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See Editorial Commentary, pp 1099–1100

Abstract—We compared patterns of blood pressure (BP) change among normotensive women, women who developed gestational hypertension or preeclampsia, and women who had essential hypertension to examine how distinct these conditions are and whether rates of BP change may help to identify women at risk for hypertensive disorders. We used antenatal clinic BP measurements (median, 14 per woman) of 13016 women from the Avon Longitudinal Study of Parents and Children who had a singleton or twin live birth surviving until ≥1 year. Linear spline models were used to describe changes in systolic and diastolic BPs in different periods of pregnancy (8–18, 18–30, 30–36, and ≥36 weeks' gestation). Women who had essential hypertension and those who developed gestational hypertension or preeclampsia had higher BP at 8 weeks' gestation (baseline) compared with normotensive women. The decrease in BP until 18 weeks was smaller in gestational hypertensive compared with normotensive pregnancies. BP rose more rapidly from 18 weeks onward in gestational hypertensive and preeclamptic pregnancies and from 30 weeks onward in essential hypertensive compared with normotensive pregnancies. Women who developed preeclampsia had a more rapid increase in BP from 30 weeks onward than those who developed gestational hypertension or had essential hypertension. Our findings indicate notable patterns of BP change that distinguish women with essential hypertension, gestational hypertension, and preeclampsia from each other and from normotensive women, even from early pregnancy. These distinct patterns may be useful for identifying women at risk of developing a hypertensive disorder later in pregnancy. (***Hypertension*. 2012;59:1241-1248.**) • **Online Data Supplement**

Key Words: blood pressure ■ preeclampsia ■ gestational hypertension ■ pregnancy ■ ALSPAC

Hypertensive disorders of pregnancy (HDP), consisting of gestational hypertension, preeclampsia, and essential hypertension, affect ≈10% of pregnancies[1] and are associated with maternal and perinatal mortality,[2,3] small-for-gestational-age infants, and preterm birth.[1,4–6] Gestational hypertension and preeclampsia are defined using blood pressure (BP) thresholds after 20 weeks' gestation, with the additional criteria of proteinuria for preeclampsia.[7]

In normal pregnancy, BP initially decreases until 18 to 20 weeks' gestation and then rises until delivery,[8–11] and studies have indicated that higher BP prepregnancy[12,13] and in the first trimester[14–16] are associated with increased risk of developing gestational hypertension and preeclampsia. The few studies that have assessed BP trajectories across gestation in different HDP groups suggest that the relative change in BP may provide additional indication of HDP risk relative to a single BP measurement. However, these studies were limited by their size (mostly N <1000), number of repeat measurements available, or outdated definitions of HDP and did not assess differences in rates of BP change between groups in different periods of pregnancy.[10,17–22] Comparing changes in BP between gestational hypertensive and preeclamptic pregnancies is useful for assessing the distinctness of these conditions and whether the greater risk associated with preeclampsia is attributable solely to its additional systemic changes, indicated by proteinuria, or also attributable to the severity of vascular problems, represented by greater increases in BP.

Our study aims to investigate whether patterns of BP change across pregnancy differ among normotensive women,

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those who have hypertension before pregnancy (referred to as "essential hypertension" throughout the article, for ease of reporting), and those who develop gestational hypertension or preeclampsia in a large prospective cohort of women. Preeclamptic pregnancies have a high risk of medically indicated preterm delivery,[23] particularly if maternal BP rises rapidly in late gestation.[24,25] We have, therefore, modeled BP change jointly with time to delivery to adjust for the shorter gestational period in women who experienced greater rises in BP.

Methods

The Avon Longitudinal Study of Parents and Children is a prospective birth cohort study aiming to investigate the health and development of children. The study has been described in full elsewhere[26] and on the Web site www.bris.ac.uk/alspac. Pregnant women with expected delivery dates between April 1, 1991, and December 31, 1992, living in Avon (United Kingdom) during their pregnancy were eligible for recruitment. Data have been collected through questionnaires, research clinics, and linkage to routine health records. Ethical approval for the study was obtained from the Avon Longitudinal Study of Parents and Children Law and Ethics Committee and from the National Health Service local ethics committee. In total, 14 541 women were enrolled, 13 796 had singleton or twin pregnancies where the offspring were alive at 1 year, and 13 578 of these women had data abstracted from obstetric records. We excluded women who had existing (N=43) or gestational (N=56) diabetes and women who had a gestational period >44 weeks (N=6), which left 13 016 women with ≥1 BP measurement available for analysis.

All of the BP and urine dipstick proteinuria measurements taken routinely as part of antenatal care by midwives, obstetricians, or other relevant health professionals, such as general practitioners, were abstracted from obstetric medical charts by 6 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 BP measurements taken in the seated position using the appropriate cuff size, and diastolic BP (DBP) was measured using Korotkoff phase V. There was a median of 14 (interquartile range, 11–16) BP measurements per woman. The gestational age at each visit was derived from the date of measurement and the expected delivery date. A questionnaire administered during pregnancy asked about previous hypertension. Women who reported having been diagnosed previously with hypertension outside of pregnancy and were aged >16 years at diagnosis were considered to have essential hypertension. For women who did not have essential hypertension, HDP was defined according to International Society for the Study of Hypertension in Pregnancy criteria,[7] with gestational hypertension defined as systolic BP (SBP) ≥140 mmHg and/or DBP ≥90 mmHg on 2 occasions after 20 weeks' gestation; preeclampsia was defined by the same criteria with proteinuria of 1+ on dipstick testing occurring at the same time as the elevated BP. This produced 4 mutually exclusive categories of no HDP, gestational hypertension, preeclampsia, and essential hypertension. Gestational age at delivery (in weeks) was calculated as the difference between the delivery date and the mother's reported last menstrual period date or updated if ultrasound information was available, which led to a reassessment of gestation. At the time of recruitment, it was not routine clinical practice to perform ultrasound gestational age dating in early pregnancy, and in the data abstracted from the clinical records it was not recorded which few women had a scan or had their gestational age adjusted.

Maternal age at delivery and offspring sex were abstracted from obstetric records. Maternal height, prepregnancy weight, parity, highest educational qualification, and smoking status were obtained from questionnaires administered during early pregnancy. Prepregnancy body mass index was calculated as weight (in kilograms)/height (in meters) squared and categorized as underweight (<18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25.0–29.9kg/m^2), and obese (≥30.0 kg/m^2). Smoking status was classed as "never" for women who did not smoke immediately before or during pregnancy, "prepregnancy/first trimester" for women who smoked only immediately before pregnancy or in the first 3 months of gestation, or "throughout" for women who continued to smoke after the first trimester.

Statistical Analysis

We first developed linear spline random-effects models for SBP and DBP changes across gestation, as described previously.[11] To take account of data clustering because of the multiple antenatal visits per woman, multilevel modeling using antenatal visits (level 1) within women (level 2) was used. We randomly sampled 1 measurement per 2-week period of gestation for each woman to prevent women with many measurements from having too great an influence on the models, leaving a median of 10 (interquartile range, 9–11) BP measurements per woman. For both SBP and DBP, the best-fitting models had knot points (indicating changes in the slope) at 18, 30, and 36 weeks' gestation, and baseline was set at 8 weeks' gestation, because there were few measurements before this. This produced 5 individual-level random-effects parameters, SBP/DBP at 8 weeks and SBP/DBP change 8 to 18 weeks, 18 to 30 weeks, 30 to 36 weeks, and 36 weeks onward.

Because women who have a greater rise in BP in late gestation are likely to deliver earlier, to have fewer BP measurements over pregnancy, and, therefore, to have less influence in statistical models, the overall average increase in BP in the population would be underestimated by these univariate models. This problem could not be overcome by simply conditioning on gestational age at delivery in our analysis, because, if length of gestation is influenced by both BP change and HDP, this would bias our estimate of the association between BP change and HDP (see Figure S1, available in the online-only Data Supplement).[27] We, therefore, combined the random-effects spline models for BP with a model for time to delivery to produce a joint model with SBP (or DBP) and time to delivery as outcome variables to adjust for this. Please see the online-only Data Supplement for further information. We included HDP category as a covariate, with normotensive pregnancies as the reference, and adjusted for maternal prepregnancy body mass index, maternal age, parity, smoking, education, and offspring sex (for singleton pregnancies) or twin pregnancy by including these as covariates also. We assessed whether the relationships of maternal characteristics with BP changes across pregnancy differed between HDP categories by testing for interactions between each of the maternal covariates and HDP category.

The correlations between BP changes and time to delivery were derived from the random effects for BP outcomes and the residual error from the time to delivery model (please see the online-only Data Supplement). Model 1 was adjusted for HDP category and maternal covariates. In model 2 we also adjusted for SBP/DBP at 8 weeks' gestation and SBP/DBP change in earlier periods of pregnancy.

To examine whether secondary causes of hypertension or the use of antihypertensive medication affected our results, we repeated analyses excluding 442 women who reported ever having had kidney disease, 41 essential hypertensive women who reported using medication to treat their hypertension, and 59 women who reported using antihypertensives, β-blockers, or calcium channel blockers (for any reason) regularly, or at any time, during their pregnancy (total excluded, 519). We also completed sensitivity analyses restricting to women who contributed ≥9 BP measurements to the spline models (N=7940) and to women with ≤11 measurements (N=7465). Statistical analyses were carried out using MLwiN version 2.23 and Stata version 11.2 combined with runmlwin.[28]

Results

The characteristics of the full cohort and the subset of women who had complete data on all maternal covariates are shown in Table 1 and by HDP category in Table S1. The distributions of each of the variables were similar in the full data set and the subset with complete data. In total, 80.0% (N=10 419) of women were normotensive throughout preg-

Table 1. Characteristics of the Full Data Set and Women Who Had Complete Data on All of the Covariables

Maternal Characteristic	Full Data Set (Total N=13 016)	Complete Data on All Variables (N=9930)
Gestational age at delivery, wk	N=13,016	
Median (IQR)	40 (39–41)	40 (39–41)
HDP, %	N=13 016	
No HDP	80.05	80.26
Gestational hypertension	14.57	14.26
Preeclampsia	2.13	1.95
Essential hypertension	3.26	3.52
Maternal prepregnancy BMI, %	N=10 839	
Underweight	5.08	4.91
Normal	74.29	74.65
Overweight	15.04	14.94
Obese	5.59	5.49
Maternal age (y), %	N=13 016	
<20	4.86	3.41
20–24	19.48	16.73
25–29	38.60	39.60
30–34	27.29	29.68
≥35	9.78	10.58
Parity, %	N=12 097	
Nulliparous	45.07	45.32
Multiparous	54.93	54.68
Smoking, %	N=12 208	
Never	66.52	69.19
Prepregnancy/first trimester	13.78	13.14
Throughout	19.70	17.66
Education, %	N=11 674	
CSE/vocational	30.00	27.64
O level	34.65	35.37
A level	22.42	23.33
Degree	12.93	13.66
Pregnancy type, %	N=13 016	
Male singleton	50.81	50.51
Female singleton	47.87	48.20
Twin	1.32	1.29

BMI indicates body mass index; CSE, certificate of secondary education; HDP, hypertensive disorder of pregnancy; IQR, interquartile range.

nancy, 14.6% (N=1896) developed gestational hypertension, 2.1% (N=277) developed preeclampsia, and 3.3% (N=424) had essential hypertension. The numbers of women who developed gestational hypertension and preeclampsia at different gestational ages are shown in Table S2. Both of these conditions most commonly developed between 35 and 39 weeks' gestation. Average BP levels at baseline and average changes in BP per week from univariate models are shown in Table S3.

Gestational age at delivery ranged from 24 to 44 weeks. Women who had essential hypertension or developed preeclampsia had a shorter average gestational period than normotensive women (Table S4).

Associations of BP Change With HDP

The Figure shows the average patterns of BP change across pregnancy by HDP category in the joint models. SBP and DBP were notably higher throughout pregnancy for women who had any of essential hypertension, gestational hypertension, or preeclampsia compared with normotensive women. Women who developed gestational hypertension had similar DBP until ≈18 weeks' gestation and SBP until ≈30 weeks' gestation to women who developed preeclampsia, after which BP increases were greater in women who developed preeclampsia compared with those who developed gestational hypertension. Women who had essential hypertension had the highest SBP and DBP at 8 weeks but similar SBP and DBP in late pregnancy to women who developed gestational hypertension.

The mean differences in SBP at 8 weeks and change in SBP in each period of pregnancy associated with gestational hypertension, preeclampsia, and essential hypertension compared with no HDP are shown in Table 2. The equivalent associations for DBP are shown in Table 3. In both unadjusted and adjusted models, gestational hypertension (compared with women remaining normotensive) was associated with a higher SBP and DBP at 8 weeks, a smaller decrease in SBP between 8 and 18 weeks, and a greater increase in SBP and DBP between 18 and 30 weeks, between 30 and 36 weeks, and after 36 weeks. Preeclampsia (compared with women remaining normotensive) was also associated with a higher SBP and DBP at 8 weeks and with a greater increase in SBP and DBP between 18 and 30 weeks, 30 and 36 weeks, and after 36 weeks. Essential hypertension (compared with women remaining normotensive) was associated with a higher SBP and DBP at 8 weeks, a greater increase in DBP between 30 and 36 weeks' gestation, and a greater increase in SBP and DBP after 36 weeks.

Women who had essential hypertension had higher SBP and DBP at 8 weeks than women who developed gestational hypertension or preeclampsia (all $P<0.05$), but there was little difference in SBP or DBP at 8 weeks between women who developed gestational hypertension or preeclampsia. Those who developed preeclampsia had a greater increase in DBP between 18 and 30 weeks and in SBP and DBP between 30 and 36 weeks and after 36 weeks than women who developed gestational hypertension or had essential hypertension (all $P<0.07$). Women who developed gestational hypertension had a greater rise in SBP and DBP between 18 and 30 weeks and in DBP from 36 weeks onward than those with essential hypertension (all $P<0.01$) but similar rates of BP change in other periods.

Figures S2 through S13 show the patterns of SBP and DBP changes across pregnancy by each of the maternal risk factors and HDP status, derived from a model including interactions of each of the maternal risk factors with HDP and SBP/DBP at 8 weeks and also with HDP and each of the splines for SBP/DBP change. These figures show that the patterns of association of each of the maternal characteristics with BP changes are similar in each HDP group.

Associations of BP Change With Time to Delivery

Table 4 shows the associations of BP at 8 weeks and changes in BP with time to delivery. Neither SBP or DBP at 8 weeks

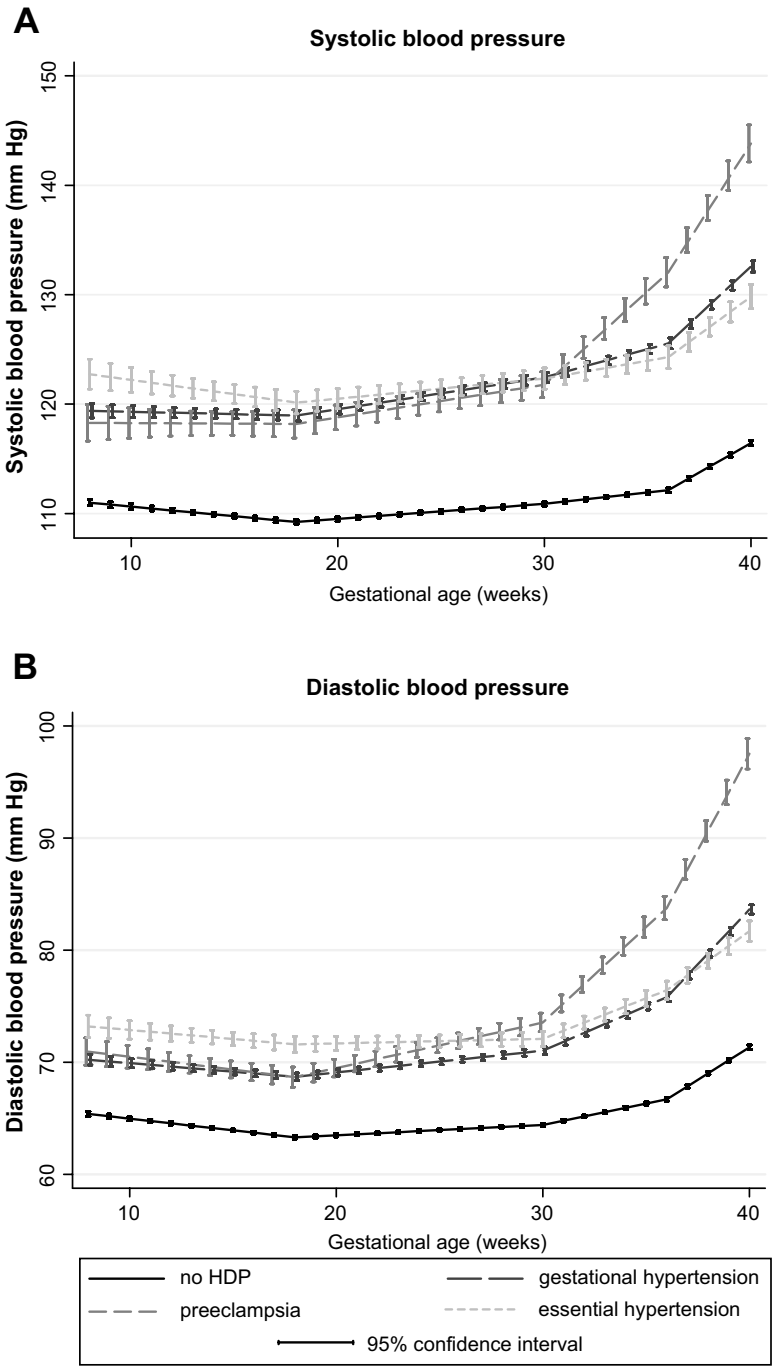

Figure. Average trajectories of systolic and diastolic blood pressures by hypertensive disorders of pregnancy in the unadjusted joint model (N=13 016). Solid black line indicates no hypertensive disorder of pregnancy; long-dashed dark-grey line, gestational hypertension; dashed grey line, preeclampsia and short-dashed light-grey line, essential hypertension.

nor change in SBP or DBP ≤18 weeks was associated with the length of gestation in any models. However, a greater rise in DBP between 18 and 30 weeks and in SBP or DBP between 30 and 36 weeks or from 36 weeks onward was associated with a shorter gestational period in models adjusted only for HDP category and maternal covariates (model 1). These associations were stronger when adjusting for baseline BP and previous BP changes (model 2). The predicted lengths of gestation at 2 SDs above and below the average BP at 8 weeks and changes in BP in each period of gestation are shown in Table S5. When we restricted analyses with length of gestation as the outcome to women who remained normotensive throughout pregnancy (N=7970), most findings were unchanged, except that SBP and DBP changes from 36 weeks onward were associated with length of gestation only in model 2.

None of the findings were meaningfully changed when we excluded women who reported having kidney disease or taking antihypertensive medication or women with <9 measurements (full results of these sensitivity analyses are available from authors). When women who had >11 measurements were excluded, findings were similar, except that SBP change between 8 and 18 weeks did not differ between gestational hypertensive and normotensive pregnancies as in the main analysis (adjusted mean difference [95% CI] in SBP change for gestational hypertensive compared with normo-

Table 2. Mean Difference (95% CI) in SBP at 8 wk and Change in SBP in Each Period of Gestation by Hypertensive Disorders of Pregnancy (N=9930)

Maternal Characteristics	Mean Difference in SBP at 8 wk, mm Hg	Mean Difference in Average SBP Change, mm Hg/wk			
		8–18 wk	18–30 wk	30–36 wk	≥36 wk
Unadjusted model					
No HDP	0	0	0	0	0
Gestational hypertension	8.189 (7.373–9.005)	0.137 (0.039–0.234)	0.148 (0.089–0.207)	0.330 (0.213–0.447)	0.707 (0.516–0.897)
Preeclampsia	7.528 (5.541–9.515)	0.117 (−0.120 to 0.355)	0.090 (−0.060 to 0.240)	1.475 (1.167–1.783)	2.418 (1.818–3.018)
Essential hypertension	11.046 (9.530–12.562)	−0.011 (−0.192 to 0.171)	0.005 (−0.108 to 0.117)	0.171 (−0.054 to 0.397)	0.397 (0.017–0.777)
Adjusted model					
No HDP	0	0	0	0	0
Gestational hypertension	7.151 (6.325–7.978)	0.107 (0.007–0.207)	0.183 (0.122–0.243)	0.330 (0.211–0.450)	0.744 (0.549–0.940)
Preeclampsia	6.513 (4.533–8.493)	0.072 (−0.167 to 0.311)	0.129 (−0.021 to 0.280)	1.463 (1.154–1.772)	2.409 (1.808–3.011)
Essential hypertension	9.900 (8.389–11.411)	−0.029 (−0.211 to 0.154)	0.043 (−0.069 to 0.156)	0.182 (−0.045 to 0.409)	0.454 (0.072–0.836)

Both models are adjusted for time to delivery; adjusted model is additionally adjusted for maternal prepregnancy BMI, age, parity, smoking during pregnancy, education, and sex/No. of fetuses. In reference category (normotensive women), for unadjusted model, mean SBP at 8 wk (mm Hg) = 111.011; mean SBP change (mm Hg/wk): 8–18 wk = −0.164; 18–30 wk=0.137; 30–36 wk=0.196; ≥36 wk=1.054. For adjusted model, mean SBP at 8 wk (mm Hg) = 111.966; mean SBP change (mm Hg/wk): 8–18 wk = −0.188; 18–30 wk=0.150; 30–36 wk=0.134; ≥36 weeks=1.222. BMI indicates body mass index; HDP, hypertensive disorder of pregnancy; SBP, systolic blood pressure.

tensive pregnancies: −0.028 mmHg per week [−0.162 to 0.106 mmHg per week]). This may be because of the later enrolment time of women who had ≤11 measurements (median, 12.3 weeks' compared with 9.7 weeks' gestation for women with >11 measurements) or may suggest that this early pregnancy difference is only apparent in women who develop more severe gestational hypertension.

Discussion

In this large prospective cohort of women, we have shown that women who developed gestational hypertension or preeclampsia had higher BP from very early in pregnancy, a reduced initial decline in SBP to 18 weeks' gestation, and a faster increase in BP from 18 weeks onward and then, in those destined to develop preeclampsia, a further marked increase in BP from 30 weeks. We also found that women who had essential hypertension had higher BP than all of the other groups in early pregnancy and a greater rise in BP than normotensive women in late pregnancy but showed a similar early pregnancy decline in BP to normotensive women.

Of note, BP levels at baseline (8 weeks), although much higher than for women who remained normotensive, were very similar in both preeclamptic women and those with gestational hypertension. This is despite some evidence that the latter 2 conditions are different from each other, with preeclampsia generally considered a 2-stage syndrome, the first stage being poor placentation and the second being maternal manifestation of hypertension and proteinuria later in pregnancy,[29] whereas gestational hypertension has been described as latent hypertension revealed by pregnancy.[30]

Table 3. Mean Difference (95% CI) in DBP at 8 wk and Change in DBP in Each Period of Gestation by Hypertensive Disorders of Pregnancy (N=9930)

Maternal Characteristics	Mean Difference in DBP at 8 wk, mm Hg	Mean Difference in Average DBP Change, mm Hg/wk			
		8–18 wk	18–30 wk	30–36 wk	≥36 wk
Unadjusted model					
No HDP	0	0	0	0	0
Gestational hypertension	4.692 (4.09–5.287)	0.044 (−0.027 to 0.115)	0.113 (0.069–0.156)	0.401 (0.311–0.491)	0.805 (0.655–0.954)
Preeclampsia	5.470 (4.020–6.920)	−0.007 (−0.180 to 0.166)	0.220 (0.110–0.331)	1.406 (1.170–1.642)	2.486 (2.017–2.956)
Essential hypertension	7.562 (6.455–8.668)	0.061 (−0.072 to 0.193)	−0.055 (−0.137 to 0.028)	0.329 (0.156–0.502)	0.274 (−0.023 to 0.572)
Adjusted model					
No HDP	0	0	0	0	0
Gestational hypertension	3.799 (3.200–4.398)	0.038 (−0.035 to 0.110)	0.132 (0.088–0.177)	0.370 (0.278–0.461)	0.833 (0.680–0.987)
Preeclampsia	4.674 (3.242–6.107)	−0.028 (−0.202 to 0.145)	0.239 (0.129–0.350)	1.336 (1.099–1.573)	2.465 (1.995–2.935)
Essential hypertension	6.585 (5.490–7.679)	0.056 (−0.077 to 0.189)	−0.029 (−0.112 to 0.054)	0.312 (0.138–0.486)	0.333 (0.035–0.632)

Both models are adjusted for time to delivery; adjusted model is additionally adjusted for maternal prepregnancy BMI, age, parity, smoking during pregnancy, education, and sex/No. of fetuses. In reference category (normotensive women), for unadjusted model, mean DBP at 8 wk (mm Hg) = 65.393; mean DBP change (mm Hg/wk): 8–18 wk = −0.202; 18–30 wk=0.091; 30–36 wk=0.375; ≥36 wk=1.155. For adjusted model, mean DBP at 8 wk (mm Hg) = 65.494; mean DBP change (mm Hg/wk): 8–18 wk = −0.175; 18–30 wk=0.109; 30–36 wk=0.463; ≥36 wk=1.252. BMI indicates body mass index; DBP, diastolic blood pressure; HDP, hypertensive disorder of pregnancy.

Table 4. Associations of Blood Pressure at 8 wk Gestation and Changes in Blood Pressure in Each Period of Pregnancy With the Time to Delivery (N=9930)

	Length of Gestation	
Blood Pressure Variable	% Increase in Gestation	95% CI
SBP at 8 wk, mm Hg		
Model 1	0.00	(−0.02, 0.02)
SBP change, mm Hg/wk		
8–18 wk		
Model 1	−0.20	(−0.63, 0.20)
Model 2	−0.22	(−0.65, 0.17)
18–30 wk		
Model 1	−0.28	(−0.73, 0.15)
Model 2	−0.47	(−0.92, −0.04)
30–36 wk		
Model 1	−0.91	(−1.16, −0.70)
Model 2	−1.17	(−1.43, −0.95)
≥36 wk		
Model 1	−0.14	(−0.26, −0.01)
Model 2	−0.54	(−0.69, −0.40)
DBP at 8 wk, mm Hg		
Model 1	0.01	(−0.02, 0.05)
DBP change, mm Hg/wk		
8–18 wk		
Model 1	−0.51	(−1.35, 0.19)
Model 2	−0.55	(−1.42, 0.18)
18–30 wk		
Model 1	−1.29	(−2.10, −0.62)
Model 2	−1.66	(−2.42, −1.00)
30–36 wk		
Model 1	−1.33	(−1.62, −1.10)
Model 2	−1.71	(−2.03, −1.46)
≥36 wk		
Model 1	−0.16	(−0.29, −0.03)
Model 2	−0.65	(−0.79, −0.50)

Model 1 was adjusted for HDP, maternal prepregnancy BMI, age, parity, smoking during pregnancy, education, and sex/No. of fetuses. Model 2 was additionally adjusted for SBP/DBP at 8 wk and SBP/DBP change in earlier periods of gestation. DBP indicates diastolic blood pressure; SBP, systolic blood pressure; HDP, hypertensive disorder of pregnancy; BMI, body mass index.

There is, however, evidence that gestational hypertension and preeclampsia share many risk factors,[31–33] suggesting that there are common mechanisms behind the development of both of these disorders. In addition, women who develop either gestational hypertension or preeclampsia have similarly increased risk of cardiovascular disease in later life.[34,35] Although preeclampsia generally carries a greater risk of intrauterine growth restriction and preterm birth than gestational hypertension,[31,33] women who have severe gestational hypertension have greater risk than those with mild preeclampsia.[4] Thus, our results are consistent with other evidence suggesting that there is important overlap between these 2 conditions.

Our finding that BP and, in particular, DBP rose more steeply from 18 weeks' gestation onward in women who developed preeclampsia compared with those who developed gestational hypertension or had essential hypertension is striking. Previous analyses of rhythm-adjusted mean BP in 202 women at risk of HDP also demonstrated equivalent BP in early pregnancy and then later discordance, with higher BP in preeclampsia than gestational hypertension.[21] However a study using clinic BP measurements (N≈8000) found that women who developed preeclampsia had lower BP in the first trimester than women who developed gestational hypertension, which may be because of the slightly later timing of measurement (median gestational age, 13.2 weeks) than our 8 weeks' baseline. In agreement with our findings, they also reported that preeclamptic women had a steeper rise in BP across pregnancy compared with gestational hypertensive women.[22] Another study (N=212) reported that women who developed preeclampsia had higher rhythm-adjusted mean BP in late pregnancy than women who had essential hypertension or developed gestational hypertension.[20] Our observed early rise in BP in preeclampsia is consistent with histological studies of impaired trophoblast invasion of myometrial arterial segments and thereby a necessity to increase baseline maternal placental perfusion,[36] as evidenced by the increase in DBP.

Given the similarities in risk factors between gestational hypertension and preeclampsia, the discordance in BP trajectory and presence of proteinuria, which would define preeclampsia, may simply be reflecting the extent of impaired placentation and an individual's renal threshold for manifesting proteinuria. Consistent with this, ≈50% of women who manifest mild hypertension before 35 weeks' gestation develop preeclampsia later in pregnancy.[29] Furthermore, even if gestational hypertension and preeclampsia are influenced by different biological mechanisms, then our results suggest that equivalent levels of early pregnancy BP predispose to both but that the biological changes related to preeclampsia produce more extreme increases in BP than those related to gestational hypertension.

The relationship that we found between a greater rise in BP after 18 weeks and a shorter time to delivery is in agreement with the study by Zhang et al,[37] which investigated BP change in 8325 nulliparous women from 6 countries. They found that women who had an early preterm birth (<34 weeks) and those who had a late preterm birth (34–36 weeks) had a greater rise in SBP and DBP between 12 to 19 weeks' and 30 to 34 weeks' gestation compared with women who delivered at term. Associations with spontaneous preterm birth were attenuated compared with those with all preterm births but remained strong.[37] We were unable to restrict to spontaneous deliveries, because we did not have these data available. However, we found that associations of DBP change from 18 weeks onward and SBP change from 30 weeks onward with length of gestation remained strong when restricting to women with normotensive pregnancies. The mechanism underlying the relationship between BP change and time to delivery is not clear, but the hypothalamic pituitary adrenal axis regulates both BP and maternal cortisol

concentrations, which are negatively associated with gestational age at birth.[38]

The strengths of our study are its large size, many repeated measurements of BP, which allowed HDP to be classified accurately, and the ability to model BP change and time to delivery in parallel. Limitations of our study include the use of routinely collected clinic measurements of BP. These are likely to be subject to a high degree of variability over the course of the day and between observers, because the method of measurement was not standardized between clinics. However, this reflects what is currently used in clinical practice to detect gestational hypertension and preeclampsia, and, thus, our results are applicable to this setting. We would not expect this to introduce bias into our findings, only random measurement error. More than 90% of women in this study attended 1 of 2 hospitals, and when we repeated the analysis for each of these separately, results were similar. Because measurements of BP before pregnancy were unavailable, we have used self-report of previous hypertension to classify essential hypertension. The higher level of BP in early pregnancy, which we found in this group compared with all of the other HDP groups, does, however, support this self-report. Although we have named this group essential hypertensives, this is likely to include a small number of women who had secondary hypertension, because we did not have information on all secondary causes. We were unable to distinguish between medically indicated induced and spontaneous deliveries; we have attempted to eliminate medically indicated deliveries related to high BP by repeating analyses in normotensive women but cannot exclude induced deliveries that were related to other conditions.

Perspectives

Our findings suggest that, as well as early pregnancy BP, the rate of increase in BP after 18 weeks may provide an early indication of those women most at risk of developing gestational hypertension or preeclampsia before the BP threshold used for diagnosis of HDP is crossed. Furthermore, women who developed gestational hypertension had a smaller decrease in SBP ≤18 weeks, compared with normotensive women, meaning that careful planned monitoring of BP change in those with high levels at their booking clinic may help earlier identification of women at risk of developing either gestational hypertension or preeclampsia.

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Disclosures

None.

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ONLINE SUPPLEMENT

BLOOD PRESSURE CHANGE IN NORMOTENSIVE, GESTATIONAL HYPERTENSIVE, PREECLAMPTIC AND ESSENTIAL HYPERTENSIVE PREGNANCIES

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Description of joint models for blood pressure change and time to delivery

We aimed to model blood pressure change jointly with time to delivery, using a joint model as described by Touloumi et al.(1) However, since gestational age at birth had a left-skewed distribution, which was difficult to model in this way, we reversed this variable to the number of weeks preterm, and centred this variable so that all values were greater than zero (this variable was calculated as 45 – gestational age in weeks, as the maximum length of gestation was 44 weeks). This variable therefore had a right-skewed distribution, which enabled us to use a lognormal model for this outcome. Covariates were included in the blood pressure change part of the models as a main effect and an interaction with each of the splines, and also in the time to delivery model as a main effect.

To regress time to delivery on blood pressure at baseline and blood pressure changes in each period of pregnancy we used the variances and pairwise covariances of the residual error from the time to delivery model and the individual-level random effects for blood pressure at 8 weeks and blood pressure change in each of the periods of gestation. Formulae described by Fisher were used to derive regression coefficients and standard errors from these variances and covariances.(2) In order to fully incorporate the uncertainty in the estimation of the variances and covariances of random effects and residuals we generated 10,000 realisations of the parameter estimates from the joint model, from a multivariate normal distribution using the means, variances and covariances of these estimates, and calculated regression coefficients for each of these realisations. Although the reverse of time to delivery was modelled, we transformed the regression coefficients to calculate the percentage difference in length of gestation associated with a unit increase in each of the blood pressure variables. These percentage differences were averaged over the 10,000 realisations, and 95% confidence intervals were formed using the 2.5^{th} and 97.5^{th} percentiles of the distributions of these values to fully incorporate the uncertainty in the estimation procedure. We therefore present the percentage mean increase in gestation per mmHg increase in SBP/DBP at 8 weeks or mmHg/week increase in rate of change in SBP/DBP, so that a greater coefficient represents a longer gestational period.

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Supplemental Tables and Figures

Table S1 Characteristics of the full dataset and women who had complete data on all covariables by hypertensive disorders of pregnancy

Maternal Characteristic	Full dataset (Total N=13,016)				Complete data on all variables (N=9,930)			
	Normotensive (N = 10,419)	Gestational Hypertension (N = 1,896)	Preeclampsia (N = 277)	Essential Hypertension (N = 424)	Normotensive (N = 7,970)	Gestational Hypertension (N = 1,416)	Preeclampsia (N=194)	Essential Hypertension (N = 350)
Gestational age at delivery (weeks)	N=10,419	N=1,896	N=277	N=424				
median (IQR)	40 (39, 41)	40 (39, 41)	39 (36, 40)	40 (38, 40)	40 (39, 41)	40 (39, 41)	39 (37, 40)	40 (38, 40)
Maternal pre-pregnancy BMI (%)	N=8,681	N=1,551	N=220	N=387				
Underweight	5.71	2.13	3.64	3.62	5.51	2.12	3.61	3.43
Normal	77.13	62.22	65.91	63.57	77.48	62.85	63.92	64.00
Overweight	13.39	23.08	17.73	18.35	13.35	22.53	19.07	18.29
Obese	3.77	12.57	12.73	14.47	3.66	12.50	13.40	14.29
Age (yrs) (%)	N=10,419	N=1,896	N=277	N=424				
15-19	5.03	3.90	8.66	2.36	3.64	2.40	5.15	1.43
20-24	19.02	21.84	25.99	15.80	16.10	19.42	27.32	14.29
25-29	38.47	39.14	34.30	42.22	39.37	40.68	35.05	42.86
30-34	28.05	24.63	18.77	25.94	30.46	26.91	21.13	27.71
35+	9.43	10.50	12.27	13.68	10.43	10.59	11.34	13.71
Parity (%)	N=9,684	N=1,761	N=248	N=404				
Nulliparous	42.14	55.99	69.35	52.72	42.27	56.64	73.71	53.14
Multiparous	57.86	44.01	30.65	47.28	57.73	43.36	26.29	46.86
Smoking in pregnancy (%)	N=9,776	N=1,773	N=249	N=410				
Never	65.41	69.66	75.10	74.39	68.19	72.46	74.74	75.71
Pre-pregnancy/1st trimester	13.61	14.95	15.66	11.46	13.05	13.77	17.01	10.57
Throughout	20.98	15.40	9.24	14.15	18.76	13.77	8.25	13.71

Education (%)	N=9,324	N=1,711	N=237	N=402				
CSE/Vocational	30.41	29.22	28.69	24.63	28.04	26.91	27.32	21.71
O Level	33.92	36.53	37.13	42.04	34.55	37.43	38.14	44.00
A Level	22.75	21.10	23.21	19.90	23.76	21.68	23.71	20.00
Degree	12.92	13.15	10.97	13.43	13.64	13.98	10.82	14.29
Pregnancy type (%)	N=10,419	N=1,896	N=277	N=424				
Male singleton	50.60	51.74	49.10	52.83	50.29	51.48	47.42	53.43
Female singleton	48.24	46.04	48.01	46.93	48.57	46.33	49.48	46.57
Twin	1.16	2.22	2.89	0.24	1.14	2.19	3.09	0.00

Abbreviations: BMI body mass index; CSE certificate of secondary education; IQR interquartile range

Table S2 Frequency distribution of the timing of onset of gestational hypertension and preeclampsia for women who developed these conditions

Hypertensive disorder of pregnancy (HDP)	Number of weeks of gestation at which HDP developed			
	< 30 weeks	**30-34 weeks**	**35-39 weeks**	**≥ 40 weeks**
Gestational hypertension				
N (%)	29 (12.1)	355 (18.7)	948 (50.0)	364 (19.2)
Preeclampsia				
N (%)	20 (7.2)	36 (13.0)	175 (63.2)	46 (16.6)

Abbreviations: HDP hypertensive disorder of pregnancy

Table S3 Average blood pressure levels at baseline and average changes in blood pressure per week in each period of gestation from univariate linear spline random effects models (N=13,016)

Blood pressure variable	Mean	Between-individual standard deviation	95% reference range
SBP at 8 weeks (mmHg)	112.78	8.66	(95.80, 129.75)
SBP change (mmHg/wk):			
8-18 weeks	-0.156	0.575	(-1.284, 0.972)
18-29 weeks	0.166	0.452	(-0.721, 1.052)
29-36 weeks	0.291	0.955	(-1.582, 2.164)
36+ weeks	1.075	1.535	(-1.933, 4.083)
DBP at 8 weeks (mmHg)	66.49	6.00	(54.72, 78.26)
DBP change (mmHg/wk):			
8-18 weeks	-0.199	0.378	(-0.941, 0.542)
18-29 weeks	0.112	0.331	(-0.537, 0.762)
29-36 weeks	0.478	0.818	(-1.126, 2.082)
36+ weeks	1.207	1.351	(-1.440, 3.855)

Table S4 Associations of hypertensive disorders of pregnancy and maternal characteristics with time to delivery (N = 9,930)

Characteristic	Length of gestation	
	% increase in gestation	95% confidence interval
HDP group		
Normotensive	0	-
Gestational hypertension	0.15	(-0.07, 0.37)
Preeclampsia	-3.27	(-3.96, -2.57)
Essential hypertension	-0.69	(-1.13, -0.25)
Pre-pregnancy BMI		
Underweight	-0.69	(-1.06, -0.31)
Normal	0	-
Overweight	0.30	(0.09, 0.52)
Obese	0.22	(-0.12, 0.56)
Maternal Age (years)		
<20	0.09	(-0.35, 0.54)
20-24	-0.04	(-0.27, 0.19)
25-29	0	-
30-34	-0.11	(-0.30, 0.08)
35+	-0.18	(-0.46, 0.09)
Parity		
Nulliparous	0	-
Multiparous	-0.09	(-0.26, 0.07)
Smoking		
Never	0	-
Pre-pregnancy/1st trimester	0.29	(0.06, 0.52)
Throughout pregnancy	-0.14	(-0.35, 0.07)
Maternal education		
CSE/vocational	-0.13	(-0.33, 0.06)
O level	0	-
A level	-0.11	(-0.32, 0.09)
Degree	0.29	(0.04, 0.54)
Pregnancy type		
Male singleton	0	-
Female singleton	0.34	(0.19, 0.50)
Twin	-6.92	(-7.96, -5.88)

Abbreviations: BMI body mass index; CSE certificate of secondary education; HDP hypertensive disorder of pregnancy

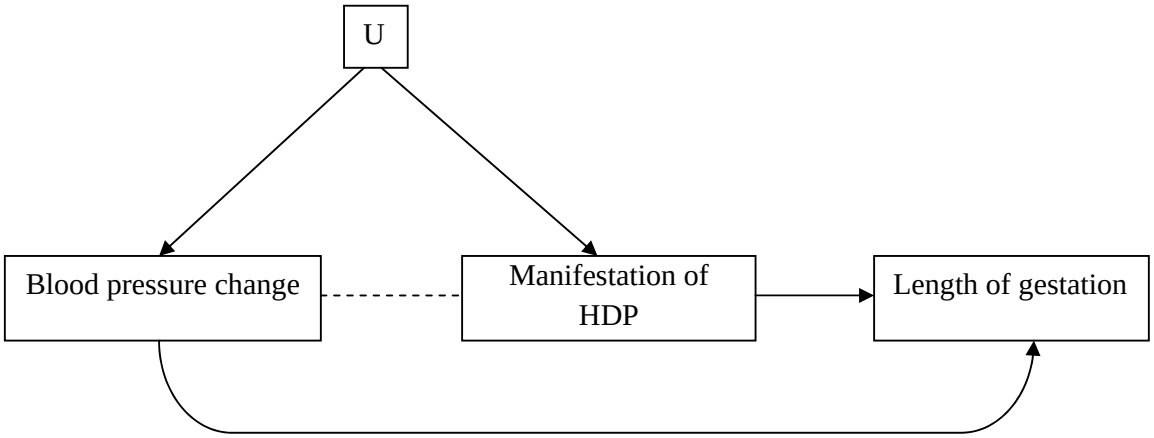
Table S5 Average length of gestation by standard deviations of blood pressure at 8 weeks gestation and change in blood pressure in each period of pregnancy in the joint model adjusted for maternal covariates*

Blood pressure variable	Length of gestation (weeks)	
	Average length of gestation	95% confidence interval
Average SBP and DBP at 8 weeks and average change in SBP and DBP in each period of gestation	39.76	(39.67, 39.84)
SBP at 8 weeks (1 SD = 7.51 mm Hg)		
+ 2 SD	39.77	(39.63, 39.92)
- 2 SD	39.74	(39.59, 39.88)
SBP change 8-18 weeks (1 SD = 0.58 mm Hg/week)		
+ 2 SD	39.67	(39.46, 39.87)
- 2 SD	39.85	(39.65, 40.05)
SBP change 18-30 weeks (1 SD = 0.44 mm Hg/week)		
+ 2 SD	39.66	(39.49, 39.83)
- 2 SD	39.85	(39.69, 40.02)
SBP change 30-36 weeks (1 SD = 0.93 mm Hg/week)		
+ 2 SD	39.06	(39.88, 39.25)
- 2 SD	40.37	(40.23, 40.52)
SBP change 36+ weeks (1 SD = 1.47 mm Hg/week)		
+ 2 SD	39.60	(39.43, 39.77)
- 2 SD	39.91	(39.75, 40.07)
DBP at 8 weeks (1 SD = 5.17 mm Hg)		
+ 2 SD	39.82	(39.67, 39.97)
- 2 SD	39.70	(39.54, 39.85)
DBP change 8-18 weeks (1 SD = 0.38 mm Hg/week)		
+ 2 SD	39.61	(39.37, 39.84)
- 2 SD	39.90	(39.69, 40.12)
DBP change 18-30 weeks (1 SD = 0.31 mm Hg/week)		
+ 2 SD	39.44	(39.26, 39.63)
- 2 SD	40.05	(39.89, 40.22)
DBP change 30-36 weeks (1 SD = 0.78 mm Hg/week)		
+ 2 SD	38.90	(38.72, 39.08)
- 2 SD	40.49	(40.36, 40.62)
DBP change 36+ weeks (1 SD = 1.28 mm Hg/week)		
+ 2 SD	39.59	(39.43, 39.75)
- 2 SD	39.92	(39.77, 40.07)

* Predictions are for women in the reference category: normotensive, normal pre-pregnancy weight, 25-29 years of age, nulliparous, never smoked in pregnancy, O level education and male singleton pregnancy and for average levels of each of the blood pressure variables other than that being varied.

Abbreviations: DBP diastolic blood pressure; SBP systolic blood pressure; SD standard deviation

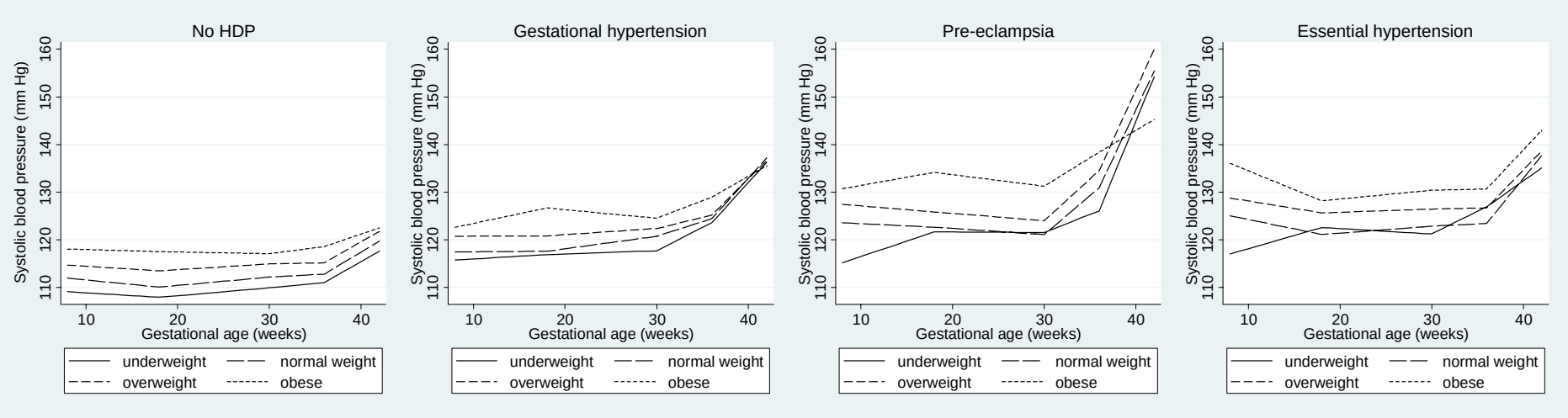
Figure S1 Hypothesised relationships between blood pressure change, hypertensive disorders of pregnancy and length of gestation*



*Arrows represent causal relationships; dashed lines represent an association. U is an unmeasured variable representing the underlying HDP, which is hypothesised to influence changes in blood pressure and the observed symptoms of HDP. Conditioning on length of gestation would bias the estimate of the association between blood pressure change and manifested HDP.

Abbreviations: HDP hypertensive disorder of pregnancy

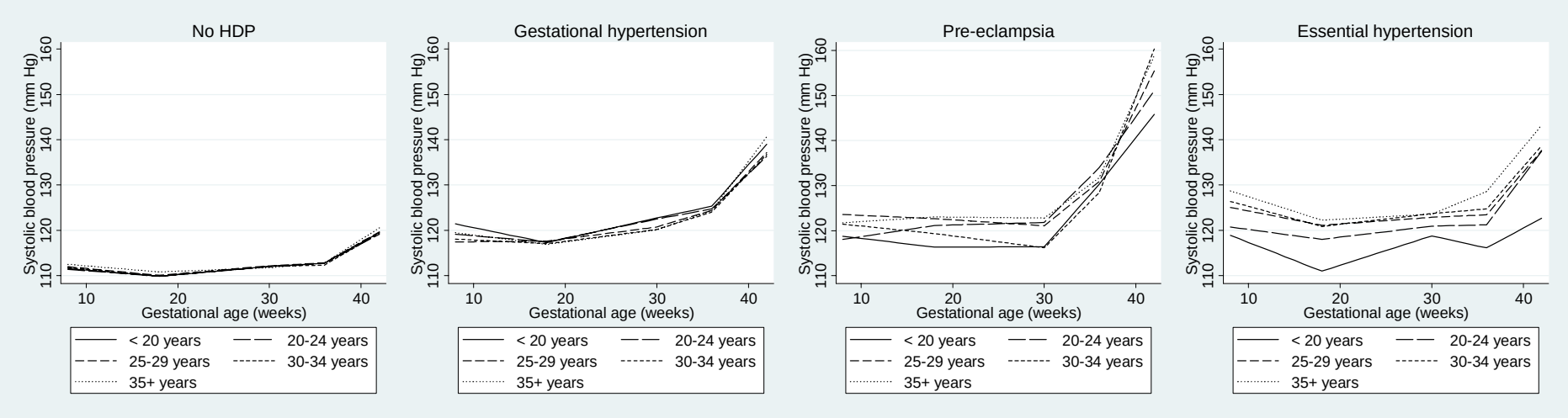
Figure S2 Predicted trajectories of systolic blood pressure across pregnancy by maternal pre-pregnancy BMI and hypertensive disorders of pregnancy (N=9,930)*



* Trajectories are predicted by the fully-adjusted joint model including interactions of each of the maternal covariates with hypertensive disorder of pregnancy group and with blood pressure at baseline and blood pressure change in each period of gestation.

Overall *P* for interaction = 0.019;
P for interaction with: SBP at 8 weeks = 0.386; SBP change 8-18 weeks = 0.149; 18-30 weeks = 0.301; 30-36 weeks = 0.755; 36+ weeks = 0.306

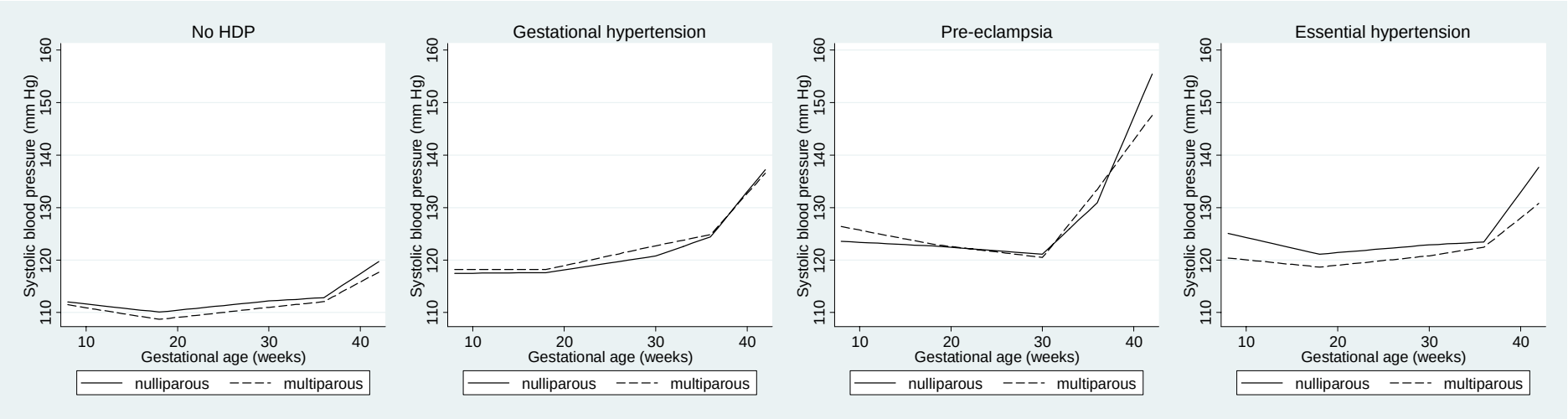
Figure S3 Predicted trajectories of systolic blood pressure across pregnancy by maternal age and hypertensive disorders of pregnancy (N=9,930)*



* Trajectories are predicted by the fully-adjusted joint model including interactions of each of the maternal covariates with hypertensive disorder of pregnancy group and with blood pressure at baseline and blood pressure change in each period of gestation.

Overall *P* for interaction = 0.068;
P for interaction with: SBP at 8 weeks = 0.202; SBP change 8-18 weeks = 0.684; 18-30 weeks = 0.770; 30-36 weeks = 0.596; 36+ weeks = 0.584

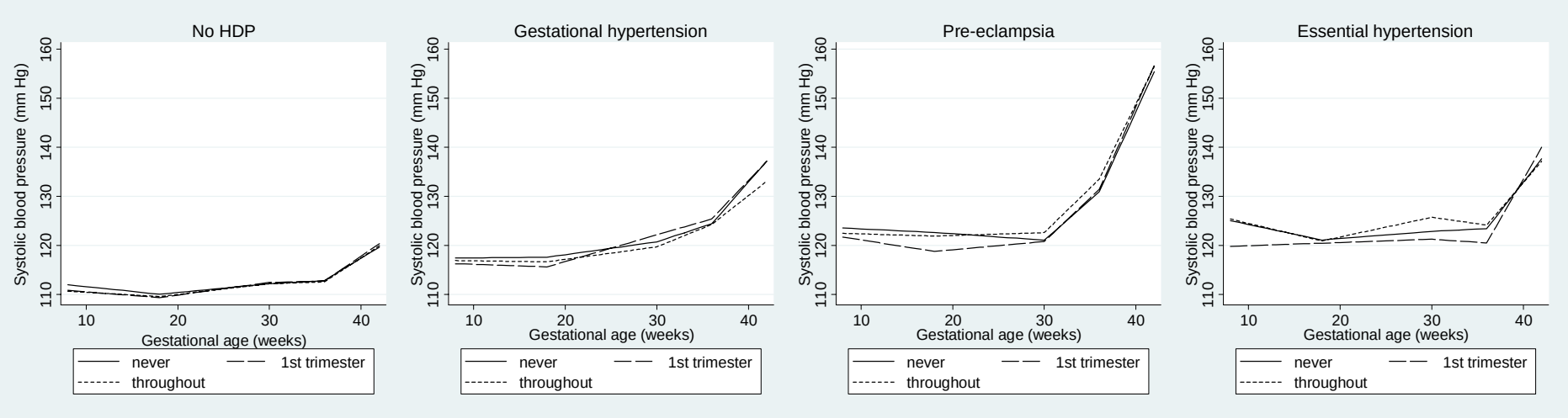
Figure S4 Predicted trajectories of systolic blood pressure across pregnancy by parity and hypertensive disorders of pregnancy (N=9,930)*



* Trajectories are predicted by the fully-adjusted joint model including interactions of each of the maternal covariates with hypertensive disorder of pregnancy group and with blood pressure at baseline and blood pressure change in each period of gestation.

Overall *P* for interaction < 0.001;
P for interaction with: SBP at 8 weeks = 0.012; SBP change 8-18 weeks = 0.387; 18-30 weeks = 0.435; 30-36 weeks = 0.029; 36+ weeks = 0.069

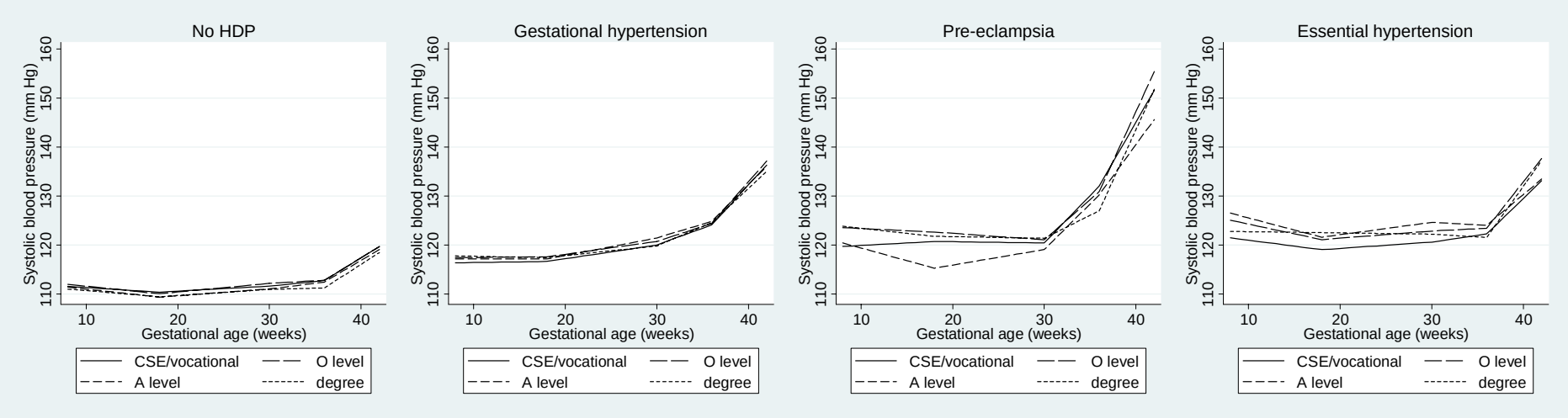
Figure S5 Predicted trajectories of systolic blood pressure across pregnancy by smoking during pregnancy and hypertensive disorders of pregnancy (N=9,930)*



* Trajectories are predicted by the fully-adjusted joint model including interactions of each of the maternal covariates with hypertensive disorder of pregnancy group and with blood pressure at baseline and blood pressure change in each period of gestation.

Overall *P* for interaction = 0.272;
P for interaction with: SBP at 8 weeks = 0.689; SBP change 8-18 weeks = 0.657; 18-30 weeks = 0.131; 30-36 weeks = 0.858; 36+ weeks = 0.182

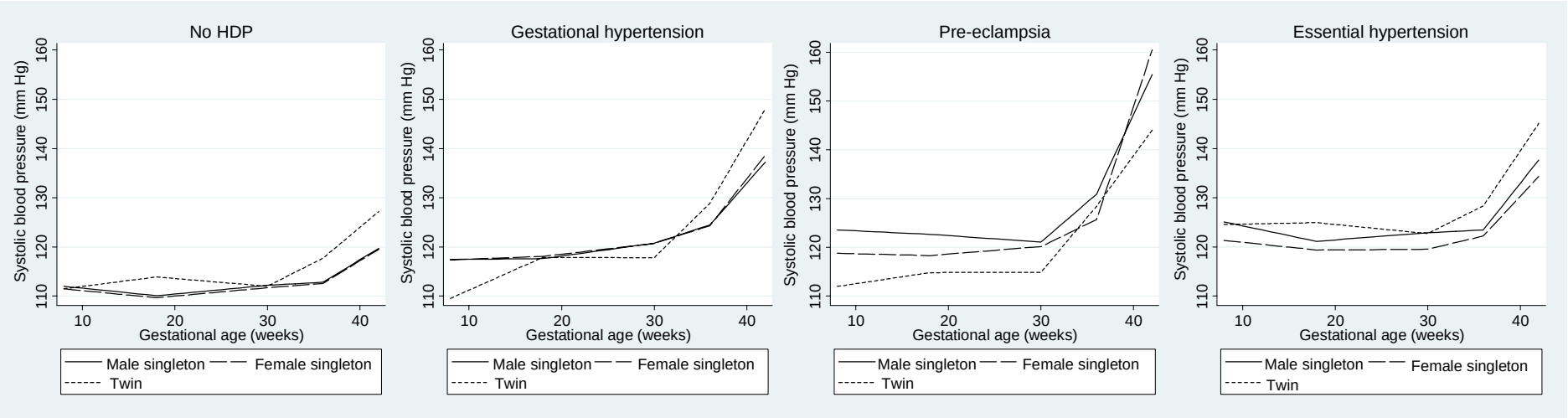
Figure S6 Predicted trajectories of systolic blood pressure across pregnancy by maternal education and hypertensive disorders of pregnancy (N=9,930)*



* Trajectories are predicted by the fully-adjusted joint model including interactions of each of the maternal covariates with hypertensive disorder of pregnancy group and with blood pressure at baseline and blood pressure change in each period of gestation.

Overall *P* for interaction = 0.148;
P for interaction with: SBP at 8 weeks = 0.429; SBP change 8-18 weeks = 0.862; 18-30 weeks = 0.328; 30-36 weeks = 0.564; 36+ weeks = 0.454

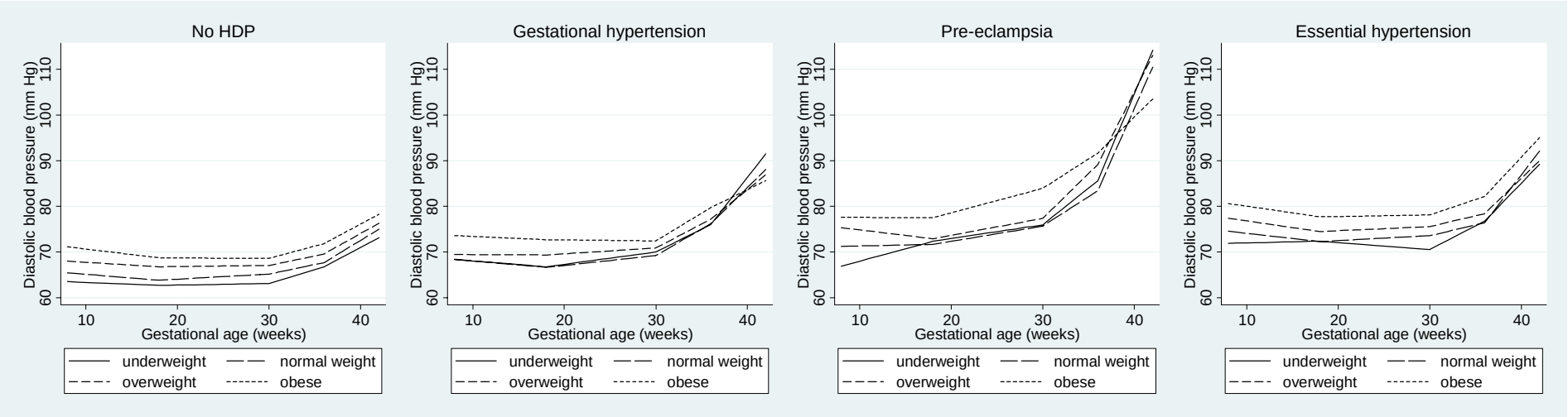
Figure S7 Predicted trajectories of systolic blood pressure across pregnancy by pregnancy type and hypertensive disorders of pregnancy (N=9,930)*



* Trajectories are predicted by the fully-adjusted joint model including interactions of each of the maternal covariates with hypertensive disorder of pregnancy group and with blood pressure at baseline and blood pressure change in each period of gestation.

Overall *P* for interaction = 0.004;
P for interaction with: SBP at 8 weeks = 0.011; SBP change 8-18 weeks = 0.847; 18-30 weeks = 0.384; 30-36 weeks = 0.169; 36+ weeks = 0.072

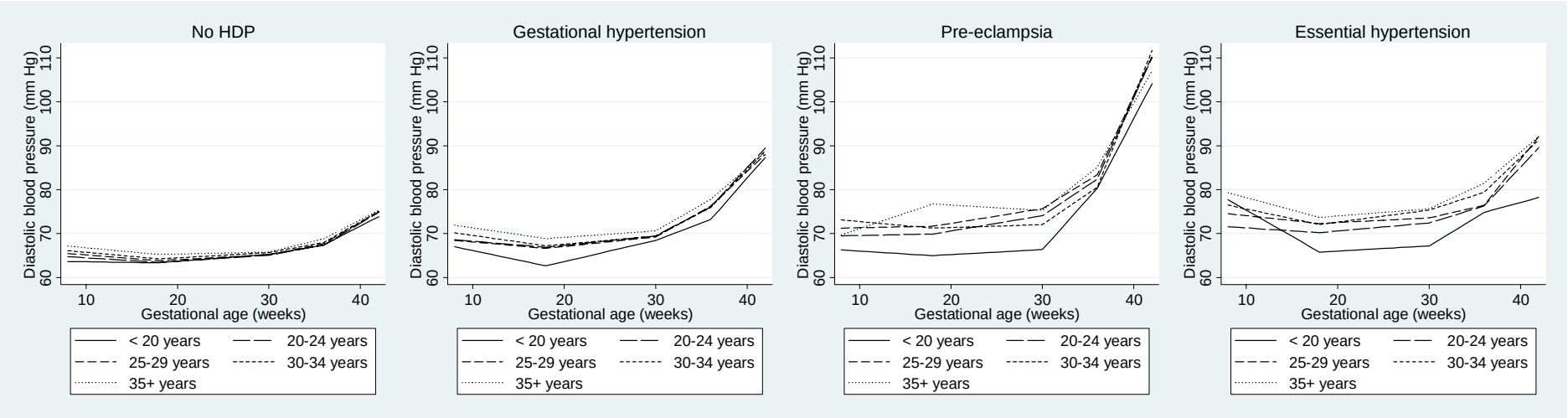
Figure S8 Predicted trajectories of diastolic blood pressure across pregnancy by maternal pre-pregnancy BMI and hypertensive disorders of pregnancy (N=9,930)*



* Trajectories are predicted by the fully-adjusted joint model including interactions of each of the maternal covariates with hypertensive disorder of pregnancy group and with blood pressure at baseline and blood pressure change in each period of gestation.

Overall *P* for interaction < 0.001;
P for interaction with: DBP at 8 weeks = 0.607; DBP change 8-18 weeks = 0.583; 18-30 weeks = 0.428; 30-36 weeks = 0.520; 36+ weeks = 0.007

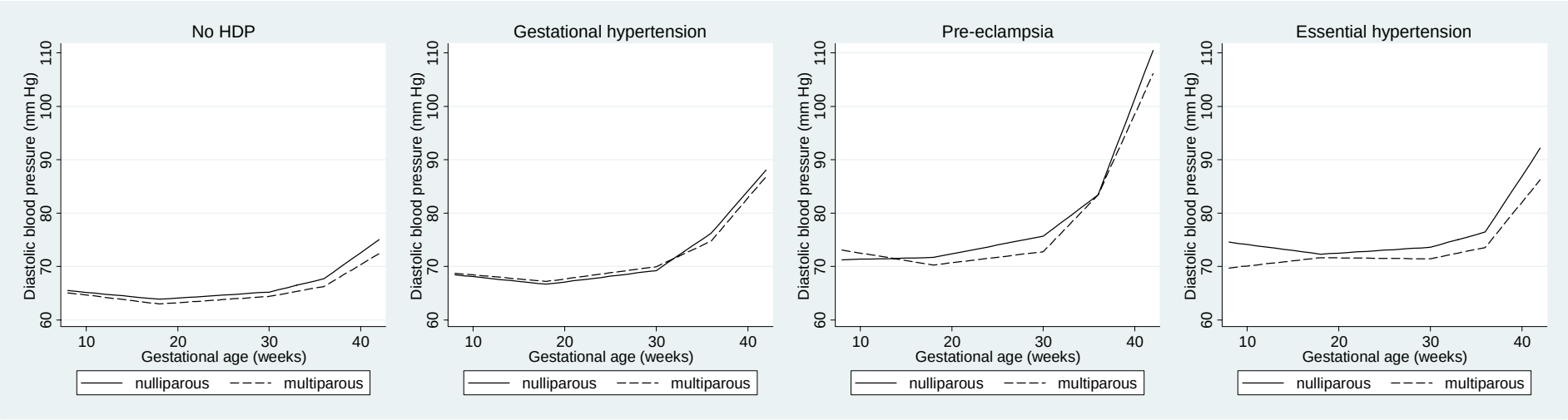
Figure S9 Predicted trajectories of diastolic blood pressure across pregnancy by maternal age and hypertensive disorders of pregnancy (N=9,930)*



*Trajectories are predicted by the fully-adjusted joint model including interactions of each of the maternal covariates with hypertensive disorder of pregnancy group and with blood pressure at baseline and blood pressure change in each period of gestation.

Overall *P* for interaction = 0.007;
P for interaction with: DBP at 8 weeks = 0.255; DBP change 8-18 weeks = 0.149; 18-30 weeks = 0.395; 30-36 weeks = 0.696; 36+ weeks = 0.480

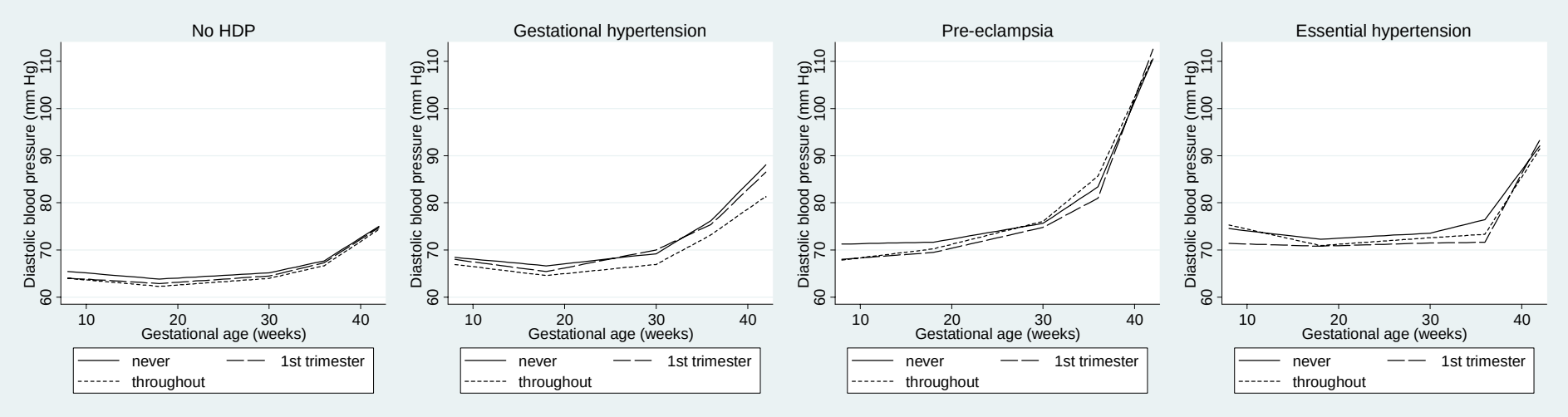
Figure S10 Predicted trajectories of diastolic blood pressure across pregnancy by parity and hypertensive disorders of pregnancy (N=9,930)*



*Trajectories are predicted by the fully-adjusted joint model including interactions of each of the maternal covariates with hypertensive disorder of pregnancy group and with blood pressure at baseline and blood pressure change in each period of gestation.

Overall *P* for interaction < 0.001;
P for interaction with: DBP at 8 weeks <0.001; DBP change 8-18 weeks = 0.005; 18-30 weeks = 0.386; 30-36 weeks = 0.007; 36+ weeks = 0.253

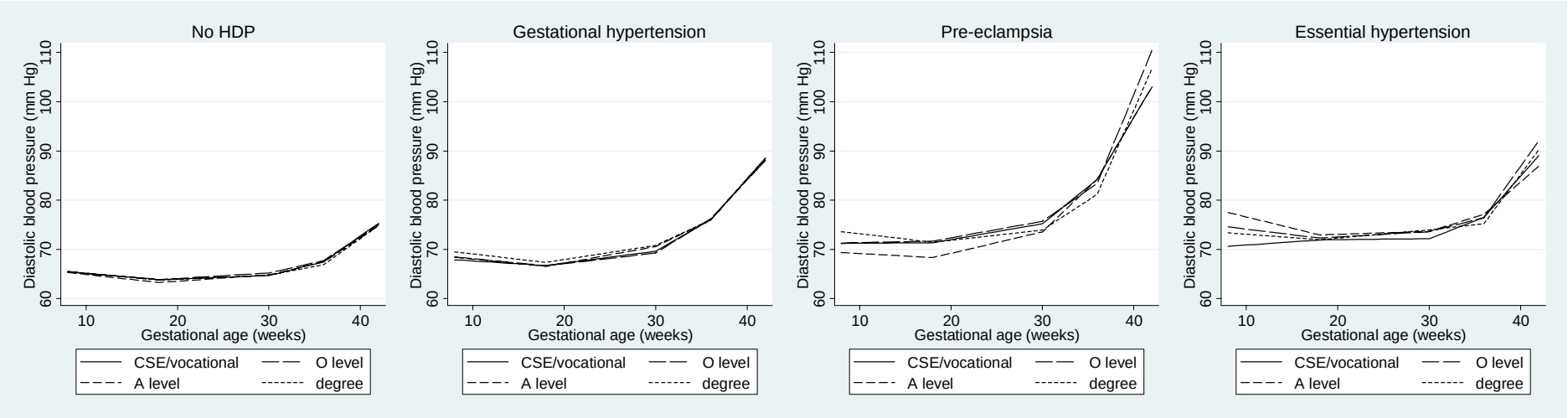
Figure S11 Predicted trajectories of diastolic blood pressure across pregnancy by smoking during pregnancy and hypertensive disorders of pregnancy (N=9,930)*



*Trajectories are predicted by the fully-adjusted joint model including interactions of each of the maternal covariates with hypertensive disorder of pregnancy group and with blood pressure at baseline and blood pressure change in each period of gestation.

Overall *P* for interaction < 0.001;
P for interaction with: DBP at 8 weeks = 0.462; DBP change 8-18 weeks = 0.772; 18-30 weeks = 0.295; 30-36 weeks = 0.117; 36+ weeks = 0.020

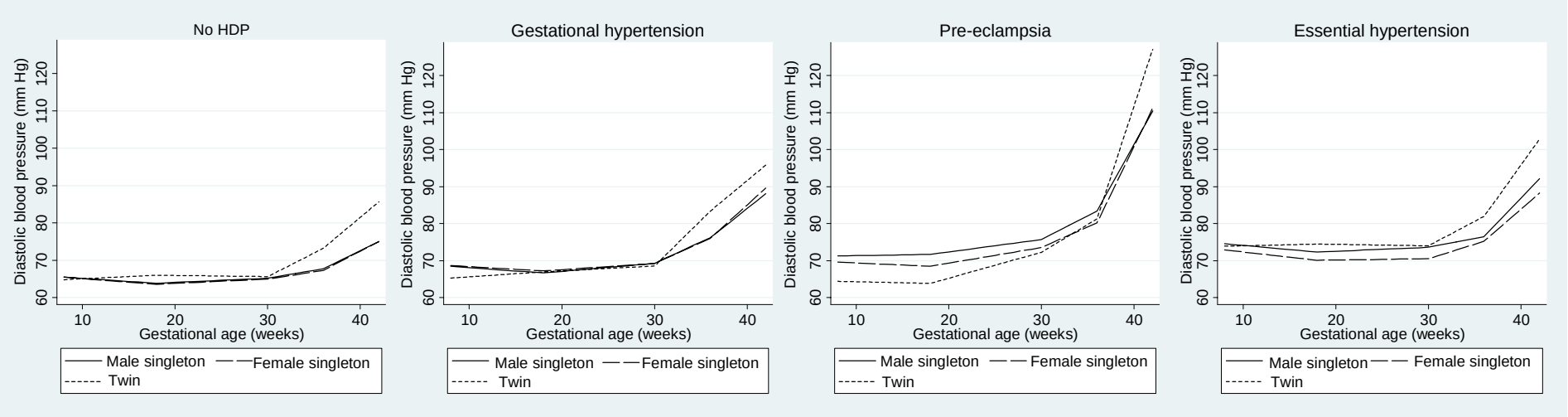
Figure S12 Predicted trajectories of diastolic blood pressure across pregnancy by maternal education and hypertensive disorders of pregnancy (N=9,930)*



*Trajectories are predicted by the fully-adjusted joint model including interactions of each of the maternal covariates with hypertensive disorder of pregnancy group and with blood pressure at baseline and blood pressure change in each period of gestation.

Overall *P* for interaction = 0.042;
P for interaction with: DBP at 8 weeks = 0.015; DBP change 8-18 weeks = 0.570; 18-30 weeks = 0.751; 30-36 weeks = 0.311; 36+ weeks = 0.129

Figure S13 Predicted trajectories of diastolic blood pressure across pregnancy by pregnancy type and hypertensive disorders of pregnancy (N=9,930)*



*Trajectories are predicted by the fully-adjusted joint model including interactions of each of the maternal covariates with hypertensive disorder of pregnancy group and with blood pressure at baseline and blood pressure change in each period of gestation.

Overall *P* for interaction < 0.001;
P for interaction with: DBP at 8 weeks = 0.336; DBP change 8-18 weeks = 0.898; 18-30 weeks = 0.441; 30-36 weeks = 0.239; 36+ weeks = 0.175