ASSOCIATIONS OF BLOOD PRESSURE IN PREGNANCY WITH OFFSPRING BLOOD PRESSURE TRAJECTORIES DURING CHILDHOOD AND ADOLESCENCE: FINDINGS FROM A PROSPECTIVE STUDY

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Short title: Maternal and offspring blood pressure trajectories

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Abstract

Background: Hypertensive disorders of pregnancy (HDP) are related to higher offspring blood pressure (BP), but it is not known whether this association strengthens or weakens as BP changes across childhood. Our aim was to assess the associations of HDP and maternal BP changes during pregnancy with trajectories of offspring BP from age 7 to 18 years.

Methods and Results: In a large UK cohort of maternal-offspring pairs (N=6619), we used routine antenatal BP measurements to derive HDP and maternal BP trajectories. These were related to offspring BP trajectories, obtained from research clinic assessments, using linear spline random effects models. After adjusting for maternal and offspring variables, including body mass index, offspring of women who had either existing hypertension, gestational hypertension or preeclampsia during pregnancy had on average higher BP at age 7 years compared to offspring of normotensive pregnancies (mean difference (95%CI) in systolic BP: 1.67mmHg (0.48,2.86), 1.98mmHg (1.32,2.65) and 1.22mmHg (-0.52,2.97) respectively). These differences were consistent across childhood to age 18 years as the patterns of BP change did not differ between offspring of hypertensive pregnancies and normotensive pregnancies. Maternal BP at 8 weeks' gestation was also positively associated with offspring BP in childhood and adolescence, but changes in BP across pregnancy were not strongly associated.

Conclusion: The differences in BP between offspring of hypertensive pregnancies and offspring of normotensive pregnancies remain consistent across childhood and adolescence. These associations appear to be most contributed to by higher maternal BP in early-pregnancy rather than by pregnancy-related BP changes.

Keywords: ALSPAC; blood pressure; change; childhood; gestational hypertension; preeclampsia; pregnancy

Introduction

Hypertensive disorders of pregnancy (HDP) include pregnancy induced hypertension (i.e. gestational hypertension and preeclampsia) and also hypertension which exists prior to pregnancy (referred to as existing hypertension here). Pregnancy induced hypertension is defined as newly elevated blood pressure (BP) after 20 weeks of gestation, with preeclampsia being distinguished from gestational hypertension by the presence of proteinuria.[1] Preeclampsia is also characterised by systemic inflammation, insulin resistance and endothelial dysfunction.[2-5]

Preeclampsia and gestational hypertension have been shown to be associated with higher BP in offspring during childhood and adolescence.[6-15] However, it is not clear how this association compares with the association of existing hypertension with offspring BP.[16] Despite the different forms of HDP having different clinical manifestations, there is clear overlap between them, and increasing evidence that they may not be entirely distinct conditions, with higher BP (even within the normal range) prior to pregnancy predisposing to the development of preeclampsia.[17] In addition, existing hypertension has recently been shown to be strongly associated with the risk of a similar range of perinatal factors, including perinatal mortality, preterm delivery and low birthweight, to preeclampsia and gestational hypertension.[18,19] Comparing BP across offspring of pregnancies affected by existing hypertension, gestational hypertension, preeclampsia and offspring of normotensive pregnancies may provide information about the mechanisms influencing the associations and whether there are distinct or common pathways involved for each of the forms of HDP.[7]

BP increases with age during childhood and adolescence,[20-27] with some studies suggesting that BP decreases in females in late adolescence.[23-27] Previous studies that examined associations of HDP with offspring BP have all focused on a single measurement occasion, and no studies to our knowledge have assessed whether HDP is associated with age-related changes in BP across childhood and adolescence using repeated measurements of BP. This would provide information

about the development of cardiovascular risk, and whether the differences seen in BP during childhood between offspring of normotensive and hypertensive pregnancies become smaller as the child ages or strengthen into adulthood.

A further way of examining the reported association between maternal HDP and offspring BP is to assess the maternal trajectory of BP change during pregnancy. Despite HDP being defined by thresholds of BP, pregnancy is a period of considerable BP change and both the BP level in early pregnancy and the rate of increase in BP in late pregnancy is greater in hypertensive pregnancies.[28] Hence identifying whether the early-pregnancy BP level or the rate of increase in BP during late pregnancy is more strongly related to changes in BP in the offspring may suggest whether the associations between HDP and higher offspring BP are driven by a common underlying predisposition to high BP between mother and child or to factors directly related to the pregnancy.

Thus, the aim of this study was to investigate the associations of HDP (existing hypertension, gestational hypertension and preeclampsia) and of maternal BP changes during pregnancy with offspring BP trajectories from age 7 to 18 years.

Methods

Study Population

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a prospective population-based birth cohort study that recruited 14,541 pregnant women resident in Avon, United Kingdom with expected dates of delivery 1st April 1991 to 31st December 1992 and is fully described elsewhere.[29,30] The study website contains details of all the data that are available through a fully searchable data dictionary (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary). All children were invited to attend research clinics between the ages of 7 and 17 years. Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. In this study we considered the 9,014 mother-offspring pairs where there was a

singleton pregnancy resulting in a live birth and where the child had their BP measured at least once. The small number of mothers with existing diabetes (N=32) or gestational diabetes (N=45) were excluded. Mothers who did not have their BP measured during pregnancy were omitted from all analyses, and mothers who had fewer than two BP measurements after 20 weeks of pregnancy were omitted from the HDP analysis. After these exclusions, 8,443 and 8,617 mother-offspring pairs were available for the HDP and maternal BP analyses, respectively.

Maternal Pregnancy Data

All maternal SBP, DBP and urine dipstick proteinuria measurements taken in routine clinical practice were abstracted from obstetric medical records by six trained research midwives. The median number (lower quartile, upper quartile) of BP and urine measurements taken during pregnancy were 14 (11, 16) and 11 (10, 14) respectively. Women who reported having previously been diagnosed with high BP outside of pregnancy are referred to as having existing hypertension throughout the remainder of this paper. For women without existing hypertension, HDP was defined according to the International Society for the Study of Hypertension in Pregnancy criteria:[1] gestational hypertension was defined as either having SBP $\geq$140mmHg or DBP$\geq$90mmHg on at least two occasions after 20 weeks of gestation; preeclampsia was defined using the same criteria with proteinuria of at least 1+ on dipstick testing occurring at the same time as the elevated BP. Thus, all the women were categorised into one of four mutually exclusive categories: no evidence of hypertension, existing hypertension, gestational hypertension or preeclampsia.

Other Maternal or Parental Characteristics

Maternal age, parity, gestational age at delivery and mode of delivery were obtained from the obstetric records. At the time of recruitment, the women were asked to report their pre-pregnancy height and weight, which were used to calculate their pre-pregnancy body mass index (BMI). Parental occupation was classified into social class groups from I (professional/managerial) to V (unskilled manual workers) using the 1991 British Office of Population and Census Statistics

classification and the highest of both parents was defined as the head of household social class. Maternal smoking was categorised as never smoked, smoked before pregnancy or in the first trimester and then stopped, and smoked throughout pregnancy. The highest educational qualification of the mother was also obtained from a questionnaire administered during pregnancy.

Offspring Characteristics

The birthweight and gender of every child were abstracted from the obstetric medical records. Current ages of the children were recorded in months upon their arrival at each of the seven follow-up clinics (7-year, 9-year, 10-year, 11-year, 13-year, 15-year, and 17-year). At all of the clinics, SBP and DBP were measured twice with the child at rest using the appropriate cuff size for the upper arm circumference and the mean of each was recorded. These SBP and DBP means were used in all the subsequent analyses. BP was measured using a Dinamap 9301 Vital Signs Monitor at the 7, 9, 11, 15 and 17-year clinics, an Omron MI-5 at the 10-year clinic and a Dinamap 8100 Vital Signs Monitor at the 13-year clinic. Height and weight measurements of the children were also recorded at each follow-up clinic, and were used to calculate the child's BMI at each clinic.

Statistical Methods

The offspring BP measurements are clustered within the offspring, and hence multilevel models with two levels (follow-up clinic (level 1) within the offspring (level 2)) were used to account for the correlation between repeated BP measurements on the same offspring.[31] There were few observations before the age of 7 years and hence this point was used as the baseline. Linear spline random-effects models with knots at 12 and 16 years of age were used to describe the trajectories of SBP and DBP change with age. Fractional polynomial curves fitted to the repeated BP measurements of all 9,014 offspring with at least one BP were used to determine these approximated knot points. This yielded four child-level random-effects parameters, SBP/DBP at 7 years, SBP/DBP change from 7 to 12 years, SBP/DBP change from 12 to 16 years, and SBP/DBP change after 16 years.

A fixed effect indicating those offspring BP measurements made at the 10-year clinic was included as the measurements made at this clinic were not consistent with those made at the 9-year and 11-year clinics due to the different measuring device used. In addition, the offspring follow-up clinic level variance was allowed to be different before and after 10 years of age as this improved the model fit.

The maternal BP measurements are clustered within mothers, and thus multilevel models were also used to account for the correlation between repeated BP measures during pregnancy on the same mother. Linear splines with knots at 18, 30, and 36 weeks' gestation, chosen according to the best fit to the data, were used for maternal BP trajectories as in previous analyses,[32] and baseline was set at 8 weeks of gestation because there were few observations before this point.

Associations of Maternal HDP with Offspring BP Change

To investigate the association of HDP with offspring BP trajectories, multivariable linear spline models were fitted to the 6,619 individuals with complete data on all covariables. We initially fitted an unadjusted model, including only HDP category as the exposure (Model 1). This was included as a categorical main effect, and as an interaction with each of the splines, in order to examine its associations with offspring BP at age 7 years and with the rates of change in BP in each period of childhood and adolescence. Model 2 adjusts for the maternal characteristics (pre-pregnancy BMI, maternal age, education, parity and smoking during pregnancy), household social class, and offspring gender, by including these as main effects and interactions with each of the splines. Model 3 additionally accounts for offspring BMI and height at ages 7-17 from each of the clinics (adjusting for weight at ages 7-17 in place of BMI gave equivalent results), by including these as time-varying confounders. Although offspring height and BMI occur after the exposure of interest (HDP), we considered them to be part of the confounding pathway through their relationship and shared determinants with maternal BMI. Model 4 also controls for perinatal factors which could be potential mediators of associations if they were acting via intrauterine mechanisms (birthweight,

gestational age, and mode of delivery), by including these as main effects and interactions with each of the splines.

Bivariate Linear Spline Models of Maternal and Offspring BP Change

To evaluate the associations of maternal BP changes during pregnancy with offspring BP trajectories we fitted bivariate linear spline models to 6,619 mother-offspring pairs where there were complete data on all covariates. Bivariate linear spline random effects models were fitted separately including maternal SBP and offspring SBP as outcomes, and including maternal DBP and offspring DBP as outcomes. To prevent mothers with many BP measurements having too much influence on the models we randomly sampled one measurement for every 2-week period of gestation. Regression coefficients of the associations between maternal BP change and offspring BP change were obtained from the covariance matrix of random effects from the bivariate models using the reffadjust command in Stata.[33]

In this analysis, we assessed three models: a minimally-adjusted model (Model 1) where we only adjusted for maternal BP at baseline (8 weeks gestation) and maternal BP changes in any earlier periods of gestation; a confounder-adjusted model (Model 2) where we additionally adjusted for maternal characteristics, household social class and offspring gender, height and BMI; and a model which controls for potential intrauterine mediators (Model 3). A detailed description of covariate adjustment is given in the footnotes of relevant tables (Tables 5 and 6). As before, all confounders and mediators were included as main effects and interactions with each of the splines, except for offspring BMI and height, which were included as time-varying confounders in the offspring BP part of the model.

To examine whether any associations found were being completely driven by women who had HDP, we repeated the analysis restricting only to mother-offspring pairs where the mother had a normotensive pregnancy.

Sensitivity Analyses

We completed several sensitivity analyses. In the first we additionally included breastfeeding up to 6 months in mediator-adjusted models to consider this as an additional potential mediator of the associations of HDP and maternal BP change with offspring BP. Secondly, we excluded offspring and mothers who had few (less than 3 and less than 5 BP measurements) and mothers who had many (more than 9 and more than 11 BP measurements) BP measurements available. Finally, to examine whether the use of antihypertensive medication affected our findings, we excluded the 33 women who had existing hypertension and reported using medication to treat their hypertension and the 26 women who reported using antihypertensives, beta blockers or calcium channel blockers (for any reason) regularly, or at any time, during their pregnancy.

Statistical analyses were carried out using MLwiN version 2.27 and Stata version 12.1 combined with runmlwin.[34]

Results

Among the 8,443 mother-offspring pairs where the mother had at least two BP measurements after 20 weeks of gestation, 6,716 (79.5%) had no HDP, 310 (3.7%) had existing hypertension, 1,256 (14.9%) had gestational hypertension and 161 (1.9%) had preeclampsia (Table 1). These proportions were similar in the 6,619 mother-offspring pairs with complete data on all covariables (Table 1). There was strong evidence (p<0.001) that HDP status was associated with maternal pre-pregnancy BMI, parity and smoking during pregnancy as well as with gestational age, birthweight and mode of delivery (Table 2).

Associations of HDP with offspring BP changes

The average SBP and DBP for those offspring whose mothers had any form of HDP: existing hypertension, gestational hypertension or preeclampsia during pregnancy were markedly higher throughout childhood and adolescence compared to those offspring whose mothers had normotensive pregnancies (Figure 1). However, the rates of offspring SBP and DBP change in each of

the age intervals were similar across hypertensive and normotensive pregnancies, with offspring SBP and DBP on average increasing through late childhood (7-12 years) and more rapidly through early adolescence (12-16 years), and then decreasing through the latter part of adolescence (16-18 years).

Existing hypertension and gestational hypertension were associated with higher average offspring SBP and DBP at 7 years of age compared with those offspring whose mothers had normotensive pregnancies in all of the models (Tables 3 and 4), with the associations attenuated towards the null after adjusting for maternal characteristics and offspring height and BMI (existing hypertension: 1.67mmHg (0.48, 2.86) for SBP, 1.32mmHg (0.41, 2.23) for DBP; gestational hypertension: 1.98mmHg (1.32, 2.65) for SBP, 0.97mmHg (0.46, 1.48) for DBP (Model 3)). There was no evidence to suggest a positive association between preeclampsia and offspring BP at 7 years of age in the dataset with complete data on all covariables (preeclampsia: 1.22mmHg (-0.52, 2.97) for SBP; 0.80mmHg (-0.53, 2.13) for DBP (Model 3)).

There was no clear further attenuation of the associations of existing hypertension and gestational hypertension with offspring SBP and DBP at 7 years of age after the additional adjustment for perinatal factors (birthweight, gestational age, and mode of delivery). However, there was a decrease in the mean differences in SBP and DBP at 7 years of age between the preeclampsia and normotensive groups after adjusting for these mediators (0.56mmHg (-1.19, 2.31) for SBP, 0.49mmHg (-0.85, 1.83) for DBP (Model 4)).

In all of the models, there was no evidence that the average linear slopes for offspring BP within each of the periods of childhood and adolescence (7-12 years, 12-16 years, and 16-18 years) differed by HDP status (Tables 3 and 4).

Associations of maternal BP changes during pregnancy and offspring BP

There was strong evidence that a higher maternal SBP at 8 weeks' gestation was associated with higher average offspring SBP at 7 years of age (Table 5), with the association attenuating but remaining strong after adjusting for the potential maternal and offspring confounders (1.13mmHg

(0.56, 1.71); Model 2). But, there was no further attenuation after the additional adjustment for birthweight, gestational age, and mode of delivery. Similarly, there was strong evidence that a higher maternal DBP at 8 weeks' gestation was associated with higher average offspring DBP at 7 years of age in the unadjusted model (Model 1; Table 6). This association attenuated but remained after adjusting for maternal and offspring characteristics (0.75mmHg (0.04, 1.47); Model 2).

There was some weak evidence of positive associations between maternal SBP changes in all periods of gestation and offspring SBP at age 7 in Model 1, although the associations of maternal SBP change in 8-18, 18-30 and >36 weeks gestation attenuated towards the null in Model 2 and the association relating to maternal SBP change in 30-36 weeks gestation attenuated after adjustment for intrauterine mediators (Model 3; Table 5). The associations of maternal DBP changes during pregnancy with offspring DBP at age 7 tended to be weaker than those for SBP with little evidence to support them, although there was some weak evidence of a positive association between maternal DBP change up to 18 weeks gestation and offspring DBP at age 7 in all models (Table 6). There was no evidence that SBP or DBP in early-pregnancy or changes in SBP or DBP during pregnancy were associated with changes in offspring BP during childhood in any models (Tables 5 and 6).

We repeated the analysis just in those mother-offspring pairs where the mothers had normotensive pregnancies (results available from authors on request). The results were similar to those of the full analysis, with the one exception that there was strong evidence in confounder-adjusted models that maternal SBP change from 8 to 18 weeks' gestation was positively associated with offspring SBP at 7 years of age (1.51mmHg (0.41, 2.64)). This association was not explained by gestational age, birthweight, and mode of delivery.

The results of each of the sensitivity analyses (adjusting for breastfeeding, excluding women/offspring with few or many BP measures or excluding women who took antihypertensive medications) were not meaningfully different from those in the main analysis (results available from from authors on request).

Discussion

In this large general population birth cohort, we found that offspring of women who had any of existing hypertension, gestational hypertension or preeclampsia had on average higher BP at 7 years of age compared with offspring whose mothers had normotensive pregnancies, although the difference in offspring BP associated with preeclampsia was not supported by strong statistical evidence and confidence intervals were consistent with the null. The difference in BP in mid-childhood remained of a similar size up to age 18 years for all hypertensive disorders as the BP trajectories across childhood and adolescence had similar shapes in offspring from all groups of maternal HDP but were consistently higher in those women with any form of hypertension, as seen in Figure 1. The associations of existing and gestational hypertension with offspring BP across childhood and adolescence remained in confounder adjusted models including after adjustment for offspring and maternal BMI. Furthermore, they did not appear to be mediated by birthweight, gestational age or mode of delivery. Despite associations of preeclampsia with offspring BP being consistent with the null in confounder adjusted models, the point estimate for the association was similar to that for gestational hypertension and was imprecisely estimated due to the relatively small number of women with preeclampsia. We also found a strong positive association of maternal BP at 8 weeks gestation with offspring BP in childhood, but much weaker associations of change in BP during pregnancy with offspring BP.

Previous studies in ALSPAC[6,7,16] and other cohorts[8-14] have shown greater BP at a single point in childhood in offspring of mothers with gestational hypertension or preeclampsia compared to offspring of mothers with normal pregnancies. Our study extends these studies, firstly by comparing associations of existing hypertension at the start of pregnancy with offspring BP to those seen for pregnancy induced hypertension and secondly by examining associations with BP change trajectories across childhood. The mean difference in offspring BP between children exposed to maternal gestational hypertension or preeclampsia that we found in this study at mean age seven years are

consistent with these previous studies, including with a recent meta-analysis.[16] This meta-analysis reported that the mean difference in SBP between offspring of preeclamptic and normotensive pregnancies at ages < 10 years was 2.91 mmHg (95% CI: 1.55-4.27) and at ages ≥ 10 years was 2.24 mmHg (1.49-2.98), suggesting a similar absolute difference in SBP at different stages of childhood. Yet it is important to note that these two estimates were based on different studies, meaning that a direct inference of how the difference in blood pressure alters with age in the same children is not possible. We found that the absolute difference in SBP and DBP between offspring of hypertensive pregnancies and offspring of normotensive pregnancies remained similar between the ages of 7-18 years. Despite the increase in BP in all groups up to the age of 16 years, the relative difference in BP (as a percentage of total BP) also remained similar over this age range, with no clear decreasing trend. Given that BP has been shown to track from childhood into adulthood,[35] and that blood pressure in young adulthood has been demonstrated to be related to mortality from cardiovascular disease, coronary heart disease and stroke in later life,[36] the differences that we have found, and their consistency across childhood and adolescence, suggest that offspring of hypertensive pregnancies may be subject to a higher cardiovascular risk across the lifecourse than offspring of normotensive pregnancies.

The associations that we have observed may be driven by shared genetic or environmental factors between the mother and child. This is supported by a study showing that genetic variants that are associated with adult BP in genome-wide association studies were associated with childhood BP from at least age 6 years, with the genetic effect on BP remaining similar from ages 6 to 17 years.[27] We have adjusted for many potential confounders to attempt to account for shared environmental factors, but it is possible that unmeasured factors could have contributed to the associations we observed. Alternatively, the associations may be explained by a direct influence of maternal HDP on the development of the fetal cardiovascular system in utero. Preeclampsia is often characterised by poor formation of the placental blood supply and could therefore affect intrauterine development via a reduced supply of nutrients to the fetus.[37] Alternatively, fetal development may be affected by

intrauterine exposure to the systemic inflammation which is associated with HDP.[38] As there are similar-sized associations of each form of HDP with offspring BP this may suggest that the mechanisms driving each of these associations are similar. However, the point estimate for the association of preeclampsia with offspring BP at 7 years of age did attenuate with adjustment for mediation by birthweight, gestational age and mode of delivery, consistent with our earlier work looking at cross-sectional associations only with offspring BP at 10 and 11 years of age in the ALSPAC study,[6,7] while the associations of gestational hypertension and existing hypertension with offspring BP remained similar. This suggests that the association of maternal preeclampsia with offspring BP may act via a different pathway to that seen for gestational hypertension and existing hypertension and that at least part of it may be explained by poor development of the fetus in utero.

Our analysis relating trajectories of maternal BP during pregnancy to offspring BP showed only weak evidence that pregnancy-related changes in BP were associated with offspring BP, but clearly demonstrated that a greater BP in early pregnancy was associated with higher offspring BP in childhood. These findings contrast with our previous study in this cohort where we have shown strong associations of greater increases in BP in the second half of pregnancy with reduced fetal growth and no association of early-pregnancy DBP with this outcome, although early-pregnancy SBP was negatively associated with size at birth. Similarly, a greater rise in BP was associated with a shorter gestation, while the early-pregnancy level of BP was not.[39] While we cannot rule out the possibility that there were small associations of maternal BP change with offspring BP which we did not have the power to detect here, the strong positive associations of early-pregnancy BP with offspring BP which we found suggest a non-pregnancy related driver of the relationship between HDP and offspring BP. This may act, for example, via a maternal predisposition to high BP rather than an adverse response to the presence of the fetus.[40] However, we had few measurements of BP prior to 8 weeks of gestation and it is possible that BP may have changed from pre-pregnancy values by this point. Early gestation is also a key period for epigenetic reprogramming and thus a specific association of BP in early pregnancy with offspring BP may be indicative of epigenetic mechanisms

which occur at this particular stage of fetal development.[41] Differences in DNA methylation patterns have been found between placentas of pregnancies affected by preeclampsia and placentas of normal pregnancies, which suggest that epigenetics plays a part in trophoblast invasion and placental development.[42]

The main strengths of this study are its size and the repeated measurements of BP taken in the mothers during pregnancy and in the offspring during childhood and adolescence. The large number of variables recorded has also allowed for in-depth consideration of potential confounders and the investigation of possible mediating variables.

As with all general population cohort studies there is loss to follow-up and there are missing data. However, the sensitivity analyses excluding mothers and offspring who had few measurements of BP available gave similar results to those of the main analyses where all mother-offspring pairs who had complete data on all covariables were included. This suggests that our results have not been markedly biased by missing BP measurements. We excluded mother-offspring pairs who did not have complete data on all covariables, and these mothers were slightly less likely to smoke during pregnancy and likely to be of a higher education level than those excluded. However, we have no reason to expect that the associations that we have observed would differ by the mother's smoking or education status. Another limitation of this study is that the measurements of BP both in the mothers and the offspring were taken using different measuring devices and by different observers. Hence these measurements of BP are likely to be subject to some degree of variability between observers and devices. Maternal measurements were also subject to end digit preference for zero. However, we would expect only random non-differential measurement error which could potentially dilute our findings. Existing hypertension was obtained through self-report of ever being diagnosed as having high BP and this may be biased. Nevertheless the fact that this is associated with higher offspring BP provides some face-validity for its accuracy. The study was also limited by the relatively small number of women who had preeclampsia. This meant that there was low power to detect a

difference in offspring BP in this group compared with normotensive pregnancies and that we obtained imprecise estimates of the associations of maternal preeclampsia with offspring BP trajectories.

Perspectives

Our findings suggest that maternal hypertension during pregnancy is associated with increased offspring BP during childhood and adolescence. These associations do not strengthen or weaken with age over the age range that we have examined (7-18 years) showing that offspring of women who experience hypertension in pregnancy have consistently higher BP from at least age 7 into early adulthood. Maternal BP at 8 weeks gestation was also positively associated with offspring BP in childhood, but changes in BP during pregnancy were not strongly associated with offspring BP. This suggests that the associations are influenced by a maternal susceptibility to high BP which precedes pregnancy.

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Conflict of interest

None

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Tables

Table 1: Characteristics in the eligible cohorts and in the subset of mother-offspring pairs with complete data on all covariables

BP Measurements	**Full data set for HDP analysis (total, N=8,443) Median (LQ, UQ)**	**Full data set for maternal BP analysis (total, N=8617) Median (LQ, UQ)**	**Complete data on all covariables (N=6619) Median (LQ, UQ)**
Offspring BP Measurements	5 (3,7)	5 (3,7)	6 (3,7)
Maternal BP Measurements	14 (11,16)	14 (11,16)	14 (12,16)
Thinned Maternal BP Measurements*	10 (9,12)	11 (9,12)	10 (9,12)
Continuous Characteristics	**Mean (SD) [N]**	**Mean (SD) [N]**	**Mean (SD)**
Maternal age (years)	28.7 (4.7) [8443]	28.7 (4.7) [8617]	29.0 (4.6)
Gestational age (weeks)	39.5 (1.8) [8443]	39.5 (1.8) [8617]	39.6 (1.7)
Birthweight (g)	3434 (534) [8360]	3432 (534) [8521]	3451 (511)
Maternal pre-pregnancy BMI (kg/m^2)	22.9 (3.8) [7483]	22.9 (3.8) [7634]	22.9 (3.8)
Categorical Characteristics	**n (%) [N]**	**n (%) [N]**	**n (%)**
HDP:			
No HDP	6716 (79.5) [8443]	6716 (79.5) [8443]	5295 (80.0)
Existing Hypertension	310 (3.7) [8443]	310 (3.7) [8443]	253 (3.8)
Gestational Hypertension	1256 (14.9) [8443]	1256 (14.9) [8443]	954 (14.4)
Preeclampsia	161 (1.9) [8443]	161 (1.9) [8443]	117 (1.8)
Smoking during pregnancy:			
Never smoked	5851 (72.0) [8130]	5985 (72.1) [8299]	4893 (73.9)
Smoked pre-pregnancy/first	979 (12.0) [8130]	995 (12.0) [8299]	763 (11.5)

trimester			
Smoked throughout pregnancy	1300 (16.0) [8130]	1319 (15.9) [8299]	963 (14.6)
Parity:			
Multiparous	4317 (53.3) [8093]	4427 (53.6) [8261]	3530 (53.3)
Nulliparous	3776 (46.7) [8093]	3834 (46.4) [8261]	3089 (46.7)
Mother's education:			
CSE/Vocational	1967 (24.5) [8008]	2001 (24.5) [8172]	1437 (21.7)
O-level	2835 (35.4) [8008]	2889 (35.3) [8172]	2388 (36.1)
A-level	2015 (25.2) [8008]	2056 (25.2) [8172]	1745 (26.4)
Degree	1191 (14.9) [8008]	1226 (15.0) [8172]	1049 (15.8)
Caesarean Section:			
Yes	874 (10.4) [8402]	879 (10.3) [8542]	670 (10.1)
No	7528 (89.6) [8402]	7663 (89.7) [8542]	5949 (89.9)
Head of household social class:			
I	1131 (14.9) [7599]	1164 (15.0) [7749]	1020 (15.4)
II	3325 (43.7) [7599]	3392 (43.8) [7749]	2934 (44.3)
III	1920 (25.3) [7599]	1947 (25.1) [7749]	1657 (25.0)
IV	864 (11.4) [7599]	876 (11.3) [7749]	713 (10.8)
V	359 (4.7) [7599]	370 (4.8) [7749]	295 (4.5)
Offspring gender:			
Male	4247 (50.3) [8443]	4334 (50.3) [8617]	3335 (50.4)
Female	4196 (49.7) [8443]	4283 (49.7) [8617]	3284 (49.6)

*To prevent mothers with many BP measurements having too much influence on the subsequent analyses we thinned the data by randomly sampling one measurement for every 2-week period of gestation. BP, blood pressure; HDP, hypertensive disorder of pregnancy; BMI, body mass index; SD, standard deviation; LQ, lower quartile; UQ, upper quartile. Head of household social class is determined using the highest parental occupation within the family, with class I referring to a professional/managerial role down to class V which referred to an unskilled manual role.

Table 2: Distributions of maternal and offspring characteristics for the full data set by HDP status (N=8443)

BP Measurements	**Median (LQ, UQ) by HDP category**				
	No HDP	**Existing Hypertension**	**Gestational hypertension**	**Preeclampsia**	
Offspring BP Measurements	5 (3,7)	6 (3,7)	5 (3,7)	5 (3,7)	
Maternal BP Measurements	13 (11,15)	15 (12,20)	16 (14,20)	19 (15,26)	
Thinned Maternal BP Measurements*	10 (9,11)	11 (10,12)	11 (9,12)	10 (9,11)	
Continuous Characteristics	**Mean (SD) [N] by HDP category**				**P-value****
	No HDP	**Existing Hypertension**	**Gestational hypertension**	**Preeclampsia**	
Maternal age (years)	28.7 (4.7) [6716]	28.8 (4.7) [310]	28.4 (4.9) [1256]	28.4 (5.4) [161]	0.344
Gestational age (weeks)	39.5 (1.7) [6716]	39.2 (2.1) [310]	39.6 (1.8) [1256]	38.0 (3.0) [161]	<0.001
Birthweight (g)	3443 (511) [6650]	3377 (597) [308]	3449 (562) [1244]	3029 (858) [158]	<0.001
Maternal pre-pregnancy BMI (kg/m^2)	22.5 (3.3) [5970]	24.6 (5.0) [285]	24.7 (4.8) [1087]	24.9 (5.3) [141]	<0.001
Categorical Characteristics	**n (%) [N] by HDP category**				**P-value†**
	No HDP	**Existing Hypertension**	**Gestational hypertension**	**Preeclampsia**	

Smoking during pregnancy:					
Never smoked	4595 (71.0) [6475]	230 (76.7) [300]	910 (75.6) [1204]	116 (76.8) [151]	<0.001
Smoked pre-pregnancy / first trimester	781 (12.0) [6475]	31 (10.3) [300]	142 (11.8) [1204]	25 (16.6) [151]	
Smoked throughout pregnancy	1099 (17.0) [6475]	39 (13.0) [300]	152 (12.6) [1204]	10 (6.6) [151]	
Parity:					
Multiparous	3648 (56.7) [6438]	141 (46.8) [301]	488 (40.5) [1204]	40 (26.7) [150]	<0.001
Nulliparous	2790 (43.3) [6438]	160 (53.2) [301]	716 (59.5) [1204]	110 (73.3) [150]	
Mother's education:					
CSE/Vocational	1598 (25.1) [6372]	62 (20.7) [299]	271 (22.9) [1185]	36 (23.7) [152]	0.032
O-level	2205 (34.6) [6372]	134 (44.8) [299]	440 (37.1) [1185]	56 (36.8) [152]	
A-level	1621 (25.4) [6372]	63 (21.1) [299]	289 (24.4) [1185]	42 (27.6) [152]	
Degree	948 (14.9) [6372]	40 (13.4) [299]	185 (15.6) [1185]	18 (11.8) [152]	
Caesarean Section:					
Yes	602 (9.0) [6682]	38 (12.3) [309]	185 (14.8) [1250]	49 (30.4) [161]	<0.001
No	6080 (91.0) [6682]	271 (87.7) [309]	1065 (85.2) [1250]	112 (69.6) [161]	
Head of household social class:					
I	916 (15.1) [6045]	32 (11.0) [292]	168 (15.0) [1123]	15 (10.8) [139]	0.696
II	2647 (43.8) [6045]	131 (44.9) [292]	481 (42.8) [1123]	66 (47.5) [139]	
II	1507 (24.9) [6045]	79 (27.0) [292]	302 (26.9) [1123]	32 (29.0) [139]	
IV	687 (11.4) [6045]	36 (12.3) [292]	122 (10.9) [1123]	19 (13.7) [139]	
V	288 (4.8) [6045]	14 (4.8) [292]	50 (4.5) [1123]	7 (5.0) [139]	
Offspring gender:					
Male	3350 (49.9)	164 (52.9)	655 (52.1)	78 (48.5)	0.354

	[6716]	[310]	[1256]	[161]
Female	3366 (50.1)	146 (47.1)	601 (47.9)	83 (51.5)
	[6716]	[310]	[1256]	[161]

*To prevent mothers with many BP measurements having too much influence on the subsequent analyses we thinned the data by randomly sampling one measurement for every 2-week period of gestation. ***F*-test for continuous characteristics on 3 DF testing the null hypothesis that the distributions of these continuous characteristics are the same across the four HDP categories. †χ^2 test for categorical characteristics on (n-1)(m-1) DF testing for associations between the variable and HDP. HDP, hypertensive disorder of pregnancy; BMI, body mass index; SD, standard deviation; LQ, lower quartile; UQ, upper quartile. Head of household social class is determined using the highest parental occupation within the family, with class I referring to a professional/managerial role down to class V which referred to an unskilled manual role.

Table 3: Mean differences (95% CI) in SBP at 7 years and average change in SBP in each period of childhood and adolescence by HDP status (N=6619)

Models	Mean difference in SBP at 7 years of age (mmHg)	Mean difference in average SBP changes (mmHg/year)		
		7-12 years	12-16 years	>16 years
Model 1:				
No HDP	0	0	0	0
Existing Hypertension	2.13 (0.87, 3.38)	0.10 (-0.19, 0.40)	0.29 (-0.22, 0.80)	-0.16 (-1.36, 1.04)
Gestational Hypertension	2.51 (1.82, 3.20)	0.02 (-0.14, 0.18)	-0.04 (-0.33, 0.25)	0.11 (-0.58, 0.80)
Preeclampsia	1.45 (-0.39, 3.29)	0.20 (-0.24, 0.64)	0.33 (-0.47, 1.13)	-0.02 (-1.84, 1.80)
Model 2:				
No HDP	0	0	0	0
Existing Hypertension	1.79 (0.53, 3.05)	0.08 (-0.22, 0.38)	0.19 (-0.31, 0.68)	-0.37 (-1.53, 0.78)
Gestational Hypertension	2.14 (1.44, 2.85)	0.01 (-0.17, 0.17)	-0.09 (-0.38, 0.19)	0.15 (-0.53, 0.83)
Preeclampsia	1.04 (-0.81, 2.88)	0.15 (-0.29, 0.59)	0.13 (-0.64, 0.90)	0.11 (-1.65, 1.88)
Model 3:				
No HDP	0	0	0	0
Existing Hypertension	1.67 (0.48, 2.86)	0.12 (-0.17, 0.41)	0.18 (-0.31, 0.66)	-0.28 (-1.40, 0.84)
Gestational Hypertension	1.98 (1.32, 2.65)	-0.03 (-0.19, 0.14)	-0.08 (-0.36, 0.20)	0.12 (-0.55, 0.78)
Preeclampsia	1.22 (-0.52, 2.97)	0.19 (-0.24, 0.61)	0.13 (-0.63, 0.89)	-0.28 (-2.00, 1.44)
Model 4:				
No HDP	0	0	0	0
Existing Hypertension	1.47 (0.28, 2.66)	0.12 (-0.17, 0.41)	0.16 (-0.32, 0.65)	-0.29 (-1.41, 0.83)
Gestational Hypertension	1.92 (1.26, 2.59)	-0.03 (-0.20, 0.13)	-0.09 (-0.37, 0.19)	0.15 (-0.52, 0.81)
Preeclampsia	0.56 (-1.19, 2.31)	0.20 (-0.24, 0.63)	0.08 (-0.68, 0.84)	-0.34 (-2.07, 1.39)

Model 1 is the unadjusted model. Model 2 is adjusted for the maternal characteristics: pre-pregnancy BMI, maternal age, parity, smoking during pregnancy and education, as well as head of household social class and offspring sex. Model 3 is additionally adjusted for offspring BMI and height. Model 4 is adjusted for birthweight, mode of delivery, and gestational age in addition to those covariables adjusted for in Model 3. In the reference category (normotensive pregnancy), for Model 1, mean SBP at 7 years (SE) [mmHg] = 97.54 (0.14); mean SBP change (SE) [mmHg/year]: 7-12 years = 1.73 (0.04), 12-16 years = 4.91 (0.06), >16 years = -4.34 (0.35). HDP, Hypertensive disorders of pregnancy; SBP, systolic blood pressure; BMI, body mass index; CI, confidence interval; SE, standard error.

Table 4: Mean differences (95% CI) in DBP at 7 years and average change in DBP in each period of childhood and adolescence by HDP status (N=6619)

Models	Mean difference in DBP at 7 years of age (mmHg)	Mean difference in average DBP changes (mmHg/year)		
		7-12 years	12-16 years	>16 years
Model 1:				
No HDP	0	0	0	0
Existing Hypertension	1.36 (0.44, 2.28)	0.01 (-0.22, 0.24)	0.19 (-0.24, 0.62)	-0.33 (-1.31, 0.65)
Gestational Hypertension	1.07 (0.57, 1.57)	-0.01 (-0.13, 0.12)	0.12 (-0.12, 0.37)	-0.29 (-0.86, 0.28)
Preeclampsia	0.84 (-0.50, 2.18)	0.06 (-0.28, 0.40)	-0.15 (-0.82, 0.52)	1.11 (-0.40, 2.61)
Model 2:				
No HDP	0	0	0	0
Existing Hypertension	1.30 (0.38, 2.22)	-0.03 (-0.26, 0.20)	0.22 (-0.21, 0.65)	-0.35 (-1.33, 0.63)
Gestational Hypertension	1.00 (0.48, 1.51)	-0.05 (-0.18, 0.08)	0.18 (-0.07, 0.43)	-0.39 (-0.98, 0.19)
Preeclampsia	0.78 (-0.56, 2.13)	-0.03 (-0.37, 0.31)	-0.04 (-0.72, 0.63)	0.88 (-0.62, 2.39)
Model 3:				
No HDP	0	0	0	0
Existing Hypertension	1.32 (0.41, 2.23)	-0.01 (-0.24, 0.22)	0.22 (-0.21, 0.65)	-0.33 (-1.31, 0.65)
Gestational Hypertension	0.97 (0.46, 1.48)	-0.06 (-0.19, 0.07)	0.19 (-0.07, 0.44)	-0.41 (-0.99, 0.17)
Preeclampsia	0.80 (-0.53, 2.13)	-0.01 (-0.35, 0.33)	-0.04 (-0.71, 0.63)	0.73 (-0.77, 2.23)
Model 4:				
No HDP	0	0	0	0
Existing Hypertension	1.22 (0.31, 2.13)	0.01 (-0.22, 0.24)	0.21 (-0.22, 0.65)	-0.34 (-1.32, 0.64)
Gestational Hypertension	0.96 (0.45, 1.47)	-0.06 (-0.19, 0.07)	0.20 (-0.06, 0.45)	-0.43 (-1.01, 0.15)
Preeclampsia	0.49 (-0.85, 1.83)	0.05 (-0.29, 0.39)	-0.05 (-0.72, 0.63)	0.67 (-0.85, 2.18)

Model 1 is the unadjusted model. Model 2 is adjusted for the maternal characteristics: pre-pregnancy BMI, maternal age, parity, smoking during pregnancy and education, as well as head of household social class and offspring sex. Model 3 is additionally adjusted for offspring BMI and height. Model 4 is adjusted for birthweight, mode of delivery, and gestational age in addition to those covariables adjusted for in Model 3. In the reference category (normotensive pregnancy), for Model 1, mean DBP at 7 years (SE) [mmHg] = 56.52 (0.10); mean DBP change (SE) [mmHg/year]: 7-12 years = 0.10 (0.03), 12-16 years = 2.66 (0.05), >16 years = -2.20 (0.11). HDP, Hypertensive disorders of pregnancy; DBP, diastolic blood pressure; BMI, body mass index; CI, confidence interval; SE, standard error.

Table 5: Mean differences (95% CI) in offspring SBP at 7 years and average changes in offspring SBP in each age interval given a 10mmHg increase in maternal SBP at 8 weeks of gestation or per 1mmHg/week increase in maternal SBP change in each period of gestation (N=6619)

			Mean difference in average offspring SBP change (mmHg/year)		
Model	**Maternal SBP variable**	**Mean difference in offspring SBP at 7 years (mmHg)**	**7-12 years**	**12-16 years**	**>16 years**
Model 1	SBP at 8 weeks (per 10mmHg)	1.53 (1.03, 2.03)	-0.03 (-0.14, 0.09)	0.09 (-0.12, 0.30)	0.03 (-0.46, 0.53)
	SBP change 8 to 18 weeks (mmHg/week)	1.43 (0.17, 2.71)	0.08 (-0.22, 0.40)	-0.06 (-0.61, 0.47)	0.30 (-0.96, 1.60)
	SBP change 18 to 30 weeks (mmHg/week)	1.36 (0.10, 2.68)	-0.04 (-0.36, 0.26)	0.13 (-0.40, 0.67)	-0.32 (-1.59, 0.96)
	SBP change 30 to 36 weeks (mmHg/week)	0.38 (-0.10, 0.88)	0.11 (-0.01, 0.23)	-0.16 (-0.38, 0.05)	0.28 (-0.22, 0.79)
	SBP change >36 weeks (mmHg/week)	0.56 (0.14, 1.00)	-0.06 (-0.16, 0.04)	0.04 (-0.14, 0.23)	-0.25 (-0.70, 0.17)
Model 2	SBP at 8 weeks (per 10mmHg)	1.13 (0.56, 1.71)	-0.07 (-0.21, 0.07)	0.10 (-0.13, 0.35)	-0.02 (-0.58, 0.55)
	SBP change 8 to 18 weeks (mmHg/week)	1.06 (-0.17, 2.32)	0.03 (-0.27, 0.34)	-0.02 (-0.56, 0.53)	0.51 (-0.75, 1.78)
	SBP change 18 to 30 weeks (mmHg/week)	0.88 (-0.43, 2.16)	-0.05 (-0.37, 0.27)	0.01 (-0.55, 0.56)	-0.07 (-1.40, 1.22)

	SBP change 30 to 36 weeks (mmHg/week)	0.52 (-0.02, 1.07)	0.09 (-0.04, 0.22)	-0.16 (-0.39, 0.07)	0.26 (-0.27, 0.78)
	SBP change >36 weeks (mmHg/week)	0.50 (0.04, 0.99)	-0.04 (-0.16, 0.08)	0.05 (-0.15, 0.25)	-0.16 (-0.65, 0.31)
Model 3	SBP at 8 weeks (per 10mmHg)	1.13 (0.55, 1.70)	-0.07 (-0.21, 0.07)	0.10 (-0.14, 0.35)	0.01 (-0.56, 0.57)
	SBP change 8 to 18 weeks (mmHg/week)	1.16 (-0.06, 2.42)	0.04 (-0.26, 0.35)	0.01 (-0.52, 0.56)	0.39 (-0.87, 1.65)
	SBP change 18 to 30 weeks (mmHg/week)	0.78 (-0.53, 2.04)	-0.05 (-0.37, 0.27)	0.01 (-0.55, 0.56)	-0.09 (-1.41, 1.19)
	SBP change 30 to 36 weeks (mmHg/week)	0.30 (-0.24, 0.85)	0.09 (-0.04, 0.23)	-0.18 (-0.42, 0.04)	0.24 (-0.28, 0.76)
	SBP change >36 weeks (mmHg/week)	0.50 (0.05, 0.99)	-0.03 (-0.15, 0.08)	0.06 (-0.14, 0.26)	-0.19 (-0.68, 0.28)

Model 1 was adjusted only for maternal SBP at 8 weeks gestation and change in maternal SBP in any earlier periods of gestation. Model 2 is adjusted for the maternal characteristics: HDP status (only in the maternal SBP part of the model, as it is wholly pregnancy related), pre-pregnancy BMI, maternal age, parity, smoking during pregnancy and education (maternal education was only included in the maternal SBP part of the model, to assist with model convergence), as well as head of household social class and offspring sex, BMI, and height (only in the offspring SBP part of the model). Model 3 is additionally adjusted for birthweight, gestational age, and mode of delivery in the offspring SBP part of the model. SBP, systolic blood pressure; BMI, body mass index; CI, confidence interval.

Table 6: Mean differences (95% CI) in offspring DBP at 7 years and average changes in offspring DBP in each age interval given a 10mmHg increase in maternal DBP at 8 weeks of gestation or per 1mmHg/week increase in maternal DBP change in each period of gestation (N=6619)

			Mean difference in average offspring DBP change (mmHg/year)		
Model	**Maternal DBP variable**	**Mean difference in offspring DBP at 7 years (mmHg)**	**7-12 years**	**12-16 years**	**>16 years**
Model 1	DBP at 8 weeks (per 10mmHg)	0.83 (0.28, 1.39)	0.05 (-0.09, 0.20)	0.06 (-0.21, 0.34)	0.27 (-0.36, 0.91)
	DBP change 8 to 18 weeks (mmHg/week)	1.47 (-0.20, 3.27)	0.02 (-0.41, 0.45)	-0.32 (-1.20, 0.55)	-0.73 (-2.82, 1.19)
	DBP change 18 to 30 weeks (mmHg/week)	1.08 (-0.25, 2.37)	-0.06 (-0.39, 0.27)	0.11 (-0.54, 0.78)	0.46 (-1.01, 2.00)
	DBP change 30 to 36 weeks (mmHg/week)	0.11 (-0.30, 0.53)	0.01 (-0.09, 0.11)	0.05 (-0.15, 0.25)	-0.19 (-0.65, 0.26)
	DBP change >36 weeks (mmHg/week)	0.24 (-0.02, 0.51)	-0.05 (-0.11, 0.02)	0.12 (-0.01, 0.25)	-0.04 (-0.34, 0.26)
Model 2	DBP at 8 weeks (per 10mmHg)	0.75 (0.04, 1.47)	0.05 (-0.13, 0.24)	0.03 (-0.33, 0.39)	0.62 (-0.20, 1.44)
	DBP change 8 to 18 weeks (mmHg/week)	1.52 (-0.21, 3.38)	-0.05 (-0.50, 0.40)	-0.19 (-1.10, 0.71)	-1.29 (-3.60, 0.70)
	DBP change 18 to 30 weeks (mmHg/week)	0.92 (-0.49, 2.30)	-0.06 (-0.42, 0.29)	0.02 (-0.67, 0.73)	0.69 (-0.88, 2.41)

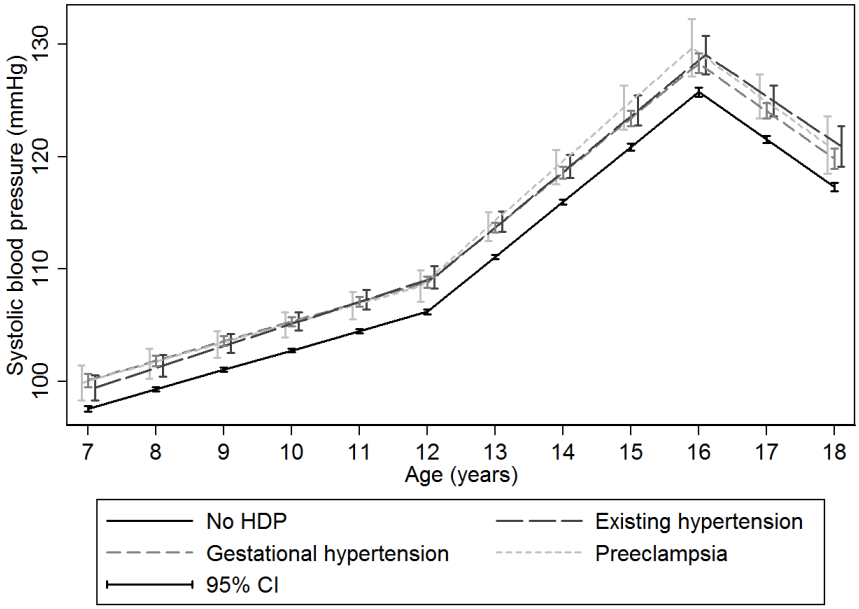
	DBP change 30 to 36 weeks (mmHg/week)	0.16 (-0.28, 0.60)	0.01 (-0.11, 0.11)	0.04 (-0.18, 0.25)	-0.15 (-0.66, 0.33)
	DBP change >36 weeks (mmHg/week)	0.24 (-0.07, 0.56)	-0.06 (-0.14, 0.02)	0.15 (-0.01, 0.30)	-0.09 (-0.47, 0.29)
Model 3	DBP at 8 weeks (per 10mmHg)	0.78 (0.06, 1.50)	0.04 (-0.14, 0.23)	0.03 (-0.32, 0.39)	0.62 (-0.20, 1.44)
	DBP change 8 to 18 weeks (mmHg/week)	1.51 (-0.21, 3.38)	-0.03 (-0.48, 0.42)	-0.22 (-1.13, 0.68)	-1.26 (-3.58, 0.73)
	DBP change 18 to 30 weeks (mmHg/week)	0.74 (-0.68, 2.11)	-0.03 (-0.39, 0.32)	0.03 (-0.66, 0.74)	0.65 (-0.93, 2.37)
	DBP change 30 to 36 weeks (mmHg/week)	0.02 (-0.42, 0.46)	0.03 (-0.08, 0.14)	0.05 (-0.17, 0.26)	-0.19 (-0.69, 0.29)
	DBP change >36 weeks (mmHg/week)	0.23 (-0.09, 0.55)	-0.05 (-0.13, 0.03)	0.14 (-0.02, 0.29)	-0.08 (-0.46, 0.29)

Model 1 was adjusted only for maternal DBP at 8 weeks gestation and change in maternal DBP in any earlier periods of gestation. Model 2 is adjusted for the maternal characteristics: HDP status (only in the maternal DBP part of the model, as it is wholly pregnancy related), pre-pregnancy BMI, maternal age, parity, smoking during pregnancy and education (maternal education was only included in the maternal DBP part of the model, to assist with model convergence), as well as head of household social class and offspring sex, BMI, and height (only in the offspring DBP part of the model). Model 3 is additionally adjusted for birthweight, gestational age, and mode of delivery in the offspring DBP part of the model. DBP, diastolic blood pressure; BMI, body mass index; CI, confidence interval.

Figures

Figure 1: Average offspring SBP and DBP trajectories by HDP status (N=8443)

A SBP



B DBP