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The Association between Preeclampsia and Childhood Development and Behavioural Outcomes

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Keywords: Preeclampsia, Childhood Development, Behavioural Issues, Epidemiology.

Significance

What is already known on this subject:

Previous literature suggests an association between preeclampsia and neurodevelopmental outcomes, such as impaired child development and behavioural issues. However, there is a lack of overall consistent findings, and much of the research examining a preeclampsia-child development relationship has been conducted on specific populations (such as preterm and very low birthweight infants) and using small sample sizes.

What this study adds:

This study examined the association between preeclampsia and child development and behavioural outcomes using a nationally representative study of children living in Ireland. Some associations between preeclampsia-exposure and subtle behavioural issues were observed after controlling for several potential confounding factors.

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Abstract

Objective: To examine the associations between preeclampsia and longitudinal child developmental and behavioural outcomes using data from a nationally representative study of children living in Ireland.

Methods: We used maternal-reported data from the Growing Up in Ireland longitudinal study of children. Data on preeclampsia and preeclampsia+small for gestational age (SGA) were collected when children were 9-months old. Data on child development and behavioural outcomes were collected at 9-months using the Ages and Stages Questionnaire (ASQ), and at 3 years, 5 years and 7-8 years using the Strengths and Difficulties Questionnaire (SDQ). Multivariate logistic regression analysis was used to examine the association between preeclampsia exposure and failure of ASQ domains, and abnormal SDQ domains. Linear spline multilevel models were used to examine the association between preeclampsia and preeclampsia+SGA and repeated measures of SDQ. All models controlled for several perinatal and sociodemographic factors.

Results: A total of 10,692 children were included in the study at baseline, representing a weighted total of 70,791. Multivariate logistic regression suggested that preeclampsia was not associated with failing any ASQ domain. Preeclampsia was associated with abnormal SDQ cut-off of Emotional (≥5) and Hyperactivity (≥7) domains at age 5 years only. In the linear spline model, mean SDQ score was higher at each time point in exposed groups.

Discussion: While we did not find strong evidence of associations between preeclampsia and child developmental and behavioural outcomes overall, some associations between preeclampsia-exposure and subtle behavioural issues did persist. Further research is needed to replicate these findings, and determine the clinical significance of changes in SDQ scores.

Keywords: Preeclampsia, Childhood Development, Behavioural Issues, Epidemiology.

Introduction

Preeclampsia is a serious obstetric complication, affecting up to 5% of all pregnancies(Rana, Lemoine, Granger, & Karumanchi, 2019), and is responsible for over 70,000 maternal deaths and 500,000 fetal deaths worldwide each year. Preeclampsia can also result in long-term consequences for both mother and baby(Rana et al., 2019), and has recently been redefined by the International Society for the Study of Hypertension in Pregnancy (ISSHP), as blood pressure ≥140/90 mmHg on/after 20 weeks' gestation, accompanied by proteinuria and/or other maternal organ dysfunction and/or uteroplacental dysfunction(Brown et al., 2018).

Previous literature suggests an association between preeclampsia and neurodevelopmental outcomes, such as impaired child development and behavioural issues(Cheng, Chou, Tsou, Fang, & Tsao, 2004; Girchenko et al., 2018; Szymonowicz & Yu, 1987), with alterations in neuroanatomical and functional connectivity in the brains of exposed offspring representing some of the potential aetiological pathways(Figueiró-Filho et al., 2017; Mak et al., 2018; Ratsep et al., 2016). However, overall consistent findings are lacking as some studies have found no association(Bohm et al., 2019; Schlapbach et al., 2010; Walker et al., 2015), while others suggest a protective association(Robinson et al., 2009; Spinillo et al., 2009). Moreover, much of the research examining a preeclampsia-child development relationship has been conducted on specific populations (such as preterm and very low birthweight infants) and using small sample sizes(Cheng et al., 2004; Johnson et al., 2015; Morsing & Marsal, 2014; Schlapbach et al., 2010; Silveira, Procianoy, Koch, Benjamin, & Schlindwein, 2007; Szymonowicz & Yu, 1987). As a result, further research should be conducted using a more representative sample of children.

Therefore, the objective of this study was to examine the association between preeclampsia and child development using the Ages and Stages Questionnaire (ASQ) at age 9-months, and behavioural outcomes using the Strengths and Difficulties Questionnaire (SDQ) at age 3 years,

5 years, and 7-8 years using data from a nationally representative study of children living in Ireland.

Methods

Study Population

Growing Up in Ireland (GUI) is a nationally representative longitudinal study of children living in Ireland and involves questionnaire-based face-to-face interviews conducted by trained interviewers(Masukume et al., 2018; The Economic and Social Research Institute, 2018). The study follows two separate cohorts over a number of years: a child cohort (beginning in 2006 when children were 9 years old) and an infant cohort (beginning in 2008 when children were 9-months old). The current study used the infant cohort recruited at 9 months of age (wave 1) and followed up at ages 3 years (wave 2), 5 years (wave 3) and 7-8 years (wave 4) of age.

The GUI study was carried out under ethical approval granted by a dedicated Research Ethics Committee set up by the Department of Health and Children, Ireland and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All persons gave their informed consent prior to their inclusion in the GUI study.

Sampling Frame

The Child Benefit Register was used as a sampling frame for the infant cohort. In Ireland, Child Benefit is paid each month to the person who cares for the child under the age of 16 years, and must be claimed within six months of the child being born or within six months of the family coming to reside in Ireland. Therefore, the Child Benefit Register is considered an up-to-date and fully comprehensive database of the population in question to identify a random sample of 9-month old infants(Quail, Williams, McCrory, Murray, & Thornton, 2011a). For children to be included in the study, they had to be registered on the Child Benefit Register, having been born between 1st December 2007 and 30th June 2008 to facilitate fieldwork when they were 9 months of age (between September 2008 and March/April 2009). A total of 41,185 children

over this period in question were deemed eligible. From this, the sample was selected on a systematic basis, pre-stratifying by marital status, county of residence, nationality and number of children in the Child Benefit claim - all variables which were available from the Child Benefit Register. A simple systematic selection procedure based on a random start and constant sampling fraction was then used(Quail et al., 2011a).

Study materials

An introductory letter, information sheet and opt-out form was sent to selected households. In the introductory letter, target participants were informed that an interviewer would be calling to their household within two weeks. If, however, they did not wish to participate in the study, they were advised to complete and return the opt-out form included with the letter within 10 days, and in which case, the interviewer would not call to their home. In addition, if a family member contacted the Study Team indicating that they did not wish to participate in the study after it had been allocated to an interviewer, the interviewer concerned was contacted and told not to visit the family in question(Quail, Williams, McCrory, Murray, & Thornton, 2011b).

A computer-assisted personal-interview (main questionnaire) and computer-assisted self-interview (sensitive questionnaire) was conducted with the respondent. These questionnaires were also available in a number of different languages in order to achieve as inclusive a sample as possible(Quail et al., 2011b). To minimize loss to follow-up, a follow-up/tracing sheet was used. The tracing sheet contained contact details of someone from outside the household who would be able to assist the Study Team in contacting the family should they move between interviews. In addition, respondents were asked to provide signed consent to allow tracing through the Child Benefit Register and whether they would be willing to take part in any further work in relation to the study(Quail et al., 2011b).

Participants included in the current study

For the current study, we used data from wave 1 (baseline), wave 2, wave 3 and wave 4 of the infant cohort. Wave 1 of the infant cohort was collected when the children were 9-months, wave 2 follow-up data was collected when the children were 3 years old, wave 3 follow-up data was collected when the children were 5 years old and wave 4 follow-up data was collected when the children were 7-8 years old (postal survey). The overall response rate at wave 1 was 65% of those sampled (n=11,134), the response rate at wave 2 was 88% (n=9,793), the response rate at wave 3 was 81% (n=9,001), and the response rate at wave 4 was 48% (n=5,344).

Exposure

Preeclampsia: Data on preeclampsia were obtained when children were 9-months old (wave 1) through a questionnaire-based face-to-face interview with the mother. We excluded children from the study if their primary caregiver was not their biological mother to ensure data on preeclampsia were accurate, and because the majority of potential confounders relate to maternal characteristics. The mother was asked the following question: "Were there any of the following complications with the pregnancy?" and instructed to tick all that apply from a list of complications. The list included "raised blood pressure and protein in the urine (Pre-eclampsia)". If she ticked this box, then a diagnosis of preeclampsia was assumed.

Preeclampsia and small for gestational age (SGA) combined: Preeclampsia is associated with impaired placentation, and as a result, can leave the fetus vulnerable to the effects of placental pathology, such as fetal growth restriction (FGR). As likelihood of FGR is higher in some (but not all) SGA infants, we combined preeclampsia and SGA as a crude proxy for preeclampsia with placental dysfunction(Royal College of Obstetricians and Gynaecologists, 2014). SGA was defined as birthweight <10th percentile for gestational age and sex of child and based on maternal-reporting of child's birthweight, gestational age and sex.

Outcomes

Ages and Stages Questionnaire (ASQ)

The ASQ was developed as a way to monitor development in infants and children to allow for further investigation if results are indicative of developmental delay(Squires, Potter, & Bricker, 1995). The ASQ contains 30 items relating to five developmental domains: communication, gross motor, fine motor, problem solving and personal/social issues. The child's mother completed the ASQ when the infants were 9-months old by selecting 'yes', 'sometimes', or 'not yet' for items in each domain, with each of these responses assigned a score of ten, five or zero, respectively(Al Khalaf et al., 2015). Scores for each domain range from 0-60, with higher scores indicating more positive outcomes. A total ASQ score for each domain was calculated, in addition to a pass/fail cut-off for each domain defined as follows: communication≤25, gross motor≤15, fine motor≤35, problem solving≤30, and personal/social issues≤30(Al Khalaf et al., 2015).

Strengths and Difficulties Questionnaire (SDQ)

The SDQ was developed as a screening tool to assess emotional and behavioural problems in children. The SDQ is a 25-item questionnaire with five subscales: emotional, conduct, hyperactivity, peer problems and prosocial behaviours(Goodman, 1997). Data were collected using the parent-administered SDQ when children were aged 3 years (wave 2), 5 years (wave 3), and 7-8 years (wave 4); while a teacher administered SDQ was also administered when children were 5 years (wave 3). Mothers and teachers replied "not true", "somewhat true", and "certainly true" to series of questions, with 'somewhat true' always scored as 1, and the scoring of 'not true' and 'certainly true' varying with the item. (Full scoring procedures are available online: https://www.sdqinfo.com). Scores for each domain range from 0-10, with lower scores indicating more positive outcomes, with the exception of prosocial behaviour which is reversed

scored (i.e. higher scores indicate more positive outcomes). Similar to other childhood behavioural outcome studies conducted in Ireland and the United Kingdom(Al Khalaf et al., 2015; Heikkilä, Sacker, Kelly, Renfrew, & Quigley, 2011; Kelly et al., 2009), abnormal SDQ cut-off points were defined as follows: total SDQ≥17, emotional≥5, conduct≥4, hyperactivity≥7, peer problems≥4 and prosocial behaviour≤4 (see eTable 1 in the Supplement for a summary of the data collection process).

Confounding Variables

We selected covariates using a directed acyclic graph (DAG) to encode our causal knowledge of this research question. In summary, we have included only covariates in our model, which we believe to be common causes of the exposure and outcome, and have excluded any variables that might be potential mediators of the association, since our goal in this paper was to estimate the total effect of preeclampsia on outcomes. Therefore, we controlled for the following potential confounders, all of which were measured at baseline: maternal education, maternal age, maternal ethnicity, maternal body mass index (BMI) at time of wave 1 interview, family social class, gestational diabetes, and infant sex, all of which have been proposed to influence child developmental and behavioural outcomes(Al Khalaf et al., 2015).

Statistical Analysis

Data were analysed using Stata/MP 14.2. All data were weighted to represent the national sample of infants aged less than one year, and who were on the Child Benefit Register in the 2008 calendar year (n=73,662)(Quail et al., 2011a). The weighting was constructed by adjusting the distribution of the sample to known population figures using Irish Census data and the Child Benefit Register.

Multivariate logistic regression analysis estimated odds ratios (OR) and 95% confidence intervals (CI) for preeclampsia-failure of ASQ domains (at age 9-months) and preeclampsia-abnormal SDQ domains (at ages 3, 5 and 7-8 years).

Model 1 represented the crude model. Model 2 was fully adjusted for maternal education, maternal age, maternal ethnicity, maternal body mass index (BMI), family social class, gestational diabetes, and infant sex. Model 3 stratified by infant sex and adjusted for the same variables as model 2 (with exception of infant sex).

Repeated Measures Analysis: As the SDQ was measured at three time points (ages 3, 5 and 7-8 years), we conducted linear spline multilevel modelling (placing 'knot points' at age 5 and 7-8 years). Multilevel models take non-independence of repeated measures on the same individual into account, therefore addressing the issue of correlations between measurements from the same individual over time (Howe et al., 2016; O'Keeffe et al., 2018). Furthermore, the multilevel approach can estimate the SDQ trajectory for all participants regardless of the number and timing of their measurements, while also taking non-linearity in the trajectory into account(Tilling et al., 2011). We modelled trajectories for preeclampsia-SDQ score and preeclampsia+SGA-SDQ score, with random effects at two levels: measurement occasion and individual. (Preeclampsia+SGA could be combined in this linear spline analysis only due to small numbers). We conducted sex-specific analyses but as there was no evidence of sex-specific effects, all results were sex-combined. We also modelled trajectories for preeclampsia-SDQ domains. In all models, the starting point was centred at age 3 (when SDQ was first measured). Similar to above, model 1 represented the crude model and model 2 represented the fully adjusted model. Finally, we assessed model fit by comparing mean SDQ scores predicted by the multilevel model to mean observed scores.

Sensitivity Analysis: In an attempt to isolate more certain cases of preeclampsia, we examined the association between preeclampsia and ASQ/SDQ in primiparous women only as

preeclampsia is more common in this group. Furthermore, as the SDQ was measured using both parent and teacher-reported data at age 5 years, multivariate linear regression estimated coefficients and 95% confidence intervals for preeclampsia-total SDQ score at 5 years. Parent-reported SDQ score was compared to teacher-reported SDQ score using the Bland-Altman agreement plot. This method assumes that differences in measurements are from an approximately normal distribution and recommends that 95% of the data points should lie between the upper and lower 95% agreement limits(Bland & Altman, 2003).

As our classification of SGA does not take ethnicity into account, we modelled trajectories for preeclampsia+SGA-SDQ score, limiting the study population to Irish/other white background. Finally, preterm birth may be a mediator or a potential confounder of the association between preeclampsia and our outcome. Thus, we performed a sensitivity analysis examining the association between preeclampsia and ASQ/SDQ domains in children born <37 weeks' gestation and ≥37 weeks' gestation compared to no preeclampsia in children born at ≥37 weeks' gestation.

Results

The GUI study contained a total of 11,134 children, representing a weighted national sample of 73,662 children who were aged less than one year, and who were on the Child Benefit Register in the 2008 calendar year. We excluded 45 children from the study because their primary caregiver was not their biological mother. In addition, we excluded 397 non-singleton children. Therefore, a total of 10,692 children were included in the study at baseline, representing a weighted total of 70,791. Mother and child characteristics are outlined in Table 1, and are based on weighted data. Of the study cohort, over 6% (n=709, [weighted sample n=4,899]) had preeclampsia. Among women with preeclampsia, over 11% (n=84, [weighted sample=548]) had preeclampsia+SGA. The vast majority of respondents were white, had a secondary level of education, were of normal weight, with a mean maternal age of 31 years, while the majority of infants in the study were born at term.

Preeclampsia and ASQ (age 9-months)

Preeclampsia was not significantly associated with failing an ASQ domain, and stratifying results by infant sex did not materially change results (Table 2).

Preeclampsia and SDQ (ages 3 years, 5 years and 7-8 years)

Logistic regression: Adjusted results in Table 3 suggested that preeclampsia was not associated with abnormal SDQ score in any of the domains at age 3 years and age 7-8 years. At age 5 years, adjusted results from parent-reported data suggested that preeclampsia was associated with a 50% increase in odds of having an abnormal SDQ score in the Emotional domain (OR: 1.50, 95% CI: 1.04, 2.17). When stratified by infant sex, results spanned the null for males (OR: 1.21, 95% CI: 0.69, 2.14), however the OR for females increased to 1.83, 95% CI: 1.13, 2.97. In addition, exposure to preeclampsia was associated with increased odds of abnormal

SDQ score in the Hyperactivity domain (OR: 1.57, 95% CI: 1.19, 2.08). In sex-stratified analyses, the OR increased to 2.15 (95% CI: 1.42, 3.24) for females, while it spanned the null for males (OR: 1.28, 95% CI: 0.89, 1.84). Preeclampsia was not associated with abnormal Conduct (OR: 1.12, 95% CI: 0.81, 1.54), Peer Problem (OR: 1.41, 95% CI: 0.97, 2.06) or Prosocial Behaviour (OR: 1.40, 95% CI: 0.75, 2.62) in the adjusted models at age 5 years.

Repeated Measures Analysis

Adjusted mean trajectories of SDQ from 3 to 7-8 years comparing exposed and unexposed groups are shown in Fig. 1. Adjusted results suggested that children exposed to preeclampsia had a higher mean SDQ score compared to the unexposed group at age 3 years, although the difference spanned the null value (mean difference: -0.10, 95% CI: -0.45, 0.25). SDQ mean scores decreased by -1.27 (95% CI: -5.54, 3.00) in the unexposed group from age 3 to 5 years, with a slower decrease in the exposed group (mean difference: -0.69, 95% CI: -0.32, -1.07). From age 5 to 7-8 years, SDQ scores increased again in both groups, with a slower rate of increase in the exposed group (mean difference: 0.66, 95% CI: 0.13, 1.18). (Fig. 1 and Table 4). Similarly, the group exposed to preeclampsia and born SGA, had a higher mean SDQ score at age 3 compared to the unexposed group and not born SGA, (mean difference: -0.37, 95% CI: -1.32, 0.59) however the difference was not statistically significant. From age 3 to 5 years, mean SDQ scores decreased by -1.16 (95% CI: -6.15, 3.82) in the unexposed group, with a slower rate of decrease in the exposed group (mean difference: -0.60, 95% CI: -1.62, 0.42). Scores increased from ages 5 to 7-8 years in both groups, again at a slower rate in the exposed group (mean difference: 0.88, 95% CI: -0.60, 2.35) (Fig. 1 and Table 4). When we modelled trajectories for preeclampsia-SDQ domains separately, preeclampsia was associated with a higher SDQ score at each time point for the Emotional domain only (eTable 2). Finally,

comparison of predicted and observed values indicated that the model was a suitable fit for the data (eTable 3 in the Supplement).

Sensitivity Analysis

Results of the analysis including primiparous women only were not significantly different from the main findings (eTable 4). Adjusted estimates suggested preeclampsia was associated with a higher SDQ score at age 5 years in both maternal-reported and teacher-reported data compared to non-exposure to preeclampsia (eTable 4). eFig. 1 compares parent-reported SDQ scores to teacher-reported SDQ scores at age 5 years on a Bland-Altman agreement plot. Differences appear to follow a normal distribution (i.e. negative differences and positive differences appear to be even), The mean difference was 1.10, with limits of agreement between -10.46 and 12.67. For example, for 95% of individuals, parent-reported SDQ scores would be between 10.46 units less and 12.67 units greater than teacher-reported SDQ scores. Limiting the study population to Irish/other white background did not have a significant impact on findings (eTable 5). Finally, results are indicative of an association between preeclampsia and some domains of the ASQ/SDQ in children born <37 weeks' gestation. However, when we limited the analysis to children born ≥37 weeks' gestation, results were not materially different from the main findings (eTable 6).

Discussion

This study aimed to examine the association between preeclampsia and child development (using the ASQ) at age 9-months, and preeclampsia and emotional/behavioural problems (using the SDQ) at age 3 years, 5 years and 7-8 years using data from a nationally representative longitudinal study of children living in Ireland. These analyses have yielded three principal findings.

First, preeclampsia was not associated with failing an ASQ domain. In comparison to previous literature, Warshafsky et al investigated the relationship between "severe" preeclampsia and failure of ASQ categories in a 5 year follow-up study(Warshafsky, Pudwell, Walker, Wen, & Smith, 2016). While Warshafsky and colleagues did not find a significant difference in the proportion of ASQ categories failed in the preeclampsia group compared to the control group at age 1, a significant difference was found at age 3. In addition, a recent study conducted in Finland found an association between preeclampsia and the Communication domain of the ASQ in children aged 23-69 months, however did not find an association in the other ASQ domains(Girchenko et al., 2018).

Second, preeclampsia was not significantly associated with abnormal SDQ score in any of the domains at age 3 years and age 7-8 years. However, at age 5 years, children exposed to preeclampsia had a 50% increased odds of failing the Emotional domain of the SDQ, and almost 60% increased odds of failing the Hyperactivity domain compared to unexposed children. Our results are in line with previous evidence that suggests behavioural difficulties identified in young children may not always be stable throughout childhood as children can sometimes transition in or out of the abnormal range for behavioural issues(D'Souza, Underwood, Peterson, Morton, & Waldie, 2019). Studies examining the association between preeclampsia and abnormal SDQ specifically are scarce. Bohm et al examined the association between hypertensive disorders of pregnancy (which included raised blood pressure,

eclampsia/preeclampsia, or toxaemia) and the risk of abnormal SDQ scores at age 7, but did not find evidence to support an association. However, the authors did not examine preeclampsia-SDQ score specifically(Bohm et al., 2019).

Third, the repeated measures analysis suggested that the group exposed to preeclampsia or preeclampsia+SGA had a higher mean SDQ score at age 3 years compared to the unexposed group. From age 3 to 5 years, we observed a decrease in mean score in unexposed and exposed groups, with a slower rate of decrease in the exposed group. Finally, from age 5 to 7-8 years, SDQ scores increased in both groups, with a slower increase in the exposed group. While changes in SDQ scores did not always reach statistical significance, a consensus about what constitutes a clinical meaningful change remains an issue as reports of changes in a child's behaviour may have a large impact on the child or family, however may not be statistically significant(Wolpert et al., 2015).

The apparent relationship observed between preeclampsia and some domains of the SDQ in this study may lack specificity however as previous research also suggests a link between preeclampsia and other neurodevelopmental outcomes such as ASD and ADHD(Dachew, Scott, Mamun, & Alati, 2018; Maher et al., 2018). For example, using population-based registry data from Sweden, (with data on over two million children), we have previously shown that exposure to preeclampsia is associated with an increase in the likelihood of autism spectrum disorder (ASD)(Maher et al., 2020) after controlling for several confounders, including confounding due to shared genetics and familial factors. Therefore, preeclampsia may be associated with adverse neurodevelopmental outcomes in general, and is not specific to one particular outcome.

With regards to potential mechanisms, the association between preeclampsia exposure and a failure in specific SDQ domains may result from neuroanatomical alterations in the brains of offspring. For example, brain imaging studies have described anatomical(Figueiró-Filho et al.,

2017; Ratsep et al., 2016) and altered functional connectivity in preeclampsia exposed children aged 7-10 years in brain regions that are collectively referred to as the 'social brain'(Mak et al., 2018). One such region is the amygdala which as part of the social brain, functions to attach emotional value to faces, and enable the recognition of different facial expressions(Veer et al., 2011). This work is consistent with our finding that preeclampsia was associated with abnormal SDQ cut-off in the Emotional domain.

Strengths and Limitations

The current study contains some limitations. First, data on exposure status (preeclampsia and preeclampsia+SGA) was collected 9-months post-delivery and was based on maternal reporting, therefore recall bias cannot be ruled out. However, the validity of maternal recall of preeclampsia is estimated to be moderate(Coolman et al., 2010), while maternal recall of infant characteristics such as gestational age and birthweight was found to be excellent and therefore a valid alternative to medical record data(Adegboye & Heitmann, 2008; Bat-Erdene, Metcalfe, McDonald, & Tough, 2013; Carter et al., 2015; Petersen, Mitchell, Van Bennekom, & Werler, 2019). Nonetheless, respondents may have for example, incorrectly reported gestational hypertension as a diagnosis of preeclampsia, potentially leading to biased results. Second, ascertainment of our outcome at age 3 years and 7-8 years was reliant on the subjective evaluation of the child's mother only. While it can be difficult to assess child development and behavioural outcomes by anyone other than the child's parents at a young age(Al Khalaf et al., 2015), we were able to include information on the SDQ from both mother and teacher at age 5 years, which may have improved the detection of emotional/behavioural problems(Goodman, Ford, Corbin, & Meltzer, 2004). Third, loss to follow-up may also be an issue. The response rate at wave 1 was 65%. Of this, 88% responded at wave 2, 81% at wave 3, and 48% at wave 4. Loss to follow-up was most likely to occur among younger mothers with lower levels of

education, and of non-white ethnic origin, while previous evidence suggests that children with behavioural disorders are more prone to loss to follow-up, which may have affected study findings(Wolke et al., 2009). Fourth, despite controlling for several confounding factors, residual confounding cannot be ruled out in observational studies. Finally, preterm birth may be a confounder of the association between preeclampsia and ASQ/SDQ but could also be a mediator of the preeclampsia-outcome association. Adjusting for a mediator in the presence of unmeasured or uncontrolled mediator-outcome confounders can induce collider bias. Thus, our results of the sensitivity analysis stratified by preterm and term birth (eTable 6) should be interpreted with caution.

However, this study also contains several strengths. First, we used data from a nationally representative study of children living in Ireland to examine the association between preeclampsia and childhood development, emotional and behavioural problems at age 9-months, 3 years, 5 years and 7-8 years. Registry data, such as the data previously used in Sweden lack information on childhood development and emotional/behavioural problems, therefore cannot be used to examine such associations. Second, SDQ was measured at three time points, therefore enabling us to conduct repeated measures analysis using linear spline multilevel modelling, which allows for change in SDQ score over time. Reassuringly, similar SDQ score trajectories in children aged 3-7 years were observed in previous studies using data from the Millennium Cohort Study in the United Kingdom(Dillenburger, Jordan, McKerr, & Keenan, 2015; Zilanawala, Sacker, & Kelly, 2018). Third, data were weighted to represent the national sample of infants aged less than one year in 2008. Fourth, we controlled for a wide range of confounding variables including maternal age and education, maternal ethnicity, maternal BMI, family social class, gestational diabetes, and infant sex. Finally, our decision to include preeclampsia+SGA as a crude proxy for preeclampsia with placental dysfunction is in

line with the recent guidelines put forward by ISSHP to include placental insufficiency in the definition of preeclampsia(Brown et al., 2018).

Conclusion

While we did not find strong evidence of associations between preeclampsia and child developmental and behavioural outcomes overall, exposure to preeclampsia was associated with an increased likelihood of subtle behavioural issues. However, further research is needed to replicate these findings, (while also taking account of repeated measurement in the SDQ over time), and determine the clinical significance of such changes in SDQ scores.

Supplementary Material

Refer to Web version for supplementary material

Conflicts of interest: none

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Data: Data for the Growing Up in Ireland cohort is collected under the provisions of 1993 Statistics Act of the Central Statistics Office, and funding is provided by the Government of Ireland through the Department of Children and Youth Affairs. The data was accessed via the Irish Social Science Data Archive - www.ucd.ie/issda. The Growing Up in Ireland Study team composed of Economic and Social Research Institute (ESRI), and Trinity College Dublin (TCD) staff designed and implements the project.

Table 1: Perinatal and Sociodemographic Characteristics Related to Preeclampsia and Childhood Behavioural Outcomes Among Singleton Live Births in Ireland		
Characteristic	**Total Population**	**Preeclampsia**
Total Population, N (%)	70,791	4899 (6.92)
Infant Sex, n (%)		
Male	36,406 (51.43)	2438 (49.86)
Female	34,385 (48.57)	2,461 (50.14)
Gestational age, n (%)		
<32 weeks	471 (0.66)	49 (1.01)
32 weeks	276 (0.39)	88 (1.80)
33 weeks	320 (0.45)	84 (1.71)
34 weeks	575 (0.81)	125 (2.56)
35 weeks	652 (0.92)	100 (2.04)
36 weeks	1,425 (2.01)	170 (3.48)
37 weeks	3,029 (4.28)	320 (6.54)
38 weeks	7,466 (10.55)	549 (11.20)
39 weeks	12,710 (17.95)	803 (16.40)
40 weeks	21,706 (30.66)	1,202 (24.55)
>40 weeks	22,004 (31.09)	1,402 (28.59)
Unknown	157 (0.23)	<30
Maternal age, years, mean (SD)	31.6 (5.49)	30.6 (5.79)
SGA		
Yes	7,015 (10.03)	548 (11.34)
No	62,950 (89.97)	4,283 (88.66)
Maternal Ethnicity, n (%)		
White	66,657 (94.16)	4,711 (96.16)
Black	1,848 (2.61)	122 (2.50)
Asian	1,741 (2.46)	54 (1.11)
Maternal Education completed, n (%)		
Primary or less	2,556 (3.61)	154 (3.15)
Second level	47,536 (67.15)	3,824 (78.06)
Third level degree or higher	20,628 (29.14)	920 (18.79)
Maternal BMI, n (%)		
Underweight	1,508 (2.13)	83 (1.70)
Normal weight	36,203 (51.14)	1,762 (35.96)
Overweight	18,583 (26.25)	1,549 (31.62)
Obese	8,934 (12.62)	1,156 (23.59)
Failure of ASQ domain, n (%)		
Communication	4,550 (6.43)	316 (6.45)
Gross Motor	10,655 (15.05)	789 (16.11)
Fine Motor	6,798 (9.60)	478 (9.76)
Problem Solving	9,478 (13.39)	594 (12.13)
Personal Social	12,305 (17.38)	797 (16.28)
Total SDQ: Maternal-reported (age 3 years), mean (SD)	7.77 (4.53)	8.25 (4.62)
Total SDQ: Maternal-reported (age 5 years), mean (SD)	7.18 (4.75)	8.34 (5.07)
Total SDQ: Maternal-reported (age 7-8 years), mean (SD)	7.10 (5.30)	7.73 (5.49)
Total SDQ: Teacher-reported (age 5 years), mean (SD)	6.04 (5.32)	7.05 (5.81)
Data refer to the weighted n (%) or mean and standard deviation (SD) where appropriate. Where cell counts are <30, n cannot be provided. Abbreviations: SGA, small for gestational age; BMI, body mass index; ASQ, Ages and Stages Questionnaire; SDQ, Strengths and Difficulties Questionnaire; SD, standard deviation.		

Table 2: Association between Preeclampsia and Child Development Among Singleton Live Births in Ireland					
	Exposed Cases	**Model 1[a]**	**Model 2[b]**	**Model 3 Stratified for Infant Sex[c]**	
		OR (95% CI)	**OR (95% CI)**	**Males**	**Females**
Failure of ASQ domains					
Communication					
Preeclampsia	316	0.99 (0.70, 1.42)	1.10 (0.77, 1.58)	1.20 (0.76, 1.92)	0.95 (0.54, 1.65)
Gross Motor					
Preeclampsia	789	1.09 (0.85, 1.40)	1.07 (0.88, 1.37)	1.27 (0.91, 1.78)	0.90 (0.63, 1.30)
Fine Motor					
Preeclampsia	478	1.01 (0.75, 1.36)	0.92 (0.68, 1.25)	1.09 (0.74, 1.61)	0.74 (0.45, 1.20)
Problem Solving					
Preeclampsia	594	0.88 (0.68, 1.15)	0.87 (0.67, 1.13)	0.98 (0.69, 1.39)	0.77 (0.51, 1.15)
Personal Social					
Preeclampsia	797	0.92 (0.72, 1.17)	0.95 (0.74, 1.22)	1.17 (0.84, 1.62)	0.72 (0.49, 1.05)

[a]Crude analysis.
[b]Adjusted for maternal education, maternal age, maternal ethnicity, maternal body mass index (BMI) at time of interview, family social class, gestational diabetes, and infant sex
[c]Adjusted for the same potential confounders as above with the exception of infant sex.
Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval ASQ, Ages and Stages Questionnaire.

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Table 3: Association between Preeclampsia and Emotional/Behavioural Problems Among Singleton Live Births in Ireland					
	Exposed Cases	**Model 1[a]**	**Model 2[b]**	**Model 3 Stratified for Infant Sex[b]**	
		OR (95% CI)	**OR (95% CI)**	**Males**	**Females**
Abnormal SDQ (age 3 years) Maternal-reported					
Emotional					
Preeclampsia	194	1.41 (0.90, 2.22)	1.26 (0.79, 2.01)	1.06 (0.54, 2.10)	1.51 (0.80, 2.85)
Conduct					
Preeclampsia	1093	1.20 (0.96, 1.50)	1.05 (0.84, 1.31)	0.94 (0.70, 1.27)	1.20 (0.88, 1.65)
Hyperactivity					
Preeclampsia	382	1.11 (0.77, 1.58)	0.95 (0.66, 1.35)	0.78 (0.50, 1.22)	1.20 (0.69, 2.10)
Peer Problems					
Preeclampsia	302	0.90 (0.63, 1.29)	0.84 (0.59, 1.20)	0.73 (0.45, 1.16)	1.02 (0.59, 1.76)
Prosocial Behaviour					
Preeclampsia	172	1.05 (0.63, 1.76)	1.13 (0.67, 1.91)	0.82 (0.43, 1.59)	1.96 (0.85, 4.54)
Abnormal SDQ (age 5 years) Maternal-reported					
Emotional					
Preeclampsia	396	**1.62 (1.12, 2.34)**	**1.50 (1.04, 2.17)**	1.21 (0.69, 2.14)	**1.83 (1.13, 2.97)**
Conduct					
Preeclampsia	490	1.30 (0.95, 1.78)	1.12 (0.81, 1.54)	1.13 (0.74, 1.73)	1.13 (0.69, 1.86)
Hyperactivity					
Preeclampsia	731	**1.74 (1.33, 2.28)**	**1.57 (1.19, 2.08)**	1.28 (0.89, 1.84)	**2.15 (1.42, 3.24)**
Peer Problems					
Preeclampsia	337	**1.60 (1.10, 2.34)**	1.41 (0.97, 2.06)	1.35 (0.85, 2.15)	1.49 (0.78, 2.83)
Prosocial Behaviour					
Preeclampsia	110	1.41 (0.74, 2.66)	1.40 (0.75, 2.62)	1.30 (0.64, 2.62)	1.90 (0.52, 6.95)
Abnormal SDQ (age 7-8 years) Maternal-reported					
Emotional					
Preeclampsia	314	1.31 (0.90, 1.92)	1.16 (0.79, 1.70)	1.57 (0.95, 2.60)	0.78 (0.41, 1.48)
Conduct					
Preeclampsia	168	0.93 (0.58, 1.47)	0.85 (0.53, 1.36)	0.87 (0.47, 1.62)	0.85 (0.40, 1.80)
Hyperactivity					
Preeclampsia	183	0.96 (0.62, 1.50)	0.82 (0.51, 1.33)	0.93 (0.55, 1.60)	0.63 (0.22, 1.83)
Peer Problems					
Preeclampsia	171	0.90 (0.54, 1.49)	0.76 (0.45, 1.27)	0.93 (0.49, 1.75)	0.49 (0.19, 1.25)
Prosocial Behaviour					
Preeclampsia	36	0.61 (0.23, 1.65)	0.58 (0.21, 1.59)	0.74 (0.26, 2.05)	-
[a]Crude analysis.					

[b]Adjusted for maternal education, maternal age, maternal ethnicity, maternal body mass index (BMI) at time of interview, family social class, gestational diabetes, and infant sex.
Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval; SDQ, Strengths and Difficulties Questionnaire.
Reason for empty cells: n too small to estimate.

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Table 4: Repeated Measures Analysis Examining the Association between Preeclampsia and Emotional/Behavioural Problems (using Total SDQ Score) Among Singleton Live Births in Ireland			
Model 1[a]	**Mean trajectory (95% CI) (No Preeclampsia)**	**Mean trajectory (95% CI) (Preeclampsia)**	**Mean difference in trajectory (95% CI) comparing no preeclampsia to preeclampsia**
Age 3 SDQ	7.75 (7.66, 7.84)	8.23 (7.88, 8.58)	-0.48 (-0.12, -0.84)
Change SDQ Age 5	-0.60 (-0.50, -0.69)	0.12 (-0.24, 0.48)	-0.72 (-0.35, -1.09)
Change SDQ Age 7-8	0.24 (0.11, 0.37)	-0.29 (-0.80, 0.21)	0.53 (0.01, 1.05)
Age 7-8 SDQ	7.39 (7.25, 7.53)	8.06 (7.51, 8.60)	-0.67 (-0.10, -1.22)
Model 2[b]			
Age SDQ3	12.19 (10.89, 13.49)	12.29 (10.95, 13.63)	-0.10 (-0.45, 0.25)
Change SDQ Age 5	-1.27 (-5.54, 3.00)	-0.58 (-4.87, 3.71)	-0.69 (-0.32, -1.07)
Change SDQ Age 7-8	1.12 (-7.62, 9.87)	0.47 (-8.29, 9.23)	0.66 (0.13, 1.18)
Age 7-8 SDQ	12.05 (3.10, 20.99)	12.18 (3.22, 21.14)	-0.14 (-0.41, 0.69)
Model 1[a]	**Mean trajectory (95% CI) (No Preeclampsia/No SGA)**	**Mean trajectory (95% CI) (Preeclampsia+SGA)**	**Mean difference in trajectory (95% CI) comparing no preeclampsia/no SGA to preeclampsia+SGA**
Age 3 SDQ	7.71 (7.61, 7.81)	8.74 (7.75, 9.72)	-1.03 (-0.04, -2.01)
Change SDQ Age 5	-0.59 (-0.49, -0.69)	0.02 (-0.99, 1.03)	-0.61 (-1.63, 0.41)
Change SDQ Age 7-8	0.16 (0.02, 0.30)	-0.47 (-1.94, 0.99)	0.63 (-0.84, 2.11)
Age 7-8 SDQ	7.28 (7.13, 7.43)	8.28 (6.72, 9.85)	-1.00 (-2.58, 0.57)
Model 2[b]			
Age 3 SDQ	11.99 (10.54, 13.44)	12.36 (10.63, 14.10)	-0.37 (-1.32, 0.59)
Change SDQ Age 5	-1.16 (-6.15, 3.82)	-0.57 (-5.65, 4.52)	-0.60 (-1.62, 0.42)
Change SDQ Age 7-8	0.99 (-7.81, 9.79)	0.12 (-8.80, 9.03)	0.88 (-0.60, 2.35)
Age 7-8 SDQ	11.82 (2.75, 20.89)	11.91 (2.71, 21.11)	-0.09 (-1.64, 1.46)

[a]Crude analysis.
[b]Adjusted for maternal education, maternal age, maternal ethnicity, maternal body mass index (BMI) at time of interview, family social class, gestational diabetes, and infant sex.
Abbreviations: 95% CI, 95% confidence interval; SDQ, Strengths and Difficulties Questionnaire; SGA, small for gestational age.

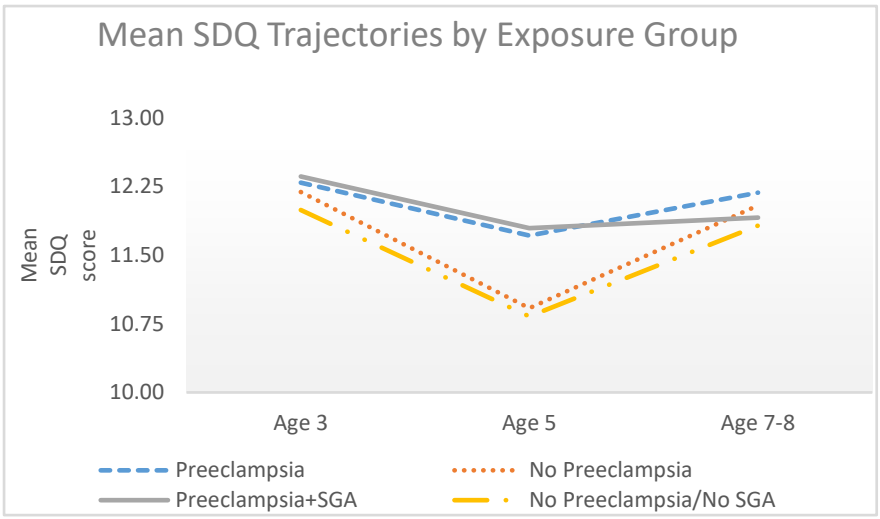


Fig. 1 Predicted trajectory of mean SDQ scores in waves 2-4 (adjusted model)

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