Development and Psychopathology (2020), **32**, 845–851
doi:10.1017/S0954579419000944

CAMBRIDGE UNIVERSITY PRESS

Regular Article

Hypertensive disorders of pregnancy and the risk of offspring depression in childhood: Findings from the Avon Longitudinal Study of Parents and Children

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Abstract

Hypertensive disorders of pregnancy (HDP) may increase the risk of offspring depression in childhood. Low birth weight is also associated with increased risk of mental health problems, including depression. This study sought to investigate (a) whether there is an association between HDP and the risk of depression in childhood and (b) whether low birth weight mediates this association. The current study is based on the Avon Longitudinal Study of Parents and Children (ALSPAC), a prospective, population-based study that has followed a cohort of offspring since their mothers were pregnant ($n = 6{,}739$). Depression at the age of 7 years was diagnosed using parent reports via the Development and Well-Being Assessment (DAWBA). Log-binomial regression and mediation analyses were used. Children exposed to HDP were 2.3 times more likely to have a depression diagnosis compared with nonexposed children, adjusted Risk Ratio [RR], 2.31; 95% CI, [1.20, 4.47]. Low birth weight was a weak mediator of this association. Results were adjusted for confounding variables including antenatal depression and anxiety during pregnancy.This study suggests that fetal exposure to maternal hypertensive disorders of pregnancy increased the risk of childhood depression. The study adds to the evidence suggesting that the uterine environment is a critical determinant of neurodevelopmental and psychiatric outcomes.

Keywords: ALSPAC, childhood depression, hypertensive disorders of pregnancy, offspring

(Received 8 November 2018; revised 24 April 2019; accepted 24 May 2019)

Introduction

The Developmental Origins of Health and Disease (DOHaD) hypothesis suggests that early life exposure to environmental insults in utero can result in alterations to the development of the fetus and lead to an increase risk of disease later in life (Barker, 2006). In support of this premise, existing evidence suggests that exposure to specific prenatal risk factors increases the risk of mental disorders later in life (Brander et al., 2016; Hultman et al., 1999; Kolevzon, Gross & Reichenberg, 2007).

Hypertensive disorders of pregnancy (HDP), a common prenatal condition that complicates up to 10% of pregnancies globally (Roberts et al., 2013), are a major cause of maternal morbidity and mortality worldwide (Global Burden of Disease Study 2013 Collaborators, 2015; Say et al., 2014). HDP are also responsible for stillbirth (Flenady et al., 2011) and infant death (Basso et al., 2006), and they are a risk factor for adverse perinatal outcomes such as preterm birth, low birth weight, and intrauterine growth restriction (Bakker et al., 2011; Ferrazzani et al., 2011). Existing evidence also shows that children exposed to HDP are at an increased risk of cardiovascular, endocrine, nutritional, and metabolic diseases later in life compared with unexposed children (Ferreira, Peeters & Stehouwer, 2009; Mamun et al., 2012; Pinheiro et al., 2016). However, little is known about the effects of HDP on offspring mental health outcomes and no study has yet investigated the association between HDP and the risk of depression in childhood.

HDP may increase the risk of childhood depression through utero-placental underperfusion, placental ischemia, hypoxia, and oxidative stress (Mol et al., 2016; Shamshirsaz, Paidas & Krikun, 2012). Depleted oxygen supply to the fetus may impair neurodevelopment and thus contribute to greater risk of depression later in life (Walker et al., 2015). Limited nutrients and oxygen can also cause oxidative stress, and there is evidence suggesting that oxidative stress may increase the risk of depression (Palta et al., 2014; Salim, 2014). The fetus may also be overexposed to maternal circulating glucocorticoids, since HDP are associated with reduced function of the placental 11β-hydroxysteroid-dehydrogenase–2 enzyme, which catalyses the conversion of maternal circulating cortisol to inactive cortisone (Causevic & Mohaupt, 2007). Exposure of the fetus to increased levels of glucocorticoids can

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Cite this article: Dachew BA, Scott JG, Betts K, Mamun A, Alati R (2020). Hypertensive disorders of pregnancy and the risk of offspring depression in childhood: Findings from the Avon Longitudinal Study of Parents and Children. *Development and Psychopathology* **32**, 845–851. https://doi.org/10.1017/S0954579419000944

affect long-term programming of hypothalamic–pituitary–adrenal (HPA) function, which is highly relevant to the biology of underlying depression (Moisiadis & Matthews, 2014a; Moisiadis & Matthews, 2014b).

To our knowledge, no study has yet investigated the association between HDP and the risk of depression in childhood. One study has reported a positive association between maternal HDP and depression in adult offspring (Tuovinen et al., 2010). However, the sample size was relatively small ($n = 788$) and the authors acknowledged that the study did not account for important confounding variables such as maternal smoking, maternal alcohol use, and maternal psychopathology during pregnancy. Therefore, further investigation of this association using large prospective studies with the capacity to address these possible confounders is needed.

Previous studies assessing the relationship between HDP and offspring psychopathology have not explored mediation via birth outcomes. There is evidence that HDP are associated with low birth weight (Ferrazzani et al., 2011), and low birth weight babies have a higher risk of developing mental health problems, including depression, later in life (Loret de Mola et al., 2014; Mathewson et al., 2017; Serati et al., 2017). Thus, it is possible that any association between HDP and depression in offspring could be mediated via low birth weight. If such an intermediary factor was evident, this would increase confidence that the relationship between HDP and depression was causal by partly elucidating its biological mechanism.

The main purpose of this study was, therefore, to investigate the association between HDP and risk of childhood depression. We will add to the existing evidence by addressing issues of confounding in a large sample size and examining the possible mediating role of low birth weight.

Methods

Design and participants

Data came from the Avon Longitudinal Study of Parents and Children (ALSPAC), a prospective longitudinal birth cohort study in Avon, United Kingdom. All pregnant women living in Avon, Southwest England, with estimated delivery dates between April 1, 1991 and December 31, 1992 were enrolled ($n = 14{,}541$). Information about ALSPAC recruitment and data collection strategies has been previously reported (Boyd et al., 2013; Fraser et al., 2013), and the study website contains details of data that is available through a fully searchable data dictionary (http://ww.bris.ac.uk/alspac/researchers/data-access/data-dictionary).

A total of 13,397 mothers had complete data on the exposure variable, HDP. Outcome data, depression diagnosis, were available for 7,909 singleton children at age 7. Of this sample, 7,847 children had data on both outcome and exposure variables. The final analyses were conducted on 6,739 children who had complete data on exposure, outcome, and confounder variables (Figure. 1).

Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Initial ethical approval was obtained for gaining written, informed consent from pregnant mothers. At each follow-up clinic assessment, mothers provided informed written consent and children provided verbal assent after receiving a full explanation of the study. The details of ethical approval including the dates of approval and associated reference numbers are available on the ALSPAC website (http://www.bristol.ac.uk/alspac/researchers/research-ethics/).

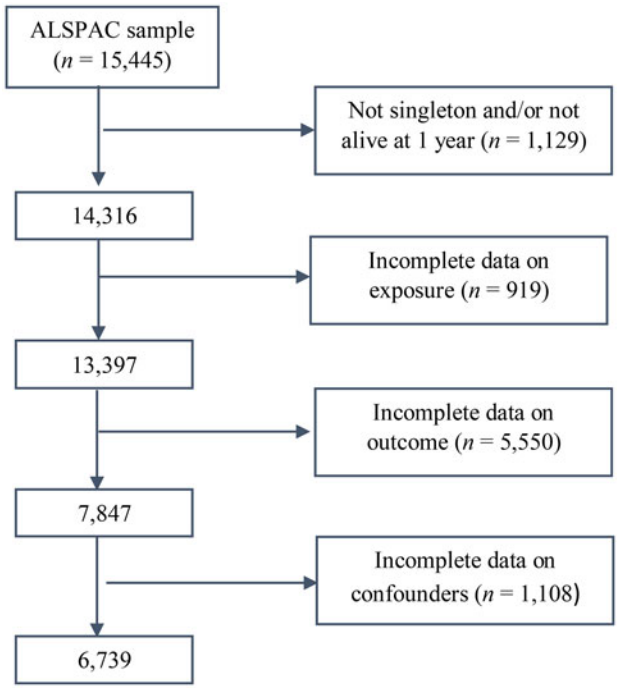

Figure 1. Flow diagram of study participants.

Measures

Outcome

Depression at 7 years of age was assessed by using parental reports of the Development and Well-Being Assessment (DAWBA). The DAWBA is a validated diagnostic instrument consisting of structured questions that establish the presence of child and adolescent mental health disorders and their effects (Goodman et al., 2011; Goodman et al., 2000). The questions for each disorder closely follow the diagnostic criteria operationalized in the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* (DSM-IV) or the *International Classification of Diseases, 10th revision* (ICD-10). The responses were entered into a computer program that integrates the information and provides likely diagnoses where appropriate. These were then assessed by experienced clinical raters who decided whether to accept or overturn the computer diagnosis (or lack of diagnosis). Validation studies show substantial agreement between diagnoses generated by the DAWBA and clinician diagnoses. The tool has been used in British nationwide surveys of child and adolescent mental health and their effects (Goodman et al., 2011; Goodman et al., 2000).

Exposure

Six trained research midwives extracted all measurements of blood pressure and proteinuria from maternal obstetric records that were documented as part of routine antenatal care by midwives or obstetricians. There was no between-midwife variation in mean values of the data abstracted, and error rates were consistently < 1% in repeated data entry checks (Macdonald-Wallis et al., 2014). We applied the International Society for the Study of Hypertension in Pregnancy to determine women with HDP (pre-eclampsia or gestational hypertension) (Brown et al., 2001). Pre-eclampsia was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, measured on ≥ 2 occasions after 20 weeks of gestation, with

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proteinuria (≥1+ on urine dipstick testing occurring at the same time as the elevated blood pressure), in a mother who did not report having hypertension prior to pregnancy. Gestational hypertension was defined as the same pattern of elevated blood pressure but without proteinuria. Hence, all women were categorized into two mutually exclusive categories of no HDP or HDP (including gestational hypertension or pre-eclampsia).

Mediating variable

Birth weight was extracted from hospital delivery records and dichotomized as low birthweight (under 2500 g) and normal birth weight.

Confounding variables

Variables associated with both HDP and childhood depression, and not considered to be on the causal pathway, were selected as confounders and included in the regression models. These included maternal age (in years), parity (nullipara and mutipara), maternal alcohol use during the first 3 months of pregnancy (*never*, less than 1 glass a week, and 1 or more glasses a week), maternal smoking during the first 3 months of pregnancy (smoker and nonsmoker), and maternal depression and anxiety during pregnancy. Maternal depression was measured at 18 weeks of gestation using the Edinburgh Postnatal Depression Scale (EPDS; Cox, Holden & Sagovsky, 1987). Scale scores were subsequently dichotomized using the recommended cut-off score for depression, 12 out of 30 (Gibson et al., 2009). Symptoms of anxiety were measured with the Crown-Crisp Experiential Index, a validated self-rating inventory (Birtchnell, Evans & Kennard, 1988).

Statistical Analysis

Main effect

Descriptive analyses were performed, followed by a series of log-binomial regression analyses assessing the association between HDP and childhood depression, firstly without and then with adjustment for confounding variables. Model 1 was unadjusted. Model 2 adjusted for maternal age and parity. Model 3 additionally adjusted for maternal smoking and alcohol use during pregnancy. Model 4 additionally adjusted for maternal depression and anxiety during pregnancy.

Mediation (indirect effects)

Mediation analyses were conducted to test whether low birth weight mediates the association between HDP and offspring depression in childhood. We investigated mediation by quantifying direct pathways between HDP and offspring depression and indirect pathways through low birthweight. We used the user-written "binary_mediation" command in Stata to compute indirect effects using the product coefficients approach, with bootstrap bias-corrected 95% confidence intervals (CI) for the indirect effects to account for non-normality in the sampling distribution of the indirect effect estimates. In the adjusted mediation analysis model, all confounding factors (i.e. maternal age, parity, maternal smoking and maternal alcohol use during pregnancy, maternal depression, and anxiety symptoms during pregnancy) were entered as covariates.

Missing data

To account for missing data, we conducted multivariate multiple imputation by chained equations using the "ice" command in Stata (Royston, 2005), drawing on the substantial information on sociodemographic variables collected at baseline. We used 50 cycles of regression switching and generated 50 imputed datasets. All covariates included in the regression model and additional auxiliary variables predictive of incomplete variables and/or missingness were imputed and the analyses were repeated. All statistical analyses were conducted using STATA 14 software (StataCorp, 2015).

Results

Descriptive Analysis

Table 1 compares characteristics of participants with and without a depression diagnosis. Mothers of children with depression at age 7 had more antenatal depressive and anxiety symptoms and were more likely to be smokers compared with mothers of children without depression diagnosis (Table 1).

Characteristics of mothers of children with data on depression compared with those without data are also shown in Supplementary table 1. In comparison with those retained in the analyses, mothers of children who were lost to follow-up or missing data were younger at childbirth, more likely to be multiparous, smoke tobacco, drink alcohol, and have more antenatal depressive and anxiety symptoms (Supplementary table 1).

Associations Between Maternal HDP and Childhood Depression

Among those children who had complete data at age 7 ($n = 6{,}739$), 15.5% were exposed to HDP. The prevalence of depression at age 7 was 0.64%. Table 2 shows univariable and multivariable associations between maternal HDP and offspring depression at the age of 7 years. The univariable logistic regression analysis (Model 1) showed that children exposed to HDP were nearly two and a half times more likely to have a diagnosis of depression at the age of 7 years compared with unexposed children, RR, 2.44; 95% CI [1.27, 4.67]. The association remained similar after adjustments were made for confounding factors in both Model 2 and Model 3. In the fully adjusted model (Model 4), HDP remained strongly associated with an increased risk of offspring depression at the age of 7 years, RR, 2.31; 95% CI [1.20, 4.47]. When we re-ran the models using the imputed dataset, we found the results did not differ substantively (Supplementary table 2).

Mediation Analysis Results: Pathways From HDP to Offspring Childhood Depression

The prevalence of low birth weight was 4.38%. The prevalence was higher in offspring of mothers with HDP, 7.6% compared with 3.8% of offspring of mothers without HDP, $\chi^2 = 62.04$, $p < .001$. Low birth weight was associated with childhood depression, $\chi^2 = 6.02$, $p = .01$.

Figure 2 and Table S3 show the mediation role of low birth weight in the association between HDP and childhood depression. As shown in Figure 2, maternal HDP predicted low birth weight, $\beta = 0.81$, $p < .001$. Taking into account the effect of low birth weight, the path between maternal HDP and offspring depression was also significant, $\beta = 0.8$, $p = .02$. Table S3 summarizes the regression coefficients for tests of direct and indirect effects of maternal HDP on childhood depression. The effect of HDP on childhood depression was weakly mediated by low birth weight, $\beta = 0.013$; 95% CI [0.01, 0.02]. The proportion of the total effect mediated by low birth weight was 7.7%. This effect was small,

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Table 1. Characteristics of mothers and children included in the analysis ($n = 6,739$)

Variables	*n* (%)
Mothers age at birth	
<25	1009 (15.0)
25–30	3298 (48.9)
>30	2432 (36.1)
Parity	
Nullipara	3111 (46.2)
Multipara	3628 (53.8)
Alcohol consumption in pregnancy	
Never	2967 (44.0)
<1 glass per week	2737 (40.6)
1 or more glasses per week	1035 (15.4)
Smoking in pregnancy	
Nonsmoker	5476 (81.3)
Smoker	1263 (18.7)
Antenatal depression	
No	5762 (85.5)
Yes	977 (14.5)
Antenatal anxiety	
No	5377 (79.8)
Yes	1362 (20.2)
HDP	
No	5693 (84.5)
Yes	1046 (15.5)
Child's sex	
Male	3459 (51.3)
Female	3280 (48.7)
Birth weight (kg)#	3.45 (0.51)

Note: # Values are expressed as mean (standard deviation).

12 times lower than the direct effect. We found a stronger direct effect of maternal HDP on offspring depression, $\beta = 0.16$; 95% CI [0.12, 0.22].

Discussion

To our knowledge, this is the first study to investigate associations between maternal HDP and childhood depression. We showed that children exposed to HDP were more than two times more likely to meet the diagnostic criteria for depression compared with unexposed children. This association was not confounded by maternal age, parity, maternal alcohol use and smoking during pregnancy, and maternal psychopathology, suggesting HDP as an independent risk factor for childhood depression. The mediational role of low birth weight in the association between HDP and childhood depression was small, suggesting a direct association between HDP and childhood depression in offspring.

Although no previous studies have examined associations between HDP and depression in childhood, our findings are consistent with results from the Helsinki birth cohort study that has reported higher depressive symptoms in offspring (ages 60 +) who were exposed to pre-eclampsia when compared to nonexposed offspring (Tuovinen et al., 2010). Our study was able to account for some of the limitations from the Helsinki study where the conclusions were limited by a relatively small sample and an inability to adjust for important confounding factors. In our study, we used a much larger sample of mothers and children and were able to account for maternal smoking, alcohol use, and maternal mental health problems experienced during pregnancy, therefore increasing confidence of a direct relationship between HDP and depression in offspring. Recently, studies using both animals and human subjects have identified strong associations between maternal HDP and increased risk for offspring psychopathology later in life (Dachew et al., 2017; Dachew et al., 2018; Liu et al., 2016; Pinheiro et al., 2016; Warshafsky et al., 2016). For example, an experimental study that used an established animal model identified a positive association between pre-eclampsia, a severe form of HDP, and atypical brain development in rats (Liu et al., 2016). Recent systematic review and meta-analysis studies conducted by this group showed that offspring who had intrauterine exposure to pre-eclampsia had a 32% and 37% higher risk of ASD (Dachew et al., 2018) and schizophrenia (Dachew et al., 2017), respectively, compared with nonexposed offspring. Findings from the South Carolina birth cohort study have also reported associations between HDP and higher risk of ADHD in offspring (Mann & McDermott, 2011).

Table 2. Associations between HDP and offspring depression at the age of 7 years ($n = 6,739$)

		Childhood depression	
		RR (95% CI)	*p*
HDP	Model 1	2.44 (1.27–4.67)	.007
	Model 2	2.38 (1.23–4.60)	.01
	Model 3	2.46 (1.27–4.76)	.008
	Model 4	2.31 (1.20–4.47)	.01

Note: Model 1 was the unadjusted model. Model 2 adjusted for maternal age and parity. Model 3 additionally adjusted for maternal smoking and alcohol use during pregnancy. Model 4 additionally adjusted maternal depression and anxiety during pregnancy.

Possible Biological Mechanisms

There are several possible mechanisms by which HDP could increase the risk of childhood depression. HDP, particularly pre-eclampsia, is a common cause of low birth weight (Ferrazzani et al., 2011), and existing evidence shows that low birth weight is risk factor for childhood mental health disorders, including depression (Loret de Mola et al., 2014; Mathewson et al., 2017; Serati et al., 2017). Thus, it is possible that HDP affects offspring depression via impaired fetal development. However, our results suggest that low birth weight only accounted for a small fraction of the observed association between HDP and depression.

Another potential mechanism underlying the associations between HDP and childhood depression may be that they are spuriously related via a common genetic predisposition. Studies have reported an association between maternal HDP and prenatal depression (Avalos, Chen, & Li, 2015; Hu et al., 2015; Kurki et al., 2000). Maternal prenatal depression may also predict risk

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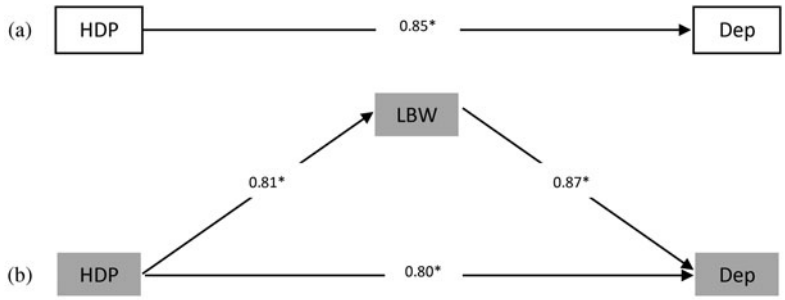

Note: Numbers refer to standardized beta coefficients. The effect values on (b) and (a) were coefficients with and without mediators, respectively. All path estimates were adjusted for maternal age, parity, maternal smoking, and alcohol use during pregnancy, and maternal depression and anxiety symptoms during pregnancy. LBW, low birth weight. Dep, childhood depression. *$p < .05$.

Figure 2. The mediation role of low birth weight in the association between HDP and childhood depression.

for depression in the offspring by genetic mechanisms or by compromising early attachment (Pearson et al., 2013). However, the association we identified here was only slightly attenuated by maternal mental health during pregnancy.

It is plausible that prenatal exposure to maternal hypertension and the resulting adverse intrauterine environment affect fetal brain development, which in turn leads to an increased risk of psychopathology, including depression, later in life (Barker, 2007; Braithwaite, Murphy, & Ramchandani, 2014; Kim, Bale, & Epperson, 2015; Newman et al., 2016). The most plausible underlying mechanism may involve a decrease in oxygen and nutrient supply to the fetus as a result of utero-placental underperfusion, placental ischemia, and hypoxia (Mol et al., 2016; Shamshirsaz et al., 2012). Depleted oxygen supply to the fetus may impair neurodevelopment and thus contribute to greater risk of depression later in life (Walker et al., 2015). Limited nutrients and oxygen can also cause oxidative stress, and there is evidence suggesting that oxidative stress may increase the risk of depression (Palta et al., 2014; Salim, 2014). The fetus may also be overexposed to maternal circulating glucocorticoids, since HDP are associated with reduced function of the placental 11-β-hydroxysteroid-dehydrogenase–2 enzyme, which catalyses the conversion of maternal circulating cortisol to inactive cortisone (Causevic & Mohaupt, 2007). Exposure of the fetus to increased levels of glucocorticoids can affect long-term programming of hypothalamic–pituitary–adrenal (HPA) function, which is highly relevant to the biology of underlying depression (Moisiadis & Matthews, 2014a; Moisiadis & Matthews, 2014b).

Another possible mechanism may involve elevated levels of serotonin (5-hydroxytryptamine, 5-HT) during pregnancy. Because platelets are the principal source of circulating serotonin, the increased platelet aggregation in HDP, especially in pre-eclampsia, causes an increase in serotonin levels in the placenta and the fetal brain (Bolte, van Geijn, & Dekker, 2001). This increased amount of exogenous serotonin in the fetal brain may impair the growth of serotonin nerve cells through negative feedback and reduced production of endogenous serotonin later in life (Goeden et al., 2016; Hadjikhani, 2010). The role of serotonin in the pathophysiology of depression is well documented (Field et al., 2008; Owens & Nemeroff, 1994). Research using animal models will be needed to clarify the biological mechanism(s) for this association.

Strength and Limitations

This study has considerable strengths. We used one of the most established and largest longitudinal cohort studies in the world, the ALSPAC. Good measures of exposure and outcome diagnosis and the availability of a wide range of confounders were other strengths of our study. Therefore, our findings should be considered as carrying the strongest evidence yet reported for an association between HDP and child depression, warranting replications in other cohort studies of comparable value to the ALSPAC study.

This study also had limitations. There were lost to follow-ups which may limit the generalizability of our findings. However, the rate of exposure to HDP in offspring who were and were not followed-up did not differ substantively and reanalysis using the imputed dataset revealed consistent finding, suggesting our results were robust. Reporter bias is likely since information on outcome were obtained by maternal report. However, the DAWBA is a well-validated instrument combining structured and semistructured questions related to DSM-IV and ICD diagnostic criteria and has been shown to be sufficiently accurate at diagnosing child mental health (Goodman et al., 2011; Goodman et al., 2000). The power of our analysis was limited by the relatively small number of children with depression diagnosis at the age of 7 years in the study sample (0.67%), and we were unable see them at the latest follow-up visits due to the high attrition rate. However, this is consistent with the prevalence of childhood depression in the general population (0.4–2.5%) (Birmaher et al., 1996). We were unable to establish a dose-response relationship between exposure to HDP and offspring depression, which would have provided stronger evidence of a causal relationship. We did not include genetic information in our analysis, but by adjusting for maternal depression during pregnancy, we provided evidence that there is an independent effect of HDP in addition to possibly inherited confounders. Finally, even though our data allowed us to adjust for a wide range of confounding factors, we cannot rule out the possibility of residual confounding.

Conclusions

Our study showed that children exposed to HDP had higher risk for depression compared with unexposed children. The association showed some evidence of mediation by low birth weight.

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The study adds to the body evidence indicating that the uterine environment is a critical determinant of neurodevelopmental outcomes and suggests that early screening for childhood emotional problems in offspring of women with HDP may be warranted. Further studies delineating underlying mechanisms between HDP and depression in children are also needed.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0954579419000944.

Acknowledgments. We are extremely grateful to all of the families who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists, and nurses.

Funding. The UK Medical Research Council and Wellcome Trust (Grant ref: 102215/2/13/2) and the University of Bristol provide core support for ALSPAC. A comprehensive list of grants funding is available on the ALSPAC website: (http://www.bristol.ac.uk/alspac/external/documents/grant-acknowledgements.pdf).

This publication is the work of the authors and Berihun Assefa Dachew, James G. Scott, Kim Betts, Abdullah Mamun, and Rosa Alati, who will serve as guarantors for the contents of this paper. Berihun is supported by the Australian Government Research Training Program (RTP). James is supported by a NHMRC Practitioner Fellowship Grant (1105807). The funders had no role in the design and conduct of the study; collection, analysis, or interpretation of data; drafting the manuscript; or the decision to submit the manuscript for publication.

Conflict of interest. The authors declare no conflicts of interest.

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https://doi.org/10.1017/S0954579419000944 Published online by Cambridge University Press