Maternal Hypertensive Disorders of Pregnancy and Depression or Anxiety in Adolescence: Findings from the Millennium Cohort Study

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Abstract

Background: The short-term effects of hypertensive disorders of pregnancy (HDP) on the health of the fetus are well known; however, their impacts on the risk of mental health in the exposed offspring are not fully understood. Our aim was to examine the association between HDP and depression/anxiety at age 17 years.

Methods: We used data from The Millennium Cohort Study, a nationally representative longitudinal study of children born in the United Kingdom. Data on HDP and potential confounders were collected when children were 9-months. Data on depression and anxiety were collected as one variable when children were aged 17 years using self-reported doctor diagnosis, and reclassified as depression/anxiety (overall), depression/anxiety with treatment, and depression/anxiety without treatment. Crude and adjusted logistic regression models were performed to examine the association between HDP and depression/anxiety, adjusting for several maternal and socio-economic factors.

Results: There were 9,517 singleton mother-child pairs included in the analyses. Adjusted logistic regression suggested an association between HDP and depression/anxiety (adjusted odds ratio, (aOR):1.30 [95% CI, 1.02–1.66]) at age 17 years. A similar association was observed for HDP and depression/anxiety with treatment (aOR:1.33 [95% CI, 1.01–1.73]) and HDP and depression/anxiety without treatment (aOR: 1.30 [95% CI, 0.80–2.12]), although the latter did not reach statistical significance.

Limitations: Data on severity and classifications of HDP were not available.

Conclusion: Exposure to HDP may be associated with an increased likelihood of depression or anxiety at age 17 years. Future research should consider severity and different classifications of HDP.

Keywords: Adolescence; anxiety; depression; hypertension; hypertensive disorders of pregnancy; pregnancy

Introduction

Hypertensive disorders of pregnancy (HDP) encompass a diverse range of diagnoses including chronic hypertension, gestational hypertension, and preeclampsia. Chronic hypertension is defined as hypertension before pregnancy or before 20 weeks gestation (Magee et al., 2022). Gestational hypertension is hypertension arising de novo at 20 weeks gestation or more in the absence of proteinuria or other findings suggestive of preeclampsia (Magee et al., 2022). Pre-eclampsia is defined as gestational hypertension accompanied by one or more of the following 1) proteinuria 2) maternal end-organ dysfunction or 3) uteroplacental dysfunction (Magee et al., 2022).

The harmful effects of HDP on the health of offspring are well known, including an increased risk of cardiovascular, endocrine, nutritional, and metabolic disorders as adults (Pinheiro et al., 2016; Ferreira, Peeters and Stehouwer, 2009; Davis et al., 2012). Furthermore, multiple studies have reported links between HDP and several adverse perinatal outcomes such as preterm birth, stillbirth, and intrauterine growth restriction in the offspring (Dachew et al., 2018; Maher et al., 2018).

Conversely, there is still ongoing debate as to whether exposure to HDP has an effect on mental health in the exposed offspring (De Boo and Harding., 2006; Sakurai, Shishido and Horiuchi, 2022). A recent systematic review and meta-analysis examined the relationship between HDP and offspring mental and behavioural problems and reported a 37% higher risk of schizophrenia in offspring exposed to preeclampsia (Dachew et al., 2018). However, fewer studies were identified that examined the association between HDP and depression/anxiety specifically. Furthermore, there is a lack of evidence in later adolescence in particular, with review authors suggesting the need for large sample birth cohorts to further investigate an HDP-mental health relationship in offspring (Dachew et al., 2018).

Therefore, the objective of this study was to investigate the association between HDP and depression or anxiety at age 17 years using data from the Millennium Cohort Study, a nationally representative longitudinal study of children born in the United Kingdom.

Methods

Millennium cohort study

The Millennium Cohort Study (MCS) is a nationally representative longitudinal study of children born between 2000 and 2002 in the United Kingdom. The study has followed the lives of these young people born across 398 areas in England, Scotland, Wales, and Northern Ireland. To date, there has been 7 waves of survey data collected from this cohort at ages 9 months (MCS1), 3 years (MCS2), 5 years (MCS3), 7 years (MCS4), 11 years (MCS5), 14 years (MCS6) and 17 years (MCS7). The recent MCS7 data sweep of 17-year-olds deliberately concentrated on interacting with these cohort members by carrying out face-to-face interviews with the adolescent cohort for the first time and parental involvement at MCS7 was minimal.[10] Ethical approval was obtained from an NHS Research Ethics Committee (MREC), and informed consent was obtained from both parents and children within the cohort (Connelly and Platt, 2014).

Study Population

Stratified cluster sampling by region and electoral ward was used to select the participants for the MCS. The cohort sample was designed using geographic clusters to be representative of the UK. This allowed for the oversampling of populations that are typically difficult to reach, specific areas with sizable ethnic minorities, high levels of child poverty, and the smaller UK nations of Scotland, Wales, and Northern Ireland (Connelly and Platt, 2014). At the beginning of the new millennium the MCS initially recruited 18,552 families into the study. Only

singleton births were considered in the current study, so after exclusion of multiple births, there remained 18,274 singleton mother–offspring pairs at baseline with data on HDP. The baseline participants reduced at each data survey sweep as follows 15,590 (MCS2), 15,246 (MCS3), 13,857 (MCS4), 13,287 (MCS5), 11,726 (MCS6) (Connelly and Platt, 2014). There were 9,774 singleton mother-child pairs remaining in the study for the most recent MCS7 survey data sweep of 17-year-olds. Of these, 9,521 answered survey questions on depression and anxiety (of which 9,517 had data on HDP). See Figure S1 for flow chart of study participants.

Exposure

Data on HDP were self-reported and collected from mothers during the first data sweep when the children were aged approximately 9 months old via face-to-face computer-assisted personal interview. The mothers of the birth cohort were asked "Did you have any illness or other problems during the pregnancy that required medical attention or treatment?" Those who responded yes to this question were instructed to choose all that apply from a list of illnesses. The list of illnesses included "raised blood pressure, eclampsia/preeclampsia or toxaemia" and ticking "yes" to this option assumed a diagnosis of HDP.

Outcome

Data on offspring depression and anxiety were collected as one variable when children were aged 17 years. This was a self-reported doctor diagnosis of anxiety or depression. Data were collected from adolescents via face-to-face interviews using a validated questionnaire during the seventh sweep of data in 2018. Question testing was deemed necessary to ensure cohort members understood the questions, felt willing and able to answer them, and could provide accurate and valid responses (Centre for Longitudinal Studies, 2018a). The MCS carried out pilot and dress rehearsals which tested all aspects of the survey (Centre for Longitudinal

Studies, 2018a). Outcomes of interest included offspring depression/anxiety (overall), offspring depression/anxiety with (current/ever) treatment, and offspring depression/anxiety without (current/ever) treatment. Depression/anxiety (overall) was generated from binary (yes/no) responses to the following question: "Has a doctor ever told you that you suffer from depression or serious anxiety?" If the answer to the question was "yes", then depression/anxiety with treatment, and depression/anxiety without treatment were generated using both of the following two questions: "Are you currently being treated for depression or serious anxiety?" and "Have you ever received treatment for depression or serious anxiety?" For example, if a respondent answered "no" to the question on currently being treated and "yes" to the question on ever receiving treatment, then they were classified as 'depression/anxiety with treatment'

Confounding Variables

In the analysis, only covariates were included in the models which were deemed to be associated with both the exposure and outcome. The following maternal and socio-economic factors collected at MCS1 were considered as potential confounders: maternal age, maternal education, maternal smoking status, maternal alcohol consumption during pregnancy, maternal body mass index (BMI), income, infant sex, and parity. The definitions for all potential confounders are described in Supplementary Table S1. As small for gestational age (SGA) may be a potential mediator or confounder for the association between HDP and depression/anxiety, an interaction term between HDP and SGA was separately analysed. SGA was defined as birthweight below the 10^{th} percentile for gestational age and sex. Similarly, as low birthweight and preterm birth may be potential mediators or confounders, interaction terms for HDP and low birthweight, and HDP and preterm birth were analysed separately. Low birthweight was defined as maternal reported birthweight of <2,500 grams. Preterm birth was defined as maternal reported delivery at <37 weeks' gestation.

Maternal depression/anxiety was recorded nine months post-partum through doctor-diagnosed self-reporting. Therefore, it could be a potential confounder or potential mediator, because the onset could have been before or during pregnancy or after birth.

Statistical Analysis

Descriptive analysis was performed to describe the baseline characteristics of the study population. The association between HDP and offspring depression/anxiety were analysed using logistic regression models to estimate the crude and adjusted odds ratios (OR) and accompanying 95% confidence intervals (CI). Sub-group analyses were performed for maternal age (≤ 35yrs and >35yrs.) and infant sex. Interaction terms were used between the exposure variable (HDP) and SGA, between HDP and low birthweight, between HDP and preterm birth and between HDP and maternal depression/serious anxiety. We further adjusted for maternal depression/serious anxiety to assess its impact on the reported results. Missing data on confounding variables was minimum, the highest percentage of missing data was on BMI (8.68%), and this was handled in the analysis by adding a missing data category in the variable. All analyses were performed using the statistical software Stata SE/17.

Results

Descriptive Analysis

The current study comprised 9,517 singleton mother-child pairs with data on HDP and offspring depression/anxiety. The characteristics of these paired study participants according to the mothers HDP status are outlined in Table 1. Of the study cohort, 10.27% (n= 978) had a self-reported doctor diagnosis of depression/anxiety. The number of females in this population with a depression or severe anxiety diagnosis was more than double [69% (n=675)] that of their male counterparts [31% (n=303)]. Furthermore, supplementary Table S2 compares the baseline

characteristics of the paired cohort with the characteristics of the MCS7 pairs remaining in the study according to the mother's HDP status. The only noteworthy difference in those that were retained in the analysis was that they were better educated than those mothers lost to follow-up, with 33% having attained a diploma or higher compared to 25% at baseline.

Associations between HDP and depression/severe anxiety in the offspring at age 17

Table 2 outlines the univariable and multivariable associations between HDP and depression/anxiety (overall), depression/anxiety with treatment, and depression/anxiety without treatment in the offspring at age 17. The univariable logistic regression analysis found that adolescents exposed to HDP had a 29% increase in the odds of having a diagnosis of depression/anxiety (overall) compared with those who were unexposed (OR:1.29 [95% CI, 1.02–1.62]). Similar effect estimates to HDP-depression/anxiety overall were found for both HDP-depression/anxiety with treatment (OR:1.32 [95% CI, 1.01–1.71]) and HDP-depression/anxiety with no treatment (OR:1.20 [95% CI, 0.74–1.93], although the latter did not reach statistical significance. The associations remained similar in the multivariable models after adjusting for potential confounders (Table 2). For example, the adjusted OR (aOR) of depression/anxiety increased by 30% in those who were exposed to HDP compared to those that were unexposed to HDP (aOR:1.30 [95% CI, 1.02–1.66]). This observation was repeatedly found when looking at both treated depression/anxiety (aOR:1.33 [95% CI, 1.01–1.73]) and untreated depression/anxiety (aOR:1.30 [95% CI, 0.80–2.12]).

Subgroup analysis and interaction terms

The results of the subgroup models, interaction terms and post-hoc analysis are presented in Table 3. In model 1, the association between HDP and depression/anxiety in those born to women ≤35yrs was similar (aOR:1.31 [95% CI, 1.01–1.70]) to those found in our primary

analysis. However, the association for those born to women >35yrs was not statistically significant (aOR:1.22, 95% CI, 0.62–2.41]). In model 2, the likelihood of depression/anxiety increased to 44% (aOR:1.44 [95% CI, 1.08–1.93]) for females exposed to HDP compared to females not exposed to HDP. In contrast, the subgroup analysis for males was not statistically significant (aOR:1.05 [95% CI, (0.67–1.63]). Model 3 examined the following groups within the study, (1) those with HDP but without SGA, (2) those with both HDP and SGA, (3) and those without HDP but with SGA. The adjusted odds of depression/anxiety in those three groups suggested higher odds of depression/anxiety compared to those not born to hypertensive mothers and not born SGA, although all estimated ORs did not reach a statistically significant level in this model. The OR for those exposed to HDP and low birthweight increased to 1.91 (95% CI, 1.06-3.43) in model 4, while the odds ratio for HDP and preterm birth increased to 2.13 (95% CI, 1.22-3.72) in model 5. In model 6, the OR was almost unchanged for participants who had HDP without maternal depression. Finally, the adjusted effect estimate for the overall depression/anxiety was slightly attenuated from 1.30 [95% CI, 1.02–1.66]) to 1.23 [95% CI, (0.97–1.57] when we additionally adjusted for maternal depression/anxiety in a post-hoc analysis in model 7.

Discussion

Main findings

This study examined the association between HDP and depression or anxiety in the offspring at age 17 years. The principal finding of the analysis is that exposure to HDP increased the odds of depression or anxiety in this cohort by approximately 30%. This finding was observed in both univariable and multivariable analysis indicating that the association was not confounded by maternal age, maternal education, maternal smoking status, maternal alcohol consumption during pregnancy, maternal BMI, income, infant sex, or parity which suggests

that maternal HDP may be an independent risk factor for depression/serious anxiety in the offspring. The observed multivariable association was similar for those that reported receiving treatment for depression/anxiety and those not receiving treatment. It should be noted however that the association was slightly attenuated after further controlling for maternal depression, although the OR remained unchanged in participants without maternal depression.

Comparison with other studies

The observations found in our study are comparable to other studies which examined the association between HDP and mental health outcomes. The Helsinki Birth Cohort found that those exposed to hypertension without proteinuria had a hazard ratio of 1.44 [95% CI, 1.11–1.88] for developing any mental health disorder over their lifetime compared to those who were not exposed to HDP (Tuovinen et al., 2012). Furthermore, results from our study agree with findings from a recent review by Robinson et al which demonstrated a positive relationship between HDP and the development of mental and behavioural disorders in children (Robinson et al., 2021). The reported pooled effect estimates ranged from 1.3 to 1.7 with 95% CI ranging from 1.0 to 2.2 (Robinson et al., 2021). In addition, the review found that the observed associations were independent of similar known confounding factors.

The Avon Longitudinal Study of Parents and Children (ALSPAC) study also examined a HDP-anxiety relationship and reported more than a two-fold increase in odds of anxiety in those exposed to HDP (2.4 [95% CI, 1.2–3.4]) (Dachew et al., 2019). It should be noted that anxiety was measured using the DAWBA tool, while depression/anxiety were based on self-reported doctor diagnosis in the current study (Dachew et al., 2019), which may partly explain the difference in the magnitude of the association.

Biological mechanisms

One of the possible aetiological paths linking severe HDP and neurodevelopment disorders is altered neuroanatomical and functional connection, which may cause behavioural problems in

exposed children (Rätsep et al., 2016; Figueiro-Filho et al., 2017). Several complex but plausible biological mechanisms exist, such as oxidative stress, utero-placental vascular insufficiency, overexposure to maternal glucocorticoids and fetal malnutrition. Dachew et al argue that maternal uterine spiral arteries do not sufficiently invade the placental trophoblast in those women with HDP (Tuovinen et al., 2012). Due to inadequate placental perfusion, this results in fetal and placental hypoxia. Reduced oxygen flow to the fetus during pregnancy may alter neurodevelopmental trajectories neurodevelopment and increase the likelihood of anxiety disorders in later life. Oxidative stress can also be a result of inadequate nutrition and oxygen (Phoswa and Khaliq, 2021). An imbalance between the creation of free radicals and antioxidant defences leads to oxidative stress, a complex biological process (Figueiro-Filho et al., 2017; Phoswa and Khaliq, 2021). Due to its rapid rate of oxygen consumption, significant amount of polyunsaturated fatty acids, regionally high iron levels, and comparatively insufficient antioxidant defences, the brain is sensitive to oxidative stress (Dachew et al., 2020). Animal and human studies have revealed a substantial link between anxiety disorders and oxidative stress (Phoswa and Khaliq, 2021; Dachew et al., 2020; Peter Stein, 2008). HDP can cause irregular fetal blood flow to the placenta, which can eventually result in fetal starvation and poor brain development (Gagnon, 2003). Given that maternal inflammation is a recognized risk factor for poor neurodevelopmental outcomes, it is also possible that the interplay between inflammatory response and oxidative stress linked to HDP could be involved (Barron, McCarthy and O'Keeffe, 2021).

Strengths and limitations

This study has several strengths. First, it uses a large contemporary population-based prospective birth cohort study which is nationally representative of children in the UK. Secondly, the study used valid, reliable methods for the exposure variable and outcome measurements. In addition, the prevalence of HDP which was reported in this study (7.33%) is

in line with the national estimate for HDP (7%) for the same time period minimizing the likelihood of this exposure being misclassified (Government Statistical Service, 2002). However, the possibility of recall bias for the exposure cannot be ruled out as data on HDP were collected approximately nine months after delivery. While this is less likely for the outcome measurements as the data were collected prospectively for depression/anxiety when children were 17 years. Thirdly, the study controlled for many maternal and socio-economic factors including maternal age, maternal education, maternal smoking status, maternal alcohol consumption during pregnancy, maternal BMI, income, infant sex, and parity and maternal mental depression/anxiety.

However, there are some limitations of this study that should be noted. First, due to a lack of data collected on different subgroups or severities of HDP categories, it was not possible to separately analyse the impact of gestational hypertension and preeclampsia. As a result, there was limited overlap with other research, which frequently concentrate on a single hypertension condition. Second, the sample size was reduced from 18,818 pairs at baseline to 9,517 pairs at MCS7, which may potentially indicate selection bias. However, when comparing the baseline characteristics of the paired cohort to those remaining in the study at MCS7 the rate of exposure (HDP) in offspring between those retained in the study and those lost to follow-up was similar (supplementary Table S2). Overall, the characteristics of both cohorts are very closely similar with the only noteworthy difference being those that were retained in the analysis were better educated than those mothers lost to follow up which indicates that loss to follow-up bias in this study may not be an issue. Third, self-reported doctor diagnoses of depression/anxiety are subject to social desirability bias. Social desirability bias is the propensity to overreport more desirable characteristics while underreporting socially unfavourable attitudes and behaviours (Krumpal, 2013). However, this is likely to be minimised here as these participants have grown up for 17 years under observation in this study and are therefore likely to be characteristically

different from the general population in terms of answering health related questions. Furthermore, when questionnaires contained more sensitive and personal questions, interviewers encouraged cohort members to complete them somewhere privately where they would not need to worry about other household members (Centre for Longitudinal Studies, 2018b). Fourth, the participants in the MCS are anonymised so it was not possible to validate reported HDP or depression/anxiety to medical records. However, Carter et al., tested the validity of a questionnaire to characterise maternal recall of pregnancy pregnancy-associated hypertension (including preeclampsia or gestational hypertension) and they reported a sensitivity of 60%, specificity of 95%, positive predictive value of 64%, and negative predictive value of 94%, from three to six years after pregnancy (Carter et al., 2015). Therefore, it is unlikely that self-reported exposure data on HDP would be inaccurately reported or subject to recall bias as it was collected from mothers nine months post-delivery. Fifth, depression/anxiety were measured as an overall doctor diagnosis so different classifications of depressive states or anxieties were not possible in this study.

Conclusion

This study found that exposure to HDP may be associated with an increased likelihood of depression/anxiety at age 17 years. If observed associations were causal, children of women with HDP may also benefit from early screening for anxiety disorders as well as other emotional, behavioural, and developmental issues. Future research should consider severity and different classifications of HDP, while potential mechanisms for the observed associations should be explored.

Author Statement

Authors MK, GM, and SA undertook the statistical analysis. MK and SA drafted the manuscript with support from all authors. All authors edited and provided critical input to improve the manuscript, and all authors approved the submitted version.

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Declaration of Interest

No conflicts of interest, including financial interest.

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Table 1: Descriptive characteristics of mother and adolescent pairs included in the analysis

Characteristics	HDP	No HDP
Total Population N (%)	698 (7.33%)	8,819 (92.63%)
Depression or Severe Anxiety (overall)		
Yes	88 (12.61%)	890 (10.09%)
No	610 (87.39%)	7,929 (89.91%)
Infant Sex		
Male	342 (49%)	4,300 (48.76%)
Female	356 (51%)	4,519 (51.24%)
Parity		
First born	391 (56.02%)	3,662 (41.52%)
Not first born	307 (43.98%)	5,157 (58.48%)
Smoking		
Smoked during pregnancy	104 (14.90%)	1,676 (19%)
Quit during pregnancy	87 (12.46%)	1,028 (11.66%)
Non-smoker	507 (72.64%)	6,112 (69.30%)
Missing		3 (0.03%)
Maternal Alcohol Consumption		
Yes	188 (26.93%)	2,734 (31%)
No	510 (73.07%)	6,075 (68.89%)
Missing		10 (0.11%)
Maternal BMI		
Underweight (<18.5 kg/m^2)	19 (2.72%)	432 (4.90%)
Normal (18.5 to <25 kg/m^2)	336 (48.14%)	5361 (60.79%)
Overweight (25.0 to <30 kg/m^2)	173 (24.79%)	1,593 (18.06%)
Obese (≥30 kg/m^2)	116 (16.62%)	661 (7.50%)
Missing	54 (7.74%)	772 (8.75%)
Maternal Age		
≤ 35yrs	604 (86.53%)	7,658 (86.84%)
>35yrs	94 (13.47%)	1,150 (13.04%)
Missing	-	11 (0.12%)
Maternal Education		
Less than O Levels	70 (10.03%)	1,383 (15.68%)
O Levels	302 (43.27%)	3,605 (40.88%)
A Levels	76 (10.89%)	899 (10.19%)
Diploma or higher	232 (33.24%)	2,656 (30.12%)
Missing	18 (2.58%)	276 (3.13%)
Income		
1st quintile (highest)	103 (14.76%)	1,777 (20.15%)
2nd quintile	133 (19.05%)	1,849 (20.97%)
3rd quintile	148 (21.20%)	1,669 (18.93%)
4th quintile	164 (23.50%)	1,747 (19.81%)
5th quintile (lowest)	150 (21.49%)	1,756 (19.91%)
Missing		21 (0.24%)
Mode of Delivery		
Spontaneous vaginal delivery	164 (23.50%)	4,544 (51.53%)
Assisted vaginal delivery	83 (11.89%)	853 (9.67%)
Induced vaginal delivery	193 (27.65%)	1,621 (18.38%)
Emergency C section	85 (12.18%)	583 (6.61%)
Planned C section	59 (8.45%)	681 (7.72%)
Induced C section	111 (15.90%)	517 (5.86%)
Missing	3 (0.43%)	20 (0.23%)
Birthweight		
Small for gestational age	84 (12.03%)	787 (8.92%)
Not Small for gestational age	607 (86.96%)	7,925 (89.86%)
Missing	7 (1%)	107 (1.21%)

Table 2: Association between HDP and depression and severe anxiety in the offspring at aged 17 among Millennium Cohort Study Participants

	Depression/anxiety cases, n	Univariable Analysis OR (95% CI)	Multivariable Analysis[a] aOR (95% CI)
HDP and depression/anxiety (overall)	88	1.29 (1.02, 1.62)	1.30 (1.02, 1.66)
HDP and depression/anxiety with treatment	69	1.32 (1.01, 1.71)	1.33 (1.01, 1.73)
HDP and depression/anxiety without treatment	19	1.20 (0.74, 1.93)	1.30 (0.80, 2.12)

Reference group=not exposed to HDP

aOR, adjusted odds ratio; CI, confidence interval; HDP, hypertensive disorder of pregnancy, OR, odds ratio.

[a]Multivariable models adjusted for the potential confounder variables of maternal age, maternal education, maternal smoking status, maternal alcohol consumption during pregnancy, maternal BMI, income, infant sex, parity

Table 3: Subgroup analysis, interaction terms and post-hoc analysis of the association between HDP and depression and severe anxiety in the offspring at aged 17

Model 1: Sub-group analysis by maternal age[a,b]	**Depression/anxiety cases, n**	**OR (95% CI)**	**Interaction P-value**
HDP (among mothers ≤ 35yrs)	77	1.31 (1.01, 1.70)	-
HDP (among mothers >35yrs)	11	1.22 (0.62, 2.41)	-
Model 2: Sub-group analysis by Infant Sex[a,c]			
HDP (among males)	24	1.05 (0.67, 1.63)	-
HDP (among females)	64	1.44 (1.08, 1.93)	
Model 3: Interactions between HDP and SGA and association with offspring depression/anxiety[a,d]			
HDP only	75	1.26 (0.97, 1.64)	0.505
Both HDP and SGA	13	1.70 (0.93, 3.13)	
SGA only	89	1.06 (0.83, 1.35)	
Model 4: Interactions between HDP and low birthweight and association with offspring depression/anxiety[a,e]			
HDP only	69	1.18 (0.91, 1.55)	0.030
HDP and low birthweight	19	1.91 (1.06, 3.43)	
Model 5: Interactions between HDP and preterm birth and association with offspring depression/anxiety[a,f]			
HDP only	66	1.16 (0.88, 1.52)	0.008
HDP and preterm birth	22	2.13 (1.22, 3.72)	
Model 6: Interactions between HDP and maternal depression and association with offspring depression/anxiety[a,g]			
HDP only	52	1.33 (0.98, 1.81)	0.428
Both HDP and maternal depression	36	1.09 (0.74, 1.61)	
Model 7: Post-hoc analysis, further adjusting for maternal depression[h]			
HDP and depression/anxiety (overall)	36	1.23 (0.97, 1.57)	-

aOR, adjusted odds ratio; CI, confidence interval; HDP, hypertensive disorder of pregnancy; SGA, small for gestational age.

[a]Adjusted for the potential confounder variables of maternal age, maternal education, maternal smoking status, maternal alcohol consumption during pregnancy, maternal BMI, income, infant sex, parity.

[b]Reference groups=not exposed to HDP among mothers ≤35yrs and not exposed to HDP among mothers >35yrs, where applicable. [c]Reference groups=not exposed to HDP among males and not exposed to HDP among females, where applicable. [d]Reference group=not exposed to HDP and not born SGA. [e]Reference group=not exposed to HDP and not low birthweight. [f]Reference group=not exposed to HDP and not born preterm. [g]Reference group=not exposed to HDP and no maternal depression. [h]Reference groups=not exposed to HDP.