses, the best performing indexing methods for one-dimensional parameters were $BSA^{0.50}$ or TC (no exponent). BSA (no exponent) and TC squared performed best for two-dimensional parameters. For the left ventricle volume, $BSA^{1.50}$ and $BSA^{1.38}$ performed equally well (not shown). $BSA^{1.50}$ was, however, chosen due to it being intuitively relatable to volume. Interestingly, $TC^{2.50}$ performed well, while $TC^{3.0}$ had a significant ($p=0.014$) residual association.

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The impact of indexing for different exponents is illustrated in supplemental figures 1-3, and in supplemental table 1. Not indexing led to an almost exponential association between ventricular length and BSA (supplemental figure 1), indexing with BSA lead to an over indexing of the larger infants (supplemental figure 2), while indexing with $BSA^{0.50}$ removed the residual association (supplemental figure 3).

Cardiac parameters

Cardiac dimensions indexed for BSA are shown in table 2. Indexing for TC provided similar results (data not shown). For the left heart, the LGA group consistently showed a smaller aortic diameter, both for the valve and the isthmus when indexed for $BSA^{0.50}$ or TC. Similarly, the LGA group showed a decreased ventricular end-diastolic dimension, non-significant when indexed for BSA, but significant when indexed for TC. No difference between study groups was seen for left atrial area, ventricular area or volume. A non-significant trend for increased left ventricular mass indexed for BSA was found among LGA ($p=0.06$).

For the right heart, the pulmonary valve diameter was smallest in the LGA group. The right ventricular length was lowest in SGA and highest among LGA. There were no group differences in the right atrial or ventricular area.

Cardiac sphericity indices and function are summarised in table 3. Both basal and mid-cavital sphericity index varied between the groups – with the right ventricle showing a higher index for the LGA, indicating that the ventricles of the LGA group are less spherical. There was no statistically significant difference in left ventricular sphericity. Sphericity was similar between SGA and AGA overall.

For cardiac function, there were no differences among the groups in left ventricle ejection fraction. However, signs of altered diastolic function could be seen, with a significantly lower, mitral valve inflow

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E-wave peak velocity (MVE) in SGA, and higher MVE in LGA. The mitral valve E'-wave peak velocity (MVE') was decreased among LGA. This was reflected in a higher MVE/MVE' ratio among LGA, while smaller among SGA. For the right ventricle, the SGA group showed a higher fractional area change.

The intraobserver variability ranged from 3 % (aortic valve dimension) to 17 % (left ventricle end-diastolic area). Interobserver variability was assessed by comparing the measurements of RO with those of TS, and the variability ranged between 4% (pulmonary valve dimension) and 24% (left atrial systolic area).

Role of adiposity and background parameters

Using thigh to head circumference –ratio as a surrogate marker we assessed the association between adiposity and indexed cardiac dimensions with simple linear regression analyses (table 4). Overall, results were similar using BSA and TC as indexing parameters (TC data not show). Aortic valve dimension (supplemental figure 4) and left ventricle end-diastolic dimension were negatively associated with adiposity, while left ventricle mass was positively associated with adiposity (supplemental figure 5). No significant associations for atrial or ventricular areas, volumes or other atrial dimensions were found. Right ventricle length as well as right ventricle and atrial areas were positively associated with adiposity.

The left ventricle basal sphericity index was not associated with adiposity, while there was a weak association with mid-cavity index. The right ventricle sphericity indices were not associated with adiposity.

Overall, in ANCOVA, the addition of covariates to the analyses had a low impact comparing the groups. For aortic valve dimension, adding adiposity and pregestational diabetes as covariates attenuated the statistical difference between LGA and AGA, while only pregestational diabetes attenuated the differences for aortic isthmus dimension. For interventricular septum dimension, indexed for BSA, none of the covariates significantly attenuated the difference between SGA and AGA. For MVE', adiposity and

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pregestational diabetes attenuated the difference between LGA and AGA. For MVE/MVE', adiposity and PDA attenuated the group differences. For the right ventricle fractional area change, adding adiposity as a covariate attenuated the difference between SGA and AGA. Adjusting for sex had no effect on the group differences for any of the aforementioned variables.

We also examined the effect of a PDA on left and right atrial and ventricular areas and left ventricular mass. Adding PDA as a covariate did not alter the group differences.

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Discussion

Our results suggest that cardiac dimensions in neonates are associated with body size, even in the presence of excessive or restricted foetal growth. However, the association becomes more complex in the presence of significant adiposity. Furthermore, there seems to be no true difference in whether the cardiac parameters are indexed for TC or BSA. This is similar to earlier findings in the field where neonatal BSA and body weight have been determined to be almost equally good indexing methods [12].

Although we found that indexing one-dimensional parameters with the square root of BSA (or TC) was optimal for AGA and SGA neonates, certain dimensions were, however, underestimated among LGA due to the influence of adiposity on BSA. Our results question the use of BSA (or body weight) as a universal parameter to adjust cardiac dimensions in the setting of abnormal neonatal body size and increased adiposity. The negative association between left ventricle outflow tract and adiposity suggest over indexing in the LGA group. Inflow- and outflow tract dimensions are likely better predicted by lean body mass compared with BSA in the setting of significant adiposity.

Earlier studies have shown increased septal thickness in LGA or in the presence of maternal diabetes, [6-8, 22] as well as a thicker left ventricular posterior free wall [23]. Septal hypertrophy has, earlier been demonstrated in intra uterine growth restricted infants [23], but smaller ventricular walls have also been reported [25]. We found no statistically significant difference among the groups for the septal thickness, in contrast to these earlier studies. The same was true for left ventricular and right ventricular sphericity, where we found no impact of abnormal body size [1, 3, 26].

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Left ventricle mass was increased among the LGA group and displayed a positive association with adiposity. This could be related to the increased presence of both pregestational and gestational diabetes in the LGA group as previously reported [6-8] but could also be independently caused by the adiposity in itself.

Our results suggest no impact of abnormal body size on left ventricular ejection fraction. Minor alterations in diastolic function has, similar to our findings, been reported earlier among SGA at the neonate stage [2] and at 6-months of age [5], and among LGA as well [27]. The exact nature of the diastolic function and its clinical impact is somewhat unclear and requires further studies.

Our results can be seen as rigid, as our sample size is sufficient, and our inclusion criteria for the SGA and AGA groups conservative, with the two groups consisting of the 2.3 most extreme body weight percentiles for gestational age. We have also controlled for maternal disease including diabetes. A major limitation is that we did not differentiate between symmetric and asymmetric growth restriction. In addition, we had no direct measure of body composition and maternal medication during gestation was not recorded. As the variability in echocardiographic measurements at the neonate stage is rather large, our sample size may also have impacted on our ability to detect group differences. Age at examination did not differ among the groups but should however be kept in mind as a potential cofounder.

In conclusion, this study shows that the impact of adiposity on BSA limits the use of this parameter in the evaluation of ventricular in- and outflow tracts, and the aortic isthmus, in the setting of abnormal neonatal body size. Indexing with BSA leads to over indexing of these parameters and the false interpretation of diminished dimensions in the setting of excessive foetal growth and LGA body size. This also raises questions concerning the use of indexing techniques and foetal Z-scores during the third trimester in addition to the neonate stage. Earlier studies have pointed out the lack of standardised nomograms at the

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neonate stage [28], and our study raises further questions on the use of indexing measures for children with differing body composition. Further studies are thus needed to explore relations between body composition and cardiac dimensions in the SGA and LGA neonate with abnormal body size at birth and to determine Z-scores for these foetuses and neonates.

Acknowledgments

We wish to acknowledge the work of the personnel at the neonatal surveillance unit at the Helsinki Women's Hospital as well as the families who participated in our study. This study has been supported by grants from the Sigrid Jusélius Foundation, The Medical Society of Finland and the Stockmann. Foundation. The authors are not aware of any potential conflicts of interest.

Conflicts of interest: The authors have no conflicts of interest to declare.

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Figure legends

Figure 1, showing recruitment groups and distribution of maternal disease. SGA= small for gestational age, AGA= appropriate for gestational age, LGA= large for gestational age. PGDM = pre-gestational diabetes mellitus, PE= preeclampsia.

Supplemental figure 1, showing the association between left ventricular length in diastole and body surface area. AGA = appropriate for gestational age SGA= small for gestational age, LGA= large for gestational age.

Supplemental figure 2, showing the association between left ventricular length in diastole indexed with body surface area and body surface area. AGA = appropriate for gestational age SGA= small for gestational age, LGA= large for gestational age. For AGA: B=-36.014, R^2=0.374. p<0.001.

Supplemental figure 3, showing the association between left ventricular length in diastole indexed with the square root of the body surface area and the square root of body surface area. AGA = appropriate for gestational age SGA= small for gestational age, LGA= large for gestational age. For AGA: B=1.567, R^2=0.013, p=0.291.

Supplemental figure 4, showing the association between aortic valve dimension indexed with the square root of body surface area (cm/m) and thigh circumference to head circumference ratio (no unit). AGA = appropriate for gestational age, SGA= small for gestational age, LGA= large for gestational age. B=-1.080, R^2=0.166, p<0.001.

Supplemental figure 5, showing the association between left ventricle mass indexed with body surface area (g/m^2) and thigh circumference to head circumference ratio (no unit). AGA = appropriate for

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gestational age, SGA= small for gestational age, LGA= large for gestational age. B=20.073, R^2=0.032, p=0.020.

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Table 1. Study population background characteristics in appropriate for gestational age (AGA), small for gestational age (SGA) and large for gestational age (LGA) infants.

	AGA		SGA		LGA		p-value
N	90		39		45		
Maternal characteristics							
Maternal age, years	31.6	±5.4	32.5	±4.6	31.1	±4.9	p=0.422
Maternal weight, kg	63	57-73	60	55-65	68	61-89	p=0.002
Maternal height, cm	167	±5	164	±6	167	±6	p=0.038
Maternal BMI, kg/m^2	23.0	20.5-25.1	22.3	19.7-24.5	25.2*	22.5-29.2	p=0.003
Smoking, n (%)	13 (14 %)		1 (3%)		2 (4%)		p=0.094
Gestational diabetes (A1-2)	14 (16%)		4 (10%)		9 (20%)		p=0.470
Pregestational diabetes (B-D, R, RF, T)	9 (10%)		0* (0%)		34* (76%)		p<0.001
Preeclampsia	6 (7%)		13* (33%)		2 (4%)		p<0.001
Neonatal characteristics							
Sex (M/F)	51/39		14/25		20/25		p=0.075
Age at examination, h	34	22-66	56	29-84	32	18-54	p=0.026
Gestational age, weeks	35.6	34.2-39.6	36.7	34.5-38.9	36.2	35.4-37.8	p=0.962
Birth weight, g	3030	2274-3609	1910‡	1755-2350	4205‡	3818-4565	p<0.001
Birth length, cm	48	46-51	43‡	42-43	51‡	50-53	p<0.001
Head circumference, cm	33.5	31.5-35.2	31.3‡	30.0-32.0	35.2‡	34.0-36.3	p<0.001
Thigh circumference, mm	143	±22	116‡	±14	177‡	±13	p<0.001
Thigh to head circumference ratio	0.42	±0.04	0.37‡	±0.04	0.50‡	±0.03	p<0.001
Body surface area, m^2	0.205	0.172-0.232	0.152‡	0.145-0.175	0.249‡	0.234-0.264	p<0.001
Thoracic circumference, mm	318	294-340	280‡	265-300	358‡	349-370	p<0.001
Heart rate (bpm)	131	125-140	130	120-145	130	125-140	p=0.858
Systolic blood pressure, mmHg	68	63-74	69	64-76	72*	67-78	p=0.018
Diastolic blood pressure, mmHg	43	38-47	44	40-52	42	36-47	p=0.026
Pulse blood pressure, mmHg	26	21-29	25	22-27	31‡	26-36	p<0.001
Patent ductus arteriosus	27 (30%)		8 (21%)		19 (42%)		p=0.053
Type of partum (vaginal/caesarian) [§]	59/30		18/21*		19/26*		p=0.039

The data is presented as mean ± SD, or median with interquartile range, or percentage. The ± sign indicates a normal distribution, while the – sign gives the interquartile range for the non-parametric data. The p-value is the p-value of the ANOVA, Kruskal-Wallis test or Pearson Chi-Square with the asterisk indicating a significant difference from the AGA group in the post-hoc test. *, †, ‡ correspond to a p-value of <0.05, <0.01 and <0.001, respectively. [§]Type of partum missing for one patient in the AGA-group.

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Table 2. Neonatal cardiac dimensions indexed for $BSA^{0.50}$, BSA or $BSA^{1.50}$ in appropriate for gestational age (AGA), small for gestational age (SGA) and large for gestational age (LGA) infants.

Left heart	AGA		SGA		LGA		
Atrium, indexed for BSA							
Left atrial area (cm^2/m^2)	9.1	±1.9	9.2	±1.9	8.9	±1.7	p=0.740
Ventricle, indexed for $BSA^{0.50}$							
Left ventricle length (cm/m)	6.5	±0.7	6.7	±0.6	6.6	±0.5	p=0.546
Left ventricle basal dimension (cm/m)	2.9	24-3.3	3.1	2.6-3.4	2.7	2.4-3.3	p=0.284
Left ventricle end-diastolic dimension (cm/m)	4.1	±0.4	4.1	±0.4	3.9	±0.4	p=0.083
Left ventricle posterior wall dimension (cm/m)	0.53	±0.11	0.58	±0.13	0.56	±0.11	p=0.064
Interventricular septal dimension (cm/m)	0.50	0.43-0.60	0.52	0.46-0.59	0.54	0.46-0.61	p=0.260
Ventricle, indexed for BSA							
Interventricular septal dimension (cm/m^2)	1.2	1.0-1.3	1.3‡	1.2-1.5	1.1	0.9-1.2	<0.001
Left ventricle area (cm^2/m^2)	18	±4	18	±2	17	±2	p=0.472
Left ventricle mass (g/m^2)	29	25-33	29	25-32	32	27-36	p=0.060
Ventricle, indexed for $BSA^{1.50}$							
Left ventricle volume (ml/m^3)	45.2	38.8-53.0	43.3	26.9-47.2	44.1	36.4-50.8	0.165
Aortic, indexed for $BSA^{0.50}$							
Aortic valve diameter (cm/m)	1.4	±0.2	1.4	±0.1	1.3‡	±0.1	p<0.001
Aortic isthmus diameter (cm/m)	1.0	±0.2	1.0	±0.1	0.9†	±0.1	p=0.012
Right heart							
Atrium, indexed for BSA							
Right atrial area (cm^2/m^2)	10	8-12	10	8-11	10	9-11	p=0.671
Ventricle, indexed for $BSA^{0.50}$							
Right ventricle length (cm/m)	5.8	5.5-6.2	5.7	5.3-6.1	6.1*	5.8-6.6	p=0.003
Right ventricle basal dimension (cm/m)	2.9	±0.4	2.8	±0.4	2.8	±0.4	p=0.057
Right ventricle mid-cavity dimension (cm/m)	2.9	±0.5	2.7*	±0.4	2.7	±0.4	p=0.032
Ventricle, indexed for BSA							
Right ventricle area (cm^2/m^2)	14	±3	14	±3	15	±2	p=0.199

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Pulmonary, indexed for BSA$^{0.50}$							
Pulmonary valve diameter (cm/m)	1.8	1.6-2.0	1.8	1.7-1.9	1.7	1.5–1.8	p=0.046

BSA = body surface area. The data are presented as mean ± SD, or median with interquartile range, or percentage. The ± sign indicates a normal distribution, while the – sign gives the interquartile range for the non-parametric data. The p-value is the p-value of the ANOVA (normal distribution) or Kruskal-Wallis test (not normal distribution) with the asterisk indicating a significant difference from the AGA group in post-hoc tests. *, †, ‡ correspond to a P-value of <0.05, <0.01 and <0.001 respectively.

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Table 3. Neonatal cardiac geometry and function in subgroups (non-indexed) in appropriate for gestational age (AGA), small for gestational age (SGA) and large for gestational age (LGA) infants.

	AGA		SGA		LGA		
Left heart, geometry							
Left ventricle basal sphericity index (no unit)	2.3	±0.4	2.3	±0.3	2.4	±0.4	p=0.286
Left ventricle mid cavity sphericity index (no unit)	1.6	1.5-18	1.6	1.4-19	1.7	1.5-1.8	p=0.214
Right heart, geometry							
Right ventricle basal sphericity index (no unit)	2.1	±0.3	2.1	±0.3	2.2*	±0.4	p=0.026
Right ventricle mid cavity sphericity index (no unit)	2.1	1.8-2.3	2.2	2.0-2.4	2.2*	2.0-2.5	p=0.010
Left ventricle, function							
Systolic function							
Left ventricle ejection fraction (Simpson bi-plane) (%)	51	±8	51	±7.5	54	±7.5	p=0.148
Diastolic function							
MVE (cm/s)	58	51-67	50†	41-55	70‡	61-77	p<0.001
MVE' (cm/s)	7.8	6.7-8.4	7.4	6.8-8.6	6.9*	6.1-7.9	p=0.013
MVE/MVE' (no unit)	7.4	6.3-8.9	6.2*	5.1-7.7	9.9*	8.2-11.8	p<0.001
Right ventricle, function							
Systolic function							
Right ventricle fractional area change (%)	25	20-33	36‡	27-43	25	16-30	p<0.002

GA= gestational age, BSA = body surface area, MVE = mitral valve E-wave peak velocity, MVE' = mitral valve lateral E'-wave peak velocity. The data are presented as mean ± SD, or median with interquartile range, or percentage. The ± sign indicates a normal distribution, while the – sign gives the interquartile range for the non-parametric data. The p-value is the p-value of the ANOVA (normal distribution) or Kruskal-Wallis test (not normal distribution) with the asterisk indicating a significant difference from the AGA group in post-hoc tests. *, †, ‡ correspond to a p-value of <0.05, <0.01 and <0.001 respectively.

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Table 4. Simple linear regression analyses with thigh to head circumference –ratio as independent variable and cardiac dimension indexed for BSA or $BSA^{0.50}$ as dependent variable for the entire study sample. Note that sphericity indices are not indexed.	
Left heart	
Atrium	
Left atrial area (cm^2/m^2)	B=-0.266, R^2=0.000, p=0.908
Ventricle	
Left ventricle length (cm/m)	B=-0.219, R^2=0.001, p=0.771
Left ventricle basal dimension (cm/m)	B=0.041, R^2=0.001, p=0.950
Left ventricle end-diastolic dimension (cm/m)	B=-1.593, R^2=0.063, p=<0.001
Left ventricle posterior wall dimension (cm/m)	B=-0.037, R^2=0.000, p=0.801
Interventricular septal dimension (cm/m)	B=0.278, R^2=0.017, p=0.089
Interventricular septal dimension (cm/m^2)	B=-1.288, R^2=0.071, p<0.001
Left ventricle area (cm^2/m^2)	B=-1.649, R^2=0.002, p=0.581
Left ventricle mass (g/m^2)	B=20.073, R^2=0.032, p=0.020
Left ventricle volume (ml/m^3)	B=3.536, R^2=0.000, p=0.788
Left ventricle basal sphericity index (no unit)	B=-0.061, R^2=0.000, p=0.894
Left ventricle mid cavity sphericity index (no unit)	B=0.570, R^2=0.027, p=0.033
Aortic	
Aortic valve diameter (cm/m)	B=-1.080, R^2=0.166, p<0.001
Aortic isthmus diameter (cm/m)	B=-0.252, R^2=0.010, p=0.203
Right heart	
Atrium	
Right atrial area (cm^2/m^2)	B=6.151**,** R^2=0.043, p=0.007
Ventricle	
Right ventricle length (cm/m)	B=2.645, R^2=0.080, p<0.001
Right ventricle basal dimension (cm/m)	B=0.707, R^2=0.011, p=0.178
Right ventricle mid-cavity dimension (cm/m)	B=0.882, R^2=0.014, p=0.128
Right ventricle area (cm^2/m^2)	B=8.308, R^2=0.041, p=0.008
Right ventricle basal sphericity index (no unit)	B=0.516, R^2=0.009, p=0.226
Right ventricle mid cavity sphericity index (no unit)	B=24.617, R^2=0.003, p=0.493
Pulmonary	
Pulmonary valve diameter (cm/m)	B=-0.360, R^2=0.009, p=0.213
B= unstandardised coefficient, R^2 = non-adjusted R-square.	

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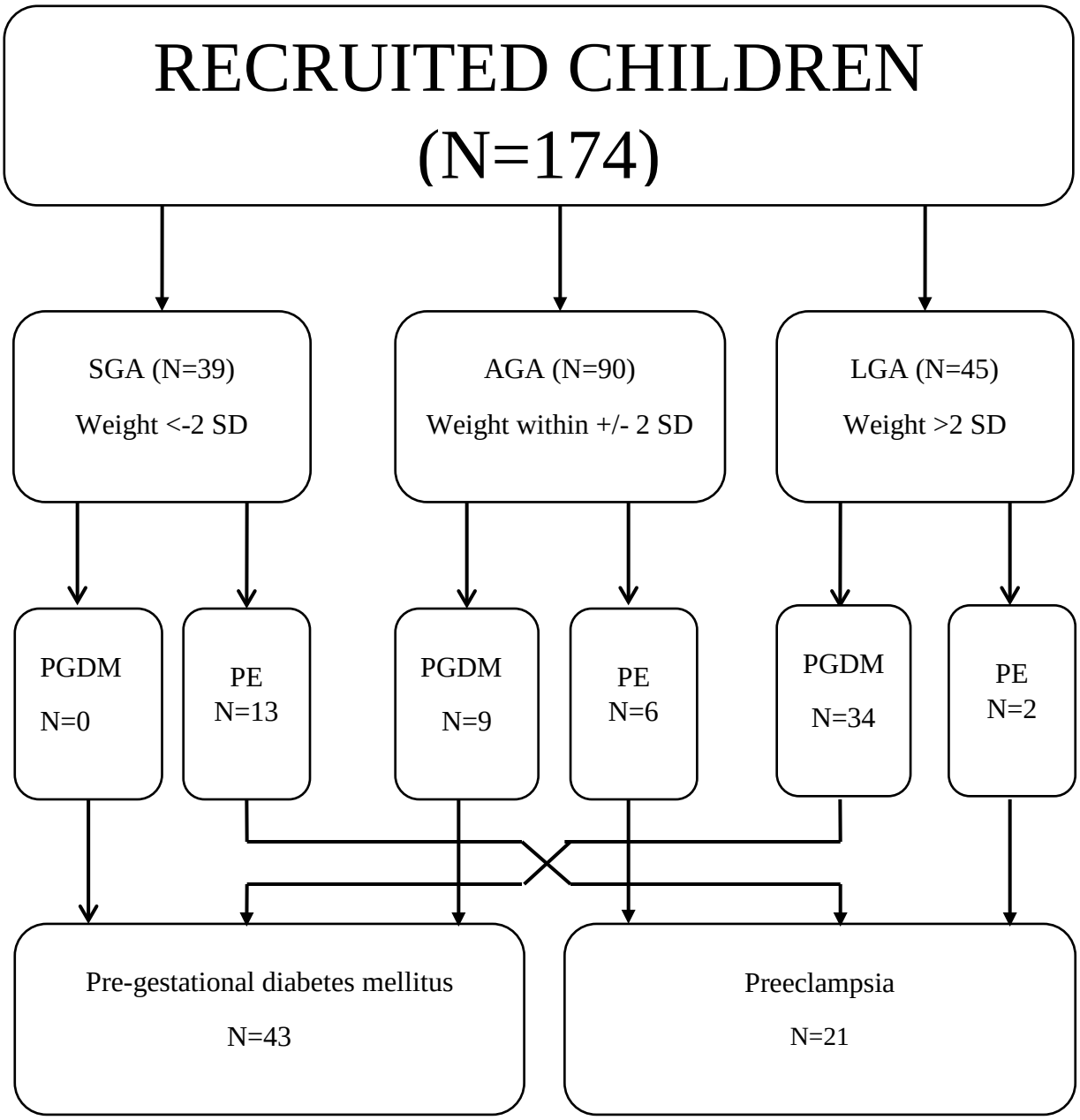

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