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# Pre-eclampsia and the risk of attention-deficit/hyperactivity disorder in offspring: Findings from the ALSPAC birth cohort study

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ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) is a prevalent heterogeneous neurodevelopmental syndrome associated with various environmental factors. This study examined the association between maternal pre-eclampsia and offspring ADHD at 7- and 10-years. The study cohort consisted of more than 7200 children who participated in Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort study. ADHD was diagnosed using parent reported Development and Wellbeing Assessment (DAWBA). Log-binomial regression and Generalized Estimating Equation (GEE) models were used. The GEE analysis showed that pre-eclampsia was associated with increased risk of ADHD in offspring (adjusted risk ratio [RR] = 2.77; 95% confidence interval [CI] = 1.42–5.38). Similarly, the results of multivariable log-binomial regression analysis at each time point showed that pre-eclampsia was associated with an almost threefold increase risk of offspring ADHD. This study suggests that offspring of mothers with pre-eclampsia are at increased risk of ADHD, although residual and unmeasured confounding by environmental and genetic factors warrants further study. If our findings are replicated by others, early screening for ADHD and other developmental delays may be recommended in offspring of women with pre-eclampsia.

## 1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the common neurodevelopmental disorders characterized by persistent symptoms of inattention, impulsivity, and hyperactivity (American Psychiatric Association, 2013). Prevalence estimates of ADHD in children ranges from 2 to 5% (Erskine et al., 2013; Polanczyk et al., 2007).

Children with ADHD have difficulty functioning at school or in other social environments (Carpenter Rich et al., 2009; Loe and Feldman, 2007) and frequently develop other comorbid disorders (Hodgkins et al., 2011; Mao and Findling, 2014). Caring for children with ADHD can also be disruptive to family life and often causes considerable stress for parents, siblings, and others who live with them (Harpin, 2005; Peasgood et al., 2016). Low occupational achievements, antisocial behaviour, drug abuse and suicide are some potential long-term outcomes in children diagnosed with ADHD (Al Ansari et al., 2017; Erskine et al., 2016; Shaw et al., 2012). Identifying early life risk factors of ADHD is therefore important to guide preventive strategies and early intervention to reduce long-term morbidity.

The causes of ADHD are not well understood. Existing evidence has identified risk factors in pregnancy that increase the likelihood of the disorder in offspring (Hanc et al., 2016; Schmitt and Romanos, 2012). One of these is pre-eclampsia which affects 3–5% of pregnancies (Mol et al., 2016). Pre-eclampsia is characterised by maternal hypertension and proteinuria occurring after 20 weeks of gestation (Roberts et al., 2013). Pre-eclampsia is commonly associated with severe placental dysfunction, which can compromise fetal blood supply and may impair neurodevelopment (Warshafsky et al., 2016). A meta-analysis conducted by our group showed that maternal pre-eclampsia was associated with increased risk of autism spectrum disorder (ASD) in offspring (Dachew et al., 2018; Maher et al., 2018). Recently, a study based on an animal model has identified a positive association between brain injury as a result of oxygen deprivation and ADHD-like behaviour in rats (Miguel et al., 2015). Therefore, it is plausible that pre-eclampsia and the associated placental dysfunction could be a risk factor for

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ADHD. However, the association between maternal pre-eclampsia and the development of ADHD in humans is not well established. Some studies have found an excess risk in children born from pre-eclamptic pregnancies (Bohm et al., 2017; Getahun et al., 2013; Golmirzaei et al., 2013; Mann and McDermott, 2011), whereas others have reported no association (Amiri et al., 2012; Gustafsson and Kallen, 2011; Halmoy et al., 2012; Ketzer et al., 2012).

Most previous studies examining this association have used small sample sizes ($n$ = 248–404) and/or based on case control study designs (Amiri et al., 2012; Golmirzaei et al., 2013; Gustafsson and Kallen, 2011; Halmoy et al., 2012; Ketzer et al., 2012). Furthermore, most of the existing studies have not accounted for important confounding variables such as parity, pre-pregnancy body mass index (BMI), alcohol use and smoking during pregnancy, pregnancy diabetes status, and maternal psychopathology (Amiri et al., 2012; Golmirzaei et al., 2013; Gustafsson and Kallen, 2011; Halmoy et al., 2012; Ketzer et al., 2012). The objective of the current study is therefore to examine the association between maternal pre-eclampsia and the risk of offspring ADHD in childhood (age 7 and 10 years) using a longitudinal birth cohort study with a comprehensive data enabling adjustment for a range of confounders in the association. Repeated measures allow us to observe ADHD risk during childhood development rather than at a single time point.

## 2. Methods

### 2.1. Data source and study participants

We used data from the Avon Longitudinal Study of Parents and Children (ALSPAC). ALSPAC is a prospective longitudinal birth cohort study in Avon, United Kingdom. All pregnant women living in Avon, South-west England with an estimated delivery date between 1st April 1991 and 31st December 1992 were enrolled ($n$ = 14,541). ALSPAC recruitment and data collection strategies are fully described elsewhere (Boyd et al., 2013; Fraser et al., 2013) and the study website contains details of available data that is available through a fully searchable data dictionary (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary).

Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees.

Data on the outcome variable, ADHD diagnosis, were available for 8033 and 7614 singleton children at the age of 7 and 10, respectively. Our sample was limited to children with data available on both maternal pre-eclampsia and ADHD. These criteria resulted in an overall sample size of 7967 and 7246 children at the age of 7 and 10, respectively. The final analyses were conducted on children who had complete data on exposure, outcome and confounder variables ($n$ = 6597 at age 7 and $n$ = 6025 at age 10).

### 2.2. Measures

#### 2.2.1. Outcome

ADHD at the age of 7 and 10 was assessed by using parental reports of the Development and Wellbeing Assessment (DAWBA). DAWBA is a validated instrument combining structured and semi-structured questions related to DSM-IV and ICD diagnostic criteria (Goodman et al., 2000). DAWBA has been used in British nationwide surveys of child and adolescent mental health, including ADHD (Goodman et al., 2000). For ADHD, the predictive value of a positive or negative DAWBA diagnosis was greater than 0.8 (Foreman et al., 2009). Details of the tool and its validation have been described elsewhere (Goodman et al., 2011; Goodman et al., 2000).

#### 2.2.2. 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 variation between midwives in mean values of the data extracted, 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 criteria to categorize pregnant women with or without pre-eclampsia (Brown et al., 2001). Maternal pre-eclampsia was defined as a systolic blood pressure (SBP) $\geq$ 140 mmHg or a diastolic blood pressure (DBP) $\geq$ 90 mmHg, measured on at least two occasions with proteinuria after 20 weeks of gestation, in mothers who were free of hypertension prior to pregnancy.

#### 2.2.3. Confounding variables

Variables associated with both pre-eclampsia and ADHD were selected as confounders and included in the regression models. These included maternal age (in years) ((Bohm et al., 2017), parity (number of times the mother had given birth prior to the birth of the study child) (Ananth and Basso, 2010), maternal alcohol use and smoking during pregnancy (Eilertsen et al., 2017; Zhu et al., 2014), maternal pre-pregnancy BMI (Mina et al., 2017), pregnancy diabetes status (Nomura et al., 2012), depression during pregnancy (Sfelinioti and Livaditis, 2017), and gestational age at delivery (Bohm et al., 2017) were considered as potential confounding variables. We did not include birth weight in the model as there was strong collinearity with gestational age at delivery.

Data on maternal age, gestational age at delivery ($<$37 weeks of gestation or $\geq$37 weeks of gestation), and maternal pregnancy diabetes status (no glycosuria or diabetes, existing diabetes, gestational diabetes and glycosuria) were obtained from the obstetric records. Maternal parity (0, 1, 2, and 3+) was obtained from questionnaires administered during pregnancy. Self-reports of alcohol use were used to assess maternal alcohol use during pregnancy. Mothers were asked how often they had consumed alcoholic drinks during the first 3 months of pregnancy (never, less than 1 glass a week, at least 1 glass a week, 1 or 2 glasses every day, at least 3–9 glasses every day, and at least 10 glasses every day). Mothers were dichotomised as smokers or non-smokers in response to self-reported smoking in the first 3 months of pregnancy. At the time of enrolment, mothers were asked to report their pre-pregnancy weight and height, which were used to calculate maternal pre-pregnancy BMI and classed as underweight ($<$18.5 kg/m$^2$), normal weight (18.5–24.9 kg/m$^2$) and overweigh/obese ($\geq$25 kg/m$^2$). Despite the possibility of report bias, maternal self-reports of pre-pregnancy weight and her measured weight at the first antenatal clinic were highly correlated (Pearson's correlation coefficient = 0.935; $p < 0.0001$). Prenatal depression was measured at 18 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).

### 2.3. Statistical analyses

We conducted descriptive analyses to explore associations with all key variables. Then we conducted a series of separate log-binomial regression models to investigate association between maternal pre-eclampsia and offspring ADHD at ages 7 and 10, computing risk ratios (RR) as a measure of risk. Model one was unadjusted. Model two was adjusted for maternal age and child's sex. Model three was adjusted for maternal pre-pregnancy BMI, maternal pregnancy diabetes status and parity, plus all confounders previously included in model two. Model four included additional adjustment for maternal depression, smoking and alcohol use during pregnancy. Model five (final model) included adjustment for all potential confounders in model four, plus gestational age at delivery.

We applied Generalized Estimating Equation (GEE) modelling to further test the association between maternal pre-eclampsia and offspring ADHD across childhood. GEE models were run using the “xtgee”

command in STATA with binomial family, log link function and unstructured correlation structure (StataCorp, 2015). This model accounts for correlation due to repeated measures being included at two different time points. The models described above (in log-binomial model) were repeated during GEE analyses.

To account for missing data, we conducted multivariate multiple imputation by chained equations using the ice command in Stata (Royston, 2005). Of children who have ADHD data at the age of 7 and 10 years, up to 20% have missing data on major covariates (Supplementary Table 1). Hence, we used 20 cycles of regression switching and generated 20 imputed data sets. All covariates included in the regression model were imputed and the analyses were repeated. We conducted a sensitivity analysis to examine associations between pre-eclampsia and the continuum of hyperactivity symptoms as measured by the Strengths and Difficulties Questionnaire (SDQ). All statistical analyses were conducted using STATA 14 software (StataCorp, 2015).

## 3. Results

### 3.1. Characteristics of participants

Table 1 compares participants with and without ADHD on key potential factors. Mothers of children with ADHD were more likely to report antenatal depressive symptoms and pregnancy diabetes compared with mothers of children without ADHD. Similarly, the prevalence of ADHD diagnosis varied substantially by maternal smoking status during pregnancy (Table 1).

We also compared characteristics of mothers and children with data on ADHD to those with missing data on this outcome. In comparison with those included in the analyses, mothers of children who were excluded, because of loss to follow-up or missing data, were younger at childbirth, had more children, had more antenatal depressive symptoms and were more likely to be smokers. However, we found no difference in terms of their pregnancy diabetes and pre-eclampsia status (Supplementary Table 2).

### 3.2. Associations of maternal pre-eclampsia and offspring ADHD

Two hundred eighty-one (2.1%) of the maternal sample had a diagnosis of pre-eclampsia in the original cohort at baseline. The overall prevalence of offspring ADHD was 2.0% ($n$ = 164) and 1.6% ($n$ = 123) at ages 7 and 10 respectively. Forty (24.4%) of children diagnosed with ADHD at age 7 years were lost at the 10-year follow-up. Excluding those who were lost to follow-up ($n$ = 40), 49.2% ($n$ = 59) of children diagnosed with ADHD at age 7 years also met the diagnostic for ADHD at age 10 years, whereas 43 (0.55%) children who had no ADHD diagnosis at 7 years, were incident cases of ADHD at 10 years as assessed by the DAWBA.

Table 2 shows univariable and multivariable associations between maternal pre-eclampsia and offspring ADHD at 7 and 10 years. In univariable analysis, children of mothers with pre-eclampsia were approximately three and four times as likely to have a diagnosis of ADHD [RR = 2.97 (95%CI: 1.33–6.61) and RR = 3.77 (95%CI: 1.68–8.47)] at 7 and 10 years respectively.

An association between maternal pre-eclampsia and offspring ADHD symptoms continued to be observed in multivariable analysis, after adjusting for a wide range of known confounders. After adjusting for maternal age and child's sex (in model 2), exposure to maternal pre-eclampsia was associated with an increased risk of offspring ADHD in both age groups. The association between maternal pre-eclampsia and offspring ADHD at 7 and 10 years remained after additional adjustments for maternal pre-pregnancy BMI, maternal pregnancy diabetes status and parity (model 3). In model 4, after additional adjustment for maternal depression, alcohol use and smoking during pregnancy, maternal pre-eclampsia was associated with increased risk of ADHD at 7 (RR = 2.85; 95%CI: 1.27–6.35) and 10 years (RR = 3.23; 95%CI: 1.42–7.34). Further adjustment for gestational age at delivery only slightly attenuated the association. When we repeated the analyses using the imputed datasets, the estimates slightly attenuated but the association remained (Supplementary Table 3).

Table 3 shows associations between maternal pre-eclampsia and offspring ADHD over two time points using GEE models. The univariable GEE analysis (model 1) showed that maternal pree-clampsia was associated with increased risk of offspring ADHD overall (RR = 3.32, 95%CI: 1.72–6.42). The association remained high after adjusting for maternal age and child's sex (RR = 3.07; 95%CI: 1.61–5.88). Further adjustment for maternal pre-pregnancy BMI, maternal pregnancy diabetes status and parity (model 3) and for maternal depression, smoking

**Table 1**
Characteristics of mothers with children diagnosed with ADHD compared with those with no ADHD diagnosis.

| Key variables | At 7 years | | At 10 years | |
|---|---|---|---|---|
| | No diagnosis of ADHD *n* (%) | Diagnosis of ADHD *n* (%) | No diagnosis of ADHD *n* (%) | Diagnosis of ADHD *n* (%) |
| **Mothers age at birth** | | | | |
| 15–19 | 173 (2.2) | 7 (4.3) | 138 (1.9) | 9 (7.7) |
| 20–24 | 1078 (13.8) | 37 (22.7) | 959 (13.4) | 20 (17.1) |
| 25–29 | 3122 (39.8) | 50 (30.7) | 2854 (39.8) | 33 (28.2) |
| 30–34 | 2531 (32.3) | 54 (33.1) | 2340 (32.7) | 42 (35.9) |
| 35+ | 935 (11.9) | 15 (9.2) | 870 (12.2) | 13 (11.1) |
| Chi-square and *p*-value | $\chi^2 = 16.7$, $p = 0.002$ | | $\chi^2 = 24.5$, $p < 0.0001$ | |
| **Parity** | | | | |
| None | 3521 (46.3) | 70 (44.6) | 3233 (46.4) | 54 (47.0) |
| 1 | 2710 (35.7) | 56 (35.7) | 2492 (37.8) | 31 (27.0) |
| 2 | 1015 (13.4) | 19 (12.1) | 910 (13.1) | 20 (17.4) |
| 3+ | 356 (4.7) | 12 (7.6) | 330 (4.8) | 10 (8.6) |
| Chi-square and *p*-value | $\chi^2 = 3.58$, $p = 0.466$ | | $\chi^2 = 7.95$, $p = 0.093$ | |
| **Pre-pregnancy BMI (kg/m$^2$)** | | | | |
| <18.5 | 321 (4.5) | 8 (5.7) | 279 (4.3) | 8 (8.0) |
| 18.5–25 | 5425 (75.8) | 107 (77.0) | 4980 (76.3) | 66 (66.0) |
| ≥25 | 1412 (19.7) | 24 (17.3) | 1270 (19.4) | 26 (26.0) |
| Chi-square and *p*-value | $\chi^2 = 0.93$, $p = 0.627$ | | $\chi^2p = 6.69$, $p = 0.035$ | |
| **Alcohol consumption in pregnancy** | | | | |
| Never | 3390 (44.2) | 74 (46.5) | 3075 (43.8) | 50 (43.5) |
| <1 glass per week | 3110 (40.6) | 53 (33.3) | 2873 (41.0) | 40 (34.8) |
| 1 + glasses per week | 1035 (13.5) | 26 (16.4) | 952 (13.6) | 19 (16.5) |
| 1 + glasses per day | 130 (1.7) | 6 (3.7) | 117 (1.6) | 6 (5.2) |
| Chi-square and *p*-value | $\chi^2 = 7.32$, $p = 0.12$ | | $\chi^2 = 15.2$, $p = 0.004$ | |
| **Smoking in pregnancy** | | | | |
| Non-smoker | 6238 (81.0) | 113 (70.6) | 5780 (82.0) | 80 (69.6) |
| Smoker | 1467 (19.0) | 47 (29.4) | 1273 (18.0) | 35 (30.4) |
| Chi-square and *p*-value | $\chi^2 = 10.8$ $p = 0.001$ | | $\chi^2 = 11.6$, $p = 0.001$ | |
| **Pregnancy diabetes status** | | | | |
| No | 7288 (96.0) | 141 (92.8) | 66,721 (96.0) | 101 (93.5) |
| Yes | 306 (4.0) | 11 (7.2) | 273 (4.0) | 7 (6.5) |
| Chi-square and *p*-value | $\chi^2 = 3.9$, $p = 0.048$ | | $\chi^2 = 1.8$, $p = 0.18$ | |
| **Gestational age at delivery** | | | | |
| <37 weeks | 331 (4.2) | 151 (92.6) | 303 (4.2) | 11 (9.4)) |
| ≥ 37 weeks | 7508 (95.8) | 12 (7.4) | 6858 (95.8) | 106 (90.6) |
| Chi-square and *p*-value | $\chi^2 = 3.84$, $p = 0.05$ | | $\chi^2 = 7.45$, $p = 0.006$ | |
| **Antenatal depression** | | | | |
| No | 6113 (85.5) | 102 (72.9) | 5637 (85.9) | 72 (72.0) |
| Yes | 1041 (14.5) | 38 (27.1) | 925 (14.1) | 28 (28.0) |
| Chi-square and *p*-value | $\chi^2 = 17.3$, $p < 0.0001$ | | $\chi^2 = 15.5$, $p < 0.0001$ | |

**Note:** Not all participants recorded data for every characteristic. Missing data were excluded from the analysis. *p*-values correspond to Pearson's chi-square test. % refers to row percentages.

**Table 2**
Associations between maternal pre-eclampsia and offspring ADHD at 7-year ($n$ = 6597) and 10-year follow-ups ($n$ = 6025).

| | | ADHD ($n$ = 117) At 7 years RR (95% CI) | $p$ | ADHD ($n$ = 87) At 10 years RR (95% CI) | $p$ |
|---|---|---|---|---|---|
| Pre-eclampsia | Model 1 | 2.97(1.33–6.61) | 0.008 | 3.77(1.68–8.47) | 0.001 |
| | Model 2 | 2.73(1.24–6.04) | 0.01 | 3.49(1.58–7.71) | 0.002 |
| | Model 3 | 2.79(1.25–6.23) | 0.01 | 3.39(1.49–7.68) | 0.003 |
| | Model 4 | 2.85(1.27–6.35) | 0.01 | 3.23(1.42–7.34) | 0.005 |
| | Model 5 | 2.72(1.21–6.09) | 0.02 | 3.04(1.31–7.01) | 0.009 |

RR: Risk Ratio; CI: Confidence interval. Model 1: unadjusted model. Model 2: adjusted for maternal age and child's sex. Model 3: adjusted for the potential confounders in model two, plus maternal pre-pregnancy BMI, maternal pregnancy diabetes status and parity. Model 4: adjusted for the potential confounders in model three, plus maternal depression, smoking and alcohol use during pregnancy. Model 5: adjusted for potential confounding variables in model four, plus gestational age at delivery.

**Table 3**
Associations between maternal pre-eclampsia and offspring ADHD over two time points (GEE model) ($n$ = 12,622).

| | | ADHD ($n$ = 204) RR (95% CI) | $p$ |
|---|---|---|---|
| Pre-eclampsia | Model 1 | 3.32(1.72–6.42) | <0.001 |
| | Model 2 | 3.07(1.61–5.88) | 0.001 |
| | Model 3 | 3.06(1.58–5.94) | 0.001 |
| | Model 4 | 2.97(1.53–5.77) | 0.001 |
| | Model 5 | 2.77(1.42–5.38) | 0.003 |

Model 1: was unadjusted model. Model 2: adjusted for maternal age and child's sex.
Model 3: adjusted for the potential confounders in model two, plus maternal pre-pregnancy BMI, maternal pregnancy diabetes status and parity. Model 4: adjusted for the potential confounders in model three, plus maternal depression, smoking and alcohol use during pregnancy. Model 5: adjusted for potential confounding variables in model four, plus gestational age at delivery.

and alcohol use during pregnancy (model 4) showed consistent results. In the fully adjusted GEE model (model 5) maternal pre-eclampsia was associated with a 2.8fold increase risk of offspring ADHD (RR = 2.77; 95%CI: 1.42–5.38). Results were comparable when we repeated the GEE analyses using the imputed datasets (Supplementary Table 4).

As symptoms of ADHD occur on a continuum, we conducted a sensitivity analysis to examine if pre-eclampsia was associated with hyperactivity symptoms as measured by the SDQ and found no associations between pre-eclampsia and hyperactivity symptoms in children (Supplementary Table 5).

## 4. Discussion

In this prospectively followed birth cohort study, we found that children exposed to maternal pre-eclampsia had higher risk of ADHD compared with unexposed children. Findings from this study add to the existing evidence by investigating the association between pre-eclampsia and ADHD in a relatively large sample of mothers and children, and by availing of clinically relevant measures as well as a wide range of potential confounders which could potentially affect the relationship between pre-eclampsia and ADHD. These findings support a developmental mechanism for ADHD in some children, as they highlight the effects of early life exposure to environmental insults in utero on short- and long-term health and disease risk (Lahti et al., 2006; Schmitt and Romanos, 2012; Van den Bergh, 2011; Van den Bergh et al., 2017). The absence of any association between pre-eclampsia or hyperactivity symptoms suggests that pre-eclampsia may be associated with higher levels of impairment with ADHD symptoms or with symptoms of inattention and disorganisation rather than the hyperkinetic symptoms.

Despite evidence suggesting no one single risk factor is responsible for the development of ADHD in offspring, ADHD heritability is well recognised ((Faraone et al., 2015) as is the role of family and the environment (Biederman et al., 1995; Ostergaard et al., 2016). Existing evidence also shows that prenatal risk factors such as smoking, alcohol use, gestational diabetes, maternal obesity and antenatal depression can increase the risk of offspring ADHD (Eilertsen et al., 2017; Mina et al., 2017; Nomura et al., 2012; Sfelinioti and Livaditis, 2017; Van Batenburg-Eddes et al., 2013; Zhu et al., 2014). In this study, the association between maternal pre-eclampsia and ADHD remained after adjusting for these prenatal risk factors. Previous studies have shown that low gestational age at birth is also associated with an increased risk of ADHD and symptoms of ADHD in childhood (Franz et al., 2018). In this study, the association between pre-eclampsia and ADHD did not attenuate even after accounting for gestational age at delivery, suggesting an independent association between maternal pre-eclampsia and ADHD. This observed relationship is supported by causal biological mechanisms observed experiments in an animal model (Miguel et al., 2015). Miguel et al. (2015) study reported long-term attentional deficits and inhibitory control failures in rats that underwent hypoxic-ischemia. One of biological mechanism reported in this study is brain damage because of hypoxic-ischemia. A range of studies have also suggested that ADHD disorder is associated with brain abnormalities such as smaller total brain and gray matter volume (Batty et al., 2010; Carmona et al., 2005) and decreased global cortical thickness (Shaw et al., 2006). In light of this, Miguel et al. (2015) study found that rats exposed to hypoxic-ischemia presented with global brain atrophy in the total hemisphere, cerebral cortex, white matter, hippocampus and striatum.

A study utilizing linked registry data ($n$ = 84,721) also reported a positive association between maternal pre-eclampsia and increased risk of ADHD in offspring, although this study lacked capacity to adjust for some important confounding factors such as parity, maternal pre-pregnancy BMI, maternal psychopathology, and pregnancy diabetes status (Mann and McDermott, 2011). Our study further supports this evidence as we were able to take these factors into consideration in our analysis. Maternal pre-eclampsia has also been associated with autism (Dachew et al., 2018) and other developmental and behavioural problems in children (Dachew et al., 2017; Pinheiro et al., 2016).

Although the mechanisms underlying associations between pre-eclampsia and ADHD are not clearly identified, pre-eclampsia can cause significant risks to the fetus through utero-placental under-perfusion, placental ischemia, and hypoxia (Shamshirsaz et al., 2012; Smith et al., 2016). Evidence from neuroimaging studies demonstrates placental ischemia and hypoxia affect fetal brain development (Penrice et al., 1996; Tolsa et al., 2004). Studies using both animal models and human subjects have also reported adverse effects of fetal hypoxia on the brain (Mallard et al., 1998; Nyakas et al., 1996). Therefore, it is plausible that the decreased oxygen and nutrient supply to the fetus in mothers with pre-eclampsia with poor placental perfusion, increases the risk of atypical neurodevelopment and thus contribute to greater risk of ADHD (Getahun et al., 2013; Smith et al., 2016).

This study has considerable strengths. Major strengths are the use of prospective birth cohort study with good measures of the exposure variable and outcome diagnosis and capacity to control for a wide range of known confounders. Additionally, repeated measures of ADHD allowed us to draw conclusions across childhood rather than being restricted to an individual time point. Information bias is unlikely since data on pregnancy were recorded prospectively.

This study also has limitations. First, as would be expected in a longitudinal study, there was attrition. Mothers of children who were excluded were younger at childbirth, had more children, had more antenatal depressive symptoms and were smokers. However, it does not seem that attrition would have fundamentally influenced our finding in a major way due to the following reasons: (i) attrition was not

associated with the exposure variable (ii) multiple imputation was used to address the limitation of missing data and reanalysis following data imputation indicated that our results were robust, (iii) in the ALSPAC sample, participant dropout according to the family variables did not alter the association between pregnancy data and DAWBA child behaviour measures (Wolke et al., 2009). Second, information on outcome was obtained by parent report. Although, DAWBA is a well-validated instrument combining structured and semi-structured questions related to DSM-IV and ICD diagnostic criteria (Goodman et al., 2011; Goodman et al., 2000) and has been widely used and shown to be sufficiently accurate at diagnosing ADHD (Foreman et al., 2009), gold standard clinical diagnosis would entail also gathering information from teachers or others involved in the care or education of the child. Third, the power of our analysis was limited by the relatively small number of children with ADHD in the study sample, which was expected considering the relatively low prevalence of ADHD in the general population. However, the prevalence of ADHD in our study was still low compared to other studies (Erskine et al., 2013; Polanczyk et al., 2007), suggesting the use of a single source of information has not lead to an excess in diagnosis of ADHD. Finally, we did not have family history of ADHD or genetic information that have been shown to reduce the strength of the association between some prenatal risk factors and offspring ADHD (Sciberras et al., 2017).

## 5. Conclusion

Our findings suggest increased the risk of ADHD in childhood following fetal exposure to pre-eclampsia. Although residual and unmeasured confounding by environmental and genetic factors warrants further study, the study adds to the building evidence that the uterine environment is a critical determinant of neurodevelopmental outcomes. Findings suggest the need for early screening of young children born to mothers with pre-eclampsia, so that atypical neurodevelopment such as inattention and hyperkinesis can be detected early and appropriate educational and parenting support offered to improve long-term outcomes. Replicating our findings using a genetically informed study design would add weight to the current evidence. Furthermore, studies of older offspring in future prospective cohorts are needed to determine if the association persists into adulthood.

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## Conflict of interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Authors' contribution

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 read and approved the final article.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2018.12.123.

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