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ASSOCIATIONS OF BLOOD PRESSURE CHANGE IN PREGNANCY WITH FETAL GROWTH AND GESTATIONAL AGE AT DELIVERY: FINDINGS FROM A PROSPECTIVE COHORT

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Abstract

Hypertensive disorders of pregnancy are associated with intrauterine growth restriction and preterm birth. However, the associations of patterns of blood pressure change during pregnancy with these outcomes have not been studied in detail. We studied repeat antenatal blood pressure measurements of 9,697 women in the Avon Longitudinal Study of Parents and Children (median (interquartile range) 10 (9, 11) measurements per woman). Bivariate linear spline models were used to relate blood pressure changes to perinatal outcomes.

Higher systolic, but not diastolic, blood pressure at baseline (8 weeks gestation) and a greater increase in systolic and diastolic blood pressure between 18 and 36 weeks gestation were associated with lower offspring birthweight and being smaller for gestational age in confounder-adjusted models. For example, the mean difference (95% CI) in birthweight per 1 mmHg/week greater increase in systolic blood pressure between 18-30 weeks was −71g (−134, −14) and between 30-36 weeks was −175g (−208, −145). A smaller decrease in systolic and diastolic blood pressure prior to 18 weeks and a greater increase between 18 and 36 weeks was associated with a shorter gestation (percentage difference in gestational duration per 1 mmHg/week greater increase in systolic blood pressure between 18-30 weeks: −0.60% (−1.01, −0.18) and 30-36 weeks: −1.01% (−1.36, −0.74)). Associations remained strong when restricting to normotensive women. We conclude that greater increases in blood pressure, from the 18-week nadir, are related to reduced fetal growth and shorter gestation even in women whose blood pressure does not cross the threshold for hypertensive disorders of pregnancy.

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Keywords

ALSPAC; Birthweight; Blood pressure; Gestational age; Pregnancy

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Introduction

The hypertensive disorders of pregnancy (HDP), gestational hypertension and preeclampsia, are major causes of intrauterine growth restriction and preterm birth.[1-6]. HDP are defined using thresholds of blood pressure after 20 weeks gestation,[7] yet pregnancy is a period of substantial change in blood pressure, with blood pressure decreasing until approximately 18-20 weeks and then increasing until delivery. [8-10] It has been shown that women who develop HDP have a greater early-pregnancy blood pressure on average and a greater increase in blood pressure in late pregnancy than women who have normotensive pregnancies.[9, 11] However, it is not currently known whether it is the initial blood pressure level, or the rate of change in blood pressure during pregnancy which is most strongly associated with adverse perinatal outcomes. One large study (N=8,623) showed that a greater second to third trimester change in blood pressure was associated with a smaller infant at birth and increased risk of preterm birth[2] but this was not adjusted for early-pregnancy blood pressure or earlier changes in blood pressure so it is unclear whether it is independent of these.

Of further interest is whether patterns of blood pressure change are associated with adverse perinatal outcomes in women who do not develop HDP. Offspring birthweight has been shown to decrease with increasing maximum blood pressure level in pregnancy,[12] suggesting a continuum of risk. Also, we previously found that risk factors for preeclampsia are associated with the rate of increase in blood pressure in late pregnancy, as well as the early pregnancy level, in women who have normal pregnancies.[13] These findings suggest that blood pressure change may be associated with risk of adverse outcomes across the whole of its distribution.

The aim of our study was to identify whether early pregnancy blood pressure and changes in blood pressure across gestation are associated with size and gestational age at birth in a large prospective cohort, and whether these associations exist across the whole distribution of blood pressure in pregnancy, or are restricted to those who develop HDP.

Methods

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a prospective birth cohort study investigating the determinants of childhood health and development. The study has been described in full elsewhere[14] and the study website contains details of available data at http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary. Women with expected delivery dates between 1st April 1991 and 31st December 1992 living in a defined area of Avon during pregnancy were eligible for recruitment. Ethical approval for the study was obtained from the ALSPAC Law and Ethics Committee and from the National Health Service (NHS) local ethics committee. All participants gave informed consent. In total 14,541 women were enrolled, 13,678 had a singleton pregnancy resulting in a live birth and

13,461 of these women had data abstracted from obstetric records. We excluded multiple pregnancies since patterns of blood pressure change and fetal growth would be different in these pregnancies. There were 13,000 women who had at least one blood pressure measurement in pregnancy and hence were eligible for inclusion.

Obstetric measurements

All blood pressure measurements which were taken as part of routine antenatal care by midwives or obstetricians were abstracted from the women's obstetric records by six trained research midwives. There was no between-midwife variation in mean values of the data abstracted and error rates were consistently <1% in repeated data entry checks. These were single blood pressure measurements taken in the seated position using the appropriate cuff size, using Korotkoff phase V for diastolic blood pressure (DBP). The gestational age at the time of measurement was derived from the measurement date and the expected delivery date. Gestational age at the time of delivery was derived from the expected delivery date and the date of birth. For most women the expected delivery date was based on the date of their last menstrual period, while for a small proportion this estimate was updated following an ultrasound scan or appearance at birth. Routine dating scans for all pregnant women were not common at this time and we do not know for which women the expected delivery date was altered in light of a scan or clinical appearance of their infant.

Birth size

Birthweight was obtained from the birth notification. Size for gestational age was derived by internally standardising birthweight for gestational age by regressing birthweight on gestational age at delivery and extracting the residuals. Since deriving size for gestational age in this way may lead to associations which are biased towards the null or may even lead to a reversal of the true effect,[15] we compared findings using this conventional method, to those using the customised UK fetal growth reference developed by Gardosi et al.[16] This reference is standardised by maternal height, pre-pregnancy weight, ethnic origin, parity and offspring sex and based on a database of 96,830 births between 2009 and 2011 from the West Midlands (see supplemental web-material for more detail).

Hypertensive disorders of pregnancy

HDP was derived using all available blood pressure measurements according to International Society for the Study of Hypertension in Pregnancy (ISSHP) criteria.[7] Gestational hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg and/or DBP ≥ 90 mmHg on two occasions after 20 weeks gestation; preeclampsia was defined by the same blood pressure criteria, with the addition of proteinuria of 1+ or more on urine dipstick testing at the same time as the elevated blood pressure. Women who responded to a questionnaire administered during pregnancy that they had ever been diagnosed with hypertension outside of pregnancy were considered to have essential hypertension. This created four mutually exclusive categories of hypertension during pregnancy: normotensive, gestational hypertensive, preeclamptic and essential hypertensive.

Maternal and offspring covariates

Maternal age at delivery and offspring sex were abstracted from obstetric records. Maternal pre-pregnancy weight and height, parity, smoking status, highest educational qualification and ethnicity were obtained from questionnaires administered during pregnancy. Pre-pregnancy BMI was calculated as weight(kg)/ height(m)^2 and classed according to World Health Organisation definitions of underweight (<18.5kg/m^2), normal (18.5-24.9kg/m^2), overweight (25.0-29.9kg/m^2) and obese (≥30.0kg/m^2). Parity was classed as nulliparous or multiparous. Smoking status was categorised as: “never” for women who did not smoke regularly immediately prior to or during pregnancy; “pre-pregnancy/first trimester” for women who smoked immediately prior to pregnancy or in the first 3 months and then stopped; and “throughout” for women who continued to smoke after the first 3 months. Maternal ethnicity was categorised as white or non-white.

Statistical Analysis

Multilevel linear spline models for blood pressure change in pregnancy have been previously fitted in this cohort.[13] These have two levels: measurement occasion (level 1) within women (level 2). Separate models were used with SBP and DBP as outcomes respectively and both had gestational age as the exposure. The rate of change in blood pressure with gestational age was modelled as four linear slopes, with knot points (indicating where the changes in slope occur) positioned according to the best fit to the data, at 18, 30 and 36 weeks gestation.[13] Baseline was set at 8 weeks gestation since there were few women who had blood pressure measurements available prior to this. Thus, the models each had 5 random effects parameters: SBP (or DBP) at 8 weeks and rate of SBP (or DBP) change between 8 and 18 weeks, 18 and 30 weeks, 30 and 36 weeks and from 36 weeks onwards.

To relate blood pressure change to the perinatal outcomes, we extended the multilevel models for blood pressure change by including the perinatal outcome as an extra response variable at the woman-level (level 2) to form a bivariate model. Regression coefficients for the associations of blood pressure at baseline and rates of blood pressure change in each period of gestation with the perinatal outcomes were derived from the level 2 variance-covariance matrix of the random effects.[17] The bivariate models were fitted in MLwiN using runmlwin[18] from Stata and regression coefficients were derived using the reffadjust command.[19] In bivariate models relating blood pressure change to length of gestation we included only blood pressure measurements taken prior to 36 weeks gestation, since for the majority of women this was prior to delivery, and included only women who had a gestation of 44 weeks or less. Since gestational age at delivery was negatively skewed, we normalised this by taking the logarithm of the reversed and re-centred variable before including it in bivariate models. Regression coefficients for this outcome are presented as percentage differences. Further information is provided in supplemental web-material.

Three models of adjustment for potential confounders/mediators were used when calculating regression coefficients: in Model 1 adjustment was made for blood pressure at baseline and earlier changes in blood pressure; in Model 2 we additionally adjusted for potential confounding by maternal pre-pregnancy BMI, height, age, parity, smoking during

pregnancy, education and ethnicity and offspring sex and in Model 3 we additionally adjusted for HDP to test whether any associations found are accounted for entirely by HDP status or whether an association of blood pressure with outcome remained after accounting for these categories, thus suggesting that they do not capture the relationship between blood pressure and outcomes in full. To further test whether any associations were driven by HDP, or only present in women who developed HDP, we repeated analyses restricting to women who had no evidence of essential hypertension or HDP.

We also performed a sensitivity analysis in which we excluded women who had essential hypertension, to assess whether any associations were influenced by this group of women.

Results

The characteristics of all women who were eligible for inclusion in analysis and those who had complete data on all maternal and offspring variables are shown in Table S1. Women who were excluded from analysis due to incomplete data were more likely to have preeclampsia and less likely to have essential hypertension, more likely to deliver preterm, to be underweight, to be in the younger age categories, to smoke during pregnancy, to be in the lowest education category and to be of non-white ethnicity than those included. They were also shorter, had offspring with a lower average birthweight and size for gestational age and had a shorter average gestation. As shown in previous publications from this study,[9, 13] and consistent with the established pattern of blood pressure change in pregnancy shown in many publications,[8, 10] both SBP and DBP in this study declined from baseline (8 weeks) to a nadir, in this study at 18 weeks, before increasing to the end of pregnancy (Figure S1).

Association s of maternal blood pressure change with offspring birthweight

Table 1 shows the associations of SBP and DBP at baseline and changes in SBP and DBP in each period of gestation defined by the linear spline model with offspring birthweight. In unadjusted models (Model 1), SBP at 8 weeks gestation was not associated with birthweight while a higher DBP at 8 weeks was associated with a heavier infant at birth. After adjustment for potential confounders (Model 2), SBP at 8 weeks was negatively associated with offspring birthweight while DBP at 8 weeks was no longer associated with birthweight. On further adjustment for HDP (Model 3), neither SBP nor DBP at 8 weeks were associated with offspring birthweight. There was no evidence that SBP or DBP change between 8 and 18 weeks gestation was associated with offspring birthweight in any models. In all models, a greater increase in SBP or DBP between 18 and 30 weeks and between 30 and 36 weeks gestation was associated with a lower offspring birthweight. A greater increase in DBP, but not SBP, from 36 weeks onwards was also associated with a lower birthweight, although this association was slightly weaker in the confounder-adjusted model (Model 2). The associations of DBP change between 18 and 30 weeks and SBP and DBP change between 30 and 36 weeks with birthweight remained strong when restricting to women who remained normotensive throughout pregnancy, while other associations attenuated.

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Associations of maternal blood pressure change with offspring size for gestational age

The associations of blood pressure at baseline and changes in blood pressure in each period of pregnancy with offspring size for gestational age, derived using internal standardisation, are shown in Table 2. In the confounder-adjusted model (Model 2), SBP at 8 weeks was negatively associated with size for gestational age, but this association attenuated on adjustment for HDP (Model 3). DBP at 8 weeks was positively associated with size for gestational age in unadjusted models (Model 1), but was not associated with size for gestational age after adjustment for maternal confounders (Model 2) or after additional adjustment for HDP (Model 3). In all models, a smaller decrease in SBP prior to 18 weeks gestation was associated with a larger infant for gestational age; but DBP change prior to 18 weeks was not associated with size for gestational age. A greater increase in DBP between 18 and 30 weeks and in SBP and DBP between 30 and 36 weeks was associated with a smaller size for gestational age in all models. Neither SBP change nor DBP change after 36 weeks was associated with size for gestational age in any models. When we restricted to women who remained normotensive throughout pregnancy, there remained strong evidence that a smaller decrease in SBP up to 18 weeks gestation was associated with a larger size for gestational age infant and a greater increase in SBP and DBP between 30 and 36 weeks was associated with a smaller size for gestational age infant. All other associations attenuated to the null.

Table S2 shows the equivalent analysis, with the external customised reference used to calculate size for gestational age. Findings were broadly similar to those using the internal standardisation method of deriving size for gestational age.

Associations of maternal blood pressure change with length of gestation

The associations of blood pressure at baseline and changes in blood pressure up to 36 weeks with the length of gestation are shown in Table 3. Neither SBP nor DBP at 8 weeks were associated with the length of gestation in any of the models. In all models, there was some evidence that a smaller decrease in SBP and DBP prior to 18 weeks gestation was associated with a shorter gestational period, and strong evidence that a greater increase in SBP and DBP between 18 and 30 weeks and between 30 and 36 weeks was associated with a shorter gestation. When restricting to normotensive women, the negative associations of DBP change between 18 and 30 weeks (although attenuated) and of SBP and DBP change between 30 and 36 weeks with length of gestation remained (Table 3). Other associations attenuated to the null.

To provide an indication of the potential clinical relevance of these associations, Table S3 shows the mean absolute change in SBP and DBP in each period of pregnancy, the expected absolute SBP and DBP change for individuals 2 SD above the mean and the difference in each of the outcomes per 2 SD increase in blood pressure change in each period. The greatest differences in outcomes were seen for blood pressure change between 30 and 36 weeks gestation.

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In the sensitivity analysis in which we excluded women who had essential hypertension (Table S4) findings were not meaningfully changed from those presented here where all women were included.

Discussion

In this large cohort, with detailed measurements of blood pressure during pregnancy, we found that higher SBP in early pregnancy, a greater decrease in SBP prior to 18 weeks and greater increases in both SBP and DBP between 18 and 36 weeks gestation were associated with a smaller child at birth. We also showed that a smaller decrease in SBP and DBP in early pregnancy and greater increases in SBP and DBP in late pregnancy, but not the early-pregnancy level of blood pressure, were associated with a shorter gestation. Associations of blood pressure change in late pregnancy with size at birth and length of gestation were found to exist on a continuum spanning normotensive and hypertensive pregnancies, while the associations of the early-pregnancy blood pressure level with size at birth were largely explained by, or specific to, women who developed HDP.

The association between higher blood pressure in early pregnancy and both lower birthweight and a smaller size for gestational age was specific to SBP; it was not seen for DBP in early pregnancy. Steer et al, in an analysis of over 200,000 women, found that there was a complex relationship between the DBP level at booking, the net increase in DBP across pregnancy and the resulting offspring birthweight.[12] For example, women with DBP greater than 80 mmHg at the first antenatal visit who had little change in DBP across pregnancy had heavier offspring on average than women with lower initial DBP. However, women with DBP over 80 mmHg at the initial visit who then had a large increase in DBP had lighter offspring than women who had a lower initial DBP and the equivalent DBP increase. The authors of that study did not examine SBP.[12] The association which we found between early-pregnancy SBP and birthweight was only apparent when we included women with HDP, and may be explained by an underlying predisposition to high blood pressure revealed by the stress of pregnancy.[20]

The relationship we found between the rise in blood pressure between 18 and 36 weeks and a smaller child at birth and shorter gestation agrees with findings by Bakker et al in analysis of 8623 women in the Generation R cohort. They reported that a greater increase in DBP between trimester 2 (~20 weeks) and trimester 3 (~30 weeks) was associated with a lower birthweight and increased risk of small for gestational age and preterm birth.[2] Bakker et al were, however, unable to examine associations of blood pressure change after 30 weeks with perinatal outcomes, did not adjust for initial blood pressure or earlier changes and included women with HDP in all analyses. We have demonstrated that the association of late pregnancy blood pressure change with fetal growth and length of gestation is independent of the level of blood pressure in early pregnancy and exists in normotensive as well as hypertensive women. Interestingly, in our study a larger decrease in SBP in early pregnancy was associated with a smaller infant for gestational age, but the change in blood pressure between trimesters 1 and 2 in the study by Bakker et al was not associated with size at birth.[2]

It is normal for blood pressure to increase in late pregnancy, and thus it is expected that some women will experience a steeper rise in blood pressure than others simply due to normal variation in this pattern of change. However, the association we have observed between a steeper increase in blood pressure and reduced fetal growth suggests that, for some women at least, this steeper increase represents an underlying pathology. In preeclampsia, it is thought that fetal growth restriction results from poor remodelling of the spiral arteries and formation of the utero-placental blood supply during placentation, leading to reduced transfer of oxygen and nutrients to the developing fetus.[21] The hypoxic placenta in turn releases antiangiogenic factors into the maternal circulation which are hypothesised to invoke the maternal inflammatory response including endothelial dysfunction and increased blood pressure.[22] Thus, abnormal placentation may explain the relationship we have found between increases in maternal blood pressure and smaller birth size of the infant. If so, our findings would suggest that this abnormal placentation also occurs in some women who do not meet the criteria for diagnosis of HDP, but may have a sub-clinical form of preeclampsia.

Essential hypertension is a well-known risk factor for preeclampsia[23] and higher blood pressure within the normal range is also associated with preeclampsia risk.[24] Most studies,[1, 3, 25] but not all,[6] have also reported that essential hypertension is associated with lower offspring birthweight and we have found similarly that higher SBP in early-pregnancy is associated with smaller size at birth. It has been suggested that the maternal endothelium plays a role in the adaptation of the spiral arteries to the presence of the fetus,[26] meaning that endothelial function could be a link between maternal predisposition to high blood pressure and intrauterine growth restriction.

It is likely that blood pressure change is related to the length of gestation predominantly due to medically indicated preterm delivery resulting from the development of HDP. However, the associations we found of blood pressure change between 30 and 36 weeks with length of gestation in normotensive pregnancies, suggests that change in blood pressure in this period may be associated with the timing of spontaneous labour. It was reported in a multi-national study of over 8000 women that a greater increase in blood pressure across gestation was associated with a greater risk of spontaneous preterm birth.[27]

An increase in blood pressure across the whole of pregnancy of 30 mmHg SBP or 15 mmHg DBP has been included in previous definitions of preeclampsia,[7] but this criterion was removed as it was not associated with adverse pregnancy outcome in women whose blood pressure did not cross the 140/90 threshold.[28] However, this definition of change did not take into account the nadir in blood pressure or focus on any specific gestational period. We found that blood pressure change between 30 and 36 weeks gestation had the strongest association with fetal growth and gestational duration. For example (see Table S3), a woman whose DBP increased from 66 mmHg (the average at 30 weeks) to 78 mmHg during this period would be expected to have a 320g lighter baby, despite having blood pressure well below the threshold for HDP at 36 weeks. There is a continuum of increased neonatal mortality with decreasing birthweight,[29,30] but defining a clinical threshold for blood pressure change given this continuous nature would be complex. Further studies assessing the frequency of a range of adverse maternal and offspring outcomes at different rates of

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blood pressure change, particularly between 30 and 36 weeks, are required in order to inform this. Thereafter if appropriate a similar consensus process as used for the recent selection of a diagnostic glucose threshold for gestational diabetes mellitus could be adopted for defining blood pressure change.[31]

The strengths of our study were its large size and the high number of blood pressure measurements available per woman, meaning that we were able to derive associations of change in blood pressure in several different periods of gestation with perinatal outcomes. We also used two definitions of size for gestational age; one based on internal standardisation of birthweight and another based on an external fetal growth reference and generally obtained similar findings using each of these approaches. A limitation of the study was that the blood pressure measurements were collected during routine antenatal appointments and therefore have inherent inter-observer variability and variability due to the different times of measurement. This would only be expected to introduce random rather than systematic error, but this may mean that associations reported here may be slightly underestimated compared to the true associations.[32] The high level of measurement error also meant that we were unable to examine associations with binary outcomes, such as small for gestational age and preterm birth, as the bivariate models would not converge. We were unable to distinguish between medically indicated and spontaneous deliveries in our analyses, however, restricting to normotensive pregnancies is likely to exclude deliveries which were indicated for reasons related to hypertension in pregnancy. Although there were differences between those included in analysis and those excluded due to incomplete data (Table S1), these differences were small and we can think of no reason to expect the associations to be different in the excluded group from what we observed here.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Perspectives

We found that greater increases in maternal blood pressure from the 18-weeks nadir onwards were associated with reduced fetal growth and a shorter gestational period, even in women who were defined as having normotensive pregnancies. These findings suggest that there is a continuum of risk across the whole distribution of blood pressure change during pregnancy and that the rate of change in blood pressure may be as important in assessing risk as whether or not the threshold for HDP is crossed.

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Novelty and Significance

1) What is new?

- Women who have a higher blood pressure in early pregnancy (8 weeks gestation) and a greater increase in blood pressure in the second half of pregnancy (18 to 36 weeks gestation) have babies who are lighter and smaller for their gestational age on average.
- Women who have a greater increase in blood pressure in the second half of pregnancy have a shorter gestation on average.

2) What is relevant?

- A greater increase in blood pressure in late pregnancy is associated with a smaller infant at birth and a shorter gestational period even in women who do not develop a hypertensive disorder of pregnancy.

Summary

The pattern of change in blood pressure during pregnancy was associated with the size of the offspring at birth and the length of gestation independently of the initial blood pressure level. Our findings suggest that changes in blood pressure may be important indicators of the risk of adverse perinatal outcomes in both normotensive and hypertensive pregnancies.

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Table 1

Mean differences in birthweight associated with a mmHg increase in blood pressure at 8 weeks and a mmHg/week increase in blood pressure change in each period of gestation*

Blood pressure variable†	Birth weight (g)			
	All women (N=9697)		Normotensive women‡(N=7766)	
	Mean difference	95% CI	Mean difference	95% CI
SBP at 8 weeks (mmHg)				
Model 1	1.63	(−0.54, 3.83)	2.65	(−0.09, 5.47)
Model 2	−2.80	(−5.23, −0.44)	−1.34	(−4.30, 1.55)
Model 3	−1.44	(−4.12, 1.24)		
SBP change (mmHg/week)				
8-18 weeks				
Model 1	46.83	(−5.84, 101.23)	41.89	(−12.30, 97.35)
Model 2	30.92	(−22.72, 88.17)	29.55	(−25.43, 86.92)
Model 3	47.32	(−7.71, 104.91)		
18-30 weeks				
Model 1	−63.88	(−120.69, −10.56)	−1.13	(−66.89, 63.16)
Model 2	−84.02	(−145.19, −29.14)	−12.08	(−82.17, 54.52)
Model 3	−71.26	(−133.59, −13.93)		
30-36 weeks				
Model 1	−143.92	(−173.16, −119.41)	−131.80	(−177.60, −95.17)
Model 2	−165.34	(−195.60, −139.50)	−158.52	(−206.75, −119.48)
Model 3	−174.51	(−207.96, −145.17)		
36+ weeks				
Model 1	−8.63	(−27.09, 11.89)	4.03	(−27.46, 41.19)
Model 2	0.62	(−19.49, 23.15)	11.67	(−22.30, 52.95)
Model 3	−3.43	(−26.97, 22.97)		
DBP at 8 weeks (mmHg)				
Model 1	5.38	(2.12, 8.60)	9.29	(5.10, 13.63)
Model 2	−0.57	(−4.42, 3.11)	3.51	(−1.17, 8.15)
Model 3	1.94	(−2.19, 6.24)		
DBP change (mmHg/week)				
8-18 weeks				
Model 1	15.88	(−79.94, 108.69)	47.85	(−54.05, 147.23)
Model 2	−60.25	(−164.17, 34.84)	−4.96	(−110.50, 95.13)
Model 3	−36.29	(−138.52, 60.25)		
18-30 weeks				
Model 1	−222.14	(−308.21, −146.42)	−122.23	(−218.45, −35.42)
Model 2	−274.41	(−361.07, −196.54)	−175.04	(−276.06, −83.85)
Model 3	−260.27	(−351.59, −178.27)		
30-36 weeks				
Model 1	−181.06	(−208.38, −156.02)	−167.45	(−217.30, −125.45)

Blood pressure variable†	Birth weight (g)			
	All women (N=9697)		Normotensive women‡(N=7766)	
	Mean difference	95% CI	Mean difference	95% CI
Model 2	−190.12	(−219.11, −164.94)	−176.09	(−227.96, −133.01)
Model 3	−204.78	(−235.47, −177.52)		
36+ weeks				
Model 1	−22.89	(−39.33, −5.96)	−25.25	(−56.04, 8.19)
Model 2	−12.17	(−28.66, 4.72)	−11.56	(−43.07, 22.03)
Model 3	−20.52	(−39.92, −0.70)		

*Model 1 is adjusted for SBP/DBP at 8 weeks and SBP/DBP change in earlier periods of gestation

Model 2 is additionally adjusted for maternal height, pre-pregnancy BMI, age, parity, smoking during pregnancy, highest educational qualification and ethnicity and offspring sex

Model 3 is additionally adjusted for maternal hypertensive disorders of pregnancy

†Mean (SD) SBP at 8 weeks: 112.8 (8.6) mmHg, SBP change 8-18 weeks: −0.15 (0.60), 18-30 weeks: 0.16 (0.45), 30-36 weeks: 0.28 (0.95), 36+ weeks: 1.06 (1.44) mmHg/week; DBP at 8 weeks: 66.5 (5.96) mmHg, DBP change 8-18 weeks: −0.20 (0.39), 18-30 weeks: 0.11 (0.32), 30-36 weeks: 0.47 (0.83), 36+ weeks: 1.20 (1.36) mmHg/week

‡Defined as women for whom there was no evidence of essential hypertension or HDP

Table 2

Mean differences in size for gestational age derived using internal standardisation associated with a mmHg increase in blood pressure at 8 weeks and a mmHg/week increase in blood pressure change in each period of gestation*

Blood pressure variable†	Size for gestational age (g)			
	All women (N=9697)		Normotensive women‡ (N=7766)	
	Mean difference	95% CI	Mean difference	95% CI
SBP at 8 weeks (mmHg)				
Model 1	1.78	(−0.08, 3.61)	1.80	(−0.64, 4.15)
Model 2	−2.15	(−4.25, −0.12)	−1.93	(−4.44, 0.66)
Model 3	−1.53	(−3.80, 0.76)		
SBP change (mmHg/week)				
8-18 weeks				
Model 1	69.96	(27.23, 117.32)	60.60	(15.28, 109.68)
Model 2	65.77	(20.63, 116.90)	58.13	(11.38, 109.29)
Model 3	75.47	(30.68, 127.60)		
18-30 weeks				
Model 1	−14.08	(−63.79, 33.41)	13.88	(−43.28, 70.38)
Model 2	−18.76	(−69.66, 29.87)	12.65	(−47.26, 71.10)
Model 3	−3.52	(−55.94, 46.83)		
30-36 weeks				
Model 1	−55.76	(−77.69, −35.22)	−50.97	(−85.08, −19.39)
Model 2	−63.41	(−87.02, −41.92)	−63.57	(−98.79, −31.02)
Model 3	−65.71	(−91.65, −41.83)		
36+ weeks				
Model 1	0.16	(−15.07, 16.47)	7.19	(−19.59, 36.64)
Model 2	10.22	(−6.24, 28.51)	16.78	(−11.43, 47.66)
Model 3	14.71	(−5.85, 36.57)		
DBP at 8 weeks (mmHg)				
Model 1	4.97	(2.31, 7.82)	7.16	(3.48, 11.06)
Model 2	−0.47	(−3.76, 2.73)	1.62	(−2.45, 5.73)
Model 3	0.78	(−2.70, 4.30)		
DBP change (mmHg/week)				
8-18 weeks				
Model 1	55.64	(−24.86, 137.24)	57.95	(−30.37, 143.72)
Model 2	−2.76	(−86.86, 80.48)	17.27	(−72.91, 109.13)
Model 3	10.00	(−73.56, 94.37)		
18-30 weeks				
Model 1	−88.68	(−158.72, −25.41)	−41.48	(−123.45, 38.26)
Model 2	−113.38	(−186.44, −47.45)	−71.94	(−155.31, 7.99)
Model 3	−99.86	(−174.49, −30.31)		
30-36 weeks				

Blood pressure variable†	Size for gestational age (g)			
	All women (N=9697)		Normotensive women‡ (N=7766)	
	Mean difference	95% CI	Mean difference	95% CI
Model 1	−65.48	(−87.06, −44.64)	−50.30	(−88.55, −13.98)
Model 2	−58.92	(−80.66, −37.48)	−42.07	(−80.51, −5.89)
Model 3	−62.32	(−86.46, −38.51)		
36+ weeks				
Model 1	−2.47	(−16.52, 11.41)	−5.22	(−31.78, 21.88)
Model 2	11.00	(−2.87, 24.99)	11.79	(−14.59, 39.63)
Model 3	13.53	(−2.77, 30.22)		

*Model 1 is adjusted for SBP/DBP at 8 weeks and SBP/DBP change in earlier periods of gestation

Model 2 is additionally adjusted for maternal height, pre-pregnancy BMI, age, parity, smoking during pregnancy, highest educational qualification and ethnicity and offspring sex

Model 3 is additionally adjusted for maternal hypertensive disorders of pregnancy

†Mean (SD) SBP at 8 weeks: 112.8 (8.6) mmHg, SBP change 8-18 weeks: −0.15 (0.60), 18-30 weeks: 0.16 (0.45), 30-36 weeks: 0.28 (0.95), 36+ weeks: 1.06 (1.44) mmHg/week; DBP at 8 weeks: 66.5 (5.96) mmHg, DBP change 8-18 weeks: −0.20 (0.39), 18-30 weeks: 0.11 (0.32), 30-36 weeks: 0.47 (0.83), 36+ weeks: 1.20 (1.36) mmHg/week

‡Defined as women for whom there was no evidence of essential hypertension or HDP

Table 3

Percentage differences in length of gestation associated with a mmHg increase in blood pressure at 8 weeks and a mmHg/week increase in blood pressure change in each period of gestation up to 36 weeks*

Blood pressure variable†	Length of gestation (weeks)			
	All women (N=9,654)		Normotensive women‡ (N=7,724)	
	% difference	95% CI	% difference	95% CI
SBP at 8 weeks (mmHg)				
Model 1	0.00	(−0.01, 0.02)	0.01	(−0.01, 0.03)
Model 2	−0.01	(−0.02, 0.01)	0.01	(−0.01, 0.03)
Model 3	0.00	(−0.02, 0.02)		
SBP change (mmHg/week)				
8-18 weeks				
Model 1	−0.26	(−0.61, 0.06)	−0.26	(−0.65, 0.10)
Model 2	−0.37	(−0.72, −0.03)	−0.35	(−0.76, 0.02)
Model 3	−0.31	(−0.68, 0.03)		
18-30 weeks				
Model 1	−0.46	(−0.84, −0.10)	−0.13	(−0.61, 0.32)
Model 2	−0.57	(−0.97, −0.20)	−0.23	(−0.71, 0.26)
Model 3	−0.60	(−1.01, −0.18)		
30-36 weeks				
Model 1	−0.88	(−1.15, −0.66)	−0.87	(−1.42, −0.49)
Model 2	−0.92	(−1.21, −0.69)	−0.92	(−1.52, −0.53)
Model 3	−1.01	(−1.36, −0.74)		
DBP at 8 weeks (mmHg)				
Model 1	0.01	(−0.01, 0.03)	0.03	(0.00, 0.06)
Model 2	0.00	(−0.02, 0.03)	0.02	(−0.01. 0.05)
Model 3	0.02	(−0.01, 0.04)		
DBP change (mmHg/week)				
8-18 weeks				
Model 1	−0.40	(−0.94, 0.09)	−0.14	(−0.75, 0.41)
Model 2	−0.55	(−1.12, −0.05)	−0.27	(−0.90, 0.30)
Model 3	−0.46	(−1.02, 0.06)		
18-30 weeks				
Model 1	−1.32	(−1.86, −0.83)	−0.84	(−1.45, −0.27)
Model 2	−1.47	(−2.02, −0.97)	−0.99	(−1.62, −0.39)
Model 3	−1.44	(−2.01, −0.91)		
30-36 weeks				
Model 1	−1.18	(−1.40, −0.98)	−1.27	(−1.69, −0.94)
Model 2	−1.22	(−1.46, −1.02)	−1.31	(−1.75, −0.97)
Model 3	−1.32	(−1.58, −1.10)		

* Model 1 is adjusted for SBP/DBP at 8 weeks and SBP/DBP change in earlier periods of gestation

Model 2 is additionally adjusted for maternal height, pre-pregnancy BMI, age, parity, smoking during pregnancy, highest educational qualification and ethnicity and offspring sex

Model 3 is additionally adjusted for maternal hypertensive disorders of pregnancy

†Mean (SD) SBP at 8 weeks: 112.8 (8.6) mmHg, SBP change 8-18 weeks: −0.15 (0.60), 18-30 weeks: 0.16 (0.45), 30-36 weeks: 0.28 (0.95) mmHg/week; DBP at 8 weeks: 66.5 (5.96) mmHg, DBP change 8-18 weeks: −0.20 (0.39), 18-30 weeks: 0.11 (0.32), 30-36 weeks: 0.47 (0.83) mmHg/week

‡Defined as women for whom there was no evidence of essential hypertension or HDP

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