Association of gestation and fetal growth restriction on cardiovascular health in preterm-born children

Christopher W. Course, MRCPCH, Sarah J. Kotecha, PhD, Michael Cousins, MRCPCH, PhD, Kylie Hart, PhD, John Lowe, PhD, W John Watkins, PhD, Sailesh Kotecha, FRCPCH, PhD

PII: S0022-3476(22)00889-7

DOI: https://doi.org/10.1016/j.jpeds.2022.09.057

Reference: YMPD 13226

To appear in: *The Journal of Pediatrics*

Received Date: 12 May 2022

Revised Date: 1 September 2022

Accepted Date: 6 September 2022

Please cite this article as: Course CW, Kotecha SJ, Cousins M, Hart K, Lowe J, Watkins WJ, Kotecha S, Association of gestation and fetal growth restriction on cardiovascular health in preterm-born children, *The Journal of Pediatrics* (2022), doi: https://doi.org/10.1016/j.jpeds.2022.09.057.

Association of gestation and fetal growth restriction on cardiovascular health in preterm-born children

Christopher W Course MRCPCH[1], Sarah J Kotecha PhD[1], Michael Cousins MRCPCH, PhD[1, 2], Kylie Hart PhD[2], John Lowe PhD[1], W John Watkins PhD[1], Sailesh Kotecha FRCPCH, PhD[1].

[1]Department of Child Health, Cardiff University School of Medicine, Cardiff, United Kingdom.

[2]Department of Paediatrics, Cardiff and Vale University Health Board, Cardiff, United Kingdom

Corresponding author:

Professor Sailesh Kotecha,

Department of Child Health

Cardiff University School of Medicine,

University Hospital of Wales,

Heath Park,

Cardiff,

CF14 4XN,

United Kingdom

kotechas@cardiff.ac.uk

Short title: Cardiovascular outcomes in preterm-born children

Conflict of interest disclosures:

Professor S Kotecha reports grants from Medical Research Council and from GSK for conduct of the current study; and grants from NIHR/HTA, Aspire Pharma and Moulton Foundation outside the

submitted work. Drs SJ Kotecha and WJ Watkins report grants from Moulton Foundation outside of this work. The other authors declare no conflicts of interest.

Sources of funding:

The RHiNO Study was funded by a Medical Research Council Experimental Medicine Challenge Grant (Reference: MR/M022552/1).

Clinical trial registration URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-003712-20/GB

Clinical Trial ID: RHiNO, EudraCT: 2015-003712-20

Data Sharing Statement: Anonymised data contained within this manuscript will be shared upon reasonable request to Professor S Kotecha.

Abbreviations:

AGA	Appropriate birth weight for gestational age
AIx	Augmentation Index
BMI	Body Mass Index
CI	Confidence Interval
CPET	Cardiopulmonary Exercise Test
DBP	Diastolic Blood Pressure
FMI	Fat Mass Index
FFMI	Fat-Free Mass Index
FGR	Fetal Growth Restriction
MAP	Mean Arterial Pressure
PWV	Pulse Wave Velocity
RHiNO	Respiratory Health Outcomes in Neonates Study
SBP	Systolic Blood Pressure
SD	Standard Deviation
SEVR	Subendocardial Viability Ratio

Abstract:

Objectives: TO prospectively evaluate the associations of early and current life factors, including gestational age, and fetal growth restriction (FGR) in preterm-born subjects, on cardiovascular health including measures of central and peripheral blood pressure and arterial stiffness and assesscardiovascular changes before and after acute exercise in preterm- and term-born school-aged children.

Study Design: From 240 children, aged 7-12 years, 204 (141 preterm-born and 63 term-born) had satisfactory data. An oscillometric device recorded cardiovascular measures before and after cycle ergometer exercise testing. Data were analysed with multivariable linear regression and mediation.

Results: Central systolic blood pressure (SBP) was 6.4mmHg (95%CI 1.2,11.6) higher in preterm-born children with FGR and 3.4mmHg (0.02,6.8) higher in those without FGR when compared with term controls. Augmentation index (AIx) was 4.1% (0.7,7.4) higher in the preterm FGR group when compared with those without FGR but was similar between the latter group and term controls. Regression modelling showed gestational age, female sex, and antenatal smoking, but not FGR, were significantly associated with SBP. In contrast, FGR and fat mass index, but not gestation, were significantly associated with AIx. Cardiovascular exercise responses were similar between all three groups studied.

Conclusions: Our data show the differential associations of prematurity and FGR on central SBP and AIx. Cardiovascular responses to exercise were similar in all three groups. Preterm-born children with and without FGR are at increased risk of cardiovascular disease in adult life.

Abstract word count: 233/249

Introduction:

Preterm birth is increasingly recognised as resulting in adverse long term cardiovascular outcomes(1). peripheral arterial blood pressure has been shown to be increased in preterm-born subjects(2, 3). Other important cardiovascular outcomes, especially those associated with endothelial function or arterial stiffness, are less well established for this population. We have previously shown increased systolic blood pressure using the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort especially in those born at 32 weeks or less gestation(2). However, markers for arterial stiffness and endothelial function including flow-mediated dilatation (FMD), distensibility coefficient (DC) and pulse wave velocity (PWV) were not increased. In a review of the literature, there were suggestions that fetal growth restriction (FGR) at birth may be associated with arterial stiffness(2) but the independent contributions of prematurity and FGR have been less studied. In contrast, an association between extremely preterm birth (<26 weeks' gestation) and increased augmentation index (AIx), an indirect measure of arterial stiffness based on aortic pulse-wave reflection, has been reported at eleven years old in the EPICure cohort, which persisted at 19 years of age(4, 5) but the investigators did not investigate the independent contributions of prematurity and FGR.

In one study of ten preterm-born young adults, systolic blood pressure remained higher throughout exercise than in the 12 term-born controls(6). In another study of 13-year-old preterm-born children, prolonged recovery time for heart rate was noted after exercise when compared with term controls but blood pressure changes after exercise were not reported(7).

We, investigated cardiovascular outcomes including central and peripheral blood pressure measurements as well as AIx and PWV before and immediately after acute exercise in preterm-born children, with and without a history of FGR, and a term-born control group. In addition, we studied

which early life factors were associated with any significant outcomes.

Methods:

The Respiratory Health Outcomes in Neonates (RHiNO) study has been described previously(8, 9). As outlined in Figure 1 (available at www.jpeds.com), children from the previous Respiratory and Neurological Outcomes in children born Preterm (RANOPs) study(10) were supplemented with additional preterm-born (≤34 weeks' gestation) and term-born children (≥37 weeks' gestation), sourced from the NHS Wales Informatics Service, and were sent a respiratory and neurodevelopment questionnaire at 7-12 years of age. Responders were invited for a home or hospital visit to obtain anthropometric details and medical history (which was supplemented by examination of the child's medical records). Children with congenital malformations, significant cardiopulmonary disorder, neuromuscular disease or neurological impairment were excluded. Ethical approval was obtained from the South-West Bristol Research Ethics Committee (15/SW/0289). Parents gave informed written consent and children provided assent to participate. From 1,122 (827 preterm-born, 295 term-born) responders, 767 were assessed at their homes and 240 from South Wales attended respiratory, cardiovascular and exercise testing conducted by a trained research nurse and a trained paediatric research fellow at Children's Hospital for Wales, Cardiff, UK, between 2017 and 2019.

Following physical examination, the child's height was measured using a stadiometer (Seca 217, Seca Deutschland, Hamburg, Germany) and weighed using calibrated bio-electrical impedance floor scales (Tanita BC-420MA, Tanita Europe B.V., Amsterdam, Holland) from which their fat-mass index (FMI) and fat-free mass index (FFMI) indices were calculated. FGR was defined as birthweight <10th percentile adjusted for sex and gestation using LMS growth version 2.77 (Medical Research Council, UK).

Vicorder® (Smart Medical, Gloucestershire, UK) was used to estimate haemodynamic measures and arterial stiffness measures including AIx, PWV and transit time(11) during the trial's baseline assessment. This oscillometric method has been validated against applanation tonometry methods (such as Sphygmocor®) in adult(12) and paediatric studies(13), and has excellent intra- and interobserver repeatability. Internal software calculates values for central blood pressure by applying a previously described transfer function to brachial pulse waveforms(11). Pulse wave analysis identifies the first and second systolic pressure peaks, which reflect the systolic pressure resulting from ventricular ejection and that resulting from the reflected aortic pulse wave respectively, allowing derivation of augmentation pressure (difference between second and first systolic peak) and AIx (augmentation pressure expressed as a percentage of the central pulse pressure). By applying a proprietary algorithm to pulse wave analysis, estimates for stroke volume and cardiac output are generated. The child was placed in a supine position with the cuffs placed over the right brachial and femoral arteries. Following baseline measurements, the child underwent a protocolised cardiopulmonary exercise testing (CPET) using a cycle ergometer (Lode, Gronigen, Netherlands) as previously described(9). Briefly, the child experienced minimally loaded peddling for three minutes after which the load was increased by 10 watts every minute as a ramp (1W/6sec). Exercising continued until participants were unable to maintain a cadence of >60rpm. A 'maximal test' fulfilled two of the following; reached 80% of their predicted maximal heart rate; reached peak oxygen consumption rate plateau; respiratory exchange ratio >1 or showing signs of volitional exhaustion (assessed by pictorial Omni scale(14)). Repeat measures were made using the Vicorder® within five minutes of completing acute exercise.

Data are presented as mean, standard deviation; 95% confidence interval (CI) or number and percentage as appropriate. Data were compared using independent samples (or paired for exercise

data) t-test or one-way ANOVA with post-hoc Bonferroni correction as appropriate. Pearson χ^2 was used to analyse categorical data. Univariable and forward stepwise multivariable linear regression modelling were performed to identify associations with cardiovascular variables. Mediation analyses was performed with MPlus version 7.4 (Muthen & Muthen, Los Angeles, CA, USA), and all other analyses were performed using SPSS version 26.0 (IBM, Armonk, NY, USA). Results with standard deviation z-score of greater than ±3.29 (representing the top and bottom 0.1% of the normal distribution) were excluded from analyses as they were considered implausible. p-value of <0.05 was considered statistically significant.

Results:

From 240 children who participated, 219 had valid cardiovascular assessments (Figure 1). An additional 12 children with measurements >±3.29 standard deviations and 3 term-born children with FGR were excluded resulting in 204 (141 preterm-born and 63 term-born) children. There were no significant differences for sex, ethnicity, or anthropometric measurements between the groups (Table I). The preterm-born children were 7 months older than term-born children at time of assessment. As anticipated, preterm-born children had lower gestational age, birthweight, and increased antenatal maternal smoking and morbidities associated with preterm birth when compared with the term-born controls.

The preterm-born children had greater peripheral [mean 120.3 (SD: 9.7)mmHg vs 116.8 (9.3)mmHg, p=0.017] and central SBP [112.2(9.2)mmHg vs 108.3(8.4)mmHg, p=0.005] when compared with term-born children (Table II). In addition, significantly more of the preterm-born children had a peripheral SBP >90th centile corrected for age, sex, and height (15) (55.3% vs 36.5% p=0.013). AIx and PWV were not different from the term-born controls. When preterm-born children who had FGR at birth were compared with the term group, they had higher central SBP (mean difference of

6.4mmHg; 95%CI 1.2,11.6, p=0.01). Preterm-born children who were AGA also had increased central SBP (3.4; 0.02,6.8, p=0.048) when compared with term-born children but the difference between the FGR and AGA preterm groups was not significantly different (3.0; -1.8,7.8, p=0.4). The difference between central and peripheral SBP was lower in the preterm FGR group when compared with the preterm AGA (-2.2; 95%CI -4.3,-0.2, p=0.029) and term-born (-2.2; -4.4,-0.02, p=0.048) groups. This difference was largely due to the higher central SBP in preterm-born children with FGR. A larger proportion of the preterm-born FGR group had peripheral SBP >90th centile when compared with term-born children (70.8% vs 36.5% p=0.012), but no significant difference was seen on comparison with the preterm-born AGA group (70.8% vs 52.1% p=0.275).

Preterm-born children with a history of FGR, when compared with term-born children, had higher mean arterial pressure [86.4 (8.8) vs 80.8 (6.8)mmHg, p=0.005], augmentation pressure [8.6(4.2) vs 6.0(4.0)mmHg, p=0.021], and AIx [15.5%(7.0) vs 11.1(6.4), p=0.009]. AIx was higher in the preterm-born FGR children when compared with preterm-born AGA children[15.5(7.0) vs 11.4(5.8), p=0.011]. No differences were noted for subendocardial viability ratio (SEVR), PWV, stroke volume, cardiac output or cardiac index between the preterm FGR group when compared with the other two groups.

We next used linear regression analysis to identify potential predictors for central systolic blood pressures and AIx (Table III). Gestational age (β -0.32, p=0.012), FMI (0.70, p=0.015), female sex (3.65, p=0.004), FGR (4.27, p = 0.029) and antenatal maternal smoking (5.82, p=0.013) were significantly associated with increased central SBP in univariable analysis. Gestational age (-0.26, p=0.037), female sex (3.53, p=0.005) and maternal antenatal smoking (5.19, p=0.025), but not FGR nor FMI, remained significantly associated with central SBP in multivariable regression. FGR (β 4.28, p=0.001), BMI (0.50, p=<0.001), FMI (0.73, p=<0.001) and FFMI (0.93, p=0.001), but not gestation,

were significantly associated with AIx in univariable analysis. In the multivariable regression model, FGR and FMI (or BMI) remained significantly associated with AIx (p=<0.001).

Next, we used mediation analyses to investigate the contributions of early life factors to increased central SBP and AIx (Figure 2; available at www.jpeds.com). Gestational age and sex had a direct effect on increased central SBP, but FGR was consequent of preterm birth and did not appear to directly affect increased central SBP. AIx was affected by FGR, but not gestational age nor sex.

We assessed the effects of CPET on cardiovascular measurements. From 216 with baseline data, 211 (98%) underwent CPET and satisfactory data were available for 177 (82%, 123 preterm-born and 54 term-born) children after quality control and outliers were removed (demographics shown in Table IV; available at www.jpeds.com). In general, the peripheral SBP, central SBP, central diastolic blood pressure (DBP) and mean arterial pressure increased in the preterm-born children with and without FGR when compared with term-born children after completing CPET (Tables V and VI; available at www.jpeds.com. Figure 3). As at baseline, measurements remained higher in the preterm groups than their term counterparts. There were no post-exercise differences in AIx or other markers of arterial stiffness between the three groups. The preterm-born AGA group increased their AIx after CPET (2.3%; 95%CI 0.6%, 3.9%; p=0.008) but a similar increase was not observed in the preterm-born FGR and term-born groups.

Discussion:

The findings show that prematurity and FGR in the preterm-born group act differently on the developing cardiovascular system. Several studies, including metanalyses(3, 16), have demonstrated that prematurity is associated with increased SBP in young adult life. The effects of prematurity and FGR on later cardiovascular health in the existing literature are not clear, possibly

due to small sample sizes available. Our data show that central SBP is associated with prematurity and not FGR; in contrast, AIx is more associated with FGR in the preterm population and less so with prematurity alone. The degree of increased SBP and sex-related differences we observed are in keeping with previously published studies and meta-analysis(2, 3, 16). Whilst these differences appear low in childhood, because SBP tracks throughout life, these differences are likely to increase with age(17). In adults, central SBP is better related to future cardiovascular events than peripheral measurements(18), and each 20mmHg increase is associated with a two-fold increased risk of cardiovascular mortality(19), hence we focussed more on central SBP. Antenatal maternal smoking has also been shown to be associated with increases in SBP in adolescence(20); and increased BMI and adiposity in childhood have also been shown to be associated with increased SBP and adverse adult cardiovascular outcomes(21). However, the majority of children included in these studies were term-born. In contrast, Flahault et al did not demonstrate an association between adiposity and increased SBP in preterm-born subjects(22). In our study, FMI was significantly associated with central SBP in univariable regression modelling but did not reach significance in multivariable modelling. Our data showed an association between FGR and central SBP in univariable regression analyses but was no longer significant in multivariable modelling. We excluded three term-born children with FGR to avoid influencing the effects of FGR associated with preterm-birth on cardiovascular outcomes. Meta-analysis has shown that adults born with low birth weight (<2500g) have an increased SBP(23), and the recent UK Biobank data showed that adults with low birthweight are at increased risk of cardiovascular disease(24), but neither study assessed the separate effects of gestational age and birthweight on cardiovascular outcomes. Preterm-born children are known to be at increased risk of sleep-disordered breathing which can impact autonomic cardiovascular control(25), however none of the children in our cohort were under the care of sleep-disorder services.

We did, however, find a relationship between FGR and AIx which appeared to be independent of gestation. Increased AIx reflects increased arterial stiffness and premature vascular ageing. Adult studies have shown that an increase in AIx of approximately 4% increases the risk of early coronary artery disease(26) highlighting the importance of identifying these individuals early in life. In our population the AIx difference was >4% when the preterm population with FGR were compared with those without FGR and term controls. This is an important finding that may be associated with the longer-term atherosclerotic morbidity in preterm-born adults as recently reported by Crump et al.(27). The existing literature on the relationship between preterm-birth and AIx is conflicting. The EPICure study did not report any differences in peripheral or central SBP at 11 years of age in extremely preterm-born survivors (<26 weeks gestation at birth) but reported 5% increase in AIx(4), which persisted to 19 years of age(5). A study of British young adults born preterm in the 1980s noted a reduction in aortic lumen size, also associated with an increased AIx of approximately 10%, in the preterm-born group(28); however, other studies have not noted a relationship between AIx and preterm-birth(29). How the findings from these studies related to fetal growth restriction were not investigated. An Australian study of 71 term- and preterm-born young adolescents with and without histories of fetal growth restriction(30) found that FGR was a stronger predictor of SBP than prematurity, but that the combination of prematurity and FGR (n = 14) had a larger effect on AIx; a difference of 9.7% was noted between the preterm growth restricted group compared with preterm control, growth restricted term and term control populations. Using a comparatively larger population of children, our study showed that AIx was significantly associated with FGR but not with prematurity in multivariable regression and mediation models. Our mediation model has demonstrated that the previously described relationship between preterm-birth and elevated AIx may be mediated by FGR.

Data for cardiovascular changes after exercise in preterm-born subjects are limited. One recent study showed that preterm-born individuals have smaller left ventricular volumes at baseline in adolescents, with a history of FGR being associated with a reduced left ventricular output(31). A Spanish study also showed reduced left ventricular size and reduced cardiac efficiency in term- and preterm-born children with severe FGR(32). This could potentially limit cardiovascular exercise tolerance. We noted that preterm- and term-born children appeared to have similar increases for peripheral and central SBP after exercise, with preterm-born children remaining generally higher than the term population as at baseline. No significant differences were noted after exercise for central DBP and mean arterial pressure compared with term-born children post-exercise. Minimal increases were noted for AIx, with the baseline relationships of highest values in the preterm group with FGR and lowest in the term controls remaining. Although limitations in exercise have been noted for preterm-born children, these are more likely to be due to respiratory dysfunction associated with prematurity(33, 34), rather than cardiovascular responses, at least in childhood.

These data suggest that long term cardiovascular assessment, including measurement of blood pressure as a minimum screening tool, is essential to prevent longer term morbidity and mortality associated with preterm birth.

Acknowledgements:

We are extremely grateful to all the children and families who took part in the RHiNO study for all their support and enthusiasm and to the nursing staff who were responsible for assessing and collecting the data. We also thank the neonatal consultants and administration teams in the South Wales neonatal units for assisting in identifying the children and for acquiring the medical notes.

References

1. Greer C, Troughton RW, Adamson PD, Harris SL. Preterm birth and cardiac function in adulthood. Heart. 2022;108(3):172-7.

2. Edwards MO, Watkins WJ, Kotecha SJ, Halcox JP, Dunstan FD, Henderson AJ, et al. Higher systolic blood pressure with normal vascular function measurements in preterm-born children. Acta Paediatr. 2014;103(9):904-12.

3. Andraweera PH, Condon B, Collett G, Gentilcore S, Lassi ZS. Cardiovascular risk factors in those born preterm - systematic review and meta-analysis. J Dev Orig Health Dis. 2021;12(4):539-54.

4. Bolton CE, Stocks J, Hennessy E, Cockcroft JR, Fawke J, Lum S, et al. The EPICure study: association between hemodynamics and lung function at 11 years after extremely preterm birth. J Pediatr. 2012;161(4):595-601 e2.

5. Hurst JR, Beckmann J, Ni Y, Bolton CE, McEniery CM, Cockcroft JR, et al. Respiratory and Cardiovascular Outcomes in Survivors of Extremely Preterm Birth at 19 Years. Am J Respir Crit Care Med. 2020;202(3):422-32.

6. Barnard CR, Peters M, Sindler AL, Farrell ET, Baker KR, Palta M, et al. Increased aortic stiffness and elevated blood pressure in response to exercise in adult survivors of prematurity. Physiol Rep. 2020;8(12):e14462.

7. Haraldsdottir K, Watson AM, Goss KN, Beshish AG, Pegelow DF, Palta M, et al. Impaired autonomic function in adolescents born preterm. Physiol Rep. 2018;6(6):e13620.

8. Hart K, Cousins M, Watkins WJ, Kotecha SJ, Henderson AJ, Kotecha S. Association of early-life factors with prematurity-associated lung disease: prospective cohort study. Eur Respir J. 2022;59(5).

9. Goulden N, Cousins M, Hart K, Jenkins A, Willetts G, Yendle L, et al. Inhaled Corticosteroids Alone and in Combination With Long-Acting beta2 Receptor Agonists to Treat Reduced Lung Function in Preterm-Born Children: A Randomized Clinical Trial. JAMA Pediatr. 2021.

10. Edwards MO, Kotecha SJ, Lowe J, Richards L, Watkins WJ, Kotecha S. Early-term birth is a risk factor for wheezing in childhood: A cross-sectional population study. J Allergy Clin Immunol. 2015;136(3):581-7 e2.

11. O'Rourke MF. Influence of ventricular ejection on the relationship between central aortic and brachial pressure pulse in man. Cardiovasc Res. 1970;4(3):291-300.

12. Pucci G, Cheriyan J, Hubsch A, Hickson SS, Gajendragadkar PR, Watson T, et al. Evaluation of the Vicorder, a novel cuff-based device for the noninvasive estimation of central blood pressure. J Hypertens. 2013;31(1):77-85.

13. Kracht D, Shroff R, Baig S, Doyon A, Jacobi C, Zeller R, et al. Validating a new oscillometric device for aortic pulse wave velocity measurements in children and adolescents. Am J Hypertens. 2011;24(12):1294-9.

14. Barkley JE, Roemmich JN. Validity of the CALER and OMNI-bike ratings of perceived exertion. Med Sci Sports Exerc. 2008;40(4):760-6.

15. Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, et al. Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents. Pediatrics. 2017;140(3).

16. de Jong F, Monuteaux MC, van Elburg RM, Gillman MW, Belfort MB. Systematic review and meta-analysis of preterm birth and later systolic blood pressure. Hypertension. 2012;59(2):226-34.

17. Chen X, Wang Y. Tracking of blood pressure from childhood to adulthood: a systematic review and meta-regression analysis. Circulation. 2008;117(25):3171-80.

18. McEniery CM, Cockcroft JR, Roman MJ, Franklin SS, Wilkinson IB. Central blood pressure: current evidence and clinical importance. Eur Heart J. 2014;35(26):1719-25.

19. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, Prospective Studies C. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360(9349):1903-13.

20. Hogberg L, Cnattingius S, Lundholm C, D'Onofrio BM, Langstrom N, Iliadou AN. Effects of maternal smoking during pregnancy on offspring blood pressure in late adolescence. J Hypertens. 2012;30(4):693-9.

21. Umer A, Kelley GA, Cottrell LE, Giacobbi P, Jr., Innes KE, Lilly CL. Childhood obesity and adult cardiovascular disease risk factors: a systematic review with meta-analysis. BMC Public Health. 2017;17(1):683.

22. Flahault A, Paquette K, Fernandes RO, Delfrate J, Cloutier A, Henderson M, et al. Increased Incidence but Lack of Association Between Cardiovascular Risk Factors in Adults Born Preterm. Hypertension. 2020;75(3):796-805.

23. Mu M, Wang SF, Sheng J, Zhao Y, Li HZ, Hu CL, et al. Birth weight and subsequent blood pressure: a meta-analysis. Arch Cardiovasc Dis. 2012;105(2):99-113.

24. Liang J, Xu C, Liu Q, Fan X, Xu J, Zhang L, et al. Association between birth weight and risk of cardiovascular disease: Evidence from UK Biobank. Nutr Metab Cardiovasc Dis. 2021;31(9):2637-43.

25. Yiallourou SR, Wallace EM, Whatley C, Odoi A, Hollis S, Weichard AJ, et al. Sleep: A Window Into Autonomic Control in Children Born Preterm and Growth Restricted. Sleep. 2017;40(5).

26. Weber T, Auer J, O'Rourke MF, Kvas E, Lassnig E, Berent R, et al. Arterial stiffness, wave reflections, and the risk of coronary artery disease. Circulation. 2004;109(2):184-9.

27. Crump C, Howell EA, Stroustrup A, McLaughlin MA, Sundquist J, Sundquist K. Association of Preterm Birth With Risk of Ischemic Heart Disease in Adulthood. JAMA Pediatr. 2019;173(8):736-43.

28. Boardman H, Birse K, Davis EF, Whitworth P, Aggarwal V, Lewandowski AJ, et al. Comprehensive multi-modality assessment of regional and global arterial structure and function in adults born preterm. Hypertens Res. 2016;39(1):39-45.

29. Flahault A, Oliveira Fernandes R, De Meulemeester J, Ravizzoni Dartora D, Cloutier A, Gyger G, et al. Arterial Structure and Stiffness Are Altered in Young Adults Born Preterm. Arterioscler Thromb Vasc Biol. 2020;40(10):2548-56.

30. Chan PY, Morris JM, Leslie GI, Kelly PJ, Gallery ED. The long-term effects of prematurity and intrauterine growth restriction on cardiovascular, renal, and metabolic function. Int J Pediatr. 2010;2010:280402.

31. Harris S, Perston L, More K, Graham P, Ellis N, Frampton C, et al. Cardiac structure and function in very preterm-born adolescents compared to term-born controls: A longitudinal cohort study. Early Hum Dev. 2021;163:105505.

32. 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):2427-36.

33. Kotecha SJ, Edwards MO, Watkins WJ, Henderson AJ, Paranjothy S, Dunstan FD, et al. Effect of preterm birth on later FEV1: a systematic review and meta-analysis. Thorax. 2013;68(8):760-6.

34. Kotecha SJ, Gibbons JTD, Course CW, Evans EE, Simpson SJ, Watkins WJ, et al. Geographical Differences and Temporal Improvements in Forced Expiratory Volume in 1 Second of Preterm-Born Children: A Systematic Review and Meta-analysis. JAMA Pediatr. 2022.

Figure 1: Flow diagram showing recruitment to RHiNO Study and the Cardiovascular assessment stage of the study.

Figure 2: Results of mediation analysis for (A)Central SBP and (B)AIx baseline data. Beta(β), standard error (SE) and p-value given for interactions between variables, with arrows showing direction of relationships. FGR: Fetal growth restriction.

Figure 3: (A)Central SBP and (B)AIx by group at baseline and after CPET (n =179). Groups colour coded and labelled. Shapes represent respective group mean, standard deviation given by vertical bars.
At Baseline and Post-CPET time points *p<0.05 compared with Term, **p<0.01 compared with Term, #p<0.05 compared with Preterm AGA. At baseline, for Central SBP both preterm-born groups had significantly higher measurements than term-born. Preterm- born FGR group significantly higher AIx than preterm-born AGA and term-born children. Post CPET Preterm-born AGA had significantly higher SBP than term-born. No differences seen in AIx post-CPET.
Horizontal brackets compare Baseline with Post-CPET: *p<0.05 **p<0.01, ***p<0.001. Preterm-born AGA and Term-born showed significant increase in their respective mean SBP between baseline and post-CPET. Only Preterm-born AGA showed a significant increase in AIx between baseline and post-CPET.

Table 1: Demographics of included children for baseline assessment

	Preterm born (all) n=141	Preterm-born FGR n=24	Preterm-born AGA n=117	Term born n= 63
Current Status				
Sex (male), n(%)	69 (48.9%)	8 (33.3)	61 (52.1)	32 (50.8)
Ethnicity (white) n(%)	133 (94.3%)	22 (91.7)	111 (94.9)	62 (98.4)
Age at testing (years), mean (SD)	11.07 (1.23)##	11.01 (1.27)	11.08 (1.23)‡‡	10.49 (1.12)
Height (cm), mean (SD)	146.06 (10.29)	141.88 (11.38)	146.91 (9.89)	144.21 (9.67)
Height (z-score), mean (SD)	0.27 (1.04)	-0.35 (0.99)**††	0.40 (1.01)	0.50 (1.01)
Weight (kg), mean (SD)	39.57 (10.62)	36.30 (10.61)	40.24 (10.55)	38.50 (10.78)
Weight (z-score), mean (SD)	0.31 (1.17)	-0.21 (1.29)*†	0.41 (1.12)	0.51 (1.05)
Body Mass Index (z-score), mean (SD)	0.19 (1.31)	-0.10 (1.49)	0.24 (1.26)	0.37 (1.11)
Fat Mass Index (kg/m^2), mean (SD)	4.03 (2.21)	3.98 (2.08)	4.04 (2.25)	3.93 (2.20)
Fat Free Mass Index (kg/m^2), mean (SD)	14.27 (1.55)	13.77 (1.65)	14.37 (1.51)	14.31 (1.33)
Neonatal History				
Gestational age (weeks), mean (SD)	30.76 (2.79)###	30.08 (2.33)†††	30.89 (2.86)‡‡‡	40.24 (1.18)
Birthweight (g), mean (SD)	1597 (578.0)###	997 (320.6)***†††	1720 (541.1)‡‡‡	3579 (493.6)
Birthweight (z-score), mean (SD)	0.10 (1.28)	-1.86 (0.67)***†††	0.50 (0.97)	0.17 (0.87)
Antenatal Smoking, n (%)	15 (10.8%)#	3 (12.5)†	12 (10.3)‡	1 (1.6)
Chronic lung disease of prematurity, n (%)	42 (29.8%)###	6 (25.0)†††	36 (30.8)‡‡‡	0 (0)
Patent ductus arteriosus, n (%)	13 (9.4%)#	3 (12.5)††	10 (8.5)‡	0 (0)
Necrotizing enterocolitis, n (%)	8 (5.8%)	2 (8.3)†	6 (5.1)	0 (0)
Retinopathy of prematurity, n (%)	9 (6.4%)#	1 (4.2)	8 (6.8)‡	0 (0)
Intraventricular haemorrhage, n (%)	17 (12.1%)##	2 (8.3)†	15 (12.8)‡‡	0 (0)

Preterm-born vs Term-born: #p<0.05, ##p<0.01 ###p<0.001
Preterm-born FGR vs Preterm-born AGA: *p<0.05, **p<0.01 ***p<0.001
Preterm-born FGR vs Term-born: †p<0.05, ††p<0.01 †††p<0.001
Preterm-born AGA vs Term-born: ‡p<0.05, ‡‡p<0.01 ‡‡‡p<0.001

FGR: Fetal Growth Restriction. AGA: Appropriate weight for gestational age.

Ant

Table 2: Effect of prematurity and FGR on cardiovascular parameters in childhood

	Preterm (all) n = 141 Mean (SD)	Preterm FGR n= 24 Mean (SD)	Preterm AGA n= 117 Mean (SD)	Term n= 63 Mean (SD)	Preterm vs Term Mean difference [95% CI]	Preterm FGR vs Preterm AGA Mean difference [95% CI]	Preterm FGR vs Term Mean difference [95% CI]	Preterm AGA vs Term Mean difference [95% CI]
Peripheral systolic BP (mmHg)	120.3 (9.7)	120.9 (11.7)	120.1 (9.3)	116.8 (9.3)	**3.5** [0.6, 6.4]**	0.8 [-4.4, 6.0]	4.2 [-1.4, 9.8]	3.4 [-0.3, 7.0]
Peripheral diastolic BP (mmHg)	57.5 (7.6)	59.8 (7.9)	57.0 (7.4)	55.7 (6.8)	1.8 [-0.4, 4.0]	2.7 [-1.2, 6.7]	4.0 [-0.2, 8.3]	1.3 [-1.4, 4.1]
Peripheral pulse pressure [mmHg]	62.7 (11.0)	61.2 (10.9)	63.1 (11.0)	61.0 (10.5)	1.7 [-1.5, 6.0]	-1.9 [-7.8, 4.0]	0.1 [-6.2, 6.4]	2.1 [-2.0, 6.1]
Central systolic BP [mmHg]	112.2 (9.2)	114.7 (10.8)	111.7 (8.8)	108.3 (8.4)	**3.9** [1.2, 6.6]**	3.0 [-1.8, 7.8]	**6.4** [1.2, 11.6]**	**3.4* [0.02, 6.8]**
Central diastolic BP [mmHg]	57.5 (7.5)	59.8 (7.9)	57.1 (7.4)	55.7 (6.8)	1.8 [-0.4, 4.0]	2.7 [-1.2, 6.6]	4.0 [-0.2, 8.3]	1.3 [-1.4, 4.1]
Central pulse pressure [mmHg]	54.7 (9.7)	55.0 (10.1)	54.7 (9.9)	52.6 (9.1)	2.1 [-0.8, 5.0]	0.3 [-4.9, 5.5]	2.4 [-3.2, 8.0]	2.1 [-1.6, 5.7]
Difference between peripheral and central systolic BP [mmHg]	8.1 (3.8)	6.2 (3.7)	8.4 (3.7)	8.4 (4.1)	-0.4 [-1.5, 0.8]	**-2.2* [-4.3, -0.2]**	**-2.2* [-4.4, -0.02]**	0.0 [-1.5, 1.4]
End systolic pressure [mmHg]	106.5 (11.4)	108.8 (11.5)	106.1 (11.3)	103.4 (11.0)	3.1 [-0.3, 6.5]	2.8 [-3.3, 8.9]	5.4 [-1.1, 12.0]	2.6 [-1.6, 6.9]
End systolic pressure index	0.9 (0.2)	0.9 (0.1)	0.9 (0.2)	0.9 (0.2)	0.0 [-0.1, 0.0]	0.0 [-0.1, 0.1]	0.0 [-0.1, 0.0]	0.0 [-0.1, 0.0]
Mean arterial pressure [mmHg]	83.3 (7.7)	86.4 (8.8)	82.6 (7.3)	80.8 (6.8)	**2.5* [0.3, 4.7]**	3.8 [-0.2, 7.8]	**5.6** [1.4, 9.9]**	1.8 [-1.0, 4.6]
Central augmentation pressure [mmHg]	6.9 (4.1)	8.6 (4.2)	6.5 (3.9)	6.0 (4.0)	0.9 [-0.3, 2.1]	2.1 [-0.1, 4.2]	**2.6* [0.3, 4.9]**	0.5 [-1.0, 2.0]
Central augmentation index [%]	12.1 (6.2)	15.5 (7.0)	11.4 (5.8)	11.1 (6.4)	1.0 [-0.8, 2.9]	**4.1* [0.7, 7.4]**	**4.4* [0.9, 8.0]**	0.4 [-2.0, 2.7]
Subendocardial viability ratio [%]	200.6 (77.0)	181.7 (68.5)	204.4 (78.3)	195.5 (68.4)	5.1 [-17.2, 27.3]	-22.7 [-62.9, 17.5]	-13.8 [-56.8, 29.2]	8.9 [-37.0, 19.1]
Pulse pressure index	1.1 (0.1)	1.2 (0.2)	1.1 (0.1)	1.1 (0.1)	0.00 [-0.04, 0.05]	**0.1* [0.001, 0.2]**	0.1 [-0.0, 0.2]	0.0 [-0.1, 0.0]

Transit time [msec]	62.7 (8.9)	60.1 (9.4)	63.3 (8.7)	60.0 (8.0)	**2.7* [0.1, 5.3]**	-3.2 [-7.8, 1.4]	0.1 [-4.9, 5.0]	**3.3* [0.03, 6.5]**
Pulse wave velocity [m/sec]	9.7 (1.4)	9.9 (1.6)	9.7 (1.4)	9.8 (1.5)	-0.1 [-0.5, 0.4]	0.3 [-0.5, 1.0]	0.1 [-0.7, 1.0]	-0.1 [-0.7, 0.4]
Stroke volume [ml]	98.8 (29.4)	99.5 (32.5)	98.7 (28.8)	102.9 (30.5)	-4.1 [-13.0, 4.8]	0.8 [-15.3, 16.9]	-3.5 [-20.7, 13.8]	-4.3 [-15.5, 7.0]
Cardiac output [L/min]	7.0 (2.4)	7.2 (2.3)	6.9 (2.4)	7.1 (2.2)	-0.1 [-0.8, 0.6]	0.3 [-1.0, 1.6]	0.1 [-1.3, 1.5]	-0.2 [-1.1, 0.7]
Cardiac index [L/min/m^2]	5.6 (2.3)	6.2 (2.7)	5.5 (2.2)	5.9 (2.2)	-0.3 [-0.9, 0.4]	0.7 [-0.5, 1.9]	0.4 [-0.9, 1.6]	0.4 [-1.2, 0.5]
Heart rate [beats/min]	70.3 (11.7)	73.8 (13.1)	69.6 (11.3)	68.8 (8.7)	1.5 [-1.7, 4.8]	4.1 [-1.7, 10.0]	4.9 [-1.3, 11.2]	0.8 [-3.3, 4.9]

*p<0.05, **p<0.01

FGR: fetal growth restriction; AGA: Appropriate birth weight for gestational age; BP: Blood Pressure

Table 3: Linear regression analysis of associations of central systolic blood pressure and augmentation ind

	Central Systolic Blood Pressure			Augmentation Index		
	Univariable analyses			Univariable analyses		
	Beta	Standard Error	Significance	Beta	Standard Error	Significance
Gestational age (weeks)	-0.32	0.13	**0.012***	-0.12	0.09	0.18
Birthweight (z-score)	-0.46	0.55	0.41	-0.50	0.37	0.18
Height (z-score)	0.30	0.62	0.63	-0.40	0.42	0.34
Body Mass Index (z-score)	0.92	0.51	0.07	1.24	0.34	**<0.001*****
Fat Mass Index	0.70	0.29	**0.015***	0.73	0.19	**<0.001*****
Fat Free Mass Index	0.65	0.43	0.42	0.93	0.29	**0.001****
Sex (ref = Male)	3.65	1.26	**0.004****	0.44	0.87	0.61
FGR (ref = No)	4.27	1.96	**0.029***	4.28	1.31	**0.001****
Antenatal Smoking (ref = No)	5.82	2.34	**0.013***	0.83	1.61	0.60

	Multivariable analysis of Central Systolic Blood Pressure		
	Beta	Standard Error	Significance
Gestational age	-0.26	0.12	**0.037***
Sex (ref = Male)	3.53	1.24	**0.005****
Antenatal Smoking (ref = No)	5.19	2.31	**0.025***
	Multivariable analysis of Augmentation Index		
	Beta	**Standard Error**	**Significance**
Fat Mass Index	0.73	0.18	**<0.001*****
FGR (ref = No)	4.29	1.26	**0.001****

*p<0.05, **p<0.01, ***p<0.001 FGR: fetal growth restriction

Table 4; online only: Demographics for Post CPET assessment

	(all) n= 123	FGR n = 21	AGA n = 102	Term born n = 54
Current Status				
Sex (male), n(%)	60 (48.8)	6 (28.6)*	54 (52.9)	25 (46.3)
Ethnicity (white), n(%)	115 (93)	19 (90.5)	96 (94.1)	53 (98)
Age at testing (years), mean (SD)	11.1 (1.2)##	11.0 (1.3)	11.1 (1.3)‡	10.5 (1.1)
Height (cm), mean (SD)	146.1 (10.4)	142.0 (12.1)	146.9 (9.9)	144.5 (9.8)
Height (z-score), mean (SD)	0.3 (1.0)	-0.32 (1.06)*††	0.38 (0.94)	0.51 (1.02)
Weight (kg), mean (SD)	39.8 (10.8)	36.2 (10.9)	40.6 (10.7)	39.0 (11.1)
Weight (z-score), mean (SD)	0.3 (1.1)	-0.21 (1.30)*†	0.45 (1.08)	0.6 (1.0)
Body Mass Index (z-score), mean (SD)	0.22 (1.31)	-0.13 (1.50)	0.30 (1.26)	0.42 (1.11)
Fat Mass Index (kg/m^2), mean (SD)	4.1 (2.2)	4.01 (2.04)	4.11 (2.30)	4.06 (2.26)
Fat Free Mass Index (kg/m^2), mean (SD)	14.3 (1.6)	13.67 (1.65)	14.45 (1.56)	14.40 (1.36)
Neonatal History				
Gestational age (weeks), mean (SD)	30.5 (2.8)###	29.67 (2.33)†††	30.65 (2.89)‡‡‡	40.00 (1.15)
Birthweight (g), mean (SD)	1593 (576)###	987 (333.0)******†††	1718 (535.4)‡‡‡	3537 (484.8)
Birthweight (z-score), mean (SD)	0.1 (1.3)	-1.83 (0.69)******†††	0.50 (0.98)‡	0.12 (0.89)
Antenatal Smoking, n(%)	12 (10)	3 (14.3)†	9 (8.8)	1 (2.0)
Chronic lung disease of prematurity, n (%)	34 (28)###	5 (23.8)†††	29 (28.4)‡‡‡	0 (0)
Patent ductus arteriosus, n (%)	11 (9)#	2 (9.5)†	9 (8.8)‡‡	0 (0)
Necrotizing enterocolitis, n (%)	7 (6)	1 (4.8)	6 (5.9)	0 (0)
Retinopathy of prematurity, n (%)	8 (7)	1 (4.8)	7 (6.9)‡	0 (0)
Intraventricular haemorrhage, n (%)	16 (13)##	2 (9.5)†	14 (13.8)‡‡	0 (0)

Preterm-born vs Term-born: #p<0.05, ##p<0.01 ###p<0.001
Preterm-born FGR vs Preterm-born AGA: *p<0.05, **p<0.01 ***p<0.001
Preterm-born FGR vs Term-born: †p<0.05, ††p<0.01 †††p<0.001
Preterm-born AGA vs Term-born: ‡p<0.05, ‡‡p<0.01 ‡‡‡p<0.001

FGR: Fetal Growth Restriction. AGA: Appropriate weight for gestational age.

Ant

Table 5; online only: Pre/Post CPET data for Preterm-born vs Term-born children.

	Preterm Born Children (n=123)			Term Born Children (n=54)			Preterm v Term	
	Baseline Mean (SD)	Post CPET Mean (SD)	Mean difference (SD) [95% CI]	Baseline Mean (SD)	Post CPET Mean (SD)	Mean difference (SD) [95% CI]	Mean Difference Post CPET [95% CI]	Mean Difference Pre vs Post CPET [95% CI]
Peripheral Systolic BP [mmHg]	120.3 (9.8)	125.8 (10.9)	**5.5*** (11.2) [3.5, 7.5]**	116.3 (9.2)	122.0 (10.3)	**5.7** (11.5) [2.5, 8.8]**	**3.8* [0.3, 7.2]**	-0.2 [-3.8, 3.5]
Peripheral Diastolic BP [mmHg]	57.3 (7.7)	61.5 (9.6)	**4.2*** (9.4) [2.5, 5.8]**	56.1 (6.8)	58.4 (9.3)	2.3 (10.7) [-0.6, 5.2]	3.1 [-0.1, 6.1]	1.8 [-1.3, 5.0]
Peripheral Pulse Pressure [mmHg]	63.0 (11.2)	64.3 (13.9)	1.4 (14.7) [-1.3, 4.0]	60.2 (10.2)	63.3 (11.4)	3.1 (11.5) [-0.0, 6.2]	1.0 [-3.2, 5.3]	-1.8 [-6.2, 2.7]
Central Systolic BP [mmHg]	112.2 (9.1)	118.7 (9.8)	**6.5*** (9.5) [4.8, 8.2]**	107.9 (8.4)	114.0 (9.8)	**6.1*** (10.6) [3.2, 9.0]**	**4.7** [1.6, 7.9]**	0.4 [-2.8, 3.5]
Central Diastolic BP [mmHg]	57.3 (7.7)	61.7 (9.2)	**4.4*** (9.5) [2.7, 6.1]**	56.1 (6.8)	58.4 (9.3)	2.3 (10.7) [-0.6, 5.2]	**3.3* [0.3, 6.3]**	2.1 [-1.1, 5.3]
Central Pulse Pressure [mmHg]	54.9 (10.0)	57.2 (12.7)	2.3 (13.3) [-0.1, 4.7]	51.7 (8.6)	55.4 (10.5)	**3.6** (9.8) [1.0, 6.3]**	1.9 [-2.0, 5.7]	-1.3 [-5.3, 2.7]
Central Augmentation Pressure [mmHg]	6.9 (3.9)	8.3 (5.6)	**1.5** (5.5) [0.5, 2.4]**	5.8 (3.9)	7.3 (5.5)	**1.6* (5.3) [0.1, 3.0]**	1.0 [-0.8, 2.8]	-0.1 [-1.9, 1.6]
Central Augmentation Index [%]	12.1 (6.0)	14.1 (8.3)	**2.0** (8.2) [0.5, 3.5]**	10.9 (6.6)	12.8 (8.8)	1.9 (8.7) [-0.4, 4.3]	1.3 [-1.4, 4.0]	0.1 [-2.6, 2.8]
Mean Arterial Pressure [mmHg]	83.0 (7.6)	90.4 (8.0)	**7.4*** (7.8) [6.0, 8.8]**	80.8 (7.1)	87.4 (8.2)	**6.6*** (9.8) [4.0, 9.3]**	**3.0* [0.4, 5.6]**	0.7 [-2.0, 3.5]
Subendocardial Viability Ratio [%]	200.7 (78.1)	116.0 (25.6)	**-84.7*** (76.7) [-98.4, -71.0]**	197.2 (68.7)	122.5 (30.2)	**-74.7*** (68.2) [-93.3, -56.1]**	-6.5 [-15.2, 2.2]	-10.0 [-33.9, 13.9]
End Systolic Pressure [mmHg]	106.4 (11.3)	105.0 (10.7)	-1.3 (10.7) [-3.2, 0.6]	103.0 (11.1)	103.6 (9.9)	0.6 (11.9) [-2.6, 3.9]	1.4 [-2.0, 4.8]	-1.9 [-5.5, 1.6]
End Systolic Pressure Index	0.9 (0.2)	0.8 (0.2)	**-0.1*** (0.1) [-3.2, 0.6]**	0.9 (0.1)	0.8 (0.1)	**-0.1*** (0.2) [-0.2, -0.1]**	**-0.05* [-0.1, -0.02]**	-0.03 [-0.08, 0.02]
Stroke Volume [ml]	98.4 (29.0)	98.5 (27.0)	0.1 (33.1) [-5.8, 6.0]	99.2 (27.4)	100.9 (26.3)	1.8 (24.0) [-4.8, 8.3]	-2.4 [-11.0, 6.3]	-1.6 [-11.5, 8.2]
Cardiac Output [L/min]	6.9 (2.4)	9.7 (2.9)	**2.8*** (3.1) [2.3, 3.4]**	6.8 (2.1)	9.7 (2.7)	**2.8*** (2.2) [2.2, 3.4]**	0.1 [-0.8, 1.0]	0.0 [-0.8, 0.8]
Cardiac Index [L/min/m^2]	5.5 (2.3)	7.8 (2.7)	**2.3*** (2.6) [1.8, 2.8]**	5.6 (2.2)	7.9 (2.7)	**2.3*** (1.9) [1.8, 2.8]**	-0.1 [-1.0, 0.7]	0.0 [-0.8, 0.8]

*p<0.05, **p<0.01, ***p<0.001. CPET: Cardiopulmonary exercise test. BP: Blood pressure.

Table 6; online only: Pre/Post CPET data for preterm-born children with and without a history of FGR.

	Preterm Born with FGR (n=21)			Preterm Born AGA (n=102)			AGA v FGR	
	Baseline Mean (SD)	Post CPET Mean (SD)	Mean difference ± SD [95% CI]	Baseline Mean (SD)	Post CPET Mean (SD)	Mean difference ± SD [95% CI]	Mean Difference Post CPET [95% CI]	Mean Difference Pre vs Post CPET [95% CI]
Peripheral Systolic BP [mmHg]	120.4 (11.0)	123.6 (11.6)	3.2 (11.7) [-2.1, 8.6]	120.3 (9.6)	126.3 (10.7)	**6.0*** (11.1) [3.8, 8.2]**	2.6 [-2.5, 7.8]	2.8 [-2.6, 8.1]
Peripheral Diastolic BP [mmHg]	59.8 (8.3)	62.6 (8.6)	2.9 (7.9) [-0.8, 6.5]	56.8 (7.5)	61.2 (9.9)	**4.4*** (9.6) [2.5, 6.3]**	-1.5 [-6.0, 3.1]	1.6 [-2.9, 6.0]
Peripheral Pulse Pressure [mmHg]	60.6 (10.7)	60.5 (9.8)	-0.1 (11.9) [-5.5, 5.5]	63.5 (11.3)	65.1 (14.5)	1.6 (15.3) [-1.4, 4.6]	4.6 [-2.0, 11.2]	1.7 [-5.3, 8.7]
Central Systolic BP [mmHg]	113.9 (9.9)	117.7 (10.4)	3.9 (9.7) [-0.5, 8.3]	111.9 (8.9)	118.9 (9.7)	**7.0*** (9.5) [5.2, 8.9]**	1.2 [-3.5, 5.8]	3.2 [-1.4, 7.7]
Central Diastolic BP [mmHg]	59.8 (8.3)	62.7 (8.6)	2.9 (7.9) [-0.8, 6.5]	56.8 (7.5)	61.5 (9.3)	**4.7*** (9.8) [2.8, 6.7]**	-1.1 [-5.5, 3.2]	1.9 [-2.6, 6.4]
Central Pulse Pressure [mmHg]	54.1 (9.8)	55.1 (9.8)	1.0 (11.1) [-4.1, 6.1]	55.1 (10.0)	57.7 (13.2)	2.6 (13.8) [-0.1, 5.3]	2.6 [-3.4, 8.6]	1.6 [-4.8, 7.9]
Central Augmentation Pressure [mmHg]	8.1 (3.9)	8.8 (4.9)	0.8 (4.3) [-1.2, 2.7]	6.6 (3.9)	8.23 (5.8)	**1.6** (5.8) [0.5, 2.7]**	-0.6 [-3.3, 2.1]	0.8 [-1.8, 3.5]
Central Augmentation Index [%]	14.9 (6.9)	15.7 (7.5)	0.8 (7.2) [-2.5, 4.1]	11.6 (5.7)	13.8 (8.4)	**2.3** (8.4) [0.6, 3.9]**	-1.9 [-5.8, 2.1]	1.4 [-2.5, 5.3]
Mean Arterial Pressure [mmHg]	86.1 (8.5)	90.8 (8.3)	**4.6** (6.5) [1.7, 7.6]**	82.4 (7.2)	90.3 (8.0)	**8.0*** (7.9) [6.4, 9.5]**	-0.4 [-4.3, 3.4]	3.3 [-0.3, 7.0]
Subendocardial Viability Ratio [%]	182.1 (73.0)	119.1 (20.2)	**-63.0** (76.7) [-97.9, -28.0]**	204.5 (78.9)	115.3 (26.6)	**-89.2*** (76.3) [-104.2, -74.2]**	-3.8 [-16.0, 8.4]	-26.2 [-62.5, 10.0]
End Systolic Pressure [mmHg]	107.9 (10.6)	106.4 (9.5)	-1.5 (10.8) [-6.5, 3.4]	106.1 (11.4)	104.8 (11.0)	-1.3 (10.7) [-3.4, 0.8]	-1.6 [-6.7, 3.5]	0.2 [-4.9, 5.3]
End Systolic Pressure Index	0.9 (0.2)	0.8 (0.1)	**-0.1** (0.1) [-0.2, -0.0]**	0.9 (0.2)	0.8 (0.2)	**-0.1*** (0.1) [-0.2, -0.1]**	-0.1 [-0.1, 0.0]	-0.1 [-0.1, 0.0]
Stroke Volume [ml]	96.1 (30.8)	92.1 (22.7)	-4.1 (33.1) [-19.2, 11.0]	98.9 (28.8)	99.9 (27.7)	1.0 (33.2) [-5.5, 7.5]	7.8 [-5.0, 20.6]	5.1 [-10.7, 20.8]
Cardiac Output [L/min]	7.1 (2.3)	8.9 (2.0)	**1.8* (3.0) [0.5, 3.2]**	6.9 (2.5)	9.9 (3.0)	**3.0*** (3.1) [2.4, 3.7]**	1.0 [-0.4, 2.4]	1.2 [-0.2, 2.7]
Cardiac Index [L/min/m^2]	6.2 (2.9)	7.6 (1.8)	**1.4* (2.8) [0.1, 2.7]**	5.4 (2.1)	7.9 (2.8)	**2.5*** (2.6) [2.0, 3.0]**	0.3 [-1.0, 1.6]	1.1 [-0.2, 2.3]

*p<0.05, **p<0.01 ***p<0.001. CPET: Cardiopulmonary exercise test. BP: Blood pressure. FGR: fetal growth restriction. AGA: Appropriate birth weight for gestational age.