Association between hypertensive disorders of pregnancy and childhood depression: the mediation role of low birth weight

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Presentation outline

• Introduction
• Aims
• Methods
• Main findings
• Conclusion
• Acknowledgment
Introduction

• Depression among children and adolescents is common but frequently unrecognized.

• It affects 2-8% of children and adolescents (Hazell, 2009)

• Children with depression
  • have difficulty functioning at school or in other social environments (Carpenter Rich et al., 2009) and
  • frequently develop other comorbid disorders (Mao and Findling, 2014)

• Identifying early life risk factors of childhood depression is important to guide preventive strategies and early intervention to reduce long-term morbidity.
Risk factors of childhood depression

• No one single risk factor is responsible for the development of depression in offspring.
  
  ➢ genetics, familial environment, personal characteristics, severe stress....

• Existing evidence showed that prenatal risk factors can increase the risk of offspring depression.
Hypertension disorders during pregnancy (HDP)

- Includes gestational hypertension and pre-eclampsia
- Complicates 10–15% of pregnancies (Mol et al., 2016)
- Responsible for up to 16% of maternal deaths worldwide (Steegers et al., 2010)
- A common factor for various adverse perinatal outcomes
  - PTB, LBW, IUGR, stillbirth, and neonatal death
- Associated with ↑ed risk of CV, immune & metabolic disorders later in life
- Little is known about the impact of HDP on offspring mental health outcomes
HDP, low birth weight and and depression

• Evidence have demonstrated that HDP is associated with low birth weight (LBW) (Ferrazzani et al., 2011)

• LBW babies have a higher risk of developing mental health problems including depression later in life (Mathewson et al., 2017, and Serati et al. 2017)

• Thus, it is possible that any association between HDP and depression in offspring could be mediated via smaller birth weight.
Objectives

- This study aimed to investigate
  i. whether there is an association between HDP and the risk of depression in childhood, and
  ii. whether LBW mediates this association
Data source and study participants

Data source
- Avon Longitudinal Study of Parents and Children (ALSPAC), Avon, United Kingdom
- All pregnant women with an estimated delivery dates between 1st April 1991 and 31st December 1992 were enrolled (n=14,541)

Sample
- 7907 children had outcome data, depression diagnosis, at age 7 years
- 7847 children had data on both outcome and exposure variables
- 6739 children had complete data on exposure, outcome and confounders
**Measurements**

**Exposure**
- Extracted from maternal obstetric records

**Outcome**
- Development and Well-Being Assessment (DAWBA)

**Mediator and confounders**
- Obstetric records
- Questionnaires administered during pregnancy

**Statistical analyses**

- Descriptive analyses
- A series of logistic regression analyses (Model 1-4)
- Mediation analysis ("binary_mediation" command in Stata)
- Sensitivity and multiple imputation analyses
## Results

### Childhood depression

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th>Adjusted (Final model)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OR (95% CI)</strong></td>
<td><strong>p</strong></td>
<td><strong>OR (95% CI)</strong></td>
</tr>
<tr>
<td>HDP</td>
<td>2.46 (1.27–4.74)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Model adjusted for: maternal age, child’s sex, parity, maternal smoking and alcohol use during pregnancy, maternal anxiety and depression during pregnancy

Note: Results were comparable when we repeated the analyses using the imputed datasets
The mediation role of LBW

- HDP was associated with LBW ($\chi^2=62.1$, $p<0.0001$)

- LBW was associated with depression ($\chi^2=5.84$, $p=0.02$)

- We used the user written “binary_mediation” command in Stata - with 95% bias corrected CI

Fig. The mediation role of low birth weight
Note: Numbers refer to standardized beta coefficients
* Significant at $p<0.05$ (after adjustment)
The mediation role of LBW cont’d

<table>
<thead>
<tr>
<th></th>
<th>β</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indirect effect (via LBW)</td>
<td>0.013</td>
<td>0.01-0.02</td>
</tr>
<tr>
<td>Direct effect</td>
<td>0.157</td>
<td>0.117-0.219</td>
</tr>
<tr>
<td>Total effect</td>
<td>0.170</td>
<td>0.105-0.223</td>
</tr>
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</table>

Numbers refer to standardized beta coefficients and their 95% CI.

The model was adjusted to maternal age, child’s sex, parity, maternal smoking and alcohol use during pregnancy, maternal depression, and anxiety symptoms during pregnancy.

95% CI indicates bootstrap bias-corrected confidence intervals.

• The proportion of the total effect mediated by low birth weight was 7.7% (0.013/0.170).

• This effect was small, 12 times lower than the direct effect (0.157/0.013).

• Suggesting a direct and strong association between HDP and childhood depression.
HDP and offspring depression cont’d

• 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 (Tuovinen et al., 2010)
Conclusions

• Our finding suggests that fetal exposure to maternal HDP increased the risk of depression in childhood.

• The association showed some evidence of mediation by low birth weight.

• The study adds to the building evidence that the uterine environment is a critical determinant of neurodevelopmental outcomes.

• Replicating our findings using a genetically informed study design would add weight to the current evidence.
We are extremely grateful to:

- All 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
- The University of Queensland and Australian Government
- The World Congress of Asian Psychiatry (WCAP) Scientific Committee
Thank You!
Possible mechanisms of association

11βHSD–2 enzyme catalyzes the conversion of maternal circulating cortisol to inactive cortisone