Title: Association of central obesity with unique cardiac remodelling in young adults born Small for Gestational Age

Authors: Gabriel Bernardino, PhD[1], Álvaro Sepúlveda-Martínez, MD, PhD[2,3], Mérida Rodríguez-López, MD, PhD[2,4], Susanna Prat-Gonzalez, MD, PhD[5,6], Carolina Pajuelo, MD[7], Rosario J Perea, MD, PhD[6,7], Maria T Caralt, MD[6,], Francesca Crovetto[2,6], MD, PhD[4], Miguel A. Gonzalez Ballester, PhD[8,9], Marta Sitges, MD, PhD[5,6], Bart Bijnens, PhD[6,9#], Fàtima Crispi, MD, PhD[2,6#*]

[#] Fàtima Crispi and Bart Bijnens contributed equally.

AFFILIATIONS:

[1]CREATIS, UMR 5220, U1294, F-69621, Univ Lyon, Université Claude Bernard Lyon 1, INSA-Lyon, CNRS, Inserm, Lyon, France

[2]BCNatal - Barcelona Center for Maternal-Fetal and Neonatal Medicine (Hospital Clínic and Hospital Sant Joan de Déu), Institut Clínic de Ginecologia Obstetricia i Neonatologia, Universitat de Barcelona, Centre for Biomedical Research on Rare Diseases (CIBER-ER), Barcelona, Spain

[3]Fetal Medicine Unit, Department of Obstetrics and Gynecology, Hospital Clínico de la Universidad de Chile, Santiago de Chile, Chile

[4]Pontificia Universidad Javeriana seccional Cali, Cali, Colombia

[5]Institut Clínic Cardiovascular, Hospital Clínic, Universitat de Barcelona, Centre for Biomedical Research on CardioVascular Diseases (CIBERCV), Barcelona, Spain.

[6]Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain.

[7]Centre de Diagnòstic per la Imatge, Hospital Clínic, Universitat de Barcelona, Barcelona, Spain

[8] BCN Medtech, Department of Information and Communication Technologies, Universitat Pompeu Fabra, Barcelona, Spain

[9]ICREA, Barcelona, Spain.

***CORRESPONDING AUTHOR:** Fàtima Crispi, MD, PhD, Fetal Medicine Research Center, BCNatal- Barcelona Center for Maternal-Fetal and Neonatal Medicine (Hospital Clínic and Hospital Sant Joan de Déu), Sabino de Arana street 1, 08028, Barcelona, Spain; e-mail: fcrispi@clinic.cat; phone: +34 932279333; fax: +34 932275605.

Conflicts of Interest: Nothing to Disclose.

Introduction

Small for gestational age (SGA) is defined as having a birth weight below the 10th percentile (thus affecting 10% of pregnancies) and predominantly includes growth-restricted fetuses. For over 30 years, epidemiological studies[1,2] have shown a consistent association between SGA and cardiovascular mortality in adults. While the precise mechanisms underlying this association are not fully clarified, fetal cardiac remodelling is proposed as a main contributor. SGA is associated with cardiac remodelling and dysfunction in fetuses,[2,3] children[4,5] and pre-adolescents[6]. However, the cardiac effects of SGA into adulthood are less investigated. Recently, we reported reduced exercise capacity and minor cardiac alterations -mainly right ventricular- in a cohort of 81 young adults born SGA[7]. In that study, statistical shape analysis was used to characterize regional structural differences between populations, exploiting its ability to treat cardiac geometry as a whole and allow an integrated approach when comparing groups[8,9]. Overall, adults born SGA present statistically significant, but subtle, changes in basal cardiac structure and function. Most studies evaluated SGA associated remodelling in the general population, while not addressing the contribution of potential, or additional, adverse stimuli to the cardiac response in some individuals.

Evaluating the effect of stressors is relevant to reveal the long-term effects of in utero adverse conditions, particularly in young patients. For instance, Scherrer et al. showed that children conceived by assisted reproductive technologies had similar baseline measures but remarkable differences in pulmonary pressure when exposed to low environmental oxygen[10]. Likewise, Huckstep et al. showed similar baseline values, but a marked reduction of ejection fraction under exercise in young adults born preterm[11]. Similarly, left ventricular structure and function in preterm adults worsens with systolic blood pressure elevation[12]. Epidemiological studies demonstrate that obesity after SGA further increases the risk of coronary events, insulin resistance and raised blood pressure[13,14]. Central obesity is recognized as a powerful predictor of obesity-related cardiovascular risk and death[15–17]. However, the effect of central obesity on cardiac remodelling and function in SGA adults has not been investigated.

We postulated that adults born SGA could have a differential, and potentially adverse, cardiac remodelling response to central obesity as both factors could potentiate each other their individual impact on cardiac performance. To test this hypothesis, we applied statistical shape analysis to study the interaction between SGA and central obesity, and its effect on cardiac structure and function in young adults.

Methodology

Study design

This study represents a sub analysis of an ambispective cohort study including young adults (30-40 years old) born SGA (n=80) and controls (n=75) with birth weight within normal ranges[7]. SGA was defined as a birth weight below the 10th centile for gestational age, and controls as normal birth weight. Exclusion criteria were neonatal macrosomia, twins, congenital malformations, genetic syndromes, major mental disorder, professional sport practice or current pregnancy. The study was approved by the local Ethics Committee and written consent was obtained for all participants.

The study protocol included medical history, physical examination, blood pressure, cardiac magnetic resonance (CMR) and incremental exercise test as described in the previous study. An international questionnaire on physical activity was used[18]. Incremental exercise test consisted in a cycloergometer (Ergoselect 100, Ergoline) permitting the measurement of oxygen uptake and heart rate at peak exercise (range 6-999 watts). Oxygen pulse was calculated as oxygen uptake divided by heart rate, and heart rate reserve by subtracting basal heart rate from heart rate at peak exercise. Anthropometric measures included weight, height, and waist and hip circumferences, were obtained by a trained physician blinded to the SGA category. Given the intrinsic relationship between SGA and height, we decided to use waist-to-hip log-ratio as a measure of central obesity[16,17], instead of BMI or waist-to-height ratios. An inelastic tape (Seca®, CA, USA) was used to measure the waist and hip circumferences, while the patient maintained the feet together and with the weight equally distributed on both feet. Waist circumference was measured horizontally midway between the lowest rib and the iliac crest. Hip circumference was measured on the area of greatest gluteal circumference. Waist-to-hip ratio was standardized by sex-specific z-score (each individual value had its sex-specific mean subtracted and divided by the sex-specific standard deviation) and used in a continuous manner. A log-transform was used to obtain a normal distribution in ratio-variables.

Cardiac magnetic resonance

CMR was performed on a 3T scanner (MAGNETOM® Trio Tim™, Siemens Healthineers, Germany) using retrospective ECG gating. Contiguous short-axis cine images covering both ventricles were acquired using a standard steady-state free-precession sequence (slice thickness 8 mm, 2 mm interslice gap) during breath hold. Long-axis cine images of 4-, 3- and 2-chamber views were also acquired. All images were stored on a digital archive for post processing with dedicated software (Argus (Siemens Medical Solutions, Germany) and Segment® (Medviso AB, Sweden)).

Shape analysis

Statistical shape analysis was used to study the regional geometric variability of the biventricular surfaces produced by central obesity and SGA. Here we provide a summary, but

a complete description of the methodology can be found in [19] and the supplementary material S1. First, biventricular surfaces of the LV endo- and epicardium and the RV endocardium were derived from each individual's CMR short axis images, using an automated algorithm[20]. Each surface contained 4446 points in point-to-point correspondence, allowing comparison between different individuals. The surfaces were previously aligned using a Partial Procrustes Algorithm[21], removing the position and orientation variability while keeping the size. Afterwards, we used principal component analysis (PCA) to derive the most significant modes of variation explaining 90% of the shape variance. Subsequently, we build a regression model to obtain the relationship between cardiac shape and central obesity (see the statistical analysis section).

To visualize and assess the regression model results, synthetic biventricular surfaces representatives of different waist-to-hip values were generated. For each waist-to-hip-ratio value between -2 and +2 standard deviations (SD), the regression coefficients of the waist-to-hip were used to construct a biventricular surface corresponding to the mean shape associated to that value of waist-to-hip-ratio for controls: representing the continuous transition from adequate weight to central obesity. The same process was performed using the regression coefficients of the interaction between SGA and waist-to-hip to obtain the equivalent surfaces associated with the central obesity cardiac remodelling of SGA. The average pointwise different between the SGA and control synthetic representative surfaces was computed for each waist-to-hip value to quantify the geometric differences between SGA and controls as a function of central obesity.

To quantitatively assess these remodelling patterns, we extracted geometrical measurements (LV and RV end-diastolic volumes, LV mass and long-axis dimension, and mitral diameter) from this spectrum of synthetic surfaces. For each surface of the SGA and control populations, we used the reverted regression model to obtain the waist-to-hip ratio expected from the surface, serving as a quantification of the presence of central obesity-induced remodelling. Associations between this remodelling index and the classical MRI-based and exercise functional parameters were tested using multivariate regression (MVR). More details on the derivation of the synthetic meshes and score are in the supplementary material.

Statistical Analysis

Statistical analysis was performed using Stata IC v14.0 (StataCorp. LP, College Station, TX, USA) and Python v3.6 (Anaconda Inc, Austin, TX, USA) and the statistical package *statsmodels* (v0.12.1). Study groups were described using mean (SD), median (interquartile range, IQR) or frequencies and compared by Student's t-test, Wilcoxon-Mann Whitney, chi-square or Fisher exact tests as appropriate. F-test was used for testing the significance of each regression coefficient in MVR, and Wilkis test for MMR. All MVR and MMR models were adjusted by sex and age as potential confounders. Benjamini-Hochberg correction for multiple testing was used. Statistical significance was established at 0.05. Multiple multivariate regression (MMR)

was used to study the relationship between central obesity, SGA and cardiac shape. This model included the shape (expressed by its PCA modes, a multi-dimensional variable) as the dependent variable, and the SGA label, waist-to-hip z-score (the main effects), together with the interaction between the two main effects as independent variables.

Results

Study populations

Perinatal and adult characteristics of the study populations are shown in Table 1. By design, SGA subjects showed lower birth weight and birth weight centile with similar gestational age at delivery as compared to controls. SGA cases showed lower height and weight, with similar body mass index and waist-to-hip ratio as compared to control subjects. The rates of body mass index above 25 was also similar among groups (controls 29 (38.8%) vs SGA 33 (41.3%)). Both groups presented similar rates of smoking habit, chronic hypertension and diabetes mellitus, values of blood pressure and plasmatic concentrations of cholesterol, triglycerides and glucose.

Cardiac shape differences between SGA and controls

Figure 1 displays the subtle ventricular shape differences between non-obese SGA and non-obese controls, mainly involving the RV (more curved base in SGA). Biventricular shape differences became more pronounced between obese SGA and obese controls, with significant changes in both ventricles. The right plot at Figure 1 demonstrates an increasing biventricular shape differences between SGA and controls with increasing waist-to-hip ratio.

Relationship between waist-to-hip ratio, SGA, and cardiac geometry

Statistical shape analysis was used to study the relationship between SGA, waist-to-hip-ratio (used in a continuous manner) and cardiac geometry. MMR identified the biventricular geometric changes associated to increases in waist-to-hip ratio in controls and SGA, which are represented in Figure 2 where the predicted geometries at ±2 STD waist-to-hip ratio and the color map represents in red the presence of local changes. A continuous transition of the biventricular shapes between the two extreme values can be found in the Supplementary Video 1. The numerical values among the different variables and covariates and the shape PCA modes are depicted in the Supplementary Materials (Table S1).

The MMR showed significant differences in biventricular shape between the overall population of SGA versus controls (smaller ventricular volumes and more curved RV base in SGA; $F=3.94$, $p<0.001$). Significant differences in biventricular shape were also observed according to waist-to-hip ratio (dilatation in the circumferential direction of both volumes and mass; $F=5.18$, $p<0.001$). In addition, the analysis demonstrated that the interaction term between waist-to-hip ratio and SGA status was a statistically significant predictor of cardiac shape ($F=2.29$, $p=0.02$). Figure 2 and both Supplementary Videos show the biventricular shape obese remodelling patterns in controls and SGA individuals shown for the lowest (-2SD waist-to-hip ratio, non-obese) and the highest (+2SD waist-to-hip ratio, obese) waist-to-hip ratio. Figure 3 shows the effect of waist-to-hip ratio on left ventricular mass, long axis and transverse dimensions, and biventricular end-diastolic volumes measured over the synthetic surfaces among SGA and controls. In controls, the obesity cardiac remodelling consisted of an increase of the myocardial mass together with a small transverse dilatation of the LV, without

an elongation of the long axis. Both obese controls and obese SGA showed basal septal hypertrophy (visible as a bulge in the basal septum below the aorta) and flattening of the left ventricular lateral wall. Dissimilar to the controls, SGA obese remodelling consisted of a shortening of the long axis, with a reduction of the cavity size, that was more pronounced in the apex.

Cardiac geometry-function relationship

For each study participant, we quantified the presence of obesity-remodelling (either the pattern specific for controls or to SGA) and expressed it as a score of obesity-remodelling. Afterwards, MVR was used to assess the relationship of this obesity-remodelling score with functional parameters (Table 2). At rest, for control participants, indexed left and right ventricular stroke volumes, cardiac outputs and heart rate, showed no relation with obesity-remodelling ($p=0.99$), suggesting a compensatory adaptation to increased body surface. On the contrary, more SGA obesity-remodelling was associated with an increasingly lower left stroke index ($p<0.001$), a tendency to higher heart rate ($p=0.07$) and preserved cardiac index ($p=0.13$). Both right stroke volume and cardiac index showed a significant lower slope in SGA as compared to controls. Both right and left ejection fractions were preserved.

When analyzing the functional results of the incremental exercise test, a different influence of central obesity was also observed in controls and SGA at peak exercise. Independently of their waist-to-hip ratio, control participants showed a preserved exercise capacity evaluated through peak oxygen consumption, oxygen pulse and heart rate ($p=0.77$, $p=0.97$, $p=0.33$ respectively). In contrast, SGA obesity-remodelling was associated with gradually lower peak oxygen consumption ($p<0.001$), oxygen pulse ($p<0.001$) and heart rate reserve ($p<0.01$) in relation to increased waist-to-hip ratio.

Sex, height, and blood pressure subanalyses

A sex-stratified subanalysis showed similar patterns in the response to central obesity for females ($F=1.97$, $p=0.07$) and males ($F=1.40$, $p=0.22$), while we found no evidence of association of neither height nor systolic blood pressure with a differential shape remodelling ($F=0.88$, $p=0.53$; $F=1.38$,$p=0.21$ respectively). The complete analysis is in the Supplementary Material (S3-5).

Discussion

This study shows a unique cardiac response to central obesity, associated to poorer exercise performance, in SGA young adults. Thus, providing supporting evidence of central obesity potentiating cardiovascular risk in SGA individuals.

SGA associates a unique cardiac adaptation to central obesity

Our data suggest for the first time a different pattern of remodelling as response to central obesity in adults born SGA and controls. Obesity represents an overload for the cardiovascular system through increased circulating blood volume and pressure. As expected, in non-SGA individuals, central obesity was associated with larger and hypertrophic hearts that permits coping with the augmented blood volume, increasing stroke volume and preserving performance at exercise. We could also observe basal septal hypertrophy (regularly found in subjects with severe hypertension), together with flattening of the lateral wall. This data is consistent with previous studies demonstrating myocardial hypertrophy and LV cavity enlargement in obese patients[22]. Our results are also concordant with previous data from 3D CMR shape analysis in large cohorts of obese adults without known comorbidities. The UK Digital Heart Project described asymmetric concentric hypertrophy and cavity dilatation with increasing body fat, with the septum being the most sensitive to changes[23]. In the UK Biobank Study, shape variants characterized by septal displacement and apical bulging had robust and strong relationships with obesity[24] In the Generation R Study, obese children present septo-lateral tilting, compression in the antero-posterior direction, and decreased eccentricity[25].

In contrast, obese adults born SGA show a unique pattern of cardiac remodelling as compared to what would be expected in obese individuals according to the previous reports, with smaller cavities and preserved ventricular mass, suggesting concentric hypertrophy. These differences were observed both in left and right ventricles. This SGA-obesity remodelling resulted in reduced stroke volume and hampered performance during exercise, suggesting that the heart is too small and needs to disproportionally increase heart rate to maintain the required cardiac output. Overall, our data suggest that while controls efficiently adapt to the increased volume loading, in SGA the response failed to meet volume and exercise requirements. The fact that obese-SGA have an early exercise capacity impairment may indicate that their reduction in cardiac sizes is not physiologically adaptive and could contribute to the previously reported worse cardiovascular outcomes in SGA individuals. No previous studies had reported cardiac shape/function in obese adults born SGA, but our data is consistent with increased cardiac events and decreased physical functioning in individuals born SGA that subsequently get obese [26–28]. It is also concordant with reduced exercise performance in SGA adults[7,29]. This is relevant as SGA individuals are a well-known group at risk of obesity, diabetes mellitus and metabolic syndrome. While the exact mechanism of this association is unclear, the '*thrifty phenotype hypothesis*' postulates that poor nutrition in early life produces permanent changes in glucose-insulin metabolism and predisposes to

subsequent obesity. Overall, our results support preventive strategies aiming to reduce obesity in individuals born SGA.

Central obesity as a second hit worsening cardiac structure and performance in SGA

Here, we confirm previous findings suggesting minor changes in cardiac shape and reduced exercise capacity in adults born SGA[7]. Central obesity seems to magnify cardiac differences between individuals born SGA and controls. While non-obese adults born SGA show subtle changes, mainly in right ventricular shape, the combination of central obesity and SGA revealed clear differences both in left and right ventricular shape as compared to obese controls.

This study provides first evidence in humans suggesting an exaggerated effect of central obesity in SGA adults. Results are consistent with experimental evidence: in SGA rats, a postnatal high-fat diet decreased aerobic cardiac performance and increased myocardial susceptibility to ischemia[30]. Together with previous studies, the findings support the hypothesis that SGA could operate as a first hit leading to latent susceptibility, which combined with subsequent risk factors -such as central obesity- could accelerate progression to cardiac disease. This notion is indirectly supported by previous epidemiologic studies. Postnatal excessive weight gain after SGA further increases the risk of coronary events, insulin resistance and raised blood pressure[26,31,32]. Likewise, it negatively affects childhood aerobic and neuromuscular fitness[33] and physical functioning in older age[28]. Conversely, breastfeeding and healthy-fat dietary intake seem to improve cardiovascular outcomes in individuals born SGA or preterm[34,35] Future research is needed to further study the impact of postnatal risk factors on individuals born SGA. Additional primary preventing strategies specifically targeting cardiovascular risk reduction in this population may be warranted.

Subanalyses regarding sex, education level, height and blood pressure

Given the observational design of this study, we acknowledge that several factors may have influenced or modified the results. A sex-stratified analysis showed similar results in men and women, although we acknowledge that our study was most likely underpowered to detect sex-related risk differences. Educational level was significantly different in the control and SGA population and therefore it could be considered a potential confounder. However, results did not statistically significantly change when adjusted by education. In a similar manner, height could also be considered a potential confounder or modifier as SGA adults were significantly shorter than controls. Thus, an interaction analysis was performed showing no significant effect of height on cardiac shape in relation to waist-to-hip ratio. However, given the negative association of the SGA obesity-remodelling with height, it cannot be discarded that the found remodelling corresponds to more severe SGA cases, since these individuals have a predisposition to develop shorter and more central obesity body types, and not a direct interaction between SGA and obesity. Finally, while not statistically significant in our cohort, a higher risk for hypertension has been reported in individuals born SGA.[14,31] Therefore, we also conducted an interaction analysis failing to demonstrate an independent

effect of blood pressure on obesity-related remodeling. The fact that no link between blood pressure for neither obesity nor shape remodelling could be demonstrated might be explained by the low precision of single cuff measurement, the lack of data on exercise-induced pressure changes or the fact that we deal with a still asymptomatic population.

Strengths and limitations

This study has some strengths and limitations that merit comment. We studied a well-phenotyped cohort selected from delivery and evaluated in adulthood. We applied 3D shape analysis to the ventricular surfaces extracted from CMR that enabled the detection cardiac shape differences among the study populations. While body surface area was not included in the analysis intentionally due to its high intrinsic correlation and interplay with obesity, comparisons were showing similar results if adjusted (data not shown). As limitations, first, it is an observational study which limits the establishment of causal relationships and is at risk of confounding. Second, we acknowledge that waist-to-hip ratio might not be the optimal surrogate of obesity, however, we considered it to be the best measure in the scenario of SGA given its strong intrinsic association with height and weight. Third, despite most baseline characteristics were similar among groups, we acknowledge that many factors may influence the outcome from birth to adulthood. Finally, given that cardiovascular adverse events occur much later in life, we could not establish a direct link between the observed remodelling and subsequent cardiovascular risk. The use of a young adult cohort avoided the interference of other comorbidities but prevented study of associations with cardiovascular events.

Conclusion

This study reveals that SGA adults experience, on top of the cardiac changes due to SGA itself, a unique cardiac remodelling in response to central obesity, that further limits their exercise capacity. This suggests that central obesity potentiates -not additive but a synergistic effect- cardiovascular risk in SGA, highlighting the importance of preventive measures promoting a healthy lifestyle in this population. Given that SGA affects 10% of live births, future studies are warranted to better understand how the heart remodels in response to other risk factors and defining preventives strategies to improve cardiovascular health of these individuals.

Acknowledgements: This work was partially supported by the French ANR (LABEX PRIMES of Univ. Lyon [ANR-11-LABX-0063] and the JCJC project ``MIC-MAC'' [ANR-19-CE45-0005]), the European Union Horizon 2020 Programme for Research and Innovation, under grant agreement No. 642676 (CardioFunXion) and the Erasmus + Programme of the European Union (Framework Agreement number: 2013-0040). This publication reflects the views only of the author, and the Commission cannot be held responsible for any use, which may be made of the information contained therein. Additionally, the research leading to these results has received funding from “la Caixa” Foundation under grant agreement LCF/PR/GN14/10270005 (Spain), the Ministerio de Educación, Cultura y Deporte under grant FPU17/05579 (Spain), the Instituto de Salud Carlos III (PI14/00226, INT21/00027, PI17/00675,

PI18/00073, PI20/00246, CM19/00140) integrados en el Plan Nacional de I+D+I y cofinanciados por el ISCIII-Subdirección General de Evaluación y el Fondo Europeo de Desarrollo Regional (FEDER) "Una manera de hacer Europa" (Spain), the Centro de Investigación Biomédica en Red de Enfermedades Raras (ERPR04G719/2016) (Spain), Cerebra Foundation for the Brain Injured Child (Carmarthen, Wales, UK), Fundación Jesus Serra (Spain), and AGAUR 2017 SGR grant nº 1531 (Spain).

Data availability statement: The data underlying this article will be shared on reasonable request to the corresponding author.

References

1. Barker DJP, Osmond C, Golding J, Kuh D, Wadsworth MEJ. Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. *BMJ (Clinical research ed)*. 1989;298(6673):564-567. doi:10.1136/bmj.298.6673.564
2. Crispi F, Miranda J, Gratacós E. Long-term cardiovascular consequences of fetal growth restriction: biology, clinical implications, and opportunities for prevention of adult disease. *American Journal of Obstetrics and Gynecology*. 2018;218(2):S869-S879. doi:10.1016/j.ajog.2017.12.012
3. Crispi F, Hernandez-Andrade E, Pelsers MMAL, Plasencia W, Benavides-Serralde A, Eixarch E, et al. Cardiac dysfunction and cell damage across clinical stages of severity in growth-restricted fetuses. *American Journal of Obstetrics and Gynecology*. 2008;199:254.e1-254.e8. doi:10.1016/j.ajog.2008.06.056
4. Sehgal A, Doctor T, Menahem S. Cardiac function and arterial indices in infants born small for gestational age: analysis by speckle tracking. *Acta Paediatrica*. 2014;103(2):e49-e54. doi:10.1111/apa.12465
5. Crispi F, Bijnens B, Figueras F, Bartrons J, Eixarch E, Le Noble F et al. Fetal Growth Restriction Results in Remodeled and Less Efficient Hearts in Children. *Circulation*. 2010;121(22):2427-2436. doi:10.1161/CIRCULATIONAHA.110.937995
6. Sarvari SI, Rodriguez-Lopez M, Nuñez-Garcia M, Sitges M, Sepulveda-Martinez A, Camara O et al. Persistence of Cardiac Remodeling in Preadolescents with Fetal Growth Restriction. *Circulation: Cardiovascular Imaging*. 2017;10:e005270. doi:10.1161/CIRCIMAGING.116.005270
7. Crispi F, Rodríguez-López M, Bernardino G, Sepulveda-Martinez A, Prat-Gonzalez S, Pajuelo C et al. Exercise Capacity in Young Adults Born Small for Gestational Age. *JAMA Cardiology*. 2021;6(11):1308. doi:10.1001/jamacardio.2021.2537
8. Bernardino G, Sanz de la Garza M, Domenech-Ximenos B, Prat-Gonzalez S, Perea RJ, Blanco I et al. Three-dimensional regional bi-ventricular shape remodeling is associated with exercise capacity in endurance athletes. *European Journal of Applied Physiology*. 2020;120(6):1227-1235. doi:10.1007/s00421-020-04335-3
9. Zhang X, Cowan BR, Bluemke DA, Finn JP, Fonseca CG, Kadish AH et al. Atlas-Based Quantification of Cardiac Remodeling Due to Myocardial Infarction. Bauer WR, ed. *PLoS ONE*. 2014;9(10):e110243. doi:10.1371/journal.pone.0110243
10. Scherrer U, Rimoldi SF, Rexhaj E, Stuber T, Duplain H, Garcin S, et al. Systemic and Pulmonary Vascular Dysfunction in Children Conceived by Assisted Reproductive Technologies. *Circulation*. 2012;125(15):1890-1896. doi:10.1161/CIRCULATIONAHA.111.071183
11. Huckstep OJ, Williamson W, Telles F, Burchert H, Bertagnolli M, Herdman C, et al. Physiological Stress Elicits Impaired Left Ventricular Function in Preterm-Born

Adults. *Journal of the American College of Cardiology*. 2018;71(12):1347-1356. doi:10.1016/j.jacc.2018.01.046
12. Mohamed A, Marciniak M, Williamson W, Huckstep OJ, Lapidaire W, McCance A, et al. Association of Systolic Blood Pressure Elevation with Disproportionate Left Ventricular Remodeling in Very Preterm-Born Young Adults: The Preterm Heart and Elevated Blood Pressure. *JAMA Cardiology*. 2021;6(7). doi:10.1001/jamacardio.2021.0961
13. Arnott C, Skilton MR, Ruohonen S, Juonala M, Viikari JSA, Kahonen M, et al. Subtle increases in heart size persist into adulthood in growth restricted babies: the Cardiovascular Risk in Young Finns Study. *Open Heart*. 2015;2(1):e000265. doi:10.1136/openhrt-2015-000265
14. Miles KL, McDonnell BJ, Maki-Petaja KM, Yasmin, Cockcroft JR, Wilkinson IB, et al. The impact of birth weight on blood pressure and arterial stiffness in later life: The Enigma Study. *Journal of Hypertension*. 2011;29(12). doi:10.1097/HJH.0b013e32834d0ca1
15. Kannel WB, Adrienne Cupples L, Ramaswami R, Stokes J, Kreger BE, Higgins M. Regional obesity and risk of cardiovascular disease; the Framingham study. *Journal of Clinical Epidemiology*. 1991;44(2):183-190. doi:10.1016/0895-4356(91)90265-B
16. Ammar KA, Redfield MM, Mahoney DW, Johnson M, Jacobsen SJ, Rodeheffer RJ. Central obesity: Association with left ventricular dysfunction and mortality in the community. *American Heart Journal*. 2008;156(5):975-981. doi:10.1016/j.ahj.2008.06.018
17. Selvaraj S, Martinez EE, Aguilar FG, Kim KYA, Peng J, Sha J, et al. Association of Central Adiposity With Adverse Cardiac Mechanics. *Circulation: Cardiovascular Imaging*. 2016;9(6). doi:10.1161/CIRCIMAGING.115.004396
18. Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE, et al. International Physical Activity Questionnaire: 12-Country Reliability and Validity. *Med Sci Sports Exerc*. 2003;35(8):1381-1395. doi:10.1249/01.MSS.0000078924.61453.FB
19. Bernardino G, Benkarim O, Sanz-de la Garza M, Prat-Gonzalez S, Sepulveda-Martinez A, Crispi F, et al. Handling confounding variables in statistical shape analysis - application to cardiac remodelling. *Medical Image Analysis*. 2020;65:101792. doi:10.1016/j.media.2020.101792
20. Peters J, Ecabert O, Meyer C, Kneser R, Weese J. Optimizing boundary detection via Simulated Search with applications to multi-modal heart segmentation. *Medical Image Analysis*. Published online 2010. doi:10.1016/j.media.2009.10.004
21. Dryden L, Mardia K V. *Statistical Shape Analysis*.; 1998.
22. Aurigemma GP, de Simone G, Fitzgibbons TP. Cardiac Remodeling in Obesity. *Circulation: Cardiovascular Imaging*. 2013;6(1):142-152. doi:10.1161/CIRCIMAGING.111.964627
23. Corden B, de Marvao A, Dawes TJ, Shi W, Rueckert D, Cook SA, et al. Relationship between body composition and left ventricular geometry using three dimensional cardiovascular magnetic resonance. *Journal of Cardiovascular Magnetic Resonance*. 2016;18(1):32. doi:10.1186/s12968-016-0251-4
24. Gilbert K, Bai W, Mauger C, Medrano-Gracia P, Suinesiaputra A, Lee AM, et al. Independent Left Ventricular Morphometric Atlases Show Consistent Relationships with Cardiovascular Risk Factors: A UK Biobank Study. *Scientific Reports*. 2019;9(1). doi:10.1038/s41598-018-37916-6
25. Marciniak M, van Deutekom AW, Toemen L, Lewandowski AJ, Gaillard R, Young AA, et al. A three-dimensional atlas of child's cardiac anatomy and the unique

morphological alterations associated with obesity. *European Heart Journal - Cardiovascular Imaging*. Published online December 21, 2021. doi:10.1093/ehjci/jeab271
26. Barker DJP, Osmond C, Forsén TJ, Kajantie E, Eriksson JG. Trajectories of Growth among Children Who Have Coronary Events as Adults. *New England Journal of Medicine*. 2005;353(17):1802-1809. doi:10.1056/NEJMoa044160
27. Fall CHD, Osmond C, Barker DJP, Clark PM, Hales CN, Stirling Y, et al. Fetal and infant growth and cardiovascular risk factors in women. *BMJ*. 1995;310(6977):428-432. doi:10.1136/bmj.310.6977.428
28. von Bonsdorff MB, Rantanen T, Sipila S, Salonen MK, Kajantie E, Osmond C, et al. Birth Size and Childhood Growth as Determinants of Physical Functioning in Older Age: The Helsinki Birth Cohort Study. *American Journal of Epidemiology*. 2011;174(12):1336-1344. doi:10.1093/aje/kwr270
29. Yang J, Epton MJ, Harris SL, Horwood J, Kingsford RA, Troghton R, et al. Reduced Exercise Capacity in Adults Born at Very Low Birth Weight: A Population-based Cohort Study. *American Journal of Respiratory and Critical Care Medicine*. 2022;205(1):88-98. doi:10.1164/rccm.202103-0755OC
30. Rueda-Clausen CF, Morton JS, Dolinsky VW, Dyck JRB, Davidge ST. Synergistic effects of prenatal hypoxia and postnatal high-fat diet in the development of cardiovascular pathology in young rats. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*. 2012;303(4):R418-R426. doi:10.1152/ajpregu.00148.2012
31. Huxley RR, Shiell AW, Law CM. The role of size at birth and postnatal catch-up growth in determining systolic blood pressure. *Journal of Hypertension*. 2000;18(7):815-831. doi:10.1097/00004872-200018070-00002
32. Eriksson JG, Forsén T, Tuomilehto J, Osmond C, Barker DJP. Early growth and coronary heart disease in later life: longitudinal study. *BMJ (Clinical research ed)*. 2001;322(7292):949-953. doi:10.1136/bmj.322.7292.949
33. van Deutekom AW, Chinapaw MJM, Vrijkotte TGM, Gemke RJBJ. The association of birth weight and infant growth with physical fitness at 8–9 years of age—the ABCD study. *International Journal of Obesity*. 2015;39(4):593-600. doi:10.1038/ijo.2014.204
34. Lewandowski AJ, Lamata P, Francis JM, Piechnik SK, Ferreira VM, Boardman H, et al. Breast Milk Consumption in Preterm Neonates and Cardiac Shape in Adulthood. *PEDIATRICS*. 2016;138(1):e20160050-e20160050. doi:10.1542/peds.2016-0050
35. Rodriguez-Lopez M, Osorio L, Acosta-Rojas R, Figueras J, Cruz-Lemini M, Figueras F, et al. Influence of breastfeeding and postnatal nutrition on cardiovascular remodeling induced by fetal growth restriction. *Pediatric Research*. 2016;79(1):100-106. doi:10.1038/pr.2015.182

FIGURES

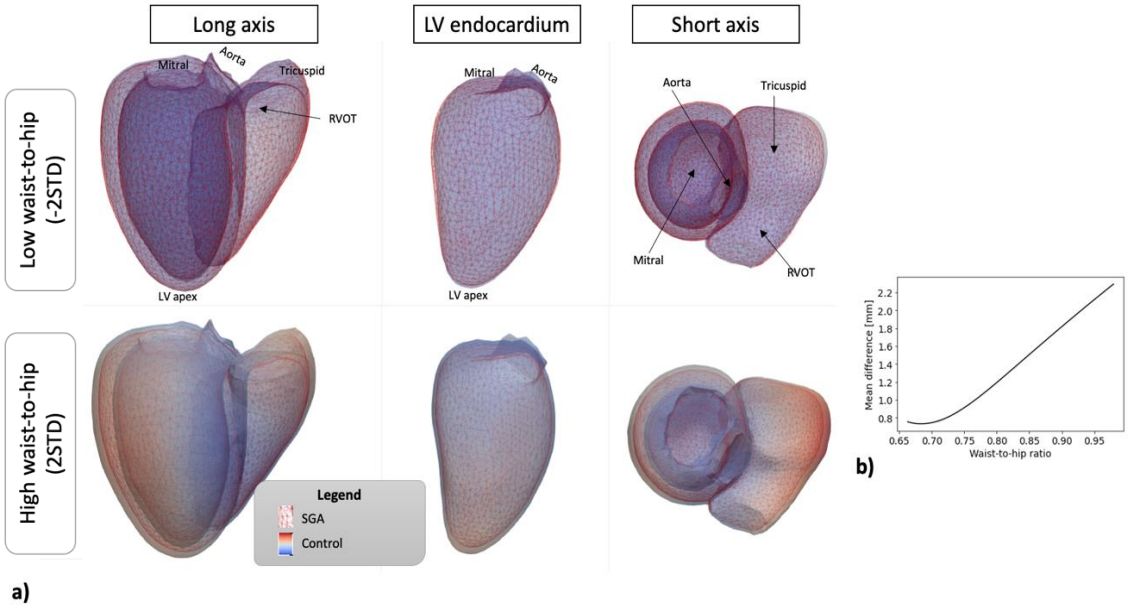

Figure 1. a) Regional differences between the synthetic representative of SGA (grid) and controls (blue-red color map, red indicating higher differences between SGA-control) for two different values of waist-to-hip ratio using our MMR model. We can see that at a low waist-to-hip (upper row), the two meshes almost overlap, except in a small region near the RV base (short-axis view), but more differences appear at higher waist-to-hip ratio (lower row). b) These differences were quantified in the plot in the right, where the mean distance between the representative biventricular surfaces of a control and a SGA is depicted as a function of the waist-to-hip ratio. It illustrates that, while the point-wise difference is small at low waist-to-hip ratio, the difference is much higher as the waist-to-hip ratio increases.

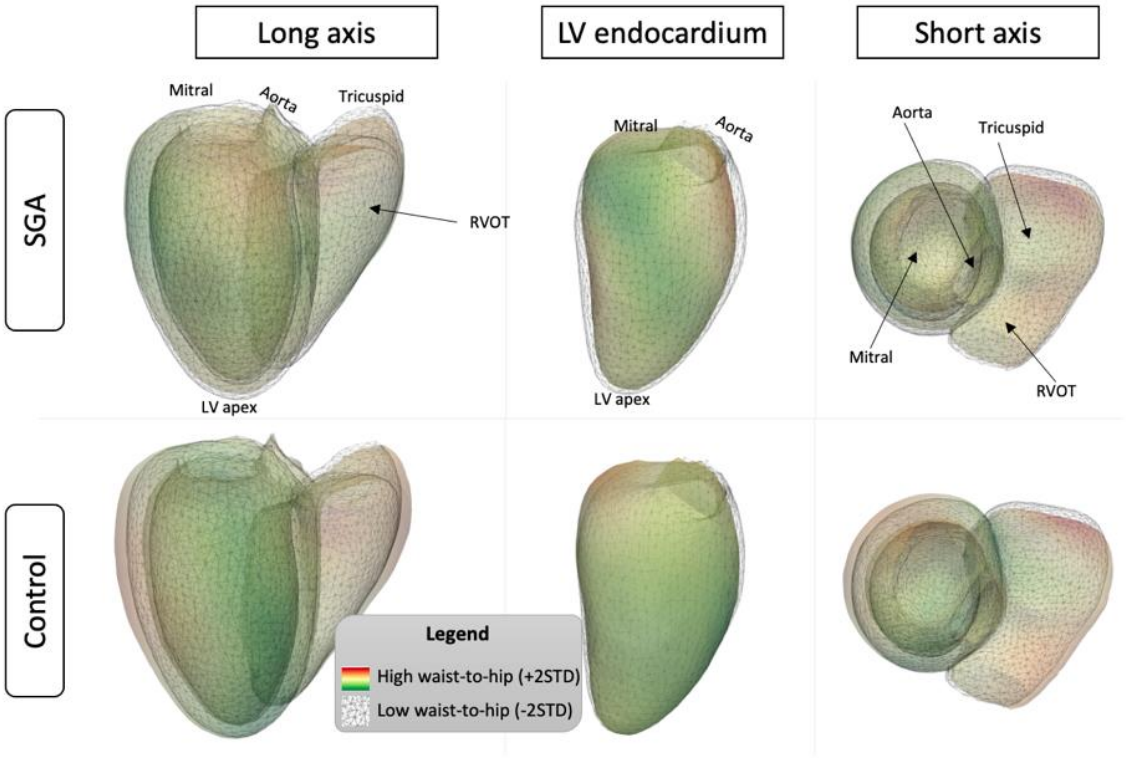

Figure 2. Synthetic biventricular surfaces representative of extreme values the waist-to-hip at +/-2 STD (-2STD corresponds to a waist-to-hip value of 0.66 displayed in the solid colormop, +2STD corresponds to a waist-to-hip value of 0.98 displayed as a grid) according to our MMR model in adults born Small for Gestational Age (SGA, above) and control patricipants (bottom). The central column represents the isolated LV endocardium for better visualisation. We can see that, in SGA (top), a higher waist-to-hip ratio is associated with a decreases of the LV volume (central view) and RV (short axis) with preserved epicardial contour. In contrast, for controls (lower row), an increase of waist-to-hip ratio is associated with a higher LV mass.

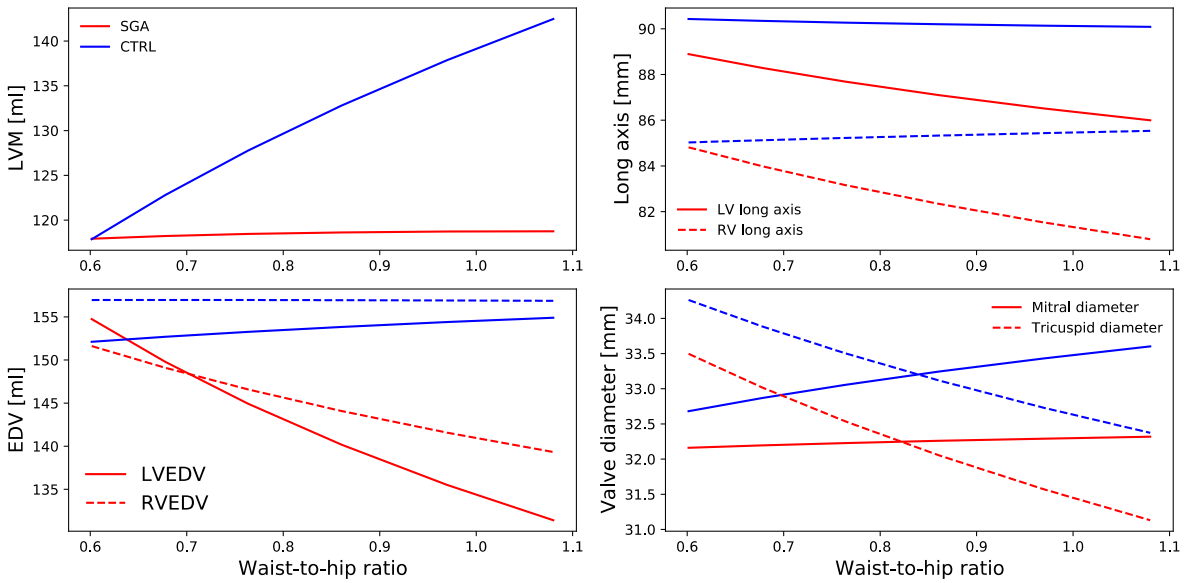

Figure 3. Continuous *changes of ventricular mass, volume and dimensions in the synthetic surfaces representative of different values of waist-to-hip ratio for control participants (blue) and adults born Small for Gestational Age (SGA, red). Controls have a preserved volumes and long-axis, but have an increasing LV mass with increments of waist-to-hip-ratio; while SGA have a preserved ventricular mass and a decrease of ventricular volumes and longitudinal dimension.*

TABLES

Table 1*. Perinatal and current baseline characteristics of the study population.*

	Controls (n=75)	**SGA** (n=80)
Perinatal characteristics		
Birthweight (g)	3380 (3195-3565)	2585 (2447-2700)*
Gestational age at delivery (weeks)	40 (39-40)	40 (39-41)
Birthweight centile	53 (40-66)	1 (1-3)*
Current baseline characteristics		
Age (years)	34.0 (30.5-36.7)	34.2 (30.1-36.5)
Female	33 (44)	43 (54)
White ethnicity	75 (100)	80 (100)
Previous familiar history of myocardial infarction	11 (14.7)	7 (8.8)
University education	48 (64)	32 (40)*
Physically active[a]	16 (21)	16 (20)
Smoking habit	44 (58.7)	43 (53.8)
Diabetes mellitus	0 (0)	3 (3.7)
Chronic hypertension	2 (2.6)	2 (2.5)
Height (m)	1.72 (1.69-1.77)	1.66 (1.58-1.72)*
Weight (kg)	73.3 (60.7-84.6)	70 (57.7-79.1)
Body surface area (m^2)[b]	1.87 (0.22)	1.78(0.23)*
Body mass index (kg/m^2)[c]	24.32 (21.4-26.6)	24.67 (21.7-28.4)
Waist-to-hip ratio	0.80 (0.73-0.86)	0.82 (0.76-0.86)
Cholesterol LDL (mg/dL)	110.6 (95.8 -133.05)	110.2 (100.6 – 125.2)
Triglyceride (mg/dL)	102.0 (70.5 – 148.5)	85.0 (69.5 – 108)
Glucose (mg/dL)	89.0 (82.0 – 97.0)	88.5 (81.0 – 96.0)
Systolic blood pressure (mmHg)[d]	118.33 (110.5-128.7)	117.5 (109.4-126.7)
Diastolic blood pressure (mmHg)[d]	71.33 (66.7-77.7)	72.0 (64.0-80.0)

Data are median (interquartile range) or number (percentage).

Abbreviations: SGA, small-for-gestational age; LDL, low-density lipoprotein.

[a]Physical activity was assessed by the International Physical Activity Questionnaire.[18]

[b]Body surface area was calculated by the Haycock formula.

[c] Body mass index calculated as the weight in kilograms divided by height in meters squared.

[d]Blood pressure was obtained at the beginning of the medical evaluation by a trained nurse while the individual was seated after having rested for 5 to 10 minutes.
*P<0.05 as compared to controls.

Table 2. *Regression slope of functional parameters at rest and at peak exercise according to waist-to-hip ratio change in control participants and adults born Small for Gestational Age (SGA).*

	Controls		SGA	
	Regression coefficient	**P-Value[c]**	**Regression coefficient**	**P-Value[c]**
Cardiac function at rest				
Left ventricular stroke index (ml/m^2) [a]	0.56	0.99	-5.45	< 0.001
Left ventricular cardiac index (ml/min/m^2)[a]	0.04	0.99	-0.12	0.16
Left ventricular ejection fraction (%)	-0.59	0.99	0.65	0.21
Right ventricular stroke index (ml/m^2)[a]	0.11	0.99	-5.99	<0.001
Right ventricular cardiac index (ml/min/m^2)[a]	0.00	0.99	-0.19	< 0.01
Right ventricular ejection fraction (%)	-1.85	0.21	0.45	0.45
Heart rate (bpm)	-1.86	0.99	4.51	0.07
Mean blood pressure (mmHg)	2.90	0.13	-0.92	0.54
Performance at peak exercise				
Oxygen uptake index (ml/min/kg) [b]	-0.36	0.99	-4.65	< 0.001
Oxygen pulse index (ml/kg)[b]	0.25	0.99	-22.31	< 0.001
Heart rate (bpm)	-1.97	0.99	-4.20	0.07
Heart rate reserve (bpm)	-0.11	0.99	-8.70	0.009
Mean blood pressure (mmHg)	3.14	0.27	-2.39	0.37

[a]Left ventricular stroke volume and cardiac output were indexed for body surface area.
[b]Oxygen uptake and pulse were indexed for weight.
[C]P-values adjusted for multiple hypothesis testing.