Childhood vascular phenotypes have differing associations with pre- and postnatal growth

Short title: Early growth and vascular phenotypes

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Abstract

Objective: In children aged 8-9 years, we examined the associations of linear and abdominal circumference (AC) growth during critical stages of pre- and post-natal development with six vascular measurements commonly used as early markers of atherosclerosis and later CVD risk.

Methods: In 724 children from the UK Southampton Women's Survey mother-offspring cohort, offspring length/height and AC measurements were collected at ten ages between 11 weeks' gestation and age 8-9 years. Using residual growth modelling and linear regression, we examined the independent associations between growth and detailed vascular measures made at 8-9 years.

Results: Postnatal linear and AC growth were associated with higher childhood systolic blood pressure and carotid-femoral pulse wave velocity, while prenatal growth was not. For example, 1SD faster AC gain between ages three and six years was associated with 2.27 (95%CI: 1.56, 2.98) mmHg higher systolic blood pressure. In contrast, faster AC gain before 19 weeks' gestation was associated with greater carotid intima media thickness (0.009 mm (0.004, 0.015) per 1SD larger 19 week AC), while later growth was not. We found no strong associations between pre- or post-natal growth and diastolic BP or measures of endothelial function.

Conclusions: Higher postnatal linear growth and adiposity gain are related to higher systolic blood pressure and carotid-femoral pulse wave velocity in childhood. In contrast, faster growth in early gestation is associated with greater childhood carotid intima media thickness, perhaps resulting from subtle changes in vascular structure that reflect physiological adaptations rather than subclinical atherosclerosis.

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Introduction

In adults, a number of haemodynamic non-invasive techniques to measure vascular structure and function have been shown to give reliable prognostic information for later risk of cardiovascular disease (CVD).[1-4] This includes blood pressure (BP), flow-mediated dilatation (FMD) and reactive hyperaemia (to assess endothelial function), carotid artery intima-media thickness (cIMT) and carotid-femoral pulse wave velocity (cfPWV; a measure of arterial stiffness). Low birth weight and adiposity gain later in life has been associated with a higher risk of hypertension, CVD and metabolic dysfunction in adulthood.[5] The heart and vascular structures start developing very early in prenatal life.[6] Hence, assessing vascular structure and function in children could thus potentially not only give an indication of childhood cardiovascular development, but also of responses to challenges, such as adiposity, and the trajectory of cardiovascular risk. However, there remains uncertainty about whether differences in vascular measures in children in relation to growth and development reflect early pathological changes or mainly represent physiological adaptations.

Several studies have explored relationships between either fetal growth or postnatal growth and vascular markers such as blood pressure in children.[7-13] Nevertheless, as far as we are aware, only one study has assessed relationships between both pre- and post-natal growth and measures of vascular structure and function in childhood, and no studies have included cIMT or measures of endothelial function.[14]

In the Southampton Women's Survey, an extensive set of cardiovascular markers was measured in children at 8-9 years of age. As women were recruited to the study before pregnancy, from a substantial number of their children we also have fetal growth measurements of length/height and AC from as early as 11 weeks' gestation, through fetal life, infancy and during early childhood. Using residual growth modelling, we have a unique opportunity to examine the independent influence of growth during critical stages of development on later vascular structure and function, and also the relative importance of linear growth compared with soft tissue growth. Further, as we also have measurements of fat and lean mass, measured by dual x-ray absorptiometry in a large sub-sample at age 8-9 years, we are able to examine the body composition correlates of AC gain.

Our main aim was therefore to examine whether conditional linear and AC growth through different stages from early pregnancy to 8-9 years of age are associated with vascular CVD risk markers at 8-9 years of age.

Methods

Study design:

The Southampton Women's Survey (SWS) is an ongoing, prospective cohort study of 12,583 initially non-pregnant women aged 20–34 years, living in Southampton, UK.[15] Assessments of lifestyle, diet and anthropometry were performed at study entry (April 1998–December 2002). Some 3,158 women in the SWS who subsequently became pregnant were followed up through pregnancy, including ultrasound measurements of the fetuses, and the offspring without congenital growth anomalies, from uncomplicated pregnancies, have been followed through infancy and childhood.

Growth variables:

Crown-rump-length and abdominal circumference (AC, a composite of liver size and adiposity) were measured by ultrasound at 11 weeks' gestation by two operators according to internationally accepted and validated methodology. At 19 and 34 weeks' gestation, fetal AC and femur length (a measure of skeletal size) were measured. Ultrasound measurements were made on still images using electronic callipers. AC and length/height were measured at birth and at ages 6 months, 12 months and 2, 3, 6-7 and 8-9 years. Crown-heel length was measured using a neonatometer (Harpenden, Wrexham, UK) at birth, and using an infantometer (Seca, Birmingham, UK) at 6 months and 1 year. At the other ages, standing height was measured with a Leicester stadiometer. Abdominal circumference from birth onwards was taken at the end of expiration using a blank tape measured against a fixed scale (measured three times and the mean was used). Of children with vascular measurements at age 8-9 years the body composition of a sub-sample of 983 children was measured by dual x-ray absorptiometry, as described previously.[16] From these, 574 children had AC measured at 2 and 8-9 years of age.

The predicted date of delivery was calculated from the date of the mother's last menstrual period and confirmed by an early dating ultrasound scan or adjusted if there were more than 14 days discordance between the two methods or the mother's menstrual dates were uncertain. Postnatal age at all time points was defined as years from predicted date of delivery (to adjust for gestational age at birth).

Vascular measures:

Details of the vascular measures have been published previously.[16] Briefly, left systolic and diastolic BP (mmHg) and cIMT (maximum thickness, the mean of up to four measures, in mm) were measured after 10-15 min rest. BP was measured by a Dinamap Critikon 8100 vital signs monitor. The BP cuff (upper arm) was inflated immediately after acquiring an optimal cIMT image. cfPWV was recorded transcutaneously (Vicorder) after 10-15 min rest. Sensor cuffs were placed on the left carotid suprasternal notch and the upper left thigh, and the time delay between two simultaneously measured cardiac cycles were measured (mean of up to four measures). Measurements of FMD and reactive hyperaemia were obtained from the right brachial artery, using high-resolution ultrasound. Brachial artery FMD was induced by a 5 min inflation of a pneumatic cuff around the forearm, followed by rapid deflation. FMD was expressed as the maximum percentage change in vessel diameter from baseline and reactive hyperaemia as percent change in flow, from baseline to maximum flow within 15 s of cuff deflation (RH%).

Confounding variables

We used a Directed Acyclic Graph (Supplemental figure 1) to determine which confounding variables to adjust for in the models. We chose only to adjust for variables extensively shown from the literature to be associated with both growth and vascular structure and function in children. These were maternal socioeconomic status (here determined by maternal educational level in six categories from none to university degree or above), pre-pregnant BMI, and smoking. We also adjusted for child's sex. As age at vascular assessment is strongly associated with vascular measures in children, even within the 8-9 year range, we also adjusted for age, as a competing exposure, to increase precision of effect size estimates.

Ethics

The SWS was approved by the Southampton and South West Hampshire Local Research Ethics Committee (reference number: 08/H0502/95). Written informed consent was obtained from all participating women and by a parent or guardian with parental responsibility on behalf of each child. The investigation conformed to the principles outlined in the Declaration of Helsinki.

Statistical analysis:

All statistical analyses were performed using Stata: Release 14. Statistical Software. StataCorp (2015). (College Station, TX: StataCorp LP). Sex-specific z-scores were derived for all biometric measurements using the LMS method for boys and girls separately.[17] Internal rather than external z-scores were used, as suitable external standards were not available for prenatal data. Crown-heel length cannot be measured by prenatal ultrasound scans, but length can be estimated from crown-rump length and femur length by assuming that they are proportional to total length. An appropriate multiplier was found by comparing the summary statistics for total length from fetal autopsies provided by Guihard-Costa et al (excluding multiple- and diabetic pregnancies, macerated fetuses and fetuses with any malformation, chromosomal abnormalities and infections),[18] with those for crown-rump length and femur length in the SWS dataset. Suggested multipliers were 1.71, 7.66 and 6.91 to predict crown-heel length from crown-rump length at 11 weeks' gestation and femur length at 19 weeks' and 34 weeks', respectively.

To assess associations with growth over distinct age periods we used residual growth modelling to eliminate collinearity problems caused by repeated measures.[19, 20] For our main analyses, conditional growth z-scores were derived from standardized residuals resulting from the regression of the z-score for a measurement at a specific time point on the z-score for the measurements at all preceding ages. Hence, the conditional variables represent how much a child's length/height or AC at a certain age differs from what would be expected based on the child's previous size, as well as the overall growth of other participants in the cohort. The successive variables are statistically independent from each other and can therefore be entered concurrently into the same regression model. We used linear regression analyses to estimate associations between fetal size at 19 weeks' gestation and fetal/child conditional growth through 8 time windows (19-34 weeks' gestation, 34 weeks' gestation-birth, birth-6 months, 6 months-12 months, 12 months-2 years, 2-3 years, 3-6 years and 6-9 years) as exposures, and vascular measures at 8-9 years of age as outcomes, adjusting for confounders.

We further performed a sensitivity analysis in a sub-sample of children who also had growth measures from 11 weeks' gestation, in order to examine if associations with fetal size at 19 weeks gestation were explained by faster/slower growth before week 11 or by growth from weeks 11-19. For this sub-sample, new conditional growth measures were developed. Lastly, we performed sensitivity analyses, including only pregnancies with certain last menstrual period dates, with similar results to when using the total study sample (data not shown). We also performed sensitivity analyses stratified by sex.

To explore whether associations with conditional growth were mainly driven by children with low (lowest quarter) or high (highest quarter) values of each vascular outcome, we undertook linear regression analyses comparing linear size and AC size z-scores from all nine time-points in the extreme quarters with the "middle" two quarters. We did similar analyses using child BMI z-scores (age- and sex-specific) from ages 6 months to 8-9 years of age as outcomes. To further examine the body composition correlates of childhood AC gain, we analysed data from the sub-samples who had AC measurements at 19 weeks' gestation and at ages 2 and 8-9 years, and measurements of fat and lean mass at age 8-9 years.

A priori, we planned to draw conclusions based on effect estimates and their CIs, rather than statistical tests using an arbitrary P-value cut-off. Nevertheless, in the figures, symbols representing the point estimates are filled reflecting the precision of the estimate (filled symbols when $p \leq 0.01$, semi-filled symbols $p<0.05$ but >0.01 and open symbols $p>0.05$).

Results

Among the 12,583 women recruited to the SWS, 3,158 women became pregnant and had a live singleton birth, constituting the total sample for the SWS offspring cohort followed up several times since birth (Supplemental Figure 2, Flow chart).[15] Of these, a sub-sample of 1,216 children participated in the 8-9 year follow-up. Due to logistical challenges and the time-consuming nature of measurements, not all measures could be taken for all participants, but at least one vascular measure was taken in 1,152 children. Of these, 724 children had growth data from all nine time points between 19 weeks' gestation and 8-9 years of age, and could be included in the comprehensive growth analyses. Maternal and child characteristics are presented for the main sample in Table 1. Except for slightly fewer mothers who smoked and slightly higher mean birthweight in the sub-sample than in mother-child pairs not included, the sub-sample seemed representative of the total cohort (data not shown).

The primary analysis, in children who had growth measures taken from 19 weeks' gestation, showed that prenatal conditional linear- and AC-growth were not associated with systolic BP at age 8-9 years. However, conditional linear growth through all postnatal time windows, as well as AC conditional growth from birth to six months of age and through all time windows from 12 months to 8-9 years (Figure 1, details in Table S1a and S2a) were associated with a higher systolic BP. The strongest association was with AC-growth between 3-6 years of age: a child in whom AC increased one SD more than expected between 3-6 years of age had 2.27 mmHg ((95% CI: 1.56, 2.98) higher systolic BP at age 8-9 years than a child growing as expected. In contrast, there was little evidence of associations between diastolic BP and the pre- or post-natal conditional growth measures, although slower AC gain in late gestation was borderline significantly associated with higher diastolic BP (-0.72 (-1.32, -0.14), p=0.01).

Prenatal conditional growth was not associated with cfPWV at age 8-9 years, but postnatal conditional linear growth from birth to 6 months, and from 6-7 to 8-9 years, and conditional AC-growth from 3 to 6 years of age were positively associated. In contrast, there were no associations between postnatal growth and cIMT at age 8-9 years, but a greater AC at 19 weeks' gestation was associated with higher cIMT (0.009 mm (0.004, 0.015), p=0.001). The sub-sample analysis in children who also had growth measures taken at 11 weeks' gestation showed that faster AC-growth from 11-19 weeks was associated with higher cIMT (0.009 (0.002, 0.017), p=0.01) (Table S1b and S2b).

Accelerated AC-growth from 6-7 to 8-9 years of age was associated with lower reactive hyperaemia at age 8-9 years. Apart from this, there were no apparent associations between conditional growth and FMD or RH% (Figure 1, details in Table S1a and S2a).

Figure 2 and Supplementary table 3 show that children with high systolic BP and children with low systolic BP at 8-9 years of age had a similar length and AC as children with middle values until birth. However, from birth onwards both growth measures started diverging in the high vs. the low systolic BP groups, so that at 2 years of age children with high systolic BP were larger, while children with low systolic BP were smaller. These differences increased further until 8-9 years of age. Analysing child BMI from 6 months to 8-9 years of age as the outcome showed that children with systolic BP in the highest quartile had a higher BMI already at 6 months, and that the difference increased further from 3 years of age (Figure 3 and Table S4).

A similar pattern was observed for children with the highest and lowest cfPWV at age 8-9 years. For cfPWV the divergence in length/height became apparent from 6 months of age, while the AC divergence emerged from three years of age. In contrast, children with the lowest cIMT at age 8-9 years tended to have smaller ACs at 19 weeks' gestation while children with cIMT in the highest quarter tended to be larger. However, these differences declined during early childhood, and no differences in AC between the groups were observed at 8-9 years of age.

Girls had slightly higher blood pressure than boys (Table 1), which as previously shown, was not explained by a higher weight or more fat mass.[16] However, stratified analyses (Supplementary figure 3 and tables S5 and S6) showed similar effects of growth on the vascular outcomes in boys and girls, although results were less robust given the smaller sample sizes.

AC may both represent fat and lean mass. In supplementary analyses we therefore examined the body composition correlates of childhood AC gain using data from the 574 children in our study sample who had measurements of fat and lean mass at age 8-9 years using dual-x-ray absorptiometry. Fetal AC at 19 weeks' gestation was not associated with child fat or lean mass at 8-9 years. However, among children whose AC z-scores increased between ages 2 and 8 years (n=347) there was a strong positive linear association between AC z-score change and fat mass at 8-9 years; each SD increase in AC z-score from 2 to 8-9 years was associated with 0.81 SD (95% CI: 0.64, 0.98) higher total fat mass, 0.89 SD (0.72, 1.07) higher truncal fat mass while only 0.37 SD (0.20, 0.54) higher total lean mass at 8-9 years of age.

Discussion

We found clear relationships of higher postnatal linear growth with higher systolic BP and cfPWV at 8-9 years of age; higher post-infancy AC gain, likely to mainly represent truncal adiposity gain, was also associated with higher late childhood systolic BP and cfPWV. In contrast, we found no robust associations between postnatal growth indices and diastolic BP, cIMT and measures of endothelial function. With the notable exception of a relation between higher AC growth before 19 weeks' gestation and greater childhood cIMT, no independent associations were observed between prenatal growth and vascular measures at 8-9 years of age.

Our results do not suggest strong independent associations between prenatal growth and systolic or diastolic BP and cfPWV at age 8-9 years, and hence differ from some previous studies indicating associations between slower last trimester linear growth and weight gain with higher BP in early childhood.[8, 13, 14] However, the reported associations from the only study assessing associations with both pre- and postnatal growth up to two years of age, were subtle.[14] We found similar effect estimates for diastolic BP in our study, although only borderline significant, which could be due to a lower sample size. However, for systolic BP our results indicate an opposite relationship, as children with the highest systolic BP at 8-9 years of age tended to be smaller at 19 weeks' gestation but had a borderline faster linear growth in late pregnancy. Our findings are in accordance with recent longitudinal studies in older children and young adults followed from birth onwards, using size at birth as a proxy measure of prenatal growth, which showed only small effects of size at birth on later BP and cfPWV, and modest effects of early postnatal growth, alongside relatively larger effects of increases in weight gain or adiposity gain in the post-infancy phase.[7, 9-12, 21] Our findings also support our previous results suggesting that associations between BMI and systolic BP and cfPWV at age 8-9 years represent both pre- and post-natal adaptations to greater lean mass and adverse effects of fat deposition in later childhood.[16] Our finding that children with high systolic BP had a higher BMI already at 6 months, and that this difference increased further from 3 years of age also support this. This endorses the importance of the first 1000 days (conception to postnatal age 2) as a period of developmental plasticity, after which perhaps adaptability is reduced and so fat and pre-pathological changes in blood vessels occur in relation to lifestyle factors. Furthermore, importantly, prenatal influences could have lasting consequences for postnatal cardiovascular structure and function without necessarily affecting early growth. Evidence for this comes from our findings linking maternal oily fish consumption during pregnancy and candidate epigenetic marks at birth with PWV in later childhood.[22, 23]

Most direct and indirect measures of fat or lean mass cannot be measured prenatally. Further, how we interpret associations between AC growth and vascular outcomes later in life will differ depending on which time window we are considering. In the first and second trimesters of fetal life, AC growth is linked to the amount and pattern of distribution of venous liver perfusion, and liver size,[24] and not fat mass, as substantial fetal fat deposition generally does not start before the third trimester. In contrast, in adults, AC gain will mainly represent relative increases in fat deposition. In late pregnancy and in the growing child, AC gain can however reflect accelerated growth of both lean and fat mass, although in the post-infancy phase it will increasingly represent fat gain. This is supported by our supplementary analyses of data from the children with measurements of AC from ages 2 and 8-9 years who also had measurements of fat and lean mass at 8-9 years of age. This suggests that the associations with post-infancy AC gain predominantly reflects effects of fat gain.

In contrast to the other vascular measures, we found that faster AC growth before 19 weeks' gestation was associated with greater cIMT at age 8-9 years, while later growth was not. cIMT is mainly a structural measure, and is much used as an early indicator of atherosclerosis. Previous studies have reported associations between high child BMI, high fat mass or "persistent high BMI trajectory" and greater cIMT in children and adolescents.[21, 25, 26] The observed association with early fetal AC growth in our study was subtle, although the effect estimate (1 SD increase in AC was associated with 0.009 mm=0.13 SD increase in cIMT) is in the same range as reported in other studies assessing relations with postnatal adiposity measures.[26] However, we and others have previously shown that in young people higher cIMT is more strongly related to the lean mass component of BMI than to fat mass.[16, [25, 27] This suggests that subtle changes in cIMT in the young may predominantly represent physiological adaptations to a larger body size as opposed to subclinical atherosclerosis.[25] Elastin accounts for almost half of the dry weight in the aorta in young people.[28] The synthesis of elastin in aorta and large arteries increases from early gestation until the perinatal period, before it drops dramatically. It has been hypothesized that impairment in the synthesis of elastin during a critical period of blood vessel development, caused by hemodynamic changes in the fetal circulation related to intra-uterine growth retardation, may underlie the association of low birthweight with hypertension in adult life.[28] From our finding we could speculate that the first half of pregnancy is such a critical period. In the long run, a relative deficiency in elastin may reduce the compliance of the aorta and large arteries, which in turn leads to higher pulse pressures, over time, leading to gradually thicker and stiffer arterial walls as elastin is replaced by collagen. We could therefore further speculate that at a young age, low rather than high cIMT may be a risk factor for later CVD, in particular if accompanied by an unhealthy diet, lack of physical activity or obesity.

In contrast to the strong relations between postnatal growth and systolic BP, we did not find strong associations with diastolic BP. It is suggested that increasing body mass (both lean and fat) in children probably results in increased systolic BP in part due to a chronic hyperaemic state and an elevated stroke volume, while diastolic BP at this age is maintained in part by peripheral vascular adaptations.[29] Our results may support this. Moreover, except for AC growth between 6-7 and 8-9 years, no associations were observed between conditional growth and measures of endothelial function, FMD and RH%. This may indicate that RH% and FMD, being mainly functional measures, remain more plastic than other aspects of body composition or vascular structure, and that these processes develop gradually over many years.

Limitations

Combining prenatal and postnatal growth measurements involves making assumptions. We have combined fetal ultrasound measures of AC with measures of AC after birth using somewhat different landmarks, and for length measurements we combined femur length, crown-heel length, length and height. Furthermore, use of the pregnancy measures was based on equations developed from pathological examinations of a large sample of fetuses.[18] Despite considerable efforts to define a reference population that was as normal as possible, the development of multipliers using a sample of fetal autopsies may involve bias, due to their possible pathological growth. Of the 3,158 women-child pairs in the total sample of the SWS cohort, only a sub-sample could be included in the present study. Although the sub-sample seemed fairly representative, this decreased statistical power to detect associations. With over 700 participants, this study is however large enough to detect clinically-relevant effects, although the clinical relevance of some of the observed subtle changes should be interpreted with caution. Moreover, there are potentially a number of environmental factors (including maternal nutrition and BP during pregnancy) which could influence both growth and vascular phenotype during different stages of early life. It is therefore possible that unmeasured confounding remains unaccounted for.

Conclusions

Early growth may point to aspects of the early life environment that induce cardiovascular adaptations, which may subsequently affect the individuals' risk of developing cardiovascular disease, for example in terms of responses to a post-natal obesogenic environment. In this study of 8-9 year old children, we showed that systolic BP and cfPWV were associated with postnatal linear growth and post-infancy AC-gain, while subtle changes in cIMT was associated with early fetal AC growth. In contrast, diastolic BP and endothelial function measures were not strongly related to growth at any time point. These differing relations with growth may point to variations in the timing, degree and duration of plasticity of different vascular phenotypes, but could also reflect varying responses to adiposity.

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Table 1. Maternal and child characteristics of main study sample (n=724). Numbers are n (%), mean (SD) or median (IQR).

	Total (n=724)	Boys (n=353)	Girls (n=371)
Maternal characteristics			
Education			
None	12 (2%)	5 (1%)	7 (2%)
CSE	55 (8%)	23 (7%)	32 (9%)
O-levels	204 (28%)	96 (27%)	108 (29%)
A-levels	217 (30%)	112 (32%)	105 (28%)
HND	49 (7%)	22 (6%)	27 (7%)
Degree	186 (26%)	94 (27%)	92 (25%)
Primiparous	362 (50%)	182 (52%)	180 (49%)
Smoker	155 (21%)	73 (21%)	82 (22%)
Pre-pregnant BMI (kg/m^2)	24.0 (22.0, 27.1)	24.2 (21.9, 27.2)	23.9 (22.0, 26.9)
Birth characteristics			
Gestational age (weeks)	40.0 (39.0, 41.0)	39.9 (39.0, 40.9)	40.1 (39.1, 41.1)
Birthweight (g)	3493 (493)	3550 (494)	3440 (488)
Crown-heel length (cm)	49.9 (2.1)	50.3 (2.1)	49.5 (2.0)
Abdominal circumference (cm)	31.7 (2.1)	31.7 (2.0)	31.7 (2.1)
Child characteristics at age 8-9 years			
Age (years)	9.2 (0.2)	9.2 (0.2)	9.2 (0.2)
Participating in sports (h/week)	2.5 (1.0, 4.0)	2.5 (1.0, 4.0)	2.0 (0.5, 4.0)
Height (cm)	135.6 (6.0)	135.7 (5.9)	135.6 (6.2)
Weight (kg)	29.9 (26.7, 34.5)	29.1 (26.5, 33.2)	30.6 (27.1, 35.4)
BMI (kg/m^2)	16.2 (15.0, 18.1)	16.1 (14.9, 17.5)	16.6 (15.2, 18.5)
BMI UK-WHO z-score	0.05 (1.11)	-0.02 (1.15)	0.12 (1.07)
Vascular outcomes			
Systolic BP (mmHg)	106.2 (9.2)	104.8 (9.0)	107.6 (9.3)
Diastolic BP (mmHg)	55.7 (7.5)	54.0 (6.8)	57.3 (7.8)
Carotid IMT (max, mm)	0.49 (0.07)	0.49 (0.07)	0.49 (0.07)
Carotid-femoral PWV (m/s)	4.58 (0.58)	4.54 (0.58)	4.62 (0.58)
Brachial FMD	6.74 (3.69)	6.43 (3.53)	7.02 (3.83)
Brachial RH%	571 (248)	542 (235)	598 (258)

BMI, body mass index; BP, blood pressure; cIMT, carotid intima media thickness (max); PWV, pulse wave velocity; FMD, flow mediated dilatation (maximum % change in brachial artery diameter after cuff-deflation); RH%, Reactive hyperaemia (per cent change in flow from baseline to maximum flow within 15 s of cuff-deflation).

Figure 1

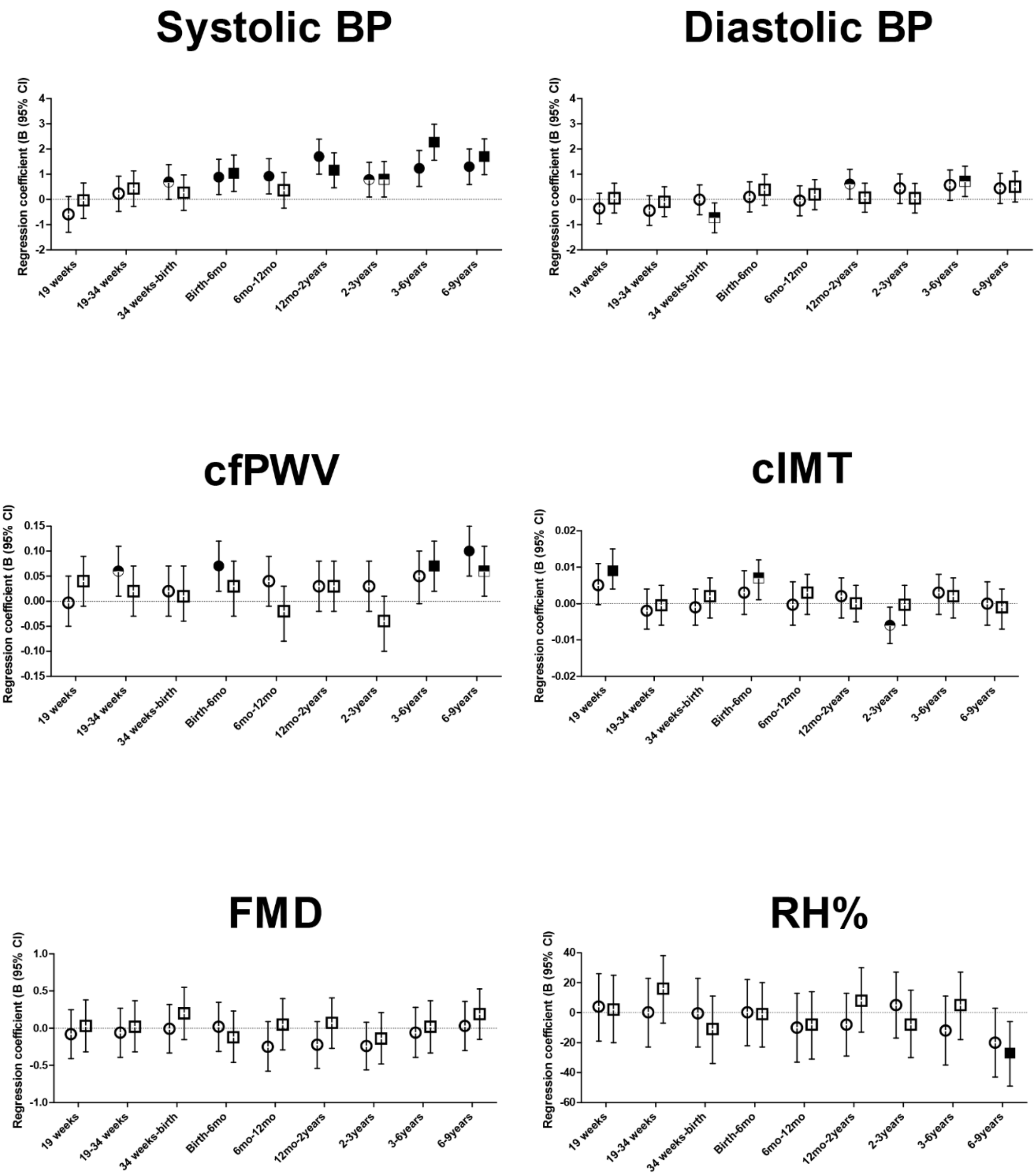


Figure legend:

Figure 1. Associations (β (95% CI)) between conditional linear growth (circles)- and AC growth (squares) through 8 time windows from 19 gestational weeks until 8-9 years of age and vascular measures; systolic BP, diastolic BP, cfPWV, cIMT, FMD (%) and RH (%). Numbers are regression coefficients (95% CI) for each time window from linear regression analyses, adjusted for confounders.

Footnote:

Filled symbols are when p≤0.01, semi-filled symbols p<0.05 but >0.01 and open symbols p>0.05.

Figure 2

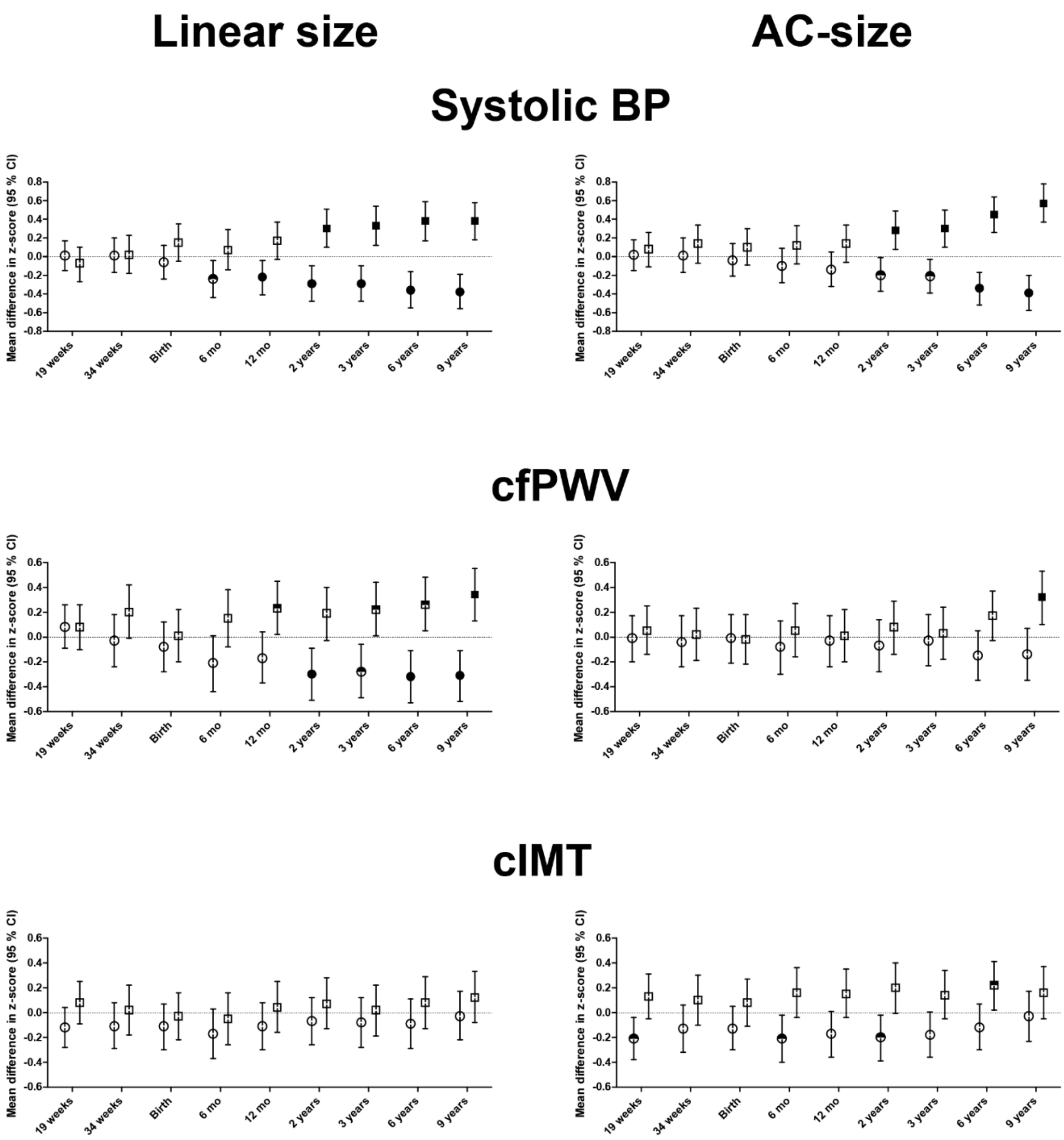


Figure legend:

Figure 2: Fetal and child growth patterns of children with highest quarter (squares) or lowest quarter (circles) levels of systolic BP, cfPWV and cIMT, compared with "middle" values (the middle two quarters, represented by the zero-line). Values are mean differences in z-scores at each time point (left panel: linear size*, right panel: AC-size*), using separate linear regression analyses.

Footnote:

Filled symbols are when p≤0.01, semi-filled symbols p<0.05 but >0.01 and open symbols p>0.05.

* Analyses were performed and is presented for the total sample (n=724). Of these, 686 had linear size and 652 had AC measured at all time points. Regression models for different time points were therefore run on slightly different numbers. However, we have rerun the analyses on consistent n's, with nearly identical results.

Figure 3

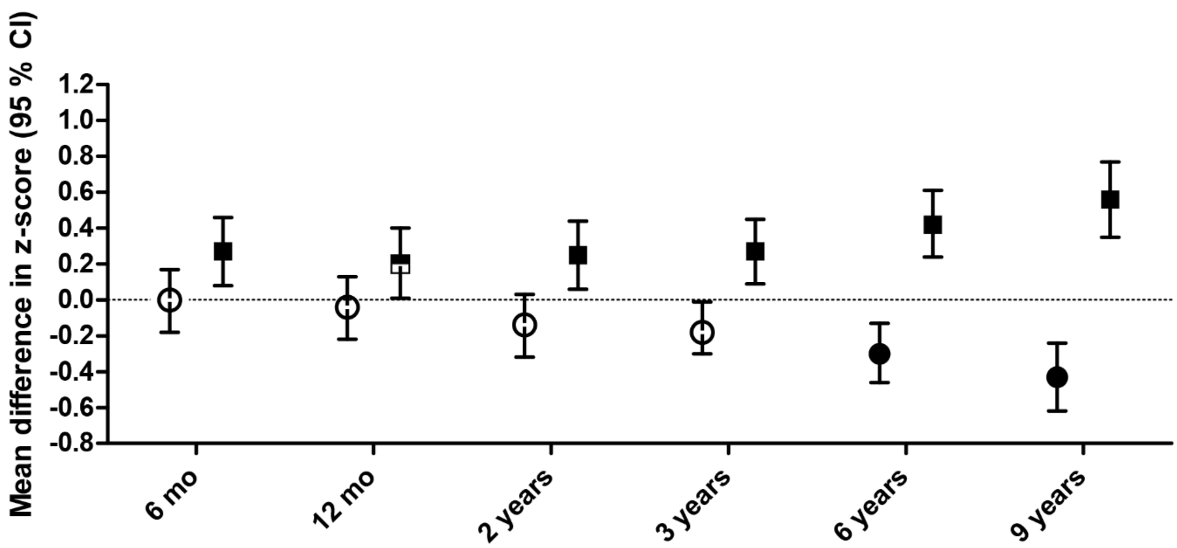


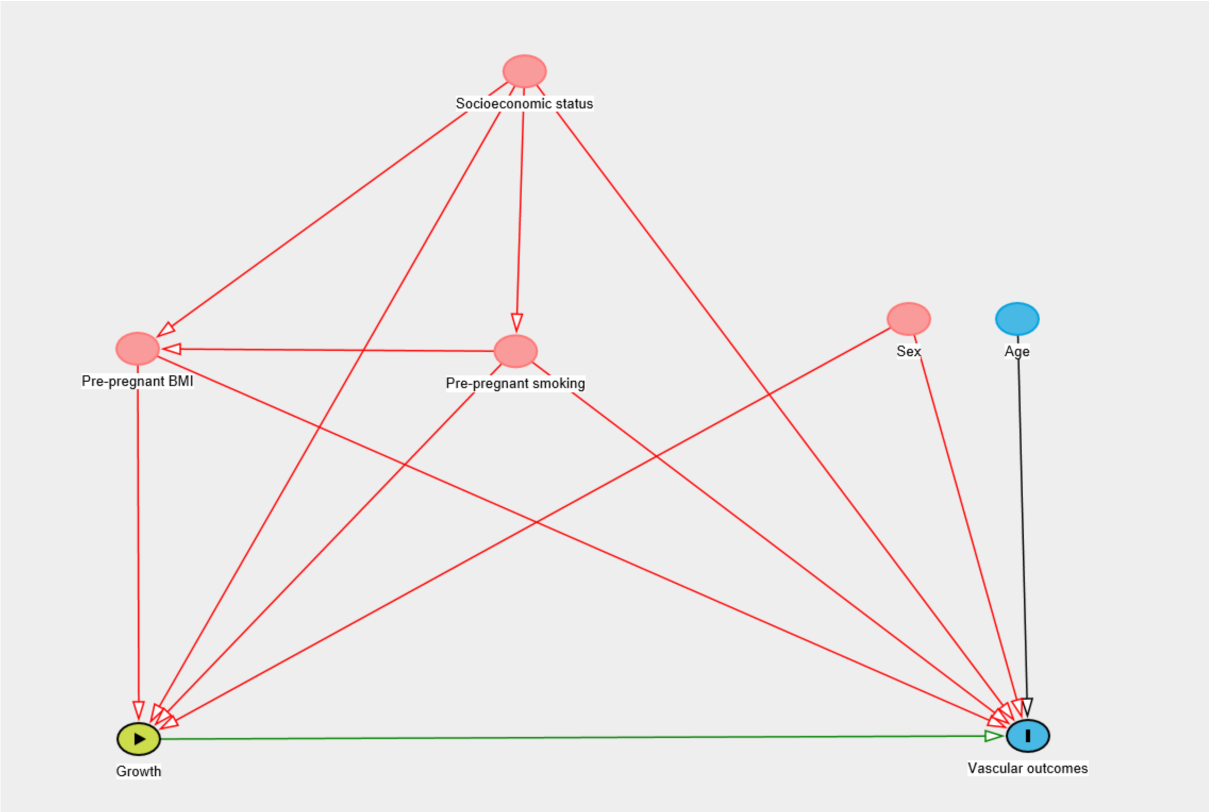
Figure legend:

Figure 2: Child BMI growth pattern from six months to 8-9 years of age of children with highest quarter (squares) or lowest quarter (circles) levels of systolic BP, compared with "middle" values (the middle two quarters, represented by the zero-line). Values are mean differences in BMI z-scores at each time point, using separate linear regression analyses.

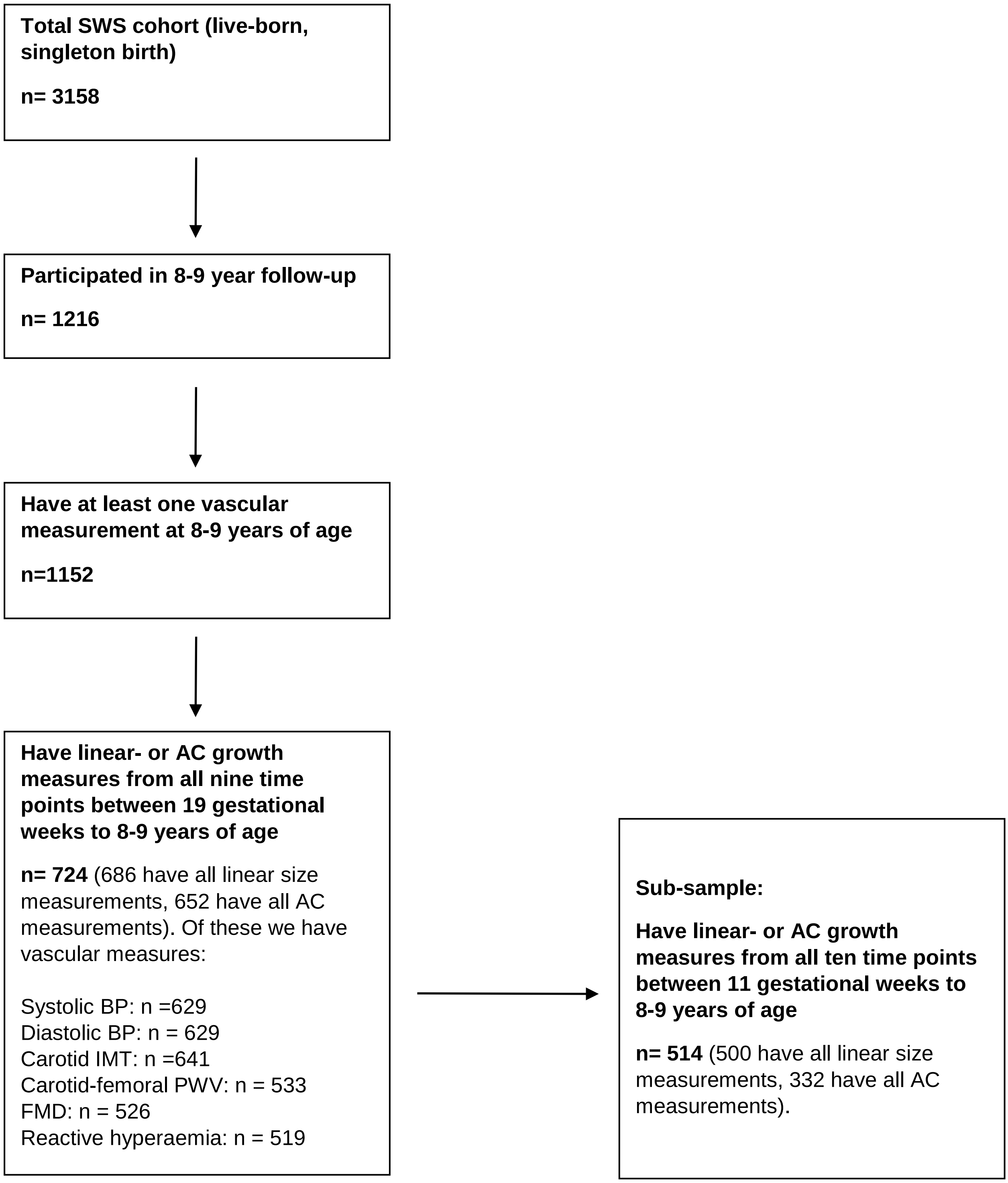
Footnote:

Filled symbols are when $p \leq 0.01$, semi-filled symbols $p<0.05$ but >0.01 and open symbols $p>0.05$.

Supplemental figure 1. Directed Acyclic Graph, showing the confounders chosen to adjust for in the models.

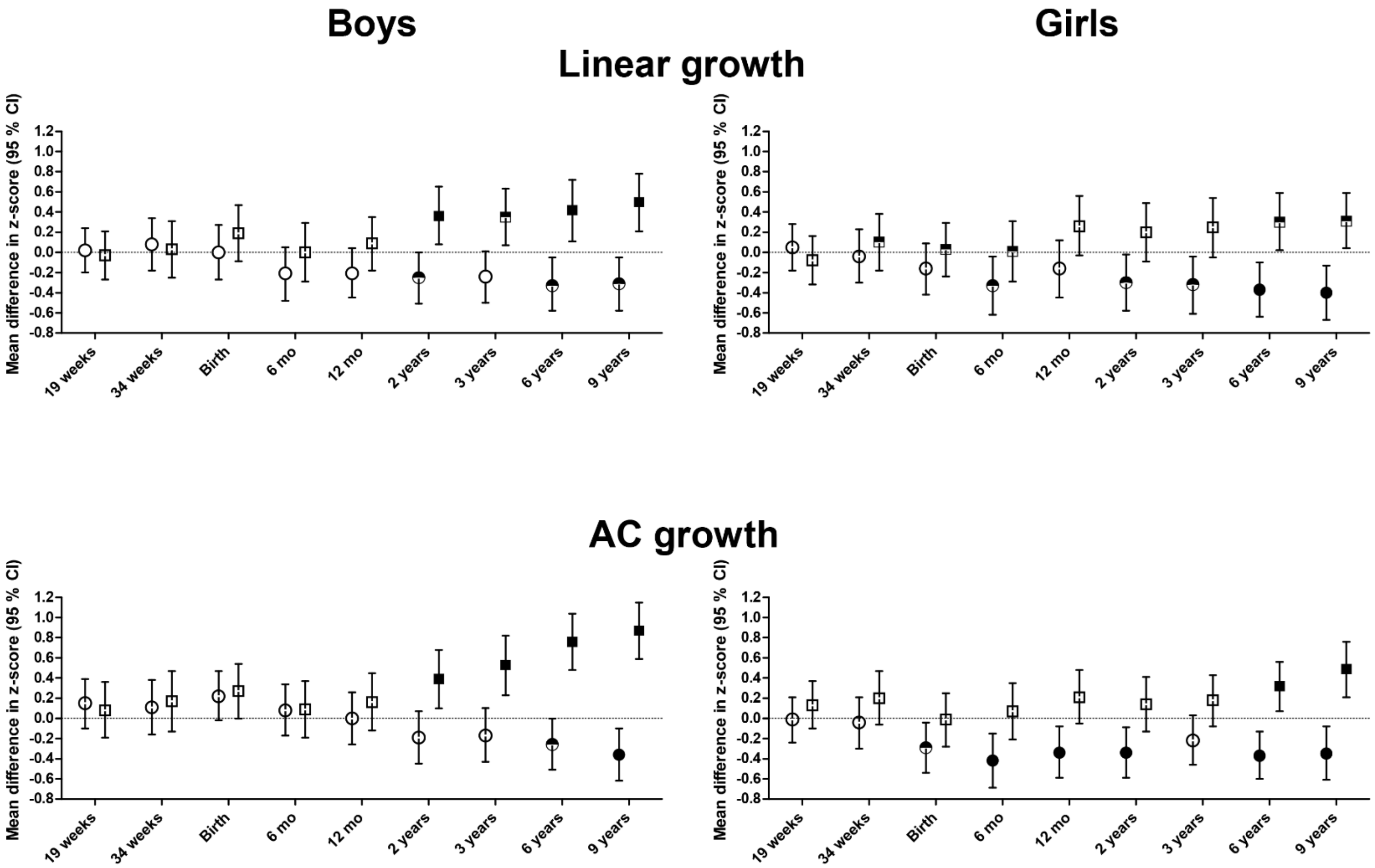


Supplemental Figure 2. Flow chart showing participating children in the Southampton Women's Survey cohort selected for analysis



BP = blood pressure; IMT = intima media thickness (max); PWV = pulse wave velocity; FMD = flow mediated dilatation (maximum % change in brachial artery diameter after cuff-deflation); Reactive hyperaemia = per cent change in flow from baseline to maximum flow within 15 s of cuff-deflation.

Supplemental Figure 3: Fetal and child growth patterns of boys and girls with highest quarter (squares) or lowest quarter (circles) levels of systolic BP compared with "middle" values (the middle two quarters, represented by the zero-line). Values are mean differences in z-scores at each time point (top panel: linear size*, bottom panel: AC-size*), using separate linear regression analyses.



Filled symbols are when p≤0.01, semi-filled symbols p<0.05 but >0.01 and open symbols p>0.05.

Supplementary tables

Table S1a. Associations between linear growth from 19 weeks gestation to 9 years of age, and vascular CVD risk factors at age 9 (using size at 19 GW as starting point and growth through eight time windows).

		19 weeks		19 weeks - 34 weeks		34 weeks - birth		Birth - 6 mo		6 mo - 12 mo		12 mo - 2 years		2 - 3 years		3 - 6 years		6 - 9 years	
	n	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p
Systolic BP	587	-0.59 (-1.30, 0.12)	0.1	0.23 (-0.47, 0.92)	0.5	0.69 (0.00, 1.38)	0.05	**0.89 (0.20, 1.59)**	**0.01**	**0.92 (0.22, 1.62)**	**0.01**	**1.70 (1.00, 2.39)**	**<0.001**	0.79 (0.10, 1.47)	0.02	**1.23 (0.52, 1.94)**	**0.001**	**1.30 (0.60, 2.00)**	**<0.001**
Diastolic BP	587	-0.35 (-0.96, 0.25)	0.3	-0.44 (-1.03, 0.15)	0.1	-0.01 (-0.60, 0.58)	1.0	0.10 (-0.49, 0.70)	0.7	-0.05 (-0.65, 0.55)	0.9	0.61 (0.02, 1.20)	0.04	0.44 (-0.15, 1.02)	0.1	0.57 (-0.04, 1.17)	0.07	0.44 (-0.16, 1.04)	0.2
Carotid IMT	599	0.005 (0.000, 0.011)	0.06	-0.002 (-0.007, 0.004)	0.5	-0.001 (-0.006, 0.004)	0.7	0.003 (-0.003, 0.009)	0.3	0.000 (-0.006, 0.005)	0.9	0.002 (-0.004, 0.007)	0.5	-0.006 (-0.011, -0.001)	0.03	0.003 (-0.003, 0.008)	0.4	0.000 (-0.006, 0.006)	1.0
Carotid-femoral PWV	502	0.00 (-0.05, 0.05)	0.9	0.06 (0.01, 0.11)	0.03	0.02 (-0.03, 0.07)	0.4	**0.07 (0.02, 0.12)**	**0.005**	0.04 (-0.01, 0.09)	0.09	0.03 (-0.02, 0.08)	0.2	0.03 (-0.02, 0.08)	0.2	0.05 (0.00, 0.10)	0.07	**0.10 (0.05, 0.15)**	**<0.001**
FMD (%)	494	-0.08 (-0.41, 0.25)	0.6	-0.06 (-0.39, 0.27)	0.7	-0.01 (-0.33, 0.32)	1.0	0.02 (-0.31, 0.35)	0.9	-0.25 (-0.58, 0.09)	0.1	-0.22 (-0.54, 0.09)	0.2	-0.24 (-0.56, 0.08)	0.1	-0.06 (-0.39, 0.28)	0.7	0.03 (-0.30, 0.36)	0.9
Reactive hyperemia (%)	485	4 (-19, 26)	0.8	0 (-23, 23)	1.0	-1 (-23, 22)	1.0	0 (-22, 23)	1.0	-10 (-33, 13)	0.4	-8 (-29, 13)	0.5	5 (-17, 27)	0.6	-12 (-35, 11)	0.3	-20 (-43, 3)	0.09

Adjusted for maternal education, prepregnant smoking and BMI and child sex and age at vascular assessment

Table S1b. Associations between linear growth from 11 weeks gestation to 9 years of age, and vascular CVD risk factors at age 9 (using size at 11 GW as starting point and growth through nine time windows).

		11 weeks		11 weeks-19 weeks		19 weeks - 34 weeks		34 weeks - birth		Birth - 6 mo		6 mo - 12 mo		12 mo - 2 years		2 - 3 years		3 - 6 years		6 - 9 years	
	n	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p
Systolic BP	424	-0.32 (-1.19, 0.54)	0.5	-0.21 (-1.08, 0.66)	0.6	0.16 (-0.67, 1.00)	0.7	0.73 (-0.10, 1.55)	0.08	**1.08 (0.23, 1.93)**	**0.01**	0.78 (-0.08, 1.64)	0.08	**1.32 (0.47, 2.16)**	**0.002**	0.71 (-0.11, 1.54)	0.09	1.07 (0.20, 1.94)	0.02	**1.57 (0.70, 2.43)**	**<0.001**
Diastolic BP	424	-0.15 (-0.87, 0.57)	0.7	-0.29 (-1.02, 0.44)	0.4	-0.73 (-1.43, -0.03)	0.04	0.17 (-0.52, 0.85)	0.6	0.24 (-0.47, 0.95)	0.5	0.01 (-0.72, 0.73)	1.0	0.51 (-0.19, 1.21)	0.2	0.33 (-0.36, 1.02)	0.3	0.44 (-0.29, 1.17)	0.2	0.35 (-0.38, 1.07)	0.3
Carotid IMT	432	0.006 (0.000, 0.012)	0.07	0.001 (-0.005, 0.007)	0.8	-0.003 (-0.009, 0.003)	0.3	-0.002 (-0.008, 0.004)	0.5	0.004 (-0.003, 0.010)	0.3	0.003 (-0.003, 0.010)	0.3	0.003 (-0.003, 0.009)	0.3	-0.007 (-0.013, -0.001)	0.03	0.004 (-0.003, 0.010)	0.2	0.001 (-0.005, 0.008)	0.7
Carotid-femoral PWV	378	0.00 (-0.06, 0.06)	0.9	0.01 (-0.05, 0.06)	0.8	0.07 (0.01, 0.13)	0.02	0.02 (-0.04, 0.07)	0.6	**0.09 (0.03, 0.15)**	**0.002**	0.01 (-0.04, 0.07)	0.7	0.03 (-0.03, 0.08)	0.4	0.03 (-0.03, 0.08)	0.4	0.05 (-0.01, 0.11)	0.1	**0.09 (0.04, 0.15)**	**0.001**
FMD (%)	361	-0.12 (-0.51, 0.26)	0.5	0.17 (-0.22, 0.57)	0.4	-0.08 (-0.47, 0.30)	0.7	0.11 (-0.28, 0.50)	0.6	-0.03 (-0.41, 0.36)	0.9	-0.12 (-0.51, 0.27)	0.5	-0.34 (-0.71, 0.03)	0.07	-0.17 (-0.55, 0.21)	0.4	0.14 (-0.27, 0.55)	0.5	0.23 (-0.16, 0.61)	0.3
Reactive hyperaemia (%)	358	11 (-16, 37)	0.4	-8 (-34, 19)	0.6	-9 (-35, 18)	0.5	7 (-19, 33)	0.6	-3 (-29, 23)	0.8	4 (-22, 30)	0.8	-13 (-38, 12)	0.3	4 (-22, 29)	0.8	4 (-24, 32)	0.8	-18 (-45, 9)	0.2

Adjusted for maternal education, prepregnant smoking and BMI and child sex and age at vascular assessment

Table S2a. Associations between AC growth from 19 weeks gestation to 8-9 years of age, and vascular CVD risk factors at age 8-9 (using size at 19 weeks' gestation as starting point and growth through eight time windows).

			19 weeks			19 weeks - 34 weeks			34 weeks - birth			Birth - 6 mo			6 mo - 12 mo			12 mo - 2 years			2 - 3 years			3 - 6 years			6 - 9 years	
			B (95% CI)	p		B (95% CI)	p		B (95% CI)	p		B (95% CI)	p		B (95% CI)	p		B (95% CI)	p		B (95% CI)	p		B (95% CI)	p		B (95% CI)	p
Systolic BP	559		-0.04 (-0.75, 0.66)	0.9		0.43 (-0.27, 1.14)	0.2		0.27 (-0.43, 0.97)	0.4		**1.04 (0.32, 1.76)**	**0.005**		0.37 (-0.35, 1.08)	0.3		**1.16 (0.46, 1.85)**	**0.001**		0.80 (0.10, 1.50)	0.03		**2.27 (1.56, 2.98)**	**<0.001**		**1.70 (0.98, 2.41)**	**<0.001**
Diastolic BP	559		0.05 (-0.54, 0.65)	0.9		-0.09 (-0.68, 0.50)	0.8		-0.73 (-1.32, -0.14)	0.01		0.38 (-0.23, 0.99)	0.2		0.20 (-0.40, 0.79)	0.5		0.07 (-0.51, 0.65)	0.8		0.05 (-0.54, 0.64)	0.9		0.72 (0.12, 1.32)	0.02		0.51 (-0.09, 1.11)	0.09
Carotid IMT	568		**0.009 (0.004, 0.015)**	**0.001**		0.000 (-0.006, 0.005)	0.9		0.002 (-0.004, 0.007)	0.5		0.007 (0.001, 0.012)	0.02		0.003 (-0.003, 0.008)	0.4		0.000 (-0.005, 0.005)	1.0		0.000 (-0.006, 0.005)	0.9		0.002 (-0.004, 0.007)	0.5		-0.001 (-0.007, 0.004)	0.6
Carotid-femoral PWV	480		0.04 (-0.01, 0.09)	0.1		0.02 (-0.03, 0.07)	0.5		0.01 (-0.04, 0.07)	0.6		0.03 (-0.03, 0.08)	0.3		-0.02 (-0.08, 0.03)	0.4		0.03 (-0.02, 0.08)	0.3		-0.04 (-0.10, 0.01)	0.1		**0.07 (0.01, 0.12)**	**0.01**		0.06 (0.01, 0.11)	0.03
FMD (%)	465		0.03 (-0.32, 0.38)	0.9		0.02 (-0.32, 0.37)	0.9		0.20 (-0.16, 0.55)	0.3		-0.11 (-0.46, 0.23)	0.5		0.05 (-0.29, 0.40)	0.8		0.07 (-0.27, 0.41)	0.7		-0.14 (-0.48, 0.21)	0.4		0.02 (-0.33, 0.37)	0.9		0.19 (-0.15, 0.53)	0.3
Reactive hyperemia (%)	460		2 (-20, 24)	0.8		16 (-7, 38)	0.2		-11 (-34, 11)	0.3		-1 (-23, 20)	0.9		-8 (-31, 14)	0.5		8 (-13, 30)	0.4		-8 (-30, 15)	0.5		5 (-18, 27)	0.7		**-27 (-49, -5)**	**0.01**

Adjusted for maternal education, prepregnant smoking and BMI and child sex and age at vascular assessment

Table S2b. Associations between AC growth from 11 weeks gestation to 8-9 years of age, and vascular CVD risk factors at age 8-9 (using size at 11 weeks' gestation as starting point and growth through nine time windows).

		11 weeks		11 weeks-19 weeks		19 weeks - 34 weeks		34 weeks - birth		Birth - 6 mo		6 mo - 12 mo		12 mo - 2 years		2 - 3 years		3 - 6 years		6 - 9 years	
	n	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p
Systolic BP	282	-0.08 (-1.19, 1.03)	0.9	0.21 (-0.81, 1.23)	0.7	0.16 (-0.87, 1.20)	0.8	0.83 (-0.21, 1.87)	0.1	0.63 (-0.42, 1.68)	0.2	1.02 (-0.04, 2.07)	0.06	0.56 (-0.46, 1.57)	0.3	0.27 (-0.75, 1.30)	0.6	**1.96 (0.88, 3.04)**	**<0.001**	**1.42 (0.38, 2.46)**	**0.008**
Diastolic BP	282	-0.07 (-1.01, 0.87)	0.9	0.07 (-0.79, 0.93)	0.9	0.14 (-0.74, 1.02)	0.8	-0.72 (-1.60, 0.16)	0.1	0.32 (-0.56, 1.21)	0.5	0.57 (-0.32, 1.46)	0.2	-0.27 (-1.12, 0.59)	0.5	-0.15 (-1.02, 0.71)	0.7	1.08 (0.17, 1.99)	0.02	0.46 (-0.41, 1.34)	0.3
Carotid IMT	288	0.007 (-0.001, 0.015)	0.09	**0.009 (0.002, 0.017)**	**0.01**	-0.005 (-0.012, 0.003)	0.2	0.003 (-0.005, 0.010)	0.5	0.003 (-0.005, 0.010)	0.5	0.004 (-0.003, 0.012)	0.2	0.000 (-0.007, 0.007)	1.0	-0.003 (-0.010, 0.005)	0.5	0.001 (-0.006, 0.009)	0.7	-0.003 (-0.010, 0.005)	0.5
Carotid-femoral PWV	250	0.03 (-0.04, 0.10)	0.5	0.06 (-0.02, 0.13)	0.1	-0.02 (-0.10, 0.06)	0.6	0.04 (-0.04, 0.11)	0.3	0.02 (-0.05, 0.09)	0.6	-0.03 (-0.10, 0.05)	0.5	-0.01 (-0.09, 0.06)	0.8	-0.08 (-0.16, 0.00)	0.05	0.05 (-0.03, 0.13)	0.2	0.05 (-0.03, 0.12)	0.2
FMD (%)	243	0.12 (-0.33, 0.57)	0.6	-0.03 (-0.50, 0.44)	0.9	0.07 (-0.40, 0.54)	0.8	-0.18 (-0.66, 0.30)	0.5	-0.29 (-0.76, 0.19)	0.2	0.00 (-0.47, 0.47)	1.0	-0.09 (-0.54, 0.36)	0.7	0.14 (-0.34, 0.62)	0.6	0.33 (-0.17, 0.83)	0.2	0.35 (-0.11, 0.82)	0.1
Reactive hyperemia (%)	241	15 (-14, 44)	0.3	-22 (-53, 9)	0.2	28 (-3, 59)	0.07	-4 (-36, 28)	0.8	1 (-30, 32)	0.9	-4 (-35, 28)	0.8	9 (-21, 39)	0.6	-28 (-60, 4)	0.08	27 (-7, 60)	0.1	-21 (-51, 9)	0.2

Adjusted for maternal education, prepregnant smoking and BMI and child sex and age at vascular assessment

Table S3.

Fetal and child growth patterns of children with low (lowest quarter) or high (highest quarter) levels of systolic and diastolic BP, cfPWV, cIMT, FMD and RH%, compared with “middle” values (the middle two quarters). Analyses were run in the total sample (n=724). Of these, 686 had linear size and 652 had AC measured at all time points. Regression models for different time points were therefore run on slightly different samples. However, we have rerun the analyses on consistent n’s, with almost identical results.

Table S3a. Fetal and child growth patterns in children with low (lowest quartile) or high (highest quartile) systolic BP, compared with “normal” systolic BP (the middle two quartiles).

	Mean difference in linear z-score				Mean difference in AC z-score			
	Lowest Q (95% CI)	p	Highest Q (95% CI)	p	Lowest Q (95% CI)	p	Highest Q (95% CI)	p
19 GW	0.01 (-0.15, 0.17)	0.9	-0.07 (-0.24, 0.10)	0.4	0.02 (-0.15, 0.18)	0.9	0.08 (-0.11, 0.26)	0.4
34 GW	0.01 (-0.17, 0.20)	0.9	0.02 (-0.18, 0.23)	0.8	0.01 (-0.17, 0.20)	0.9	0.14 (-0.07, 0.34)	0.2
Birth	-0.06 (-0.24, 0.12)	0.5	0.15 (-0.05, 0.35)	0.1	-0.04 (-0.21, 0.14)	0.7	0.10 (-0.09, 0.30)	0.3
6 months	-0.24 (-0.44, -0.04)	0.02	0.07 (-0.14, 0.29)	0.5	-0.10 (-0.28, 0.09)	0.3	0.12 (-0.08, 0.33)	0.2
12 months	-0.22 (-0.41, -0.04)	0.02	0.17 (-0.03, 0.37)	0.1	-0.14 (-0.32, 0.05)	0.1	0.14 (-0.06, 0.34)	0.2
2 years	-0.29 (-0.48, -0.10)	**0.003**	0.30 (0.10, 0.51)	**0.004**	-0.20 (-0.38, -0.01)	0.04	0.28 (0.08, 0.49)	**0.006**
3 years	-0.29 (-0.48, -0.10)	**0.003**	0.33 (0.12, 0.54)	**0.002**	-0.21 (-0.39, -0.03)	0.02	0.30 (0.10, 0.50)	**0.003**
6 years	-0.36 (-0.55, -0.16)	**<0.001**	0.38 (0.17, 0.59)	**<0.001**	-0.34 (-0.52, -0.17)	**<0.001**	0.45 (0.26, 0.64)	**<0.001**
9 years	-0.38 (-0.56, -0.19)	**<0.001**	0.38 (0.18, 0.58)	**<0.001**	-0.39 (-0.58, -0.20)	**<0.001**	0.57 (0.37, 0.78)	**<0.001**

Table S3b. Fetal and child growth patterns in children with low (lowest quartile) or high (highest quartile) diastolic BP, compared with "normal" diastolic BP (the middle two quartiles).

	Mean difference in linear z-score				Mean difference in AC z-score			
	Lowest Q (95% CI)	p	Highest Q (95% CI)	p	Lowest Q (95% CI)	p	Highest Q (95% CI)	p
19 GW	0.03 (-0.12, 0.19)	0.7	-0.02 (-0.19, 0.14)	0.8	0.04 (-0.12, 0.21)	0.6	0.21 (0.03, 0.38)	0.02
34 GW	-0.06 (-0.25, 0.13)	0.5	-0.08 (-0.27, 0.12)	0.4	0.06 (-0.13, 0.24)	0.6	0.10 (-0.10, 0.29)	0.3
Birth	0.04 (-0.15, 0.22)	0.7	0.04 (-0.15, 0.23)	0.7	0.10 (-0.08, 0.27)	0.3	-0.02 (-0.21, 0.17)	0.8
6 months	0.03 (-0.17, 0.23)	0.8	0.08 (-0.13, 0.29)	0.4	-0.14 (-0.32, 0.05)	0.2	-0.08 (-0.27, 0.12)	0.4
12 months	0.13 (-0.06, 0.32)	0.2	0.15 (-0.04, 0.35)	0.1	-0.08 (-0.27, 0.11)	0.4	-0.03 (-0.23, 0.16)	0.7
2 years	0.05 (-0.15, 0.24)	0.6	0.16 (-0.04, 0.36)	0.1	0.03 (-0.16, 0.22)	0.7	0.15 (-0.04, 0.35)	0.1
3 years	0.02 (-0.18, 0.21)	1.0	0.15 (-0.05, 0.35)	0.1	-0.05 (-0.24, 0.13)	0.6	0.08 (-0.12, 0.27)	0.4
6 years	0.01 (-0.19, 0.20)	0.9	0.19 (-0.02, 0.40)	0.07	-0.01 (-0.19, 0.18)	1.0	0.21 (0.01, 0.40)	0.04
9 years	-0.03 (-0.23, 0.16)	0.7	0.20 (0.00, 0.40)	0.06	-0.06 (-0.26, 0.13)	0.5	0.25 (0.05, 0.46)	0.02

Table S3c. Fetal and child growth patterns in children with low (lowest quartile) or high (highest quartile) cIMT, compared with "normal" cIMT (the middle two quartiles).

	Mean difference in linear z-score				Mean difference in AC z-score			
	Lowest Q (95% CI)	p	Highest Q (95% CI)	p	Lowest Q (95% CI)	p	Highest Q (95% CI)	p
19 GW	-0.12 (-0.28, 0.04)	0.1	0.08 (-0.09, 0.25)	0.4	-0.21 (-0.38, -0.04)	0.02	0.13 (-0.05, 0.31)	0.2
34 GW	-0.11 (-0.29, 0.08)	0.3	0.02 (-0.18, 0.22)	0.9	-0.13 (-0.32, 0.06)	0.2	0.10 (-0.10, 0.30)	0.3
Birth	-0.11 (-0.30, 0.07)	0.2	-0.03 (-0.22, 0.16)	0.8	-0.13 (-0.30, 0.05)	0.2	0.08 (-0.11, 0.27)	0.4
6 months	-0.17 (-0.37, 0.03)	0.09	-0.05 (-0.26, 0.16)	0.7	-0.21 (-0.40, -0.02)	0.03	0.16 (-0.04, 0.36)	0.1
12 months	-0.11 (-0.30, 0.08)	0.3	0.04 (-0.16, 0.25)	0.7	-0.17 (-0.36, 0.01)	0.06	0.15 (-0.04, 0.35)	0.1
2 years	-0.07 (-0.26, 0.12)	0.5	0.07 (-0.13, 0.28)	0.5	-0.20 (-0.39, -0.02)	0.03	0.20 (0.00, 0.40)	0.05
3 years	-0.08 (-0.28, 0.12)	0.4	0.02 (-0.19, 0.22)	0.9	-0.18 (-0.36, 0.00)	0.06	0.14 (-0.05, 0.34)	0.2
6 years	-0.09 (-0.29, 0.11)	0.4	0.08 (-0.13, 0.29)	0.5	-0.12 (-0.30, 0.07)	0.2	0.22 (0.02, 0.41)	0.03
9 years	-0.03 (-0.22, 0.17)	0.8	0.12 (-0.08, 0.33)	0.2	-0.03 (-0.23, 0.17)	0.8	0.16 (-0.05, 0.37)	0.1

Table S3d. Fetal and child growth patterns in children with low (lowest quartile) or high (highest quartile) cfPWV, compared with "normal" cfPWV (the middle two quartiles).

		Mean difference in linear z-score						Mean difference in AC z-score				
		Lowest Q (95% CI)	p		Highest Q (95% CI)	p		Lowest Q (95% CI)	p		Highest Q (95% CI)	p
19 GW		0.08 (-0.09, 0.26)	0.4		0.08 (-0.10, 0.26)	0.4		-0.01 (-0.20, 0.17)	0.9		0.05 (-0.14, 0.25)	0.6
34 GW		-0.03 (-0.24, 0.18)	0.8		0.20 (-0.01, 0.42)	0.06		-0.04 (-0.24, 0.17)	0.7		0.02 (-0.19, 0.23)	0.8
Birth		-0.08 (-0.28, 0.12)	0.4		0.01 (-0.20, 0.22)	0.9		-0.01 (-0.21, 0.19)	0.9		-0.02 (-0.22, 0.18)	0.8
6 months		-0.21 (-0.44, 0.01)	0.06		0.15 (-0.08, 0.38)	0.2		-0.08 (-0.30, 0.13)	0.4		0.06 (-0.16, 0.27)	0.6
12 months		-0.17 (-0.37, 0.04)	0.1		0.23 (0.02, 0.45)	0.03		-0.03 (-0.24, 0.17)	0.7		0.01 (-0.20, 0.22)	0.9
2 years		-0.30 (-0.51, -0.09)	**0.005**		0.19 (-0.03, 0.40)	0.09		-0.07 (-0.28, 0.14)	0.5		0.08 (-0.14, 0.29)	0.5
3 years		-0.28 (-0.49, -0.06)	**0.01**		0.22 (0.01, 0.44)	0.04		-0.03 (-0.23, 0.18)	0.8		0.03 (-0.18, 0.24)	0.8
6 years		-0.32 (-0.53, -0.11)	**0.003**		0.26 (0.05, 0.48)	0.02		-0.15 (-0.35, 0.05)	0.1		0.17 (-0.03, 0.37)	0.09
9 years		-0.31 (-0.52, -0.11)	**0.003**		0.34 (0.13, 0.54)	**0.002**		-0.14 (-0.35, 0.07)	0.2		0.32 (0.10, 0.53)	**0.004**

Table S3e. Fetal and child growth patterns in children with low (lowest quartile) or high (highest quartile) FMD, compared with "normal" FMD (the middle two quartiles).

		Mean difference in linear z-score						Mean difference in AC z-score				
		Lowest Q (95% CI)	p		Highest Q (95% CI)	p		Lowest Q (95% CI)	p		Highest Q (95% CI)	p
19 GW		0.09 (-0.09, 0.26)	0.3		-0.02 (-0.20, 0.16)	0.8		0.08 (-0.11, 0.27)	0.4		0.05 (-0.14, 0.24)	0.6
34 GW		0.02 (-0.19, 0.22)	0.9		-0.03 (-0.24, 0.18)	0.8		-0.03 (-0.23, 0.18)	0.8		-0.13 (-0.33, 0.08)	0.2
Birth		-0.09 (-0.29, 0.10)	0.4		-0.11 (-0.31, 0.09)	0.3		-0.13 (-0.32, 0.06)	0.2		-0.01 (-0.20, 0.19)	1.0
6 months		-0.08 (-0.30, 0.14)	0.5		-0.05 (-0.27, 0.17)	0.6		0.01 (-0.20, 0.23)	0.9		-0.01 (-0.23, 0.20)	0.9
12 months		0.03 (-0.18, 0.24)	0.8		-0.08 (-0.29, 0.13)	0.5		-0.07 (-0.28, 0.14)	0.5		-0.06 (-0.28, 0.15)	0.6
2 years		0.02 (-0.19, 0.24)	0.8		-0.16 (-0.38, 0.06)	0.1		-0.14 (-0.35, 0.08)	0.2		-0.01 (-0.23, 0.20)	0.9
3 years		0.02 (-0.19, 0.24)	0.8		-0.17 (-0.39, 0.05)	0.1		-0.01 (-0.22, 0.19)	0.9		-0.08 (-0.28, 0.13)	0.5
6 years		0.02 (-0.20, 0.24)	0.8		-0.13 (-0.35, 0.09)	0.2		0.04 (-0.16, 0.24)	0.7		-0.02 (-0.22, 0.18)	0.8
9 years		-0.01 (-0.23, 0.20)	0.9		-0.12 (-0.34, 0.09)	0.3		0.10 (-0.12, 0.31)	0.4		0.16 (-0.06, 0.38)	0.2

Table S3f. Fetal and child growth patterns in children with low (lowest quartile) or high (highest quartile) reactive hyperaemia, compared with "normal" reactive hyperaemia (the middle two quartiles).

		Mean difference in linear z-score						Mean difference in AC z-score				
		Lowest Q (95% CI)	p		Highest Q (95% CI)	p		Lowest Q (95% CI)	p		Highest Q (95% CI)	p
19 GW		-0.01 (-0.19, 0.17)	0.9		0.14 (-0.05, 0.32)	0.1		0.01 (-0.18, 0.19)	0.9		0.14 (-0.05, 0.33)	0.1
34 GW		0.04 (-0.17, 0.24)	0.7		0.18 (-0.03, 0.40)	0.09		-0.01 (-0.21, 0.20)	0.9		0.25 (0.04, 0.45)	0.02
Birth		0.02 (-0.17, 0.22)	0.8		0.09 (-0.11, 0.29)	0.4		0.08 (-0.11, 0.27)	0.4		0.09 (-0.10, 0.28)	0.4
6 months		-0.07 (-0.29, 0.15)	0.5		-0.04 (-0.27, 0.18)	0.7		-0.05 (-0.27, 0.16)	0.6		0.07 (-0.15, 0.29)	0.5
12 months		-0.02 (-0.23, 0.20)	0.9		-0.09 (-0.30, 0.13)	0.4		-0.01 (-0.22, 0.21)	1.0		0.04 (-0.17, 0.26)	0.7
2 years		0.06 (-0.16, 0.28)	0.6		-0.05 (-0.27, 0.18)	0.7		-0.14 (-0.35, 0.08)	0.2		0.10 (-0.11, 0.32)	0.3
3 years		-0.01 (-0.23, 0.21)	0.9		-0.05 (-0.27, 0.18)	0.7		0.01 (-0.19, 0.21)	0.9		0.08 (-0.13, 0.29)	0.4
6 years		-0.01 (-0.23, 0.21)	0.9		-0.10 (-0.32, 0.13)	0.4		-0.05 (-0.25, 0.15)	0.6		0.01 (-0.19, 0.22)	0.9
9 years		-0.03 (-0.25, 0.18)	0.8		-0.14 (-0.36, 0.07)	0.2		0.05 (-0.17, 0.27)	0.6		-0.16 (-0.39, 0.06)	0.2

Table S4. Associations with child postnatal BMI

Table S4a Child BMI patterns between 6 months and 8-9 years of age in children with low (lowest quartile) or high (highest quartile) systolic BP, compared with “normal” systolic BP (the middle two quartiles).

		Mean difference in BMI z-score			Mean difference in BMI z-score	
		Lowest Q (95% CI)	p		Highest Q (95% CI)	p
6 months		0.00 (-0.18, 0.17)	1		0.27 (0.08, 0.46)	**0.006**
12 months		-0.04 (-0.22, 0.13)	0.6		0.20 (0.01, 0.40)	0.04
2 years		-0.14 (-0.32, 0.03)	0.1		0.25 (0.06, 0.44)	**0.01**
3 years		-0.18 (-0.35, -0.01)	0.04		0.27 (0.09, 0.45)	**0.004**
6 years		-0.30 (-0.46, -0.13)	**0.001**		0.42 (0.24, 0.61)	**<0.001**
9 years		-0.43 (-0.62, -0.24)	**<0.001**		0.56 (0.35, 0.77)	**<0.001**

Table S4b Child BMI patterns between 6 months and 8-9 years of age in children with low (lowest quartile) or high (highest quartile) diastolic BP, compared with “normal” diastolic BP (the middle two quartiles).

		Mean difference in BMI z-score			Mean difference in BMI z-score	
		Lowest Q (95% CI)	p		Highest Q (95% CI)	p
6 months		-0.06 (-0.24, 0.11)	0.5		0.00 (-0.19, 0.19)	1
12 months		-0.11 (-0.29, 0.07)	0.2		0.02 (-0.17, 0.20)	0.9
2 years		-0.13 (-0.30, 0.05)	0.2		0.05 (-0.13, 0.23)	0.6
3 years		-0.13 (-0.30, 0.04)	0.1		0.13 (-0.04, 0.31)	0.1
6 years		-0.05 (-0.22, 0.13)	0.6		0.16 (-0.03, 0.34)	0.09
9 years		-0.11 (-0.30, 0.09)	0.3		0.22 (0.01, 0.43)	0.04

Table S4c Child BMI patterns between 6 months and 8-9 years of age in children with low (lowest quartile) or high (highest quartile) cIMT, compared with "normal" cIMT (the middle two quartiles).

		Mean difference in BMI z-score			Mean difference in BMI z-score	
		Lowest Q (95% CI)	p		Highest Q (95% CI)	p
6 months		-0.15 (-0.33, 0.03)	0.1		0.18 (0.00, 0.37)	0.06
12 months		-0.10 (-0.28, 0.08)	0.3		0.14 (-0.05, 0.33)	0.1
2 years		-0.16 (-0.34, 0.01)	0.07		0.05 (-0.14, 0.24)	0.6
3 years		-0.10 (-0.27, 0.07)	0.3		0.11 (-0.07, 0.30)	0.2
6 years		-0.04 (-0.22, 0.13)	0.6		0.11 (-0.08, 0.29)	0.3
9 years		-0.01 (-0.21, 0.19)	0.9		0.12 (-0.09, 0.34)	0.3

Table S4d Child BMI patterns between 6 months and 8-9 years of age in children with low (lowest quartile) or high (highest quartile) cfPWV, compared with "normal" cfPWV (the middle two quartiles).

		Mean difference in BMI z-score			Mean difference in BMI z-score	
		Lowest Q (95% CI)	p		Highest Q (95% CI)	p
6 months		0.04 (-0.16, 0.24)	0.7		0.04 (-0.16, 0.24)	0.7
12 months		0.10 (-0.09, 0.30)	0.3		-0.04 (-0.24, 0.17)	0.7
2 years		0.16 (-0.03, 0.35)	0.1		0.05 (-0.15, 0.25)	0.6
3 years		0.09 (-0.10, 0.28)	0.4		-0.11 (-0.30, 0.09)	0.3
6 years		0.05 (-0.14, 0.24)	0.6		0.08 (-0.11, 0.27)	0.4
9 years		0.01 (-0.21, 0.22)	1		0.15 (-0.07, 0.37)	0.2

Table S4e Child BMI patterns between 6 months and 8-9 years of age in children with low (lowest quartile) or high (highest quartile) FMD, compared with "normal" FMD (the middle two quartiles).

		Mean difference in BMI z-score			Mean difference in BMI z-score	
		Lowest Q (95% CI)	p		Highest Q (95% CI)	p
6 months		-0.07 (-0.27, 0.13)	0.5		-0.06 (-0.26, 0.14)	0.6
12 months		-0.01 (-0.21, 0.19)	0.9		0.12 (-0.08, 0.32)	0.2
2 years		-0.06 (-0.26, 0.13)	0.5		0.02 (-0.18, 0.22)	0.8
3 years		-0.10 (-0.29, 0.08)	0.3		0.02 (-0.17, 0.21)	0.8
6 years		0.00 (-0.19, 0.19)	1		0.06 (-0.13, 0.25)	0.5
9 years		0.02 (-0.20, 0.24)	0.9		0.15 (-0.07, 0.38)	0.2

Table S4f Child BMI patterns between 6 months and 8-9 years of age in children with low (lowest quartile) reactive hyperaemia or high (highest quartile) , compared with "normal" reactive hyperaemia (the middle two quartiles).

		Mean difference in BMI z-score			Mean difference in BMI z-score	
		Lowest Q (95% CI)	p		Highest Q (95% CI)	p
6 months		0.07 (-0.13, 0.27)	0.5		0.10 (-0.10, 0.30)	0.3
12 months		0.03 (-0.17, 0.22)	0.8		0.12 (-0.08, 0.32)	0.2
2 years		-0.05 (-0.25, 0.14)	0.6		0.07 (-0.13, 0.27)	0.5
3 years		0.04 (-0.14, 0.23)	0.6		0.08 (-0.11, 0.27)	0.4
6 years		0.02 (-0.17, 0.21)	0.8		0.04 (-0.15, 0.24)	0.7
9 years		0.06 (-0.17, 0.28)	0.6		-0.12 (-0.35, 0.11)	0.3

Analyses, (as in tables S1, S2, S3) stratified by sex

Table S5a. Associations between linear growth from 19 weeks gestation to 9 years of age, and vascular CVD risk factors at age 9, **in boys** (using size at 19 GW as starting point and growth through eight time windows).

			19 weeks			19 weeks - 34 weeks			34 weeks - birth			Birth - 6 mo			6 mo - 12 mo			12 mo - 2 years			2 - 3 years			3 - 6 years			6 - 9 years	
	n		B (95% CI)	p		B (95% CI)	p		B (95% CI)	p		B (95% CI)	p		B (95% CI)	p		B (95% CI)	p		B (95% CI)	p		B (95% CI)	p		B (95% CI)	p
Systolic BP	293		-0.67 (-1.68, 0.34)	0.2		-0.04 (-1.02, 0.95)	0.9		0.84 (-0.12, 1.80)	0.09		1.03 (-0.05, 2.11)	0.06		1.10 (0.03, 2.17)	0.04		**2.05 (1.13, 2.98)**	**<0.001**		0.52 (-0.38, 1.42)	0.3		1.08 (0.11, 2.05)	0.03		1.09 (0.09, 2.08)	0.03
Diastolic BP	293		-0.13 (-0.97, 0.71)	0.8		-0.36 (-1.18, 0.46)	0.4		-0.47 (-1.27, 0.33)	0.3		-0.28 (-1.18, 0.62)	0.5		-0.22 (-1.11, 0.67)	0.6		0.30 (-0.47, 1.06)	0.4		-0.18 (-0.92, 0.57)	0.6		0.45 (-0.36, 1.25)	0.3		0.29 (-0.54, 1.12)	0.5
Carotid IMT	300		0.008 (-0.001, 0.016)	0.07		-0.004 (-0.013, 0.004)	0.3		0.001 (-0.008, 0.009)	0.9		0.002 (-0.007, 0.011)	0.6		-0.005 (-0.014, 0.004)	0.3		0.003 (-0.004, 0.011)	0.4		**-0.011 (-0.018, -0.003)**	**0.006**		0.001 (-0.007, 0.009)	0.8		-0.004 (-0.012, 0.004)	0.3
Carotid-femoral PWV	250		-0.03 (-0.10, 0.05)	0.5		0.04 (-0.04, 0.11)	0.3		0.04 (-0.04, 0.11)	0.3		0.08 (0.00, 0.16)	0.04		0.00 (-0.07, 0.07)	1		0.02 (-0.05, 0.09)	0.6		0.00 (-0.07, 0.06)	0.9		0.05 (-0.03, 0.12)	0.2		**0.16 (0.08, 0.23)**	**<0.001**
FMD (%)	245		-0.15 (-0.62, 0.32)	0.5		0.02 (-0.43, 0.48)	0.9		0.21 (-0.25, 0.66)	0.4		0.46 (-0.03, 0.94)	0.06		-0.13 (-0.62, 0.35)	0.6		-0.13 (-0.54, 0.29)	0.5		-0.17 (-0.58, 0.25)	0.4		-0.20 (-0.65, 0.24)	0.4		-0.05 (-0.55, 0.44)	0.8
Reactive hyperemia (%)	239		6 (-26, 37)	0.7		-9 (-40, 22)	0.6		-1 (-32, 29)	0.9		20 (-12, 51)	0.2		-20 (-53, 11)	0.2		9 (-18, 36)	0.5		4 (-24, 33)	0.8		-12 (-42, 18)	0.4		-17 (-51, 16)	0.3

Adjusted for maternal education, prepregnant smoking and BMI and child age at vascular assessment

Table S5b. Associations between linear growth from 19 weeks gestation to 9 years of age, and vascular CVD risk factors at age 9 **in girls** (using size at 19 GW as starting point and growth through eight time windows).

		19 weeks		19 weeks - 34 weeks		34 weeks - birth		Birth - 6 mo		6 mo - 12 mo		12 mo - 2 years		2 - 3 years		3 - 6 years		6 - 9 years	
	n	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p
Systolic BP	294	-0.43 (-1.46, 0.61)	0.4	0.41 (-0.60, 1.42)	0.4	0.57 (-0.45, 1.59)	0.3	0.79 (-0.15, 1.74)	0.1	0.81 (-0.17, 1.79)	0.1	1.23 (0.16, 2.30)	0.02	1.20 (0.12, 2.29)	0.03	1.29 (0.21, 2.38)	0.02	**1.47 (0.41, 2.52)**	**0.006**
Diastolic BP	294	-0.47 (-1.36, 0.42)	0.3	-0.63 (-1.50, 0.24)	0.2	0.44 (-0.43, 1.32)	0.3	0.40 (-0.41, 1.21)	0.3	0.14 (-0.70, 0.98)	0.7	0.89 (-0.03, 1.81)	0.06	**1.26 (0.33, 2.19)**	**0.008**	0.89 (-0.04, 1.82)	0.06	0.30 (-0.60, 1.20)	0.5
Carotid IMT	299	0.002 (-0.006, 0.009)	0.6	0.000 (-0.007, 0.008)	0.9	-0.003 (-0.010, 0.005)	0.4	0.003 (-0.003, 0.010)	0.3	0.002 (-0.005, 0.009)	0.5	0.000 (-0.008, 0.007)	0.9	0.000 (-0.008, 0.008)	0.9	0.006 (-0.002, 0.014)	0.1	0.004 (-0.004, 0.012)	0.3
Carotid-femoral PWV	252	0.01 (-0.06, 0.08)	0.7	0.08 (0.01, 0.15)	0.03	0.01 (-0.06, 0.08)	0.8	0.06 (0.00, 0.13)	0.05	0.07 (0.00, 0.14)	0.04	0.06 (-0.01, 0.13)	0.1	0.06 (-0.02, 0.13)	0.1	0.05 (-0.02, 0.12)	0.2	0.06 (-0.02, 0.13)	0.1
FMD (%)	249	-0.04 (-0.51, 0.44)	0.9	-0.18 (-0.66, 0.31)	0.5	-0.25 (-0.74, 0.24)	0.3	-0.32 (-0.79, 0.14)	0.2	-0.29 (-0.77, 0.19)	0.2	-0.29 (-0.79, 0.21)	0.3	-0.27 (-0.79, 0.24)	0.3	-0.02 (-0.54, 0.51)	1	0.17 (-0.31, 0.65)	0.5
Reactive hyperemia (%)	246	2 (-31, 36)	0.9	11 (-23, 46)	0.5	1 (-33, 35)	0.9	-16 (-49, 16)	0.3	0 (-33, 34)	1	-31 (-65, 4)	0.08	12 (-24, 47)	0.5	-19 (-56, 19)	0.3	-20 (-54, 13)	0.2

Adjusted for maternal education, prepregnant smoking and BMI and child age at vascular assessment

Table S5c. Associations between AC growth from 19 weeks gestation to 8-9 years of age, and vascular CVD risk factors at age 8-9 **in boys** (using size at 19 weeks' gestation as starting point and growth through eight time windows).

		19 weeks		19 weeks - 34 weeks		34 weeks - birth		Birth - 6 mo		6 mo - 12 mo		12 mo - 2 years		2 - 3 years		3 - 6 years		6 - 9 years	
		B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p
Systolic BP	263	-0.35 (-1.30, 0.59)	0.5	0.26 (-0.73, 1.24)	0.6	0.07 (-0.93, 1.08)	0.9	0.34 (-0.72, 1.41)	0.5	-0.16 (-1.12, 0.80)	0.7	**1.76 (0.84, 2.69)**	**<0.001**	**1.44 (0.53, 2.35)**	**0.002**	**2.14 (1.19, 3.08)**	**<0.001**	**1.73 (0.75, 2.71)**	**0.001**
Diastolic BP	263	-0.01 (-0.80, 0.79)	1	-0.28 (-1.11, 0.56)	0.5	-0.67 (-1.52, 0.18)	0.1	0.05 (-0.85, 0.95)	0.9	-0.13 (-0.94, 0.68)	0.8	0.24 (-0.55, 1.02)	0.6	0.13 (-0.64, 0.90)	0.7	0.56 (-0.24, 1.36)	0.2	0.66 (-0.17, 1.50)	0.1
Carotid IMT	269	0.008 (0.000, 0.016)	0.04	0.005 (-0.003, 0.013)	0.2	0.004 (-0.004, 0.012)	0.3	0.009 (0.000, 0.017)	0.04	0.006 (-0.002, 0.013)	0.1	-0.003 (-0.010, 0.005)	0.5	-0.001 (-0.008, 0.007)	0.8	-0.002 (-0.010, 0.005)	0.5	0.001 (-0.007, 0.009)	0.8
Carotid-femoral PWV	228	0.02 (-0.05, 0.09)	0.6	0.03 (-0.05, 0.11)	0.5	0.02 (-0.06, 0.10)	0.7	0.06 (-0.02, 0.14)	0.1	-0.04 (-0.11, 0.03)	0.3	0.01 (-0.06, 0.09)	0.8	-0.05 (-0.12, 0.03)	0.2	0.08 (0.00, 0.15)	0.04	0.08 (0.00, 0.16)	0.05
FMD (%)	219	0.24 (-0.24, 0.71)	0.3	0.06 (-0.43, 0.56)	0.8	-0.01 (-0.56, 0.54)	1	0.30 (-0.21, 0.80)	0.3	-0.24 (-0.72, 0.25)	0.3	0.45 (-0.02, 0.91)	0.06	0.02 (-0.44, 0.48)	0.9	-0.37 (-0.88, 0.14)	0.2	0.27 (-0.21, 0.75)	0.3
Reactive hyperemia (%)	218	-16 (-45, 14)	0.3	13 (-17, 43)	0.4	-30 (-63, 3)	0.08	8 (-22, 37)	0.6	-20 (-49, 9)	0.2	15 (-13, 43)	0.3	12 (-17, 41)	0.4	1 (-30, 33)	0.9	-33 (-61, -4)	0.03

Adjusted for maternal education, prepregnant smoking and BMI and child age at vascular assessment

Table S5d. Associations between AC growth from 19 weeks gestation to 8-9 years of age, and vascular CVD risk factors at age 8-9 **in girls** (using size at 19 weeks' gestation as starting point and growth through eight time windows).

		19 weeks		19 weeks - 34 weeks		34 weeks - birth		Birth - 6 mo		6 mo - 12 mo		12 mo - 2 years		2 - 3 years		3 - 6 years		6 - 9 years	
		B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p
Systolic BP	296	0.37 (-0.70, 1.44)	0.5	0.40 (-0.62, 1.43)	0.4	0.27 (-0.73, 1.27)	0.6	**1.53 (0.52, 2.53)**	**0.003**	0.83 (-0.24, 1.90)	0.1	0.49 (-0.57, 1.55)	0.4	0.25 (-0.86, 1.37)	0.7	**2.11 (1.00, 3.22)**	**<0.001**	**1.68 (0.62, 2.75)**	**0.002**
Diastolic BP	296	0.11 (-0.80, 1.02)	0.8	-0.01 (-0.88, 0.86)	1	-0.92 (-1.77, -0.07)	0.03	0.63 (-0.22, 1.49)	0.1	0.49 (-0.42, 1.40)	0.3	-0.09 (-0.98, 0.81)	0.9	0.00 (-0.94, 0.95)	1	0.84 (-0.10, 1.79)	0.08	0.30 (-0.60, 1.20)	0.5
Carotid IMT	299	**0.010 (0.002, 0.017)**	**0.01**	-0.005 (-0.013, 0.002)	0.2	0.000 (-0.007, 0.007)	1	0.006 (-0.002, 0.013)	0.1	-0.001 (-0.009, 0.007)	0.8	0.003 (-0.005, 0.011)	0.5	0.000 (-0.008, 0.008)	1	0.009 (0.001, 0.017)	0.03	-0.005 (-0.012, 0.003)	0.2
Carotid-femoral PWV	252	0.07 (-0.01, 0.14)	0.09	0.02 (-0.06, 0.09)	0.6	0.01 (-0.06, 0.09)	0.8	0.00 (-0.07, 0.07)	0.9	0.00 (-0.09, 0.08)	0.9	0.05 (-0.03, 0.12)	0.2	-0.05 (-0.13, 0.04)	0.3	0.06 (-0.01, 0.14)	0.1	0.05 (-0.02, 0.12)	0.2
FMD (%)	246	-0.32 (-0.83, 0.18)	0.2	-0.15 (-0.63, 0.34)	0.5	0.32 (-0.16, 0.79)	0.2	-0.47 (-0.95, 0.01)	0.05	0.29 (-0.20, 0.79)	0.2	-0.20 (-0.69, 0.29)	0.4	-0.29 (-0.82, 0.25)	0.3	0.41 (-0.08, 0.89)	0.1	0.13 (-0.36, 0.62)	0.6
Reactive hyperemia (%)	242	17 (-17, 51)	0.3	17 (-16, 50)	0.3	1 (-31, 33)	1	-12 (-44, 20)	0.5	5 (-30, 39)	0.8	1 (-32, 35)	0.9	-27 (-63, 10)	0.2	2 (-32, 35)	0.9	-14 (-47, 19)	0.4

Adjusted for maternal education, prepregnant smoking and BMI and child age at vascular assessment

Table S6a. Fetal and child growth patterns in **boys** with low (lowest quartile) or high (highest quartile) systolic BP, compared with "normal" systolic BP (the middle two quartiles).

		Mean difference in linear z-score						Mean difference in AC z-score				
		Lowest Q (95% CI)	p		Highest Q (95% CI)	p		Lowest Q (95% CI)	p		Highest Q (95% CI)	p
19 GW		0.02 (-0.20, 0.24)	0.8		-0.03 (-0.27, 0.21)	0.8		0.15 (-0.10, 0.39)	0.2		0.08 (-0.19, 0.36)	0.5
34 GW		0.08 (-0.18, 0.34)	0.5		0.03 (-0.25, 0.31)	0.8		0.11 (-0.16, 0.38)	0.4		0.17 (-0.13, 0.47)	0.3
Birth		0.00 (-0.26, 0.26)	1		0.19 (-0.09, 0.47)	0.2		0.22 (-0.02, 0.47)	0.07		0.27 (0.00, 0.54)	0.05
6 months		-0.21 (-0.48, 0.05)	0.1		0.00 (-0.29, 0.29)	1		0.08 (-0.17, 0.34)	0.5		0.09 (-0.19, 0.37)	0.5
12 months		-0.21 (-0.45, 0.04)	0.1		0.09 (-0.18, 0.35)	0.5		0.00 (-0.26, 0.26)	1		0.16 (-0.12, 0.45)	0.3
2 years		-0.25 (-0.51, 0.00)	0.05		0.36 (0.08, 0.65)	**0.01**		-0.19 (-0.45, 0.07)	0.2		0.39 (0.10, 0.68)	**0.009**
3 years		-0.24 (-0.50, 0.01)	0.06		0.35 (0.07, 0.63)	0.02		-0.17 (-0.44, 0.10)	0.2		0.53 (0.23, 0.82)	**0.001**
6 years		-0.33 (-0.61, -0.05)	0.02		0.42 (0.11, 0.72)	**0.007**		-0.26 (-0.51, 0.00)	0.05		0.76 (0.48, 1.04)	**<0.001**
9 years		-0.31 (-0.58, -0.05)	0.02		0.50 (0.21, 0.78)	**0.001**		-0.36 (-0.62, -0.10)	**0.006**		0.87 (0.59, 1.15)	**<0.001**

Table S6b. Fetal and child growth patterns in **girls** with low (lowest quartile) or high (highest quartile) systolic BP, compared with "normal" systolic BP (the middle two quartiles).

		Mean difference in linear z-score						Mean difference in AC z-score				
		Lowest Q (95% CI)	p		Highest Q (95% CI)	p		Lowest Q (95% CI)	p		Highest Q (95% CI)	p
19 GW		0.05 (-0.18, 0.28)	0.7		-0.08 (-0.32, 0.16)	0.5		-0.01 (-0.24, 0.21)	0.9		0.13 (-0.10, 0.37)	0.3
34 GW		-0.04 (-0.30, 0.23)	0.8		0.10 (-0.18, 0.38)	0.5		-0.04 (-0.30, 0.21)	0.7		0.20 (-0.06, 0.47)	0.1
Birth		-0.16 (-0.42, 0.09)	0.2		0.03 (-0.24, 0.29)	0.8		-0.29 (-0.54, -0.04)	0.02		-0.01 (-0.28, 0.25)	0.9
6 months		-0.33 (-0.62, -0.04)	0.03		0.01 (-0.29, 0.31)	1		-0.42 (-0.69, -0.15)	**0.002**		0.07 (-0.21, 0.35)	0.6
12 months		-0.16 (-0.45, 0.12)	0.3		0.26 (-0.03, 0.56)	0.08		-0.34 (-0.59, -0.08)	**0.009**		0.21 (-0.05, 0.48)	0.1
2 years		-0.30 (-0.58, -0.02)	0.04		0.20 (-0.09, 0.49)	0.2		-0.34 (-0.59, -0.09)	**0.009**		0.14 (-0.13, 0.41)	0.3
3 years		-0.32 (-0.61, -0.04)	0.03		0.25 (-0.05, 0.54)	0.1		-0.22 (-0.46, 0.03)	0.08		0.18 (-0.08, 0.43)	0.2
6 years		-0.37 (-0.64, -0.10)	**0.008**		0.31 (0.02, 0.59)	0.03		-0.37 (-0.60, -0.13)	**0.003**		0.32 (0.07, 0.56)	**0.01**
9 years		-0.40 (-0.67, -0.13)	**0.004**		0.31 (0.04, 0.59)	0.03		-0.35 (-0.61, -0.08)	**0.01**		0.49 (0.21, 0.76)	**0.001**

Table S6c. Fetal and child growth patterns in **boys** with low (lowest quartile) or high (highest quartile) cIMT, compared with "normal" cIMT (the middle two quartiles).

		Mean difference in linear z-score						Mean difference in AC z-score				
		Lowest Q (95% CI)	p		Highest Q (95% CI)	p		Lowest Q (95% CI)	p		Highest Q (95% CI)	p
19 GW		-0.11 (-0.33, 0.11)	0.3		0.10 (-0.14, 0.34)	0.4		-0.27 (-0.52, -0.03)	**0.03**		0.02 (-0.24, 0.29)	0.9
34 GW		0.02 (-0.23, 0.28)	0.9		0.05 (-0.23, 0.33)	0.7		-0.15 (-0.42, 0.12)	0.3		0.16 (-0.13, 0.46)	0.3
Birth		-0.12 (-0.38, 0.14)	0.4		-0.04 (-0.32, 0.24)	0.8		-0.14 (-0.38, 0.11)	0.3		0.10 (-0.17, 0.37)	0.5
6 months		-0.18 (-0.44, 0.09)	0.2		-0.09 (-0.38, 0.19)	0.5		-0.23 (-0.48, 0.02)	0.07		0.24 (-0.04, 0.51)	0.09
12 months		-0.15 (-0.40, 0.10)	0.2		-0.09 (-0.36, 0.18)	0.5		-0.12 (-0.38, 0.13)	0.3		0.43 (0.15, 0.71)	**0.003**
2 years		-0.15 (-0.41, 0.12)	0.3		0.01 (-0.27, 0.30)	0.9		-0.14 (-0.41, 0.13)	0.3		0.36 (0.06, 0.66)	**0.02**
3 years		-0.12 (-0.39, 0.14)	0.4		-0.01 (-0.30, 0.28)	0.9		-0.13 (-0.41, 0.14)	0.3		0.27 (-0.03, 0.58)	0.08
6 years		-0.03 (-0.32, 0.25)	0.8		0.09 (-0.22, 0.40)	0.6		0.07 (-0.20, 0.34)	0.6		0.36 (0.06, 0.65)	**0.02**
9 years		0.04 (-0.24, 0.31)	0.8		0.12 (-0.17, 0.42)	0.4		0.05 (-0.23, 0.34)	0.7		0.26 (-0.05, 0.57)	0.1

Table S6d. Fetal and child growth patterns in **girls** with low (lowest quartile) or high (highest quartile) cIMT, compared with "normal" cIMT (the middle two quartiles).

		Mean difference in linear z-score						Mean difference in AC z-score				
		Lowest Q (95% CI)	p		Highest Q (95% CI)	p		Lowest Q (95% CI)	p		Highest Q (95% CI)	p
19 GW		-0.07 (-0.30, 0.15)	0.5		0.08 (-0.17, 0.32)	0.5		-0.15 (-0.37, 0.08)	0.2		0.22 (-0.02, 0.47)	0.07
34 GW		-0.14 (-0.40, 0.12)	0.3		0.02 (-0.27, 0.30)	0.9		-0.08 (-0.33, 0.16)	0.5		0.05 (-0.22, 0.32)	0.7
Birth		-0.10 (-0.35, 0.14)	0.4		-0.01 (-0.29, 0.26)	0.9		-0.11 (-0.36, 0.13)	0.4		0.07 (-0.20, 0.34)	0.6
6 months		-0.14 (-0.42, 0.14)	0.3		0.00 (-0.31, 0.31)	1		-0.25 (-0.51, 0.02)	0.07		0.06 (-0.23, 0.35)	0.7
12 months		-0.10 (-0.37, 0.18)	0.5		0.16 (-0.14, 0.47)	0.3		-0.31 (-0.56, -0.07)	**0.01**		-0.15 (-0.42, 0.12)	0.3
2 years		-0.04 (-0.31, 0.23)	0.8		0.12 (-0.18, 0.42)	0.4		-0.30 (-0.55, -0.06)	0.02		0.02 (-0.25, 0.30)	0.9
3 years		-0.09 (-0.37, 0.18)	0.5		0.03 (-0.28, 0.33)	0.9		-0.21 (-0.45, 0.02)	0.08		0.03 (-0.23, 0.29)	0.8
6 years		-0.15 (-0.42, 0.12)	0.3		0.07 (-0.23, 0.37)	0.6		-0.28 (-0.52, -0.05)	0.02		0.08 (-0.18, 0.34)	0.5
9 years		-0.12 (-0.38, 0.15)	0.4		0.12 (-0.17, 0.41)	0.4		-0.12 (-0.38, 0.15)	0.4		0.07 (-0.22, 0.36)	0.6

Table S6e. Fetal and child growth patterns in **boys** with low (lowest quartile) or high (highest quartile) cfPWV, compared with “normal” cfPWV (the middle two quartiles).

		Mean difference in linear z-score						Mean difference in AC z-score				
		Lowest Q (95% CI)	p		Highest Q (95% CI)	p		Lowest Q (95% CI)	p		Highest Q (95% CI)	p
19 GW		0.12 (-0.13, 0.37)	0.3		0.08 (-0.17, 0.34)	0.5		-0.01 (-0.29, 0.28)	1		0.04 (-0.26, 0.33)	0.8
34 GW		-0.07 (-0.37, 0.24)	0.7		0.08 (-0.23, 0.39)	0.6		0.02 (-0.29, 0.33)	0.9		0.10 (-0.22, 0.41)	0.5
Birth		0.03 (-0.26, 0.32)	0.8		0.12 (-0.18, 0.42)	0.4		0.01 (-0.28, 0.29)	1		0.05 (-0.24, 0.35)	0.7
6 months		-0.15 (-0.46, 0.15)	0.3		0.07 (-0.24, 0.39)	0.6		0.08 (-0.22, 0.38)	0.6		0.22 (-0.09, 0.53)	0.2
12 months		-0.07 (-0.37, 0.22)	0.6		0.04 (-0.26, 0.34)	0.8		0.10 (-0.20, 0.39)	0.5		0.09 (-0.21, 0.39)	0.6
2 years		-0.22 (-0.51, 0.07)	0.1		-0.09 (-0.38, 0.21)	0.6		-0.03 (-0.33, 0.28)	0.9		-0.02 (-0.34, 0.29)	0.9
3 years		-0.22 (-0.51, 0.07)	0.1		-0.13 (-0.42, 0.17)	0.4		0.06 (-0.25, 0.37)	0.7		-0.03 (-0.35, 0.28)	0.8
6 years		-0.26 (-0.57, 0.05)	0.1		-0.10 (-0.42, 0.21)	0.5		-0.15 (-0.45, 0.15)	0.3		-0.07 (-0.38, 0.23)	0.6
9 years		-0.27 (-0.56, 0.02)	0.07		0.04 (-0.26, 0.34)	0.8		-0.01 (-0.32, 0.30)	0.9		0.34 (0.02, 0.65)	**0.04**

Table S6f. Fetal and child growth patterns in **girls** with low (lowest quartile) or high (highest quartile) cfPWV, compared with “normal” cfPWV (the middle two quartiles).

		Mean difference in linear z-score						Mean difference in AC z-score				
		Lowest Q (95% CI)	p		Highest Q (95% CI)	p		Lowest Q (95% CI)	p		Highest Q (95% CI)	p
19 GW		0.09 (-0.17, 0.34)	0.5		0.13 (-0.13, 0.38)	0.3		-0.01 (-0.26, 0.24)	0.9		0.17 (-0.09, 0.42)	0.2
34 GW		0.00 (-0.30, 0.30)	1		0.29 (-0.01, 0.59)	0.06		-0.20 (-0.48, 0.08)	0.2		-0.08 (-0.36, 0.19)	0.5
Birth		-0.11 (-0.39, 0.18)	0.5		0.04 (-0.24, 0.33)	0.8		-0.01 (-0.28, 0.26)	0.9		0.00 (-0.27, 0.28)	1
6 months		-0.23 (-0.57, 0.10)	0.2		0.20 (-0.13, 0.54)	0.2		-0.19 (-0.50, 0.13)	0.2		0.01 (-0.31, 0.32)	1
12 months		-0.23 (-0.53, 0.08)	0.1		0.47 (0.17, 0.77)	**0.003**		-0.10 (-0.39, 0.19)	0.5		0.04 (-0.24, 0.33)	0.8
2 years		-0.29 (-0.59, 0.01)	0.06		0.47 (0.17, 0.77)	**0.002**		-0.16 (-0.45, 0.14)	0.3		0.17 (-0.13, 0.47)	0.3
3 years		-0.26 (-0.57, 0.04)	0.09		0.58 (0.28, 0.89)	**<0.001**		-0.09 (-0.37, 0.18)	0.5		0.09 (-0.19, 0.36)	0.5
6 years		-0.27 (-0.56, 0.02)	0.07		0.62 (0.33, 0.92)	**<0.001**		-0.17 (-0.43, 0.09)	0.2		0.32 (0.06, 0.58)	**0.02**
9 years		-0.26 (-0.55, 0.03)	0.08		0.61 (0.32, 0.90)	**<0.001**		-0.20 (-0.50, 0.09)	0.2		0.33 (0.04, 0.63)	**0.03**