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Hypertensive disorders of pregnancy and the risk of anxiety disorders in adolescence: Findings from the Avon Longitudinal Study of Parents and Children

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ABSTRACT

Background: The effect of hypertensive disorders of pregnancy (HDP) on offspring anxiety disorders in adolescence is not yet known. This study aims to examine the association between HDP and offspring anxiety disorders at age 15 years.

Methods: We used data from 5231 mother–offspring pairs from the United Kingdom based Avon Longitudinal Study of Parents and Children (ALSPAC). Anxiety disorder was diagnosed in the offspring at the age of 15 years using the Development and Well-Being Assessment (DAWBA).

Results: Among those who had anxiety disorders, 16.4% were exposed to HDP. After adjusting for a wide range of known confounders, we found that adolescents of women with HDP had a 2.43 fold (95% CI: 1.41–4.19) increase risk of anxiety disorders compared with adolescents of women without HDP.

Conclusions: Our study showed that adolescents exposed to HDP had higher risk of anxiety disorders compared with unexposed adolescents and suggests that prevention and treatment of maternal HDP could possibly prevent offspring anxiety in adolescence. Early screening for anxiety disorders in offspring of women with HDP may also be warranted. Further research is needed to explain the pathways by which HDP may increase the risk of offspring psychopathology.

1. Introduction

Anxiety disorders remain the most prevalent mental health problem experienced in adolescence (Polanczyk et al., 2015). Adolescents with anxiety disorders can experience persistent fear, worry, or dread, which can lead to lack of concentration with accompanying academic and social difficulties (Ansary and Luthar, 2009; Mazzone et al., 2007; Priest, 2013). Anxiety disorders during adolescence are also strongly associated with adult mental and substance use disorders such as anxiety, depression, conduct, alcohol, drug use disorders and suicidal behaviours (Bittner et al., 2007; Woodward and Fergusson, 2001). Identifying early life risk factors of anxiety is therefore important to guide preventive strategies and early intervention to reduce adolescent and adult health consequences (Griffiths and Fazel, 2016; Morgan et al., 2016).

Changes to the in utero environment during pregnancy could result in altered developmental outcomes in offspring (Barker et al., 2013). The developmental origins of health and disease hypothesis suggests that early life exposure to environmental insults in utero can result in alterations to the development of the foetus and lead to an increase of risk of disease later in life (Barker, 2007). Hypertensive disorders of pregnancy (HDP) are potential exposures that may alter long-term child development in this way.

There is comprehensive evidence that maternal HDP are associated with an increased risk of offspring cardiovascular, endocrine, nutrition, and metabolic diseases later in life (Ferreira et al., 2009; Mamun et al., 2012; Pinheiro et al., 2016; Tripathi et al., 2018; Wu et al., 2009). Conversely, there are relatively few studies examining the impact of HDP on neurodevelopmental and psychiatric outcomes in offspring and no study has yet investigated the association between HDP and the risk

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of anxiety disorders in adolescence. Findings from a population based nested case-control study in Southern California showed that offspring exposed to pre-eclampsia had a 34% increased risk of ADHD compared with non-exposed offspring (Getahun et al., 2013). Data from the Helsinki birth cohort study further suggest that HDP increased the risk of depression and mood disorders but not anxiety disorders in adult offspring (Tuovinen et al., 2012, 2014). The Western Australia Pregnancy Cohort Study examined the association between HDP and behavioural problems in children using the Child Behaviour Checklist (CBCL) (Robinson et al., 2009). This study found that preeclampsia was not associated with total behavioural and externalizing symptoms, but was linked to a reduction in internalizing symptoms at age 5 and 8 years. Studies reporting associations between HDP and offspring psychosis have reported conflicting findings (Tuovinen et al., 2014). One of these studies suggested that in utero exposure to preeclampsia increased the risk of offspring psychotic symptoms by fourfold (Tuovinen et al., 2014), while in two other studies no associations were observed (Bain et al., 2000; Zammit et al., 2009).

Most studies examining the association between HDP and offspring mental health problems have a number of limitations. First, the great majority have used screening tools instead of diagnostic tools to measure offspring mental health outcomes (Robinson et al., 2009, 2013; Tuovinen et al., 2014; Zammit et al., 2009). Second, most of the existing studies are based on case-control methodology and/or used small sample sizes (Bain et al., 2000; Getahun et al., 2013; Tuovinen et al., 2012, 2014; Zammit et al., 2009). Third, most have not consistently accounted for important confounding variables such as parity (Bain et al., 2000; Robinson et al., 2009; Zammit et al., 2009), pre-pregnancy body mass index (BMI) (Bain et al., 2000; Getahun et al., 2013; Robinson et al., 2009; Zammit et al., 2009), alcohol use and/or smoking during pregnancy (Bain et al., 2000; Tuovinen et al., 2012, 2014), pregnancy diabetes status (Bain et al., 2000; Getahun et al., 2013; Robinson et al., 2009, 2013; Tuovinen et al., 2012, 2014; Zammit et al., 2009), and maternal anxiety and depression during pregnancy (Bain et al., 2000; Robinson et al., 2009; Tuovinen et al., 2012, 2014). Finally, none of these studies examined the association between HDP and anxiety disorders in adolescence when most mental disorders emerge. This study therefore aims to fill this gap in the literature by investigating the relationship between maternal HDP and offspring anxiety at 15 years of age using a highly reputable birth cohort study with the capacity to control for a wide range of potential confounders.

2. Methods

2.1. Design and participants

We used data from Avon Longitudinal Study of Parents and Children (ALSPAC), a prospective longitudinal birth cohort study in Avon, United Kingdom (UK). All pregnant women living in Avon, South-west England, with estimated delivery dates between 1st April 1991 and 31st December 1992 were enrolled. ALSPAC recruited 14,541 pregnant women during this time-period. These pregnancies resulted in 14,062 live births and 13,988 children at 1 year of age. The current study uses data from the offspring sample (singletons only) completing the assessment at 15 years of age ($n = 5231$). ALSPAC recruitment and data collection strategies are fully described elsewhere (Boyd et al., 2013; Fraser et al., 2013a) and the study website contains details of available data that is available through a fully searchable data dictionary (http://ww.bris.ac.uk/alspac/researchers/data-access/data-dictionary).

Ethics 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 assent after receiving a full explanation of the study.

2.2. Measures

2.2.1. Outcome: anxiety disorders at age 15 years

Anxiety at the age of 15 years was measured by using the Development and Well-Being Assessment (DAWBA). DAWBA is a validated diagnostic instrument consisting of structured questions that establish the presence of child and adolescent mental health disorders and their impact. The questions for each disorder closely follow the diagnostic criteria operationalised in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th *edition* (DSM-IV) or the International Classification of Diseases, 10th revision (ICD-10) Diagnostic Criteria for Research (Goodman et al., 2000, 2011). DAWBA has been validated and used for the child and adolescent mental health survey in UK (Goodman et al., 2000).

2.2.2. Exposure: HDP

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 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).

2.2.3. Confounding variables

Variables that could potentially be associated with both the exposure and outcome were considered confounders. These included socio-economic position indicators (maternal education, social class, marital status, and ethnicity) (McLaughlin et al., 2012; Reiss, 2013; Russell et al., 2015), maternal age (Aitken et al., 2016; Tearne et al., 2016), parity (Lahti et al., 2014), maternal alcohol use and smoking during pregnancy (Hellemans et al., 2008; Moylan et al., 2015), pregnancy diabetes status (Zammit et al., 2009), maternal pre-pregnancy body mass index (BMI) (Van Lieshout et al., 2013), maternal depression and anxiety during pregnancy (Capron et al., 2015; Pearson et al., 2013; Schreier et al., 2008), gestational age at delivery, and birthweight (Loret de Mola et al., 2014).

All socioeconomic position indicators were obtained from questionnaires administered to the mothers during pregnancy. Maternal education status was ascertained in pregnancy and split into 4 categories: Certificate of Secondary Education (CSE)/vocational, O level (an examination taken and passed at 16 years of age), A level (examinations taken and passed at 18 years of age upon leaving secondary school), and university degree. Social class was based on the UK Registrar General's classification of occupations (Melotti et al., 2011) and grouped into four categories: I (professional), II (managerial and technical), III (skilled manual or non-manual), and IV (partly skilled or unskilled).

Maternal marital status (never married, widowed/divorced/separated, and married) and ethnicity (white and non-white) were obtained from questionnaires administered at baseline. Data on maternal age, gestational age at delivery, and maternal pregnancy diabetes status (no glycosuria or diabetes and existing diabetes, gestational diabetes or glycosuria) and parity (nullipara and mutipara) were obtained from the obstetric records and questionnaires administered during pregnancy.

Self-reports of alcohol use were used to assess maternal alcohol use during pregnancy. Mothers were asked how often they had consumed alcoholic drinks during the first 3 months of pregnancy (never, less than 1 glass a week, 1 or more glasses a week, and 1 or more glasses every day). Mothers were dichotomised as smokers or non-smokers in response to self-reported smoking in the first 3 months of pregnancy. At the time of enrolment, mothers were asked to report their pre-pregnancy weight and height, which were used to calculate maternal pre-pregnancy BMI (kg/m^2). Maternal self-reports of pre-pregnancy weight and her measured weight at the first antenatal clinic were highly correlated (Pearson's correlation coefficient = 0.94; $p < 0.0001$). Prenatal depression was measured at 32 weeks of gestation using Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987). Scale scores were dichotomized using the recommended cut-off score for depression (12 out of 30) (Gibson et al., 2009). Symptoms of antenatal anxiety at 32 weeks of gestation were measured with the Crown-Crisp Experiential Index (CCEI), a validated self-rating inventory (Birtchnell et al., 1988).

2.3. Statistical analyses

Descriptive analyses were firstly conducted for all key factors. Associations between maternal HDP and the risk of offspring anxiety were then assessed using univariable log-binomial model, computing Risk Ratio (RR) as a measure of risk. Results were then adjusted for key confounding variables; maternal education status, social class, marital status, ethnicity, maternal age at delivery, parity, maternal alcohol use and smoking during pregnancy, maternal pregnancy diabetes status, maternal pre-pregnancy BMI, maternal depression and anxiety during pregnancy, child's sex, gestational age at delivery, and birthweight through the use of multivariable log-binomial regression analysis. To account for the possibility of bias due to attrition, 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 explanatory variables included in the regression model and additional auxiliary variables predictive of incomplete variables and/or missingness were imputed and the analyses were repeated. The resulting Monte Carlo errors were less than 5% of the standard error and fraction of missing information (FMI) values were no larger than 0.2, indicating that 50 imputed datasets were sufficient. All statistical analyses were conducted using STATA 14 software (StataCorp, 2015).

3. Results

3.1. Characteristics of mothers and children

Table 1 shows the characteristics of mothers and children included in the analysis. Among 5231 offspring who were assessed for anxiety disorders using DAWBA at the age of 15 years, 52.7% were females and their mean (SD) birth weight was 3.4 (5.3) kg. The mean (SD) age of mothers included in the analysis was 29.2 (4.6) years. 49% of the mothers were nulliparous and their mean (SD) pre-pregnancy BMI was 22.9 (3.7) kg/m^2. In the first 3 months of their pregnancy, 15.7% mothers smoked tobacco and 13.9% consumed one or more glasses of alcohol per week. The prevalence of antenatal anxiety and depression (measured at 32 weeks of gestation) was 19.4% and 16.2% respectively.

A large number of participants (63.5%) did not have anxiety data at the age of 15 years. Baseline maternal characteristics of those children with data on anxiety were compared to those without data (Table S1). In comparison with those retained in the analyses, mothers of children who were lost to follow-up were younger at childbirth, had lower educational levels, were more likely to be from white ethnicity, not married, multiparous, smoke tobacco, drink alcohol, and have higher antenatal depressive and anxiety symptoms. However, we found no difference in terms of their pre-pregnancy BMI, pregnancy diabetes and HDP status (Table S1).

Table 1
Characteristics of mothers and children included in the analysis.

Categorical variables	Sample with outcome data available	*n* (%)
Maternal education status	4664	
Vocational/CSE*		768 (16.5)
O level		1670 (35.8)
A level		1365 (29.2)
Degree		861 (18.5)
Material status	4865	
Never married		647 (13.3)
Widowed/divorced/Separated		230 (4.7)
Married		3988 (82.0)
Ethnicity	4810	
White		4719 (98.1)
Non-white		91 (1.9)
Social class/occupational status	4341	
Professional		205 (4.7)
Managerial and technical		1486 (34.2)
Skilled manual or non-manual		1939 (44.7)
Partly skilled or unskilled		711 (16.4)
Parity	4818	
Nullipara		2363 (49.0)
Multipara		2455 (51.0)
Alcohol consumption in pregnancy	4865	
Never		2111 (43.4)
< 1 glass per week		2005 (41.2)
1 or more glasses per week		676 (13.9)
1 or more glasses per day		73 (1.5)
Smoking in pregnancy	4881	
Non-smoker		4117 (84.3)
Smoker		764 (15.7)
Pregnancy diabetes status	4800	
No		4605 (95.9)
Yes		195 (4.1)
Antenatal anxiety	4590	
No		3698 (80.6)
Yes		892 (19.4)
Antenatal depression	4689	
No		3928 (83.8)
Yes		761 (16.2)
Hypertension disorders of pregnancy	4956	
No		4143 (83.6)
Yes		813 (16.4)
Child's sex	5228	
Male		2475 (47.3)
Female		2753 (52.7)
Numerical variables		**Mean (SD)**
Maternal age at delivery (in years)	4977	29.2 (4.6)
Pre-pregnancy BMI(kg/m^2)	4516	22.9 (3.7)
Birth weight (in kg)	4913	3.4 (5.3)
Gestational age at delivery (in weeks)	4977	39.5 (1.7)

CSE = Certificate of Secondary Education.

3.2. Association between HDP and offspring anxiety at the age of 15 years

Of the offspring (N = 5231) assessed for anxiety disorders at age 15 using the DAWBA, 1.93% (n = 101) met diagnostic criteria. Among those offspring who had anxiety disorders, 16.4% were exposed to HDP. The prevalence of anxiety disorders was higher for those children of mothers who had HDP compared with unexposed children (2.83% vs 1.67%). Table 2 shows univariable and multivariable associations between maternal HDP and offspring anxiety at the age of 15 years. Univariable analysis showed that children exposed to HDP were two times more likely to have a diagnosis of anxiety at the age of 15 years compared with unexposed children (RR = 2.01; 95% CI: 1.19–3.38).

Table 2
Association between HDP and offspring anxiety at the age of 15 years.

Categorical variables	Unadjusted	Adjusted#
	RR (95%CI)	RR (95% CI)
HDP		
No	1	1
Yes	2.01 (1.19–3.38)	2.43 (1.41–4.19)
Maternal education status		
Vocational/CSE)	1	1
O level	0.78 (0.42–1.44)	0.93 (0.49–1.76)
A level	0.54 (0.27–1.08)	0.84 (0.39–1.84)
Degree	0.47 (0.21–1.07)	0.83 (0.32–2.180)
Material status		
Never married	1	1
Widowed/divorced/Separated	0.69 (0.23–2.06)	0.86 (0.28–2.62)
Married	0.46 (0.26–0.81)	0.64 (0.33–1.22)
Ethnicity		
White	1	1
Non-white	2.18 (0.55–8.64)	3.09 (0.79–8.15)
Social class/occupational status		
Professional/managerial and technical	1	1
Skilled manual or non-manual	1.20 (0.69–2.09)	0.87 (0.46–1.63)
Partly skilled or unskilled	2.04 (1.09–3.82)	1.14 (0.55–2.34)
Parity		
Nullipara	1	1
Multipara	1.41 (0.87–2.27)	1.92 (1.11–3.32)
Alcohol consumption in pregnancy		
Never	1	1
< 1 glass per week	0.61 (0.36–1.03)	0.64 (0.38–1.08)
1 or more glasses per week	0.58 (0.26–1.28)	0.62 (0.28–1.39)
1 or more glasses per day	0.83 (0.11–5.94)	1.07 (0.14–7.99)
Smoking in pregnancy		
Non-smoker	1	1
Smoker	1.95 (1.14–3.35)	1.44 (0.79–2.64)
Pregnancy diabetes status		
No	1	1
Yes	1.12 (0.36–3.52)	1.01 (0.32–3.14)
Antenatal anxiety		
No	1	1
Yes	1.49 (0.86–2.56)	0.74 (0.37–1.46)
Antenatal depression		
No	1	1
Yes	2.38 (1.42–3.98)	2.14 (1.11–4.12)
Child's sex		
Male	1	1
Female	4.78 (2.52–9.01)	4.75 (2.48–9.10)
Numerical variables		
Maternal age at delivery (in years)	0.92 (0.87–0.97)	0.94 (0.88–1.01)
Pre-pregnancy BMI (kg/m^2)	1.02 (0.96–1.08)	0.99 (0.93–1.05)
Birth weight (in kg)	1.00 (0.99–1.00)	1.00 (0.99–1.00)
Gestational age at delivery (in weeks)	1.07 (0.92–1.25)	1.02 (0.86–1.21)

1 = reference category, CI = Confidence interval, CSE = Certificate of Secondary Education, RR = Risk Ratio, # the model was adjusted for all variables listed in the table.

After adjusting for a wide range of known confounding factors in multivariable model, HDP remained strongly associated with an increased risk of offspring anxiety at the age of 15years (RR = 2.43; 95% CI: 1.41–4.19). When we re-ran the models using the imputed dataset we found the results did not differ substantively (Table S2).

4. Discussion

To our knowledge, this is the first study to investigate the association between maternal HDP and anxiety disorders in adolescence. The finding demonstrated a two and half fold increase in the risk of anxiety disorders in adolescent offspring who had been exposed to maternal HDP. This association was not confounded by maternal socio-economic status, maternal age, parity, maternal alcohol use, smoking, depression and anxiety during pregnancy, pregnancy diabetes status, maternal pre-pregnancy BMI, child's sex, gestational age and birthweight, suggesting HDP is an independent risk factor for anxiety disorders in adolescent offspring. The finding is compatible with the hypothesis that foetal programming may account, at least in part, for the association between maternal HDP and offspring anxiety disorders (Barker, 2007; Barker et al., 2013).

Evidence suggests maternal antenatal anxiety and depression are associated with increased risk of adverse neurodevelopmental and psychiatric outcomes including anxiety disorders in offspring (Capron et al., 2015; Pearson et al., 2013; Schreier et al., 2008). In this study, we also found strong associations between maternal depression and anxiety disorders during pregnancy and offspring anxiety disorders at age 15 years, although the effect of antenatal anxiety attenuated after adjustment. Therefore, it may be that maternal depression and anxiety disorders during pregnancy may contribute to mother–offspring aggregation of anxiety. Similar to maternal HDP, there is evidence that maternal depression and anxiety during pregnancy are associated with down regulation of the enzymes 11β-hydroxysteroid dehydrogenase type 2 (11 β-HSD2), the enzyme which catalyses the conversion of maternal circulating cortisol to inactive cortisone (O'Donnell et al., 2012). These changes may allow more cortisol to pass through the placenta, with the potential to influence a number of aspects of foetal neurodevelopment. We found no interaction between HDP and maternal depression or anxiety during pregnancy (data not shown); however, adjustment for maternal antenatal depression and anxiety disorders did not attenuate this association, suggesting an independent association between maternal HDP and anxiety disorders in offspring.

A number of studies have shown a strong association between HDP and increased risk of cardiovascular and metabolic disorders in offspring (Alsnes et al., 2017; Fraser et al., 2013b; Timpka et al., 2016). A smaller number of studies have shown that HDP is also associated with increased risk of neurodevelopmental disorders such autism and ADHD (Dachew et al., 2018; Xu et al., 2018). However, there are no studies that have explored the association between HDP and anxiety disorders in adolescence. A Helsinki birth cohort study examined the association between maternal HDP and psychiatric disorders in an aging population of offspring (aged 69 years) (Tuovinen et al., 2014). This study reported that maternal HDP is associated with increased the risk of offspring depression and but not anxiety disorders on DSM-IV-oriented scales. This lack of association could be due to lack of statistical power as the sample size was relatively small (n = 788). The authors also acknowledged that the study did not account for important confounding factors such as maternal smoking, maternal alcohol use, and maternal psychopathology during pregnancy. In our study, we used a much larger sample of mothers and children and were able to account for these confounding factors, therefore increasing confidence of a direct relationship between HDP and anxiety disorders in offspring. Recently, studies from human subjects have also identified strong associations between maternal HDP and increased risk offspring psychopathology later in life (Dachew et al., 2017; Pinheiro et al., 2016; Tearne et al., 2015). For example, a longitudinal pregnancy cohort study conducted by Tearne et al. (2015) showed that children who experienced adverse prenatal environments, including HDP, experienced increased levels of problem behaviours in childhood, and more problematic mental health trajectories. However, the study could not adjust for some important confounding factors such as parity, maternal pre-pregnancy BMI, maternal psychopathology, and pregnancy diabetes status. Our study adds confidence to this finding, as we were able to consider these factors in our analysis.

Maternal HDP may increase the risk of anxiety disorders in offspring by several plausible biological mechanisms. In HDP there is inadequate invasion of the maternal uterine spiral arteries into the placental trophoblast (Burke and Karumanchi, 2013). This result in poor placental perfusion and leads to placental and fetal hypoxia (Shamshirsaz et al., 2012). Depleted oxygen supply to the fetus may impair neurodevelopment and thus contribute to greater risk of anxiety disorders in later in life. Limited nutrients and oxygen can also cause oxidative stress (Sinha and Dabla, 2015; Walker et al., 2015). Oxidative stress is a complex

biological process, which is the result of an imbalance between the production of reactive oxygen species (free radicals) and antioxidants defences (Betteridge, 2000; van Velzen et al., 2017). The brain is sensitive to oxidative stress, due to its high rate of oxygen consumption, large content of polyunsaturated fatty acids, its regional high iron levels, and relatively modest antioxidant defences (Halliwell, 2006; van Velzen et al., 2017). Studies in both humans and animals have shown a strong association between oxidative stress and anxiety disorders (R et al., 2014; Souza et al., 2007; van Velzen et al., 2017).

There is also evidence that HDP is associated with reduced function 11β-HSD2 enzyme, in which the foetus can be overexposed to maternal circulating glucocorticoids (Causevic and Mohaupt, 2007; Kosicka et al., 2016). Exposure of the foetus to increased levels of glucocorticoids can affect long-term programming of hypothalamic–pituitary–adrenal (HPA) function (Moisiadis and Matthews, 2014). There is evidence from animal models that reduced 11b-HSD2 causes an alteration in the behaviour of the offspring (Holmes et al., 2006; Welberg et al., 2000). Administration of the 11β -HSD2 inhibitor carbenoxolone in rodent models resulted in an increase in anxiety-like behaviour (Welberg et al., 2000).

The strengths of this study include the large prospective birth cohort study, valid and reliable measures of the exposure variable and outcome diagnosis, and capacity to control for a wide range of known confounders. In addition, anxiety was measured in the whole population, as opposed to the selection biases inherent in a clinically referred sample, giving a much clearer picture of underlying risk. This study also had limitations. Attrition in our study may limit the generalizability of our finding. Because maternal HDP is also associated with other diverse pregnancy outcomes, findings may be influenced by selection bias. 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 (Table S1). Previous studies have shown that the ALSPAC cohort attrition is associated with socioeconomic disadvantage (Boyd et al., 2013). Because these factors are also associated with adverse mental health outcomes in offspring (Aitken et al., 2016; Capron et al., 2015; Hellemans et al., 2008; Lahti et al., 2014; Moylan et al., 2015; Pearson et al., 2013; Reiss, 2013; Russell et al., 2015; Schreier et al., 2008; Tearne et al., 2016), this type of loss follow-up would be more likely to increase rather than reduce any observed association between HDP and anxiety disorders in adolescence. In addition, 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 no change in the main finding, suggesting our results were robust. We were unable to examine the association between HDP and specific anxiety disorders (e.g. generalised anxiety disorder, panic disorder, etc) in adolescence due to relatively small number of children with an anxiety diagnosis in the study sample. We were also unable to establish a dose-response relationship between exposure to HDP and offspring anxiety, which would have provided stronger evidence of a causal relationship. We did not include genetic information in our analysis, but we did adjust for maternal anxiety and depression during pregnancy. The fact that this adjustment did not affect the strength of the associations detected, suggests an effect of HDP on offspring's anxiety disorders independent of familial liability for anxiety.

5. Conclusions

Our study showed that adolescents exposed to HDP had an increased risk of anxiety disorders compared with unexposed adolescents and suggests that prevention and treatment of maternal HDP could possibly prevent offspring anxiety in adolescence. Early screening for anxiety disorders and other emotional, behavioural and developmental problems in offspring of women with HDP may also be warranted. Further research is needed to explain the pathways by which HDP may increase the risk of offspring anxiety. Identifying the mechanisms underlying the association would help to design intervention strategies that can reduce the risk of anxiety disorders in children of women with HDP.

Contributors

Study concept and design, acquisition, statistical analysis and interpretation of data, and drafting of the article: BAD. Statistical analysis and interpretation of data, and critical revision of the article for important intellectual content: JS, AM and RA. All authors have approved the final article.

Conflicts of interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.01.001.

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