Selective fetal growth restriction in identical twins: from womb to adolescence

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Chapter 5

Early structural cardiovascular changes after adverse intrauterine circumstances in identical twins: a cohort study using neonatal cardiac ultrasound.

Submitted to Archives of Disease in Childhood – Fetal & Neonatal Edition. 2022 Sep.

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Abstract

Objective. To investigate early structural cardiovascular remodeling after fetal growth restriction (FGR) in a cohort of identical twins, controlling for confounding of genetic and maternal factors.

Design. Prospective observational cohort study.

Setting. Single-center, population-based.

Patients. Live-born monochorionic twins born between January 2019 – June 2021.

Interventions. Transthoracic cardiac ultrasound within one week after birth.

Main outcome measure. Z-scores for cardiac valve annuli diameters and left ventricle dimensions were calculated based on gestational age at birth and compared between smaller and larger twins. The z-score difference between birth weight and each cardiac structure per twin was tested against the intercept, to assess heart sparing. A value >0 indicates that the cardiac structure is less affected by FGR than birth weight (heart sparing). A value <0 indicates that the cardiac structure is more affected by FGR than birth weight.

Results. Median gestational age at birth of the 100 included twin pairs was 33.8 (interquartile range (IQR) 30.8-36.1) weeks, with birth weights of 1729 (IQR 1200-2115) grams for the smaller twin and 2058 (IQR 1643-2500) grams for the larger twin. All structures showed the same association in which the smaller twin had a lower z-score than the larger twin. The z-score difference in birth weight and cardiac structure was significantly higher than the intercept in all but one structure (tricuspid valve).

Conclusions. While cardiac structures are generally smaller for the twin with the lower birth weight, the deviation in birth weight tends to be more pronounced than the deviation in cardiac structure, indicative of heart sparing.

Funding: The Dutch Heart Foundation (2017T075).

Introduction

Adverse intrauterine circumstances are thought to negatively impact lifelong health. Previous research has demonstrated a strong association between fetal growth restriction (FGR) and an increased risk of cardiovascular disease (CVD) in adulthood[1,2]. The mechanism behind this association is thought to be fetal programming: structural and functional adaptations in fetal development in response to a suboptimal environment that are persistent throughout life[3].

Cardiovascular remodeling can already be observed in fetuses with FGR. The morphometry of the heart becomes more spherical with thickened myocardial walls[3]. Cardiomegaly has been implicated as an expression of 'heart sparing', i.e., blood flow redistribution favoring major organs when in a prolonged state of hypoxia[4]. These subtle but disadvantageous changes may persist after birth. Echocardiographic studies in children born after FGR have reported smaller cardiovascular dimensions and mass as well as greater arterial wall stiffness from early childhood until preadolescence[5-7]. Yet, neonatal cardiovascular changes after FGR are largely unreported, while these form the basis for tracking the lifelong cardiovascular consequences of FGR. Moreover, the scarcely available studies are limited by their study design in which small for gestational age (SGA) neonates are compared to appropriately-grown neonates, inherently subject to confounding[8,9]. A population of identical twins offers a solution.

Monochorionic (MC) twins are genetically identical and share a single placenta during pregnancy. This shared placenta can give rise to a range of complications, including a discordant antenatal growth pattern following from an unequally shared placenta[10]. A within-pair comparison in this study population thereby controls for any potential confounding of genetic and maternal factors. Therefore, this study aims to compare structural cardiac measurements and aortic pulse-wave velocity (aPWV) between the smaller and larger twin at birth and to assess whether heart sparing is present using neonatal cardiac ultrasound.

Methods

This study is part of the Twinlife study (Twin Longitudinal Investigation of FEtal discordance; Netherlands Trial Register ID NL7538). This is a prospective, longitudinal cohort study including all MC twins born in the Leiden University Medical Center (LUMC) from January 2019 onwards[11]. The Twinlife study was reviewed and approved by the ethics committee of the LUMC (P18.184) and inclusion is still ongoing. All parents are asked for informed consent. Exclusion criteria are triplet pregnancies, perinatal mortality (intrauterine fetal demise, selective reduction, termination of pregnancy or neonatal death before cardiac ultrasound), cases with twin reversed arterial perfusion or congenital abnormalities.

The following baseline characteristics were collected: maternal age, gravidity, parity, type of MC twin pathology (twin-twin transfusion syndrome (TTTS) diagnosed according to the Eurofetus criteria[12], twin anemia polycythemia sequence (TAPS)[13] and selective fetal growth restriction (sFGR), defined as a birth weight discordance (BWD) ≥ 20% in the absence of TTTS/TAPS with BWD calculated as (birth weight larger twin – birth weight smaller twin)/birth weight larger twin x 100[14]), fetoscopic laser coagulation or other treatment modalities for TTTS/TAPS (amniodrainage, intrauterine transfusion (IUT) with/without partial exchange transfusion (PET)), gestational age at birth, sex, delivery mode, BWD, birth weight with z-score (singleton curves based on gestational age and sex), proportion of neonates born SGA (defined as birth weight < 10th centile[15,16]) and the presence of a patent ductus arteriosus requiring either medical or surgical treatment.

Transthoracic cardiac ultrasound including two-dimensional M-mode was performed by a senior pediatric cardiologist (AAWR) within one week after birth according to the guidelines of the American Society for Echocardiography[17,18]. Mitral valve (MV) annulus diameter and tricuspid valve (TV) annulus diameter were measured in an apical four-chamber view. Aortic valve (AV) annulus diameter was measured in the parasternal long-axis view and pulmonary valve (PV) annulus diameter in the parasternal short-axis view. The following parameters were measured in M-mode: left atrium diameter (LA), aortic root diameter (Ao), LA/Ao ratio, left ventricular internal diameter in diastole (LIVDD) and systole (LVIDS), left ventricular posterior wall thickness in diastole (LVPWD) and systole (LVPWS), LV mass[19], ejection fraction, fractional shortening calculated as (LVIDD – LVIDS)/LVIDD x 100, and relative wall thickness (RWT) calculated as (2 x LVPWD)/LVIDD)[18-20]. All measurements were performed by a single investigator (SGG) under supervision of a senior pediatric

cardiologist (AAWR). Z-scores for the cardiac vale annuli diameters and LV parameters were calculated based on gestational age at birth[21,22].

To determine aPWV, a measure of aortic stiffness, two pulsed Doppler recordings of the aorta were made at the level of the AV and the descending aorta (Figure 1)[23-25]. A similar time point in the electrocardiogram was chosen for both recordings and the time until onset of flow was measured three times in both recordings to calculate an average. The transit time was calculated as: average time of onset of flow at descending aorta – average time of onset of flow at AV. The length of the aorta from the location of the first Doppler recording to the other was determined using Osirix DICOM viewer[26]. aPWV was calculated as: (aortic length)/(100 x transit time)[25].

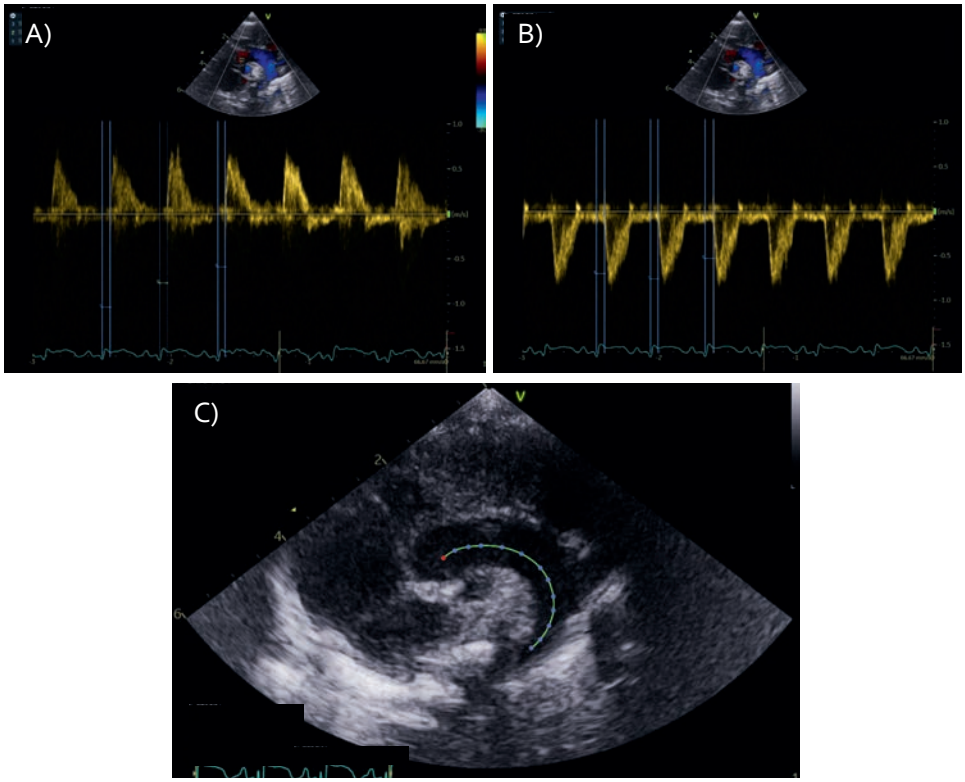

Figure 1. Measurement of the aPWV; A) pulsed Doppler recording at the level of the AV with three measurements of time until flow, B) pulsed Doppler recording at the descending aorta with three measurements of time until flow, C) length of the aorta from the location of pulsed Doppler recording A to pulsed Doppler recording B.

The difference between the z-score of birth weight and the z-score of each cardiac structure was calculated per individual twin to assess the presence of heart sparing. A value >0 indicates that the deviation of the cardiac structure is less than the deviation of birth weight in relation to gestational age at birth, i.e., the cardiac structure is less affected than birth weight (heart sparing). A value <0 indicates that the deviation of the cardiac structure is more than the deviation of birth weight in relation to gestational age at birth, i.e., the cardiac structure is more affected than birth weight. The relationship between the z-scores of birth weight and the cardiac structures was plotted with a line depicting x = y (representing a one-to-one relationship). Values above this line indicate that the cardiac structure was less affected than birth weight relative to gestational age at birth and values below the line indicate that the cardiac structure was more affected than birth weight relative to gestational age at birth.

To test for association between 1) twin size (smaller/larger) and the cardiovascular outcomes and 2) the difference in z-scores of birth weight and cardiac structures and the intercept (representing the absence of a difference in these z-scores), a Generalized Estimating Equation (GEE) was used. This method accounts for the fact that we study paired data (twin pairs) while also allowing us to control for covariates. It is well-known that in MC twins TTTS can influence fetal cardiac development, differentially for the donor and recipient, due to intertwin hemodynamic imbalances[27]. The same is presumed for TAPS, albeit not thoroughly researched. As prenatal growth is our primary focus, we have chosen to examine the effect of twin size (smaller/larger) in this study and regard the group of included MC twins as a whole. To take into account any potential influences of the different types of MC twin complications (TTTS, TAPS, sFGR, uncomplicated) on the cardiac parameters, we first tested this association using a GEE. When there was a statistically significant association, the analysis of twin size for that outcome parameter was corrected for the type of complication. Statistical analyses were performed using IBM Statistics Version 25.0 (SPSS, Inc. an IBM company, Chicago, IL, USA) and R Version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria). Data are presented as median (interquartile range (IQR)), n/N (%) or n (%). A *p*-value of < 0.05 was considered statistically significant.

Results

Between January 2019 and June 2021, 105 parents agreed to participate in the study (inclusion rate 89% (105/118); Figure 2). In four cases, we were unable to perform a cardiac ultrasound for logistic reasons (fast transfer to a peripheral hospital after birth, unavailability of the pediatric cardiologist and parental COVID-19 infection). In one case, a congenital abnormality was detected within the first weeks after birth with subsequent exclusion. aPWV was missing in 24 cases due to unavailability of staff trained to perform this measurement at the time of these ultrasounds.

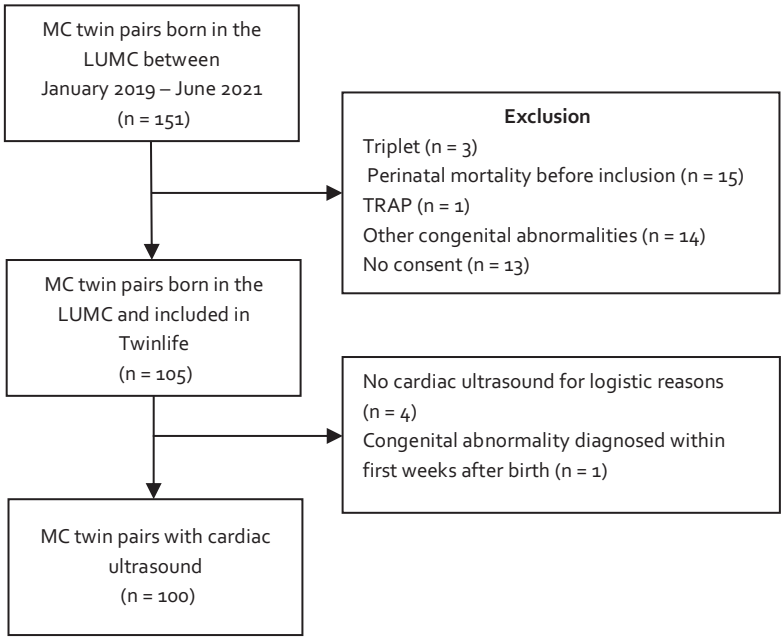

Figure 2. Flowchart of study inclusion.

Median gestational age at birth was 33.8 (IQR 30.8-36.1) weeks (Table 1). The smaller twin had a median birth weight of 1729 (IQR 1200-2115) grams and the larger twin of 2058 (IQR 1643-2500) grams. Patent ductus arteriosus requiring treatment was present in four cases (three smaller twins, one larger twin born between 27-34 weeks (p = 0.340)). Of all pregnancies, 41% (41/100) was complicated by TTTS, of which 90% (37/41) were treated with fetoscopic laser coagulation which was successful in 36/37 cases; 17% (17/100) was complicated by TAPS of which 13% (2/17) were successfully treated with fetoscopic laser coagulation in the TAPS trial (ClinicalTrails.gov ID NCT04432168); 19% (19/100) was complicated by sFGR in the absence of TTTS or TAPS; and 23% (23/100) was uncomplicated.

Table 1. Baseline maternal, obstetrical and neonatal characteristics for included twins.

Characteristics	**MC twins (n=200; 100 pregnancies)**
Maternal age – *years*	32 (29-34)
Gravidity	2 (1-3)
Parity	1 (0-1)
MC twin pathology	
Uncomplicated	23 (23)
TTTS	41 (41)
Fetoscopic laser coagulation	37 (90)
Other treatment	4 (10)
TAPS	17 (17)
Fetoscopic laser coagulation	2 (13)
Other treatment	15 (87)
sFGR	19 (19)
Gestational age at birth – *weeks*	33.8 (30.8-36.1)
Female	96 (48)
Caesarean	123 (62)
Birth weight discordance – *%*	13 (7-27)
Birth weight – *grams*	
Smaller twin	1729 (1200-2115)
z-score	-1.1 (-1.7--0.7)
Larger twin	2058 (1643-2500)
z-score	-0.3 (-0.7-0.1)
Small for gestational age	
Smaller twin	63 (63)
Larger twin	17 (17)

MC: monochorionic, TTTS: twin-twin transfusion syndrome, TAPS: twin anemia-polycythemia sequence, sFGR: selective fetal growth restriction.
Outcomes are presented as median (interquartile range (IQR)).

All cardiac valve annuli diameters showed the same association in which the smaller twin had a lower z-score (0.6 difference for MV, 0.5 difference for TV and AV, 0.3 difference for PV, with $p < 0.0001$ for MV, TV and AV and $p = 0.019$ for PV; Table 2). Similarly, both the LA diameter and Ao diameter were smaller in the smaller twin, with a 0.8 mm ($p = 0.002$) and a 0.4 mm difference ($p = 0.002$). A similar association was observed for the z-scores of the LV dimensions with lower z-scores for the smaller twin (0.3 difference for LVIDD ($p = 0.001$) and LVIDS ($p = 0.002$), 0.1 difference for LVPWD ($p = 0.020$) and LVPWS ($p = 0.010$)). The analysis of LVPWD was corrected for type of complication, following the significant association of $p = 0.033$ (Table S1). LV mass was lower for the smaller twin as opposed to the larger twin (5.1 (IQR 4.0-6.6)

grams vs. 6.0 (IQR 4.5-7.7) grams, $p < 0.0001$), as was RWT (0.34 (IQR 0.29-0.40) vs. 0.36 (IQR 0.29-0.47), $p = 0.020$). Functional parameters did not differ within twin pairs. No significant difference was found for aPWV, with 3.1 (IQR 2.4-5.3) m/s in the smaller twin and 3.3 (IQR 2.5-4.4) m/s in the larger twin ($p = 0.259$).

Table 2. Structural and functional cardiac parameters for the smaller and larger twin.

Outcomes	Smaller twin (n=100)	Larger twin (n=100)	*p*-value
Cardiac valve annuli diameter			
MV – mm	9.9 (9.1-11.1)	10.8 (9.8-11.9)	
z-score	-0.8 (-1.6--0.2)	-0.2 (-0.9-0.5)	**<0.0001**
TV – mm	10.4 (8.9-11.7)	11.0 (9.8-11.9)	
z-score	-1.3 (-2.4--0.3)	-0.8 (-1.6--0.1)	**<0.0001**
AV – mm	5.9 (5.3-6.5)	6.1 (5.8-6.7)	
z-score	-0.5 (-1.2-0.2)	0.0 (-0.7-0.7)	**<0.0001**
PV – mm	6.6 (5.9-7.4)	6.9 (6.2-7.5)	
z-score	0.8 (-0.2-1.7)	1.1 (0.2-2.0)	**0.019**
LA diameter – mm	10.7 (9.4-12.1)	11.5 (10.2-12.7)	**0.002**
Ao diameter – mm	8.2 (7.2-9.0)	8.6 (7.7-9.7)	**0.002**
LA/Ao ratio	1.3 (1.2-1.5)	1.3 (1.1-1.5)	0.347
Left ventricular dimensions			
LVIDD – mm	14.8 (13.3-16.2)	15.5 (13.7-16.8)	
z-score	0.5 (-0.1-1.3)	0.8 (0.2-1.7)	**0.001**
LVPWD – mm	2.5 (2.2-2.9)	2.7 (2.3-3.3)	
z-score	-0.2 (-0.9--0.1)	-0.1 (-0.8-0.2)	**0.020***
LVIDS – mm	9.6 (8.8-11.4)	10.7 (9.4-11.9)	
z-score	0.4 (-0.4-1.1)	0.7 (0.1-1.4)	**0.002**
LVPWS – mm	3.6 (3.1-4.0)	3.7 (3.3-4.6)	
z-score	-0.5 (-1.1-0.0)	-0.4 (-1.2-0.9)	**0.010**
LV mass – grams	5.1 (4.0-6.6)	6.0 (4.5-7.7)	**<0.0001**
LV ejection fraction – %	64.0 (57.7-70.5)	61.2 (56.0-69.2)	0.108
Fractional shortening – %	31.6 (27.9-36.6)	30.0 (26.6-35.7)	0.220
RWT	0.34 (0.29-0.40)	0.36 (0.29-0.47)	**0.020**
aPWV – m/s	3.1 (2.4-5.3)	3.3 (2.5-4.4)	0.259

MV: mitral valve, TV: tricuspid valve, AV: aortic valve, PV: pulmonary valve, LA: left atrium, Ao: aortic root, LV: left ventricular, LVIDD: end-diastolic left ventricular internal diameter, LVPWD: end-diastolic left ventricular posterior wall thickness, LVIDS: end-systolic left ventricular internal diameter, LVPWS: end-systolic left ventricular posterior wall thickness, RWT: relative wall thickness, aPWV: aortic pulse-wave velocity.

RWT calculated as (2 x LVPWD)/LVIDD

Outcomes are presented as median (IQR).

*corrected for type of complication.

Table S1. *p*-values per tested measurement for the association with type of complication (divided into TTTS, TAPS, sFGR or uncomplicated twins).

Outcomes	*p*-value
Cardiac valve annuli diameter	
MV z-score	0.772
TV z-score	0.127
AV z-score	0.377
PV z-score	0.292
LA diameter – mm	0.627
Aortic root diameter – mm	0.196
LA/Ao ratio	0.104
Left ventricular dimensions	
LVIDD z-score	0.141
LVPWD z-score	**0.033**
LVIDS z-score	0.734
LVPWS z-score	0.527
LV mass – grams	0.186
LV ejection fraction – %	0.100
Fractional shortening – %	0.108
RWT	0.059
aPWV – m/s	0.184

MV: mitral valve, TV: tricuspid valve, AV: aortic valve, PV: pulmonary valve, LA: left atrium, Ao: aortic, LV: left ventricular, LVIDD: end-diastolic left ventricular internal diameter, LVPWD: end-diastolic left ventricular posterior wall thickness, LVIDS: end-systolic left ventricular internal diameter, LVPWS: end-systolic left ventricular posterior wall thickness, RWT: relative wall thickness, aPWV: aortic pulse-wave velocity.

The cardiac structures were less affected than birth weight in relation to gestational age at birth, indicated by a significantly higher difference in z-scores compared to the intercept in all but one parameter (Table 3): 0.2 (IQR -0.6-1.2) for MV (p =0.011), 0.5 (IQR -0.4-1.3) for AV (p = 0.002), 1.6 (IQR 0.6-2.7) for PV, 0.4 (IQR -0.2-1.1) for LVIDD, 0.8 (IQR 0.1-1.4) for LVPWD, 1.3 (IQR 0.4-2.1) for LVIDS and 0.3 (IQR -0.4-1.4) for LVPWS, all with $p < 0.0001$. The sole structure that was affected to a greater extent than birth weight in relation to gestational age at birth, i.e., significantly lower than the intercept, was the TV (-0.5 (IQR -1.2-0.5), $p < 0.0001$). These associations are also depicted in Figure 3, illustrating that the majority of twins is above the x = y line.

Table 3. The difference in z-score of birth weight and z-score of the cardiac structure tested against the intercept.

Differences in z-scores	MC twins (n=200)	*p*-value
Cardiac valve annuli diameter		
Birth weight - MV	0.2 (-0.6-1.2)	**0.011**
Birth weight - TV	-0.5 (-1.2-0.5)	**0.002**
Birth weight - AV	0.5 (-0.4-1.3)	**<0.0001**
Birth weight - PV	1.6 (0.6-2.7)	**<0.0001**
Left ventricular dimensions		
Birth weight - LVIDD	0.4 (-0.2-1.1)	**<0.0001**
Birth weight - LVPWD	0.8 (0.1-1.4)	**<0.0001**
Birth weight - LVIDS	1.3 (0.4-2.1)	**<0.0001**
Birth weight - LVPWS	0.3 (-0.4-1.4)	**<0.0001**

MV: mitral valve, TV: tricuspid valve, AV: aortic valve, PV: pulmonary valve, LVIDD: end-diastolic left ventricular internal diameter, LVPWD: end-diastolic left ventricular posterior wall thickness, LVIDS: end-systolic left ventricular internal diameter, LVPWS: end-systolic left ventricular posterior wall thickness, Outcomes are presented as median (IQR).

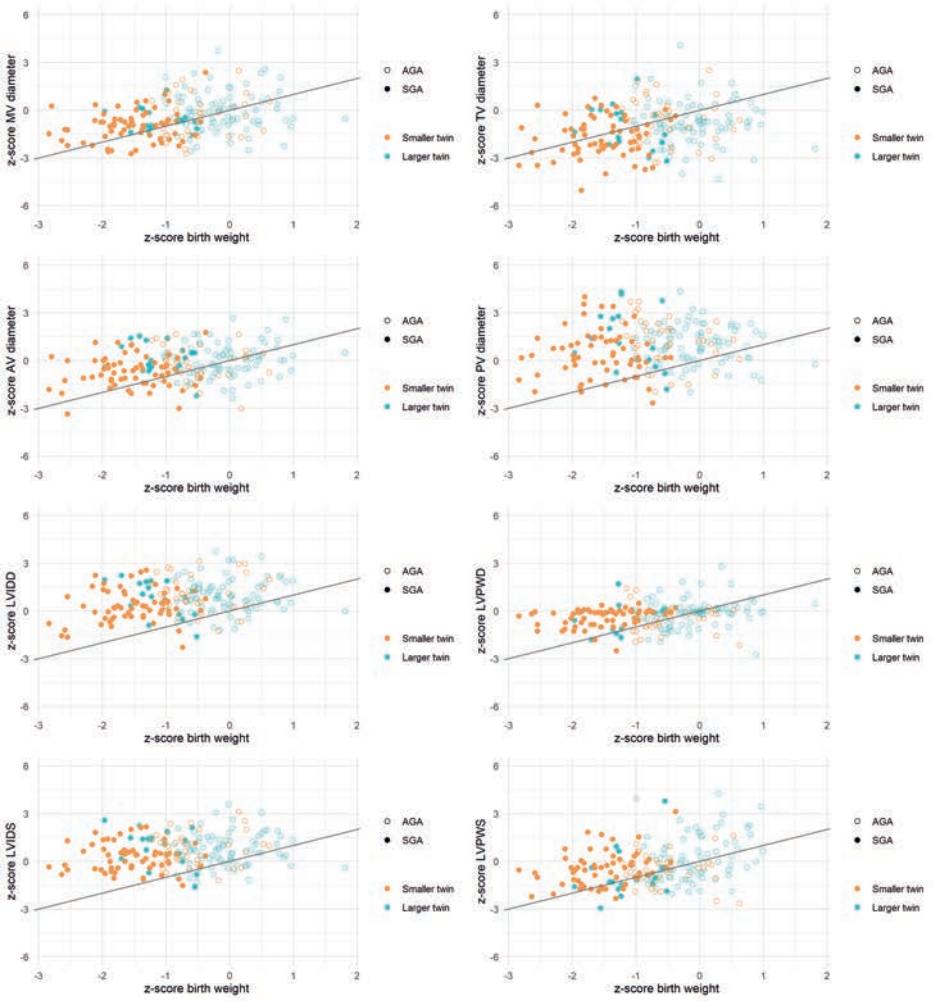

Figure 3. Scatterplots of the relationship between the z-score of the birth weight (x-axis) and the z-score of the cardiac structures (y-axis), with the line depicting x = y. Values above this line indicate that the cardiac structure was less affected than birth weight relative to gestational age at birth and values below the line indicate that the cardiac structure was more affected than birth weight relative to gestational age at birth.

Discussion

In MC twins, the smaller twin presents with a structurally smaller heart (including cardiac valve annuli, LA, Ao and LV dimensions) at birth when compared to the larger twin. Despite having smaller cardiac structures, the heart (except for the TV) appears to be less affected by FGR than body size for a given gestational age. This finding is indicative of heart sparing.

A fetus experiencing FGR adapts by redistributing blood flow towards major organs. This 'sparing' has been elaborately described in the context of the brain and is reflected by a larger head circumference relative to body size[28-30]. We have now observed a similar phenomenon for the heart in which the cardiac structures are less affected by FGR than body size. Redistribution of cardiac output is facilitated by vasodilation and increased blood flow towards essential vascular beds and vasoconstriction and decreased blood flow towards non-essential vascular beds[29]. This may be the cause of the smaller TV annulus diameter relative to birth weight as observed in our study, following preferential blood flow towards the brain through the left side of the heart, thereby favoring the MV over the TV. Yet, one would expect the PV to also be affected and this was not the case. Nonetheless, when these hemodynamic changes continue for an extended period of time, structural cardiovascular remodeling occurs that can in turn result in functional deficits as well[3,29,31].

Our results are in line with available literature in singletons. Preterm SGA neonates are reported to already have an altered cardiac morphology within days after birth when compared to appropriately-grown controls[32]. A similar study at two years of age demonstrated that SGA infants presented with significantly smaller LV dimensions and that any alterations were strongly related to birth weight[5]. The unique aspect of our population in which we compare identical twins that were exposed to different intrauterine environments sets us apart from previous studies, eliminating any other known and unknown influences.

Tracking cardiovascular structure and functioning over a longer period of time is crucial to understand the pathophysiological processes that underlie CVD risk[33,34]. We have now focused on neonatal cardiovascular remodeling. It is plausible that changes in some parameters, such as the aPWV, are yet to occur if this adaptive process is more gradual throughout childhood. This is supported by a study reporting a higher aPWV for preschool children born SGA compared to AGA children, as well as by a

study that found that measures at two years were stronger predictors for outcome at ten years than measures at 1.5 months[33,35]. In addition, we do not yet know whether the observed changes at birth will also persist into childhood or if these are (partially) reversible. This information is essential in devising targeted interventions to potentially induce this reversal in the future.

Our study has limitations. We have included a range of MC twin complications that can each have a different impact on cardiovascular structure. TTTS and TAPS twins experience hemodynamic imbalances in utero, which can affect postnatal cardiac dimensions despite reversibility after fetal therapy[27,36,37]. Similarly, in TAPS the donor experiences anemia and the recipient polycythemia, resulting in distinct circulatory adaptations[13]. In sFGR, hemodynamic changes are different in origin and expressed by abnormal umbilical artery Doppler flow patterns[38]. Additionally, prenatal growth is affected differently by each MC twin complication. Where isolated sFGR is primarily caused by unequal placental sharing, growth discrepancies in TTTS and TAPS can also occur due to oliguria or anemia in the donor. This influences direct extrapolation of our results to FGR in singletons, as this is primarily caused by placental insufficiency. To control for heterogeneity in our population, we assessed whether there was an association between the type of complication and each cardiac measurement. This was only the case LVPWD that stayed significant even after correction for the complications, illustrative of a limited influence.

To conclude, we report a structurally smaller heart for the smaller twins in our population. While cardiac structures are generally smaller, the deviation in birth weight tends to be more pronounced than the deviation in cardiac structure, indicative of heart sparing. These findings are suggestive of early cardiovascular changes after FGR. We used an identical twin cohort controlling for genetic and maternal factors, in which epigenetic profiling and cardiovascular follow-up will also be performed in the near future. Tracking cardiovascular structure and functioning over a longer period of time is crucial to understand the pathophysiological processes that underlie CVD risk[33,34]. Individualized risk assessments can be formed, allowing for consecutive timely and targeted interventions to minimalize the burden of disease in later life.

Acknowledgements
We wish to thank the parents and their twins participating in the Twinlife study for their time and efforts.

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