The influence of birth weight on fetal cardiac indices at 35–37 weeks' gestation

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What are the novel findings of this work

Fetuses with birthweight <10th percentile, compared to those with birthweight ≥10th percentile, had more globular right ventricles and reduced left and right ventricular function. There was a linear association between cardiac morphological and functional indices with birthweight z-score, but not with uterine artery pulsatility index z-score or cerebroplacental ratio z-score, which are indirect markers of placental perfusion and fetal oxygenation, respectively.

What are the clinical implications of this work

The differences in fetal cardiac indices between small and appropriately grown fetuses may be part of a normal physiological response to change in fetal size rather than part of a pathological adaptation to abnormal placental perfusion and fetal oxygenation.

ABSTRACT

Background: Echocardiographic studies have reported that fetuses with low birth weight, compared to those with normal birthweight, have globular hearts and reduced cardiac function. Dichotomizing continuous variables, such as birthweight, may be helpful in describing pathology in small studies but can prevent us from identifying physiological responses in relation to change in size.

Objective: To explore associations between fetal cardiac morphology and function, with birthweight, as a continuous variable, as well as uterine artery pulsatility index (UtA-PI), as an indirect measure of placental perfusion, and the cerebroplacental ratio (CPR), as an indirect measure of fetal oxygenation.

Methods: Prospective study of 1,498 women with singleton pregnancies undergoing routine ultrasound examination at 35^{+0} - 36^{+6} weeks' gestation. Pregnancies complicated by pregestational and gestational diabetes mellitus, chronic hypertension, pregnancy induced hypertension, or preeclampsia were excluded from the analysis. Conventional and more advanced echocardiographic modalities, such as speckle tracking, were used to assess fetal cardiac function in the right and left ventricle. The morphology of the fetal heart was assessed by calculating the right and left sphericity index. In addition, the pulsatility index of the uterine arteries (UtA-PI), umbilical arteries (UA-PI) and middle cerebral arteries (MCA-PI) was determined and the cerebroplacental ratio (CPR) was calculated by dividing MCA-PI by UA-PI. Multiple linear regression models were used to assess determinants of fetal echocardiographic parameters.

Results: The study population included 146 (9.7%) small for gestational age (SGA) fetuses with birthweight <10^{th} percentile and 68 (4.5%) with fetal growth restriction (FGR). In the SGA and FGR groups, compared to the non-SGA and non-FGR fetuses, there was a more globular right ventricle, reduced left and right ventricular systolic function, and from the left ventricular diastolic functional indices, the E/A ratio was increased. There was a linear association between right ventricular sphericity index, indices of left and right ventricular systolic function and E/A ratio with birthweight z-score. There were no significant associations between cardiac morphological and functional indices with UtA-PI z-score or CPR z-score.

Conclusion: This screening study at 35-37 weeks' gestation has demonstrated that the only determinant of fetal cardiac morphology and function is birthweight. This suggests

that the differences in fetal cardiac indices between small and appropriately grown fetuses may be part of a normal physiological response to change in fetal size rather than part of a pathological adaptation to abnormal placental perfusion and fetal oxygenation.

INTRODUCTION

Fetal echocardiographic studies have consistently reported that fetuses with low birth weight, compared to those with normal birthweight, have globular hearts and reduced cardiac function.[1-11] However, defining smallness relies on arbitrary birthweight cut-offs, such as the 10th or 3rd percentile [12,13] and although dichotomizing continuous variables, such as birthweight, may be helpful in describing pathology in small studies it can prevent us from identifying physiological responses in relation to change in size.

We carried out comprehensive assessment of fetal cardiac morphology and function in a large screening study at 35-37 weeks of gestation. We used two different approaches to understand physiology: first, we replicated previous studies and compared fetal cardiac function and morphology between small for gestational age (SGA) and non-SGA fetuses and between fetal growth restriction (FGR) and non-FGR groups, and second, we explored associations between fetal cardiac indices, with birthweight, as a continuous variable, as well as uterine artery pulsatility index (UtA-PI), as a measure of placental perfusion, and the cerebroplacental ratio (CPR), as a measure of fetal oxygenation.

METHODS

Study design and participants

This prospective study was conducted at Kings' College Hospital as a substudy of the Advanced Cardiovascular Imaging Study (REC No 18/NI/0013, IRAS ID:237936). Inclusion criteria were singleton pregnancies undergoing routine ultrasound examination at 35^{+0} - 36^{+6} weeks of gestation. Women were not eligible to participate if they had multiple pregnancy or fetuses with chromosomal and structural abnormalities including cardiac defects, or they were not able to consent for the study due to mental or physical illness or were <16 years of age. Pregnancies complicated by pregestational and gestational diabetes mellitus, chronic hypertension, pregnancy induced hypertension or preeclampsia were excluded from the analysis. All patients gave written informed consent to participate in the study which was approved by the National Research Ethics Committee.

Maternal and fetal characteristics

During the clinical visit, maternal characteristics (age, race, weight and height to calculate body mass index) were recorded and additional information for pregnancy outcome, including gestational age at delivery and birthweight was retrieved from maternal hospital records.

Fetal ultrasound examination

Gestational age was determined by the crown–rump length measurement in the first trimester.[14] The visit at 35-37 weeks included assessment of fetal growth and use of Doppler ultrasound to measure UtA-PI and pulsatility index of the umbilical artery (UA-PI) and middle cerebral artery (MCA-PI).[15,16] The CPR was determined by dividing MCA-PI by UA-PI. The estimated fetal weight (EFW) was derived from the measurements of head circumference, abdominal circumference and femur length using the Hadlock formula,[17] because a systematic review identified this as being the most accurate model.[18] The term SGA was used to refer to babies which, according to the Fetal Medicine Foundation fetal and neonatal population weight charts, had a birthweight below the 10th percentile.[19] Fetal growth restriction was defined as birthweight below the 3rd percentile or birthweight between the 3rd and 10th percentile in the presence of either UtA-PI >95th percentile or CPR <5th percentile; this is a simplified version of a previous classification which included both birthweight and EFW.[20] In this study we relied on birthweight because EFW is not accurate; in a previous screening study, involving 45,847 singleton pregnancies at 35^{+0} - 36^{+6} weeks' gestation, we found that in screening by EFW <10th percentile the predictive performance for SGA neonates with birthweight <10th percentile was 69% for those born within 2 weeks of assessment, 45% for those born at 2-4 weeks and 30% for those born at >4 weeks.[21]

Fetal echocardiography (Figure 1)

A comprehensive fetal cardiac functional assessment was carried out using Canon Aplio i900 machines with a convex transducer (i8CX1) (Canon Medical Systems Europe BV, ZOETERMEER, The Netherlands). Measurements were performed using conventional pulsed wave Doppler (PW-Doppler) and M-Mode as well as more advanced imaging modalities, such as tissue Doppler imaging (TDI) and speckle tracking echocardiography (STE). Right systolic ventricular function was assessed by measuring tricuspid annular plane systolic excursion (TAPSE)[22] and right ventricular global longitudinal strain using speckle tracking. Left ventricular systolic function was assessed by calculating myocardial performance index[23] and left ventricular global longitudinal strain. Image acquisition for speckle tracking analysis was performed in a four-chamber view at an "apex up or down" projection.[25] A clip of 3-5 seconds with a minimum of 100 frames per second was obtained for each case in accordance with recent guidelines[17] and analysis was carried out using proprietary software (Vitrea, Canon Medical Systems, Crawley, UK). Markers were manually placed along the endocardium, which was subsequently tracked automatically throughout the entire cycle to calculate global longitudinal strain in the right and left ventricle.[25,26] Left ventricular diastolic function was assessed by calculating E/A ratio by measuring the mitral valve early (E) and late (A) diastolic filling peak Doppler velocities [27] and E/e' from tissue Doppler as previously described.[28, 29] The morphology of the left and right ventricle was assessed in an apical or basal four-chamber view and the length and width of the left and right ventricles were measured in end-diastole. The sphericity index was calculated by dividing base-to-apex length by transverse diameter. Fetal cardiac examinations were carried out by seven trained fetal medicine fellows who also performed the analysis of the Doppler indices. Analysis of speckle tracking was carried out by two operators. The operators carrying out the fetal cardiac examinations were blinded to EFW and birthweight. Inter and intra analyzer reproducibility for the Doppler indices was assessed in 20 fetuses. We have previously reported on reproducibility of speckle tracking analysis. [25]

Statistical analysis

Distribution of continuous variables was graphically examined by histograms and quantile-quantile plots to assess normality. Normally distributed continuous variables are presented as mean (± standard deviation) and variables not following a normal distribution are presented as median (25^{th} - 75^{th} percentile). Comparisons of variables between SGA, FGR and normal growth fetuses were made using independent samples Student's T Test or the Mann-Whitney U Test and the chi-squared test for continuous and categorical variables, respectively. The reproducibility of cardiac measurements was assessed by intraclass correlation coefficient.

Multiple linear regression models were used to assess determinants of a range of fetal echocardiographic parameters which differed in our primary comparisons between SGA/FGR and normally grown fetuses. To ensure normality assumptions in regression analyses, we employed the inverse ranking normalization for all continuous variables used as dependent variables in respective models. Analysis was further adjusted for a pre-specified set of confounders, including maternal characteristics (age, body mass index, race, and gestational age), birthweight, UtA-PI z-score, CPR z-score. Repeat analysis was performed after normalizing the cardiac indices for EFW z-score, which was carried out by creating the ratio of the cardiac indices to EFW z-score.

Statistical analyses were conducted with STATA package, version 13.1 (StataCorp, College Station, Texas USA). We deemed statistical significance at $p < 0.05$.

RESULTS

Patient characteristics

The study population of 1,498 participants included 146 (9.7%) SGA fetuses with birthweight <10th percentile (SGA group) and 1,352 (90.3%) with birthweight ≥10th percentile (non-SGA group), and 68 (4.5%) FGR and 1,430 (95.5%) non-FGR fetuses (Table 1). In the FGR group, the birth weight was <3rd percentile in 55 (80.9%) cases and between the 3rd and 10th percentiles in 13 (19.1%) and the UtA-PI was >95th percentile or the CPR was <5th percentile in 20 (29.4%) cases. In the SGA or FGR group, compared to the non-SGA or non-FGR group, respectively, the maternal body mass index was lower and the percentage of women of Asian racial origin was higher. In the FGR group, compared to the non-FGR group, gestational age at delivery and CPR were lower.

Reproducibility of echocardiographic measurements

The inter-observer reproducibility of cardiac measurements was moderate to excellent (intraclass correlation coefficient was 0.733 for isovolumic relaxation time and 0.963 E/A. The intra-observer reproducibility was good to excellent (intraclass correlation coefficient was 0.768 for isovolumic relaxation time and 0.994 for tricuspid annular systolic plane excursion) (Supplementary Table 1).

Fetal cardiac indices in the SGA and FGR groups

In the SGA or FGR group, compared to the non-SGA or non-FGR group, the right heart was more globular and there was reduced right and left ventricular systolic function as measured by TAPSE and global longitudinal strain, but there was no significant difference between groups in myocardial performance index (Table 1). From the left ventricular diastolic functional indices, the E/A ratio was increased in the SGA and FGR groups, but there was no significant difference in E/e' (Table 1).

Determinants of fetal cardiac indices

There were significant associations between fetal cardiac indices and birthweight z-score (Figure 2), but not with maternal age, body mass index, racial origin, UtA-PI z-score or CRP z-score (Table 2). Lower birthweight was associated with reduced left and right global longitudinal strain (less negative strain values) and decreased right sphericity index. A linear association was also noted between tricuspid annular plane systolic excursion and birthweight z-score. There was no significant association between myocardial performance index and birthweight z-score. From left ventricular diastolic indices, an inverse association was noted between E/A ratio and birthweight z-score, but there was no significant association between E/e' and birthweight z-score. The associations between cardiac indices and birthweight z-score remained even after normalizing the cardiac indices for EFW z-score (Supplementary Table 2).

DISCUSSION

Main findings of the study

In this large screening study at 35-37 weeks of gestation, we showed that there is a linear association between birthweight and fetal cardiac functional and morphological indices, whereas indirect markers of placental perfusion and fetal oxygenation had no significant impact on fetal cardiac indices. These findings suggest that the differences in fetal cardiac indices between small and appropriately grown fetuses may be part of a normal physiological response to change in size rather than part of a pathological adaptation to abnormal placental perfusion and fetal oxygenation.

Comparison with existing literature and interpretation of results

Previous case control studies reported that FGR or SGA fetuses have altered cardiac morphology and function. [1-11] These changes in SGA and FGR have been attributed to placental dysfunction resulting in increased cardiac afterload causing right ventricular hypertrophy and increase in right ventricular sphericity index.[30] Additionally, growth restricted fetuses may suffer from hypoxia with consequent redistribution in the fetal circulation and increased blood flow to the brain resulting in increase in the left ventricular volume. Moreover, there is evidence to suggest that hypoxia leads to changes in the function of the cardiomyocyte at cellular level resulting in impaired contractility of the heart.[31] Crispi *et al* have speculated that the observed cardiac changes in SGA and FGR may identify those fetuses that are at increased risk for development of adult cardiovascular disease.[30]

In our large screening study, which included 147 SGA fetuses and 67 with FGR, we confirmed that the SGA and FGR groups, compared to non-SGA and non-FGR groups, have more globular hearts, [3, 5-11] increased diastolic filling ratios[1, 5, 11] and less TAPSE.[5, 6, 11] In addition, by using more advanced imaging modalities, such as fetal speckle tracking, we showed that in FGR and SGA fetuses there were signs of reduced left and right ventricular systolic function. However, in contrast to previous

reports [1, 4, 5, 9] we found no significant difference between the FGR and non-FGR groups in the myocardial performance index and there is no obvious explanation for this discordance.

In our study we could not test causal relationships, but we had the opportunity to explore association between fetal cardiac indices, birthweight and ultrasound markers of placental perfusion and fetal oxygenation. We used UtA-PI to assess placental perfusion and CPR as a marker of fetal hypoxia[32-34]. We demonstrated that UtA-PI and CPR were not associated with fetal cardiac functional and morphological indices; this finding is in line with a recent study showing that SGA fetuses display alterations in cardiac morphology independent of UA-PI and CPR.[10] In addition, we showed for the first time with advanced echocardiographic modalities that there is a linear relationship between birthweight and cardiac function and this relationship stands through the whole spectrum of birthweights regardless of whether fetuses are defined as growth restricted or normally grown. These findings challenge the approach that fetuses under a certain percentile have a pathologically altered heart function and suggest that fetal cardiac function is modified according to fetal demands with bigger fetuses showing more vigorous contractility and small fetuses having reduced ventricular contraction.

Strengths and limitations

The main strengths of the study are: first, this is the largest prospective study where detailed fetal cardiac assessment was performed in a healthy unselected population at 35-37 weeks' gestation; and second, we followed a strict protocol for image acquisition and analysis and confirmed that the SGA and FGR groups have reduced cardiac function and altered cardiac morphology and demonstrated that these findings are due to physiological differences in size rather than due to changes in placental perfusion and fetal oxygenation. The main limitation of the study is that the findings at 35-37 weeks' gestation may not be applicable to earlier gestations or for fetuses with adverse perinatal outcome and that in severe early onset FGR there

may indeed be distinct pathological cardiac findings. Additionally, in our FGR group only 29% had UtA-PI >95th percentile or CPR <5th percentile.

Implications for clinical practice

This study provides information on the determinants of fetal heart function in an unselected population. It shows that in uncomplicated pregnancies birthweight is the only determinant of fetal cardiac function in the third trimester and highlights the need to account for differences in fetal size when comparing fetal cardiac indices in pathological pregnancies, such as those affected by preeclampsia or diabetes mellitus. It also suggests that we should be cautious in the interpretation of results when dichotomizing continuous cardiac variables because extreme comparisons may mask the presence of important linear physiological associations.

Conclusion

This study demonstrates a linear relationship between birthweight and fetal heart function, showing a gradual reduction of cardiac heart function with decreasing birthweight. The absence of associations between indirect markers of placental perfusion and fetal oxygenation with fetal cardiac indices challenges the presence of a pathological fetal cardiac response in growth restricted fetuses in the third trimester.

Conflict of interest: The authors report no conflict of interest

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FIGURE LEGENDS

Figure 1. Fetal cardiac assessment.

Global longitudinal strain of the right and left ventricle, measurement of the tricuspid annular plane systolic excursion (TAPSE) by M-mode, myocardial performance index using pulse spectral Doppler, tissue Doppler imaging, and right and left sphericity index.

Figure 2. Relationship between birthweight z-score and cardiac indices.

The graphs demonstrate the presence of a linear association between birthweight z-score and right and left ventricular global longitudinal strain, right ventricular sphericity index and tricuspid annular plane systolic excursion.

Table 1. Comparison of characteristics and cardiac indices in small for gestational age vs. non-small for gestational age fetuses and in fetal growth restricted vs. non-fetal growth restricted fetuses.

Variable	Non-SGA N: 1352	SGA N:146	P value	Non-FGR N=1430	FGR N=68	P value
Age in years	33.2 (4.9)	32.1 (5.2)	0.011	33.1 (4.9)	32.0 (5.0)	0.087
Body mass index in kg/m^2	29.1 (4.6)	27.5 (3.9)	<0.001	29.0 (4.5)	27.2(4.1)	0.001
Racial origin			<0.001			<0.001
White	990 (73.2)	82 (56.2)		1038 (72.6)	34 (50.0)	
Black	214 (15.8)	31 (21. 2)		229 (16.0)	16 (23.5)	
Asian	91 (6.7)	27 (18.5)		102 (7.1)	16 (23.5)	
Mixed	57 (4.2)	6 (4.1)		61 (4.3)	2 (3.0)	
Gestational age at scan in weeks	36.1 (0.4)	36.1 (0.5)	0.264	36 (0.5)	36.1 (0.5)	0.987
Conception			0.332			0.823
Assisted fertilisation	63 (4.66)	6 (4.1)		66 (4.6)	3 (4.4)	
Ovulation drugs	6 (0.44)	2 (1.4)		8 (0.6)	0 (0)	
Natural	1283 (94.9)	138 (94.5)		1356 (94.8)	65 (95.6)	
Uterine artery PI z-score	-0.15 (-0.8, 0.6)	-0.05 (-0.7, 0.7)	0.196	-0.1 (-0.8, 0.6)	0.01 (-0.7, 0.8)	0.053
Cerebroplacental ratio z-score	-0.1 (-0.7, 0.6)	-0.5 (-1.0, 0.2)	<0.001	-0.1 (-0.8, 0.6)	-0.6 (-1.3, -0.1)	<0.001
Birthweight z-score	0.08 (-0.4, 0.7)	-1.7 (-2.1, -1.5)	<0.001	0.02 (-0.6, 0.6)	-2.1 (-2.5, -1.9)	<0.001
Fetal heart rate in beats/min	140 (14)	140(13)	0.963	140 (14)	137 (12)	0.165
Gestational age at delivery in weeks	40(1.2)	39.6(1.4)	<0.001	40 (1.2)	39.4 (1.5)	<0.001
Systolic parameters						
LV-MPI	0.6 (0.5, 0.7)	0.6 (0.5, 0.6)	0.478	0.6 (0.5, 0.7)	0.6 (0.5, 0.7)	0.429
Isovolumic contraction time in sec	0.04 (0.03, 0.05)	0.04 (0.03, 0.05)	0.295	0.04 (0.03, 0.05)	0.04 (0.03, 0.05)	0.718
Ejection time in sec	0.16 (0.15, 0.17)	0.16 (0.15, 0.17)	0.445	0.16 (0.15, 0.17)	0.16 (0.15, 0.17)	0.928
LV-GLS in %	-20.9 (-23.3, -18.4)	-19.4 (-21.1, -17.6)	<0.001	-20.7 (-22.9, -18.4)	-18.7 (-21.2, -17)	<0.001
RV-GLS in %	-19.2 (-21.3, -17.5)	-17.4 (-19.4, -15.4)	<0.001	-19.1 (-21.1, -17.3)	-17.3 (-19.8, -15.4)	<0.001
TAPSE in mm	7.5 (6.5, 8.5)	7.0 (6.1, 8.2)	0.007	7.5 (6.5, 8.5)	6.4 (5.6, 7.6)	<0.001
LV diastolic parameters						
E/A	0.82 (0.72, 0.92)	0.84 (0.76, 0.95)	0.040	0.82 (0.73, 0.92)	0.87 (0.8, 1.0)	0.001
E/e'	9.1 (7.8, 10.9)	9.1 (7.8, 10.5)	0.419	9.1 (7.8, 10.9)	9.0 (7.8, 10.8)	0.731
Isovolumic relaxation time in sec	0.05 (0.05, 0.06)	0.05 (0.05, 0.06)	0.154	0.05 (0.05, 0.06)	0.06 (0.05, 0.06)	0.050
Morphology						
LV sphericity index	1.9 (1.8, 2.1)	1.9 (1.7, 2.2)	0.697	1.9 (1.8, 2.1)	1.95 (1.7, 2.2)	0.927
RV sphericity index	1.7 (1.6, 1.9)	1.6 (1.5, 1.8)	<0.001	1.7 (1.6, 1.9)	1.6 (1.4, 1.8)	0.007

SGA: small for gestational age, FGR: fetal growth restriction, PI: pulsatility index, CRP: cerebroplacental ratio, LV: left ventricle, RV: right ventricle, MPI: myocardial performance index, GLS: global longitudinal strain, TAPSE: tricuspid annular plane systolic excursion.

Table 2. Multivariable analysis of fetal cardiac indices.

Variable	Left ventricle global longitudinal strain		Right ventricle global longitudinal strain		Tricuspid annular place systolic excursion		E/A		Right ventricle sphericity index	
	Coefficient [95% CI]	**P value**	**Coefficient [95% CI]**	**P value**	**Coefficient [95% CI]**	**P value**	**Coefficient [95% CI]**	**P value**	**Coefficient [95% CI]**	**P value**
Age in years	0.004 (-0.01, 0.02)	0.560	0.01 (-0.01, 0.02)	0.248	0.007 (-0.003, 0.02)	0.179	0.003 (-0.01, 0.01)	0.607	-0.01 (-0.03, 0.003)	0.129
Body mass index in kg/m^2	0.01 (-0.004, 0.03)	0.142	-0.005 (-0.02, 0.12)	0.550	0.002 (-0.01, 0.01)	0.701	0.001 (-0.01, 0.01)	0.910	-0.001 (-0.02, 0.02)	0.911
Racial origin										
White (ref)										
Black	0.20 (0.00, 0.39)	0.050	0.07 (-0.13, 0.27)	0.489	0.22 (0.07, 0.37)	0.003	0.08 (-0.07, 0.23)	0.293	-0.16 (-0.35, 0.04)	0.121
Asian	0.09 (-0.17, 0.34)	0.513	-0.01 (-0.27, 0.25)	0.955	-0.24(-0.43, -0.05)	0.014	-0.19 (-0.39, 0.01)	0.056	-0.13 (-0.40, 0.13	0.314
Mixed	0.21 (-0.14, 0.54)	0.242	-0.01 (-0.36, 0.34)	0.951	0.06 (-0.20, 0.32)	0.647	0.24 (-0.02, -0.04)	0.072	0.12 (0.01, 0.16)	0.499
Gestational age at scan in weeks	0.08 (-0.07, 0.23)	0.304	0.13 (-0.02, 0.29)	0.094	0.23 (0.12, 0.35)	<0.001	0.05 (-0.06, 0.02)	0.350	-0.08 (-0.24, 0.07)	0.273
Uterine artery PI z-score	-0.002 (-0.07, 0.06)	0.947	0.01 (-0.05, 0.08)	0.715	-0.024 (-0.07, 0.02)	0.319	-0.03 (-0.08, 0.02)	0.182	0.01 (-0.05, 0.08)	0.675
Cerebroplacental ratio z-score	-0.02 (-0.09, 0.06)	0.646	0.07 (-0.01, 0.14)	0.070	0.04 (-0.02, 0.09)	0.193	0.01 (-0.04, 0.07)	0.647	0.02 (-0.05, 0.09)	0.590
Birthweight z-score	-0.13 (-0.20, -0.06)	<0.001	-0.17 (-0.24, -0.09)	<0.001	0.15 (0.10, 0.21)	<0.001	-0.099 (-0.15, -0.04)	0.001	0.09 (0.01, 0.16)	0.020

Outcome variables have been inverse rank normalized. Abbreviations: PI: pulsatility index

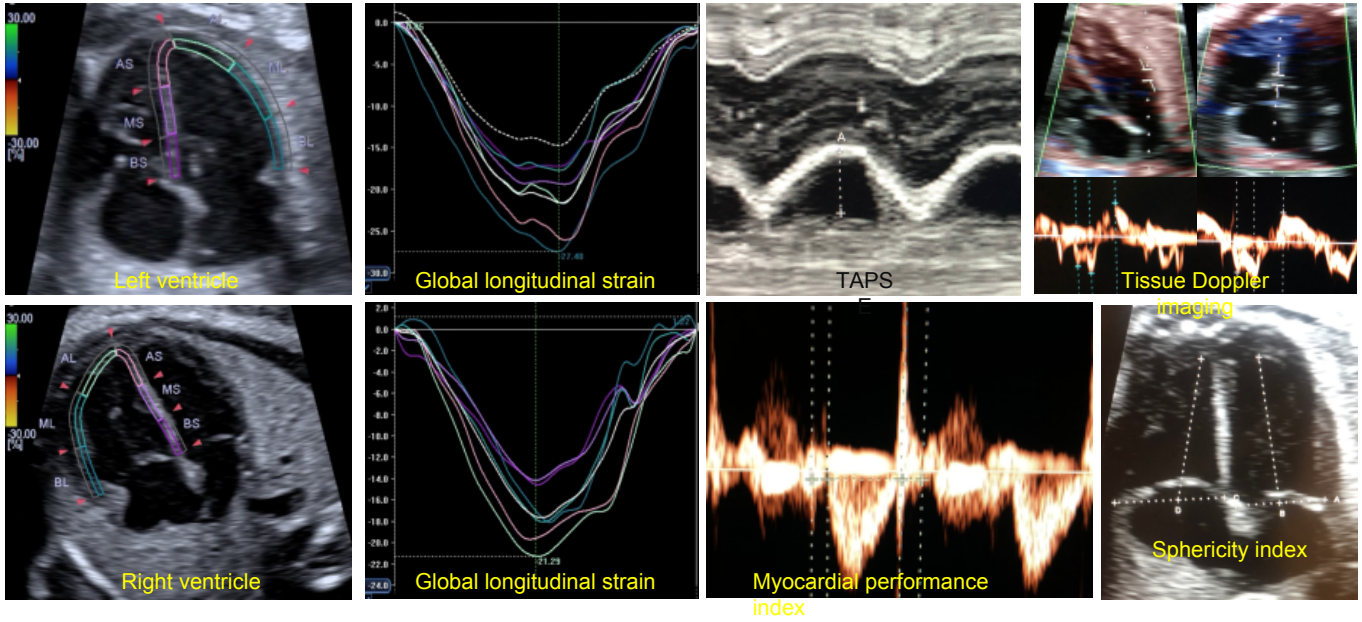

Figure 1

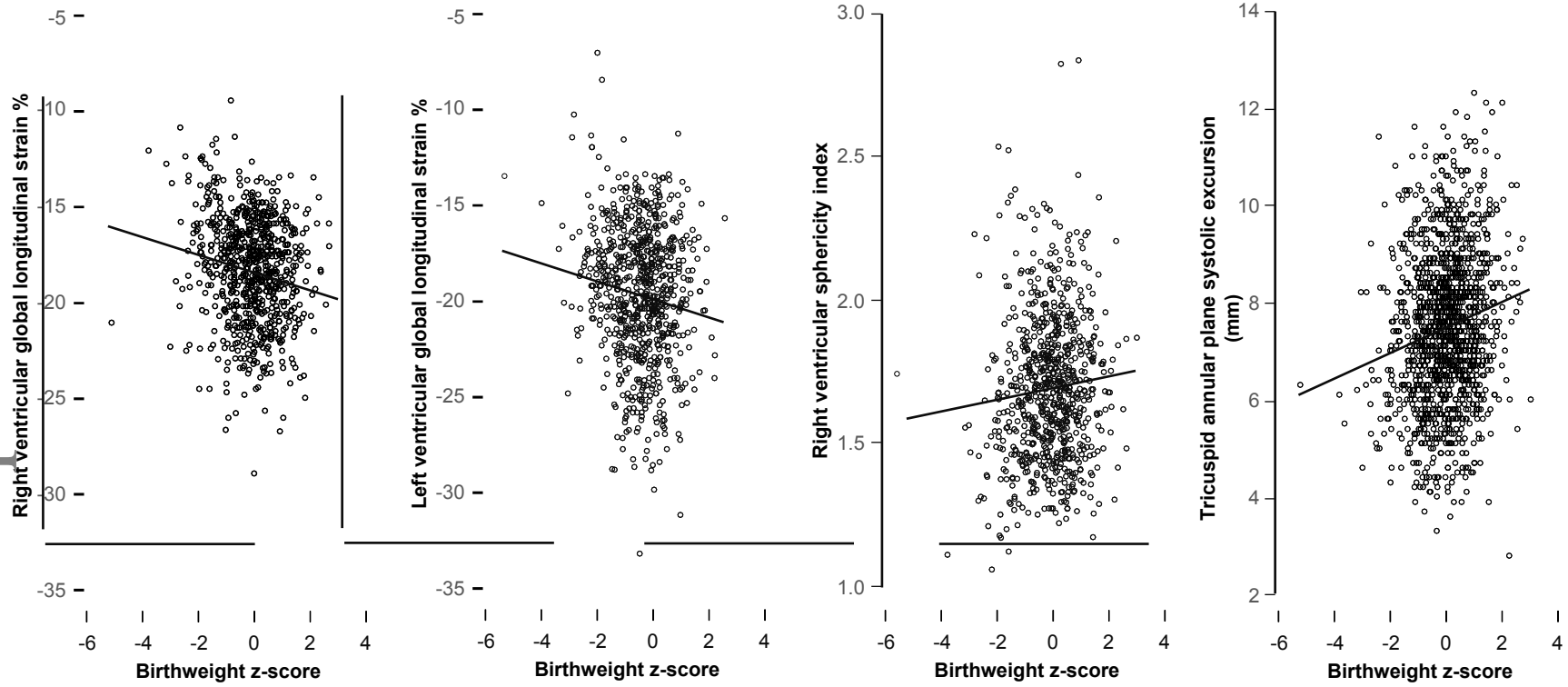

Figure 2