

Sex-specific programming of cardiovascular physiology in children

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Aims

Increasing evidence suggests that adverse prenatal environments, as indicated by low birth weight, cause long-term changes in cardiovascular physiology that predispose to circulatory disease. The mechanisms are poorly understood, most human studies have been carried out in adults and little is known about early pathophysiological changes. Therefore, we have assessed the relationship between birth weight and cardiovascular physiology in children.

Methods and results

In 140 healthy boys and girls (aged 7–9 years), born at term and followed prospectively, we continuously recorded blood pressure, electrocardiograms and cardiac impedance before, during, and after 10 min of psychosocial stress (Trier Social Stress Test for Children). In boys, an association of lower birth weight with higher resting systemic arterial pressure ($\beta = -6.8$ mmHg/kg, $P = 0.03$) and a trend towards higher vascular resistance ($\beta = -87$ dyne s/cm⁵/kg, ns) were substantially strengthened following stress ($\beta = -9.5$ mmHg/kg, $P = 0.003$ and $\beta = -139$ dyne s/cm⁵/kg, $P = 0.02$, respectively). In girls, lower birth weight was associated with a shorter pre-ejection period ($\beta = 8.0$ ms/kg, $P = 0.005$) and corrected QT interval ($\beta = 11.9$ ms/kg, $P = 0.003$) at rest and little changed by stress.

Conclusion

Smaller size at birth is associated with sex-specific alterations in cardiac physiology; boys had higher systemic vascular resistance and girls had increased cardiac sympathetic activation.

Keywords

Foetal programming • Epidemiology • Paediatrics • Physiology • Stress

Introduction

Small size at birth is associated with major cardiovascular pathologies, including hypertension and coronary heart disease in later life.¹ These findings have led to the concept of the Developmental Origins of Health and Disease.² This proposes that an adverse foetal environment, usually reflected by reduced birth size, causes adaptive physiological responses with persistent effects on disease risk. Although the epidemiological findings have been replicated in several studies and are paralleled by animal experiments, the nature of the underlying adaptive physiological responses is still poorly understood. Previous studies have been of adults in middle or later life and have examined endpoints such as the prevalence of cardiovascular disease or hypertension, which have complex pathogeneses. Fewer studies have been carried out in children and little is known about the age at which early pathophysiological changes are discernible.

Raised blood pressure appears to be an early feature and is accompanied by alterations of both arterial structure and function, indicated by impaired endothelial function and increased arterial stiffness.^{3,4} Of particular interest are recent findings that birth weight may be associated with altered autonomic function. In adults, lower birth weight is associated with a greater risk of 'white coat' hypertension rather than blood pressure measured by 24 h ambulatory monitoring,⁵ and in both adults and children, is linked with indices of increased sympathetic nervous system activity. These include resting heart rate (HR),⁶ blood pressure and HR responses to psychological stressors,⁷ and measurements of cardiac pre-ejection period (PEP; an index of cardiac sympathetic activation).⁸ However, studies of muscle sympathetic nerve activity give conflicting results.^{9,10}

The current study was designed to examine the influence of prenatal growth on cardiovascular function in normal healthy children, using non-invasive techniques. Studies of children are important in

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detecting early abnormalities, which may lead to cardiovascular disease. They also have an advantage over those in older subjects, as they are less likely to be affected by life-course experiences and the development of overt, non-congenital cardiovascular disease. We studied children undergoing a psychosocial stress test as there is increasing evidence that measures of cardiovascular function during stress may reveal individual phenotypes associated with a greater risk of hypertension and cardiovascular disease whereas those taken at rest may not.^{11,12}

Methods

The children were recruited from a prospective study of mothers who took part in an earlier study of foetal growth in Southampton, UK.¹³ Of these, 374 (74%) were still living in the Regional Health Authority Area. We initially approached the children's general practitioners enquiring whether there was any reason (social or medical) why the child should not be approached. Following this, we approached and recruited a sample of healthy children (68 boys and 72 girls, aged 7–9 years) for the study, which was carried out over a 12 month period. Their birth weight was recorded and duration of gestation was estimated from menstrual history and ultrasound scan. Data on family history of hypertension and maternal alcohol or tobacco use during pregnancy were obtained by questionnaires and clinical notes review, carried out at several stages during pregnancy. Mother's social class (UK National Statistics Socio-Economic Classification) and the children's educational achievements in their national Standard Assessment Test (SAT) at age seven were recorded during their follow-up visit.

The children attended a clinical research facility for the study and underwent dual-energy X-ray absorptiometry (DXA) to measure body composition. Stress tests were carried out at the same time in the afternoon. To assess cardiovascular function, an optimal array¹⁴ of nine spot electrodes (Blue Sensor—Ambu Ltd, St Ives, UK) for impedance cardiography and two spot electrodes for a lead II electrocardiogram (ECG) were applied. The thoracic impedance electrodes were sited using a laser levelling device which, together with careful postural adjustment, allowed repeatable and highly accurate positioning (within a few millimetres) in the standing subject. The distance between the inner set of these electrodes (*I*) defines the volume of the thorax in which impedance is measured and, therefore, has a marked effect on the values obtained. This distance was fixed at 17% of the subject's height. A blood pressure tonometer was attached over the site of the radial artery of the non-dominant hand (VasoTrac APM205A—MedWave Inc., St Paul, MN, USA). This intermittently applies a cushioned pressure sensor over the site of the radial artery, partially compressing the artery against the head of the radius, allowing blood pressure estimation every 12–15 heartbeats. In comparison with measures obtained invasively from the radial artery, this device performs better than oscillometric devices in children¹⁵ with the advantages of being better tolerated, particularly by children, and allowing more frequent measurements. The non-dominant wrist and hand were splinted on their dorsal aspect to minimize motion artefact in the blood pressure recordings and the arm was supported with a sling. To control for the influence of movement, blood pressure readings were corrected to a reference level (insertion of the deltoid tendon) using a fluid-filled tube and calibrated pressure-sensing device that continuously measured and adjusted for the 'hand to heart' differential. Analogue signals from these electrodes and devices were digitally sampled at 1000 Hz and recorded by a PC-based data acquisition system connected to a series of bioamplifiers (MP150, EBI100C and ECG100C—BIOPAC Systems Inc., Goleta, CA, USA) calibrated and configured according to

manufacturer's instructions. Impedance measurement was calibrated with a series of high-precision resistors. A detailed description of the processing used to derive cardiovascular measures from this data is given in the online supplement.

The children were asked to perform a public speaking task involving storytelling for 5 min followed by a mental arithmetic task lasting 5 min for a panel of three unknown adult 'judges' in front of a video camera and microphone (Trier Social Stress Test for Children, TSST-C).¹⁶ Motivation was increased by offering toys as a potential reward for high performance. This type of stressor is known to be a reliable stimulant of both the Hypothalamic-Pituitary-Adrenal axis (HPAA)¹⁷ and autonomic¹⁸ limbs of the stress response. Prior to and following the stressor, the children rested by watching a calming video for 5 min. The children were standing during all of these tasks. Finally, the children were given a voucher for toys worth £10. The Local Research Ethics Committee approved the study and both parents and children gave written informed consent.

Previous studies have suggested that there may be important sex differences in the programming of cardiovascular physiology. In a recent study,¹⁹ small size at birth predicted greater sympathetic activation, parasympathetic withdrawal, and reduced baroreflex sensitivity during psychological stress in young adult women but not men. Similar sex-specific associations were found in a Dutch study using the same stress protocol.²⁰ These findings are supported by animal studies,^{21,22} which show stronger associations between an adverse prenatal environment and increased sympathetic activation during stress in females compared with that in males. Therefore, we designed our study to assess equal number of boys and girls with an *a priori* intention of sex-specific analysis.

Statistical analysis

We estimated that a sample size of 150 children would have a 90% power of detecting a 4 mmHg change in blood pressure per kilogram of birth weight during psychological stress at the 0.05 significance level. For all parameters, mean values for the duration of each task (both stress tasks and the pre- and post-stress periods) were obtained. As obesity affects autonomic function, analyses were adjusted for current BMI (adjustment for percentage body fat estimated by DXA yielded almost identical results which are not presented). The majority (80%) of the clinical sessions was carried out by the same investigator. A second investigator (also male) performed the remainder and this was allowed for in our analysis. To exclude the possibility that associations between cardiovascular parameters and measures of size at birth were dependent on variations in the duration of gestation, we adjusted for gestational age in the analyses using multiple linear regression. Further adjustment for HR and systolic blood pressure was made for analyses using cardiac time intervals. All statistical tests were two-sided and *P*-values of less than 0.05 were taken to denote statistical significance. No adjustments for multiple testing were made to significance levels due to the exploratory nature of this study.

Results

Table 1 shows the birth and current characteristics of the subjects by sex. Table 2 shows the median values of the cardiovascular parameters before, during and following stress for boys and girls. In both sexes, HR and arterial pressure (SAP and DAP) increased during stress. Stroke volume (SV) and cardiac output (CO) fell whereas systemic vascular resistance (SVR) increased. PEP and left-ventricular ejection time (LVET) fell. Whilst these intervals might be expected to shorten with increased HR, corrected QT (QTc)

interval and systolic time ratio (STR) are independent of HR and shortened too, suggesting increased sympathetic cardiac stimulation was also responsible. *Table 3* outlines the relationships between the cardiovascular parameters and birth weight. In boys, lower birth weight was associated with increased SVR and arterial pressure, particularly in the immediate post-stress period, 25–30 min after the onset of the stress test. Similar but weaker associations were present in the other periods reaching statistical significance only for SAP during the pre-stress period. In girls, there were no associations between the parameters in *Table 3* and birth weight. In further regression models, the sex interaction terms for birth weight effects on SVR and SAP in the post-stress period were close to significant ($P = 0.07$ and 0.08 , respectively). Repeating all analyses using indices of SV, CO and SVR normalized for body surface area yielded virtually identical results (not presented).

Table 4 shows the relationships between birth weight and cardiac time intervals in both sexes. Lower birth weight in boys was associated with longer LVET, which was statistically significant during the pre- and post-stress periods and close to significant during stress. In contrast, lower birth weight in girls was associated with significantly shorter PEP and QTc and a lower STR throughout the tasks. In further regression models, the sex interaction terms for the birth weight effects on LVET and PEP were statistically significant ($P = 0.009$ and 0.04 , respectively) and close to significant for QTc ($P = 0.06$).

Because other potential confounders, such as family history of hypertension, social class, education and maternal smoking or alcohol consumption during pregnancy, might explain our results, we repeated our analyses with these variables included. In no case was any of these parental variables significant predictors of cardiovascular parameters in childhood and relationships between size at birth and later cardiovascular function were not significantly altered by their inclusion.

Table 1 Birth and current characteristics of study subjects, median (interquartile range)

Characteristics	Boys	Girls
Birth characteristics		
Gestational age (days)	281 (275–288)	281 (271–287)
Birth weight (kg)	3.56 (3.34–3.90)	3.41 (3.08–3.74)
Current characteristics		
Age (years)	8.9 (8.7–9.1)	8.8 (8.4–9.0)
Weight (kg)	28.9 (24.4–32.5)	29.5 (27.5–33.4)
Height (cm)	134.4 (128.7–137.9)	131.4 (128.1–135.2)
BMI (kg/m ²)	16.1 (15.2–17.5)	17.2 (15.6–18.6)
Body fat by DXA scan (%)	19.2 (16.5–23.7)	27.6 (23.9–33.0)
Manual social class ^a	12/68 (18%)	17/72 (24%)
SAT reading score ^b	2.2 (0.8)	2.4 (0.9)
SAT maths score ^b	2.5 (0.6)	2.5 (0.5)

^aFraction (%), includes social classes 3, 4 and 5 m. ^bMean (SD), pupils taking UK standard assessment tests at age seven are expected to achieve a score of two.

Discussion

We present the first evidence in children of relationships between size at birth and later cardiovascular function. The sex-specific patterns of these relationships were striking. As highlighted in *Tables 3* and *4*, boys who had a lower birth weight demonstrated higher blood pressure and vascular resistance following stress, whereas girls who had a lower birth weight had shorter PEP and QTc. As these associations were seen with measures of size at birth adjusted for gestational age, these findings are due to growth restriction and not prematurity.

We recruited normal healthy children from a community-based cohort study of mothers and their children. The anthropometric measurements and assessment of gestational age at birth (*Table 1*) were obtained using standardized techniques, including the use of ultrasound confirmation of gestational age in early pregnancy. We used an established stress test that has been validated for use in children,¹⁶ which recreates a stressful environment similar to the moderate stressors that most adults and children experience in day-to-day living. Unlike many milder stressors, the TSST-C reliably activates the HPAA, which modulates the actions of the sympathetic nervous system.²³ Therefore, in this context, a more complete picture of cardiovascular function during stress can be obtained.

A potential weakness of our study is reliance upon impedance cardiography to derive measures of SV, CO, and SVR. Although this has been a source of controversy, a meta-analysis of 154 published comparisons between impedance cardiography and reference measures of CO concluded that it is sufficiently accurate, particularly in healthy subjects, for use in research.²⁴ Indeed, in healthy children, impedance cardiography compares well to the indirect Fick method for assessment of CO²⁵ and yields repeatable and consistent measures of reactions to a range of mental and physical stressors.²⁶ Although our measures of SV and CO were somewhat higher than those from a study of seated children experiencing mild stressors,²⁶ this may be because our subjects were standing and experiencing greater stress. Furthermore, although they are supported by these impedance-derived measures, our findings are not reliant upon them and impedance cardiography remains an accurate method for timing of events in the cardiac cycle.²⁷ Another feature of our results is that no adjustment has been made for multiple testing. However, the majority of the measures are not independent of one another and measurements taken over the four periods (pre- and post-stress and during stress) are essentially repeated measures, with similar or identical relationships generally seen with outcomes in each period.

Table 2 shows that the TSST-C resulted in marked pressor responses. Blood pressure increased with a mean increment of 24 mmHg in the girls and 22 mmHg in the boys accompanied by simultaneous increases in HR. Impedance data show that SVR also increased, generating the blood pressure increments, whereas SV and CO fell. At the same time, STR decreased, suggesting greater myocardial contractility and PEP and QTc fell, indicating that greater sympathetic cardiac stimulation is responsible for this. Unlike previous studies using milder psychological stressors in children, we did not see a dramatic beta-adrenergic response to the stress tasks, as indicated by modest changes in

Table 2 Median (interquartile range) of cardiovascular variables prior to, during and following stress

Cardiovascular variable	Boys				Girls			
	Pre-stress	Speech	Maths	Post-stress	Pre-stress	Speech	Maths	Post-stress
HR (bpm)	102 (93–108)	105 (99–112), 0.00001	104 (95–113), 0.00002	99 (93–107), 0.4	108 (100–114)	112 (104–117), 0.00004	108 (101–115), 0.04	106 (99–112), 0.04
SV (mL)	75 (62–87)	67 (56–81), <0.00001	64 (54–80), <0.00001	71 (62–88), 0.01	65 (58–78)	62 (52–71), <0.00001	63 (53–71), <0.00001	66 (59–77), 0.7
CO (L/min)	7.6 (6.4–8.7)	6.9 (5.9–7.8), <0.00001	6.9 (5.8–7.8), <0.00001	7.6 (6.2–8.2), 0.0002	7.0 (6.5–7.9)	6.9 (6.1–7.6), 0.04	6.6 (6.0–7.4), 0.00003	7.0 (6.3–8.0), 0.2
SVR (dyne s/cm ⁵)	713 (617–848)	938 (840–1056), <0.00001	959 (828–1112), <0.00001	754 (641–861), 0.04	806 (693–917)	994 (899–1156), <0.00001	985 (889–1112), <0.00001	786 (706–896), 0.6
SAP (mmHg)	97 (92–106)	119 (113–129), <0.00001	118 (113–126), <0.00001	101 (95–109), 0.006	101 (96–105)	125 (118–131), <0.00001	119 (109–129), <0.00001	102 (96–110), 0.01
DAP (mmHg)	56 (53–62)	71 (66–75), <0.00001	68 (65–73), <0.00001	56 (53–62), 0.8	59 (56–63)	74 (68–77), <0.00001	70 (64–75), <0.00001	58 (54–62), 0.03
LVET (ms)	227 (211–238)	226 (214–235), 0.1	224 (208–234), 0.004	228 (215–243), 0.09	225 (207–233)	218 (211–233), 0.7	221 (212–238), 0.2	228 (215–236), 0.00005
PEP (ms)	76 (72–82)	73 (69–79), 0.00007	74 (70–80), 0.09	75 (72–82), 0.3	73 (68–78)	69 (63–74), <0.00001	71 (65–77), 0.01	72 (67–77), 0.1
QTc (ms)	311 (296–326)	308 (294–321), <0.00001	308 (295–322), <0.00001	311 (298–326), 0.7	307 (292–318)	301 (290–313), <0.00001	303 (293–318), 0.0005	306 (296–320), 0.2
STR (%)	33.4 (31.3–36.4)	33.0 (30.7–35.3), 0.01	33.6 (31.3–36.9), 0.9	33.3 (30.2–36.3), 0.03	32.5 (29.4–37.3)	30.7 (27.2–34.4), <0.00001	31.4 (27.7–35.5), 0.003	31.9 (29.1–36.0), 0.0004

HR, heart rate; SV, stroke volume; CO, cardiac output; SVR, systemic vascular resistance; SAP and DAP, systolic and diastolic arterial pressure; LVET, left ventricular ejection time; PEP, pre-ejection period; STR, systolic time ratio (PEP/LVET). Subjects were standing during all four periods and watching a restful video pre- and post-stress. *P*-values (given below figures) refer to paired comparisons with the pre-stress rest period using Wilcoxon matched-pairs signed-ranks tests.

Table 3 Regression coefficients (95% CI) relating birth weight (kg) to cardiovascular variables prior to, during and following stress

Cardiovascular variable	Boys				Girls			
	Pre-stress	Speech	Maths	Post-stress	Pre-stress	Speech	Maths	Post-stress
HR (bpm)	4.3 (−3.3, 11.9), 0.26	−1.1 (−6.9, 4.8), 0.72	2.6 (−4.1, 9.4), 0.44	5.5 (−1.7, 12.7), 0.13	−1.3 (−8.9, 6.3), 0.74	−3.3 (−10.9, 4.2), 0.38	−3.9 (−11.1, 3.4), 0.29	−3.2 (−10.1, 3.7), 0.36
SV (mL)	−1.1 (−12.8, 10.6), 0.85	0.6 (−10.6, 11.9), 0.91	−2.9 (−14.4, 8.6), 0.61	−0.3 (−12.9, 12.3), 0.96	−3.1 (−13.0, 6.9), 0.54	0.6 (−9.1, 10.4), 0.89	2.1 (−6.9, 11.1), 0.65	1.2 (−8.4, 10.8), 0.80
CO (L/min)	0.3 (−0.72, 1.27), 0.58	0.1 (−0.99, 1.17), 0.87	−0.1 (−1.12, 0.96), 0.88	0.4 (−0.69, 1.45), 0.49	−0.3 (−1.1, 0.4), 0.39	−0.1 (−0.9, 0.7), 0.81	0.0 (−0.7, 0.8), 0.96	0.0 (−0.8, 0.8), 0.99
SVR (dyne s/cm ⁵)	−87 (−205, 31), 0.15	−99 (−259, 61), 0.22	−88 (−242, 66), 0.26	−139 (−259, −21), 0.02	26 (−71, 123), 0.59	53 (−92, 198), 0.47	4 (−116, 124), 0.95	10 (−96, 116), 0.85
SAP (mmHg)	−6.8 (−12.9, −0.8), 0.03	−6.8 (−14.5, 0.9), 0.09	−6.5 (−13.9, 0.9), 0.09	−9.5 (−15.8, −3.3), 0.003	−0.2 (−5.1, 4.7), 0.94	−1.3 (−9.1, 6.5), 0.74	2.7 (−4.6, 9.9), 0.45	2.9 (−2.6, 8.5), 0.29
DAP (mmHg)	−3.6 (−7.9, 0.7), 0.09	−3.9 (−9.6, 1.7), 0.17	−4.6 (−9.7, 0.4), 0.07	−6.5 (−10.9, −2.1), 0.005	−0.4 (−4.1, 3.3), 0.83	0.0 (−5.8, 5.8), 0.99	2.5 (−2.5, 7.5), 0.32	1.3 (−2.7, 5.3), 0.52

HR, heart rate; SV, stroke volume; CO, cardiac output; SVR, systemic vascular resistance; SAP and DAP, systolic and diastolic arterial pressure. Subjects were standing during all four periods and watching a restful video pre- and post-stress. Coefficients are corrected for current BMI, investigator and gestational age. *P*-values are given below the coefficients.

Table 4 Regression coefficients (95% CI) relating birth weight (kg) to cardiovascular variables prior to, during and following stress

Cardiovascular variable	Boys				Girls			
	Pre-stress	Speech	Maths	Post-stress	Pre-stress	Speech	Maths	Post-stress
LVET (ms)	−8.0 (−13.4, −2.6), 0.005	−5.9 (−12.2, 0.3), 0.06	−5.9 (−12.1, 0.3), 0.06	−6.1 (−11.6, −0.7), 0.03	−4.2 (−10.6, 2.2), 0.19	−0.0 (−8.5, 8.4), 0.99	2.7 (−6.0, 11.5), 0.53	0.8 (−4.9, 6.6), 0.78
PEP (ms)	0.3 (−5.6, 6.2), 0.91	−1.2 (−7.1, 4.8), 0.70	0.8 (−5.2, 6.8), 0.78	0.8 (−5.2, 6.7), 0.79	8.0 (2.5, 13.5), 0.005	8.5 (2.0, 14.9), 0.01	8.9 (3.1, 14.7), 0.003	6.7 (1.2, 12.2), 0.02
QTc (ms)	2.6 (−6.9, 12.1), 0.59	−0.9 (−9.8, 8.1), 0.85	1.9 (−7.8, 11.5), 0.70	2.7 (−6.9, 12.3), 0.57	11.9 (4.2, 19.7), 0.003	9.8 (2.4, 17.1), 0.01	11.4 (4.2, 18.6), 0.003	11.2 (5.1, 17.4), 0.0006
STR (%)	1.4 (−1.7, 4.4), 0.37	0.6 (−2.6, 3.8), 0.72	1.6 (−1.5, 4.8), 0.31	1.4 (−1.6, 4.3), 0.37	4.6 (1.4, 7.8), 0.006	4.5 (0.9, 8.1), 0.02	4.0 (0.9, 7.1), 0.01	3.0 (0.2, 5.8), 0.04

LVET, left ventricular ejection time; PEP, pre-ejection period; STR, systolic time ratio (PEP/LVET). Subjects were standing during all four periods and watching a restful video pre- and post-stress. Coefficients are corrected for current BMI, investigator, gestational age, heart rate and systolic arterial pressure. *P*-values are given below the coefficients.

HR and PEP. For example, a previous study in pre-pubertal children of the same age²⁸ showed a 5.6% increase of CO with a modest 3.6% increase of SVR in response to a reaction time task, a 3% increase of CO with an 8.4% increase of SVR in response to a mirror-tracing task, and a 1.3% fall of CO with an 18.2% increase of SVR in response to a cold pressor test. The pattern of responses to the TSST-C in our study is even more biased towards vascular response with the greatest similarity to the cold pressor test from that study, which also showed a fall of CO during stress. Boys showed an 8.8% fall of CO and a 29% increase of SVR, whereas girls showed a 4.1% fall of CO and a 24% increase of SVR. Therefore, our data add to this emerging story of a high degree of specificity of cardiovascular responses to the nature of the stressor.

Our study also adds to growing evidence of major sex differences in the relationships between reduced foetal growth and physiological alterations that may predispose to cardiovascular disease. The pattern of shortened PEP and QTc seen in girls who were smaller at birth is consistent with up-regulation of sympathetic cardiac activation at rest and during stress. We recently found that young women, but not men, who were smaller at birth not only had greater sympathetic activation, but also enhanced blood pressure responses,⁷ greater parasympathetic withdrawal and reduced baroreflex sensitivity during stress.¹⁹ The common finding of these studies, therefore, is an association in females between smaller birth size and indicators of greater sympathetic cardiac stimulation. However, these studies differed in that birth weight was also associated with blood pressure in the women but not in the girls. A possible explanation for this may be that lower birth weight females have enhanced sympathetic activity from a young age but that abnormal baroreflex function, which may lead to exaggerated blood pressure responses to stress, takes time to develop. Longitudinal studies of a single cohort into adulthood would be required to establish this but, given the known associations between blood pressure reactivity and hypertension,¹² such sympathetic hyperactivity may be an important mediator of the known associations between small size at birth and hypertension in females.

In contrast to the girls, boys who were smaller at birth had higher arterial pressures, particularly following the stress test. However, like the girls, they did not have significantly different HR, SV or CO. Therefore, the finding of greater SVR in the boys who were smaller at birth suggests that their greater arterial pressures were generated by peripheral vascular constriction rather than increased CO. These patterns suggest that boys who were smaller at birth have a predominantly vascular (as opposed to myocardial) response to stress. Given that a predominance of vascular rather than myocardial activity is associated with early hypertension,²⁹ this suggests a potential mechanism by which they may develop hypertension. There is evidence that a predominantly vascular response to stress is linked with prolongation of the response. This is consistent with our findings in boys (Table 3) which were most marked during the post-stress period.

An additional finding was that boys who were smaller at birth showed longer LVET. There is evidence from a study of men³⁰ that LVET is inversely related to arterial stiffness, as measured by pulse-wave velocity. Therefore, one possible explanation of our finding is that arterial stiffness is greater in the boys who were

smaller at birth but we have not measured pulse-wave velocity in our study and, therefore, this is speculative. This accords with evidence, however, that increased arterial stiffness, as assessed by the augmentation index, is associated with low birth weight in children,³¹ although, as yet, it is uncertain whether the effects are sex-specific.

We have shown for the first time that there are marked sex differences in the way that size at birth is associated with alterations in cardiovascular physiology established in childhood. Specifically, we found that smaller size at birth is associated with higher SVR following stress in boys and evidence of increased cardiac sympathetic activation at rest and during stress in girls. This suggests that, as in animals, intrauterine influences can have lasting effects on cardiovascular function that differ by sex but are likely to promote the development of hypertension and cardiovascular disease in both sexes.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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The above article uses a new reference style being piloted by the EHJ that shall soon be used for all articles.