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The Association between Preeclampsia and Childhood Development and Behavioural Outcomes

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

2

3 **Significance**

4 *What is already known on this subject:*

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

10 *What this study adds:*

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

15

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27 **Abstract**

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

31 **Methods:** We used maternal-reported data from the Growing Up in Ireland longitudinal study
32 of children. Data on preeclampsia and preeclampsia+small for gestational age (SGA) were
33 collected when children were 9-months old. Data on child development and behavioural
34 outcomes were collected at 9-months using the Ages and Stages Questionnaire (ASQ), and at
35 3 years, 5 years and 7-8 years using the Strengths and Difficulties Questionnaire (SDQ).
36 Multivariate logistic regression analysis was used to examine the association between
37 preeclampsia exposure and failure of ASQ domains, and abnormal SDQ domains. Linear spline
38 multilevel models were used to examine the association between preeclampsia and
39 preeclampsia+SGA and repeated measures of SDQ. All models controlled for several perinatal
40 and sociodemographic factors.

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

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

50

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

52 **Introduction**

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

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

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

77 5 years, and 7-8 years using data from a nationally representative study of children living in
78 Ireland.

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102 **Methods**

103 **Study Population**

104 Growing Up in Ireland (GUI) is a nationally representative longitudinal study of children living
105 in Ireland and involves questionnaire-based face-to-face interviews conducted by trained
106 interviewers(Masukume et al., 2018; The Economic and Social Research Institute, 2018). The
107 study follows two separate cohorts over a number of years: a child cohort (beginning in 2006
108 when children were 9 years old) and an infant cohort (beginning in 2008 when children were
109 9-months old). The current study used the infant cohort recruited at 9 months of age (wave 1)
110 and followed up at ages 3 years (wave 2), 5 years (wave 3) and 7-8 years (wave 4) of age.

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

116

117 **Sampling Frame**

118 The Child Benefit Register was used as a sampling frame for the infant cohort. In Ireland, Child
119 Benefit is paid each month to the person who cares for the child under the age of 16 years, and
120 must be claimed within six months of the child being born or within six months of the family
121 coming to reside in Ireland. Therefore, the Child Benefit Register is considered an up-to-date
122 and fully comprehensive database of the population in question to identify a random sample of
123 9-month old infants(Quail, Williams, McCrory, Murray, & Thornton, 2011a). For children to
124 be included in the study, they had to be registered on the Child Benefit Register, having been
125 born between 1st December 2007 and 30th June 2008 to facilitate fieldwork when they were 9
126 months of age (between September 2008 and March/April 2009). A total of 41,185 children

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

132

133 **Study materials**

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

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

151

152 **Participants included in the current study**

153 For the current study, we used data from wave 1 (baseline), wave 2, wave 3 and wave 4 of the
154 infant cohort. Wave 1 of the infant cohort was collected when the children were 9-months,
155 wave 2 follow-up data was collected when the children were 3 years old, wave 3 follow-up
156 data was collected when the children were 5 years old and wave 4 follow-up data was collected
157 when the children were 7-8 years old (postal survey). The overall response rate at wave 1 was
158 65% of those sampled (n=11,134), the response rate at wave 2 was 88% (n=9,793), the response
159 rate at wave 3 was 81% (n=9,001), and the response rate at wave 4 was 48% (n=5,344).

160

161 **Exposure**

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

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

177 **Outcomes**

178 **Ages and Stages Questionnaire (ASQ)**

179 The ASQ was developed as a way to monitor development in infants and children to allow for
180 further investigation if results are indicative of developmental delay(Squires, Potter, & Bricker,
181 1995). The ASQ contains 30 items relating to five developmental domains: communication,
182 gross motor, fine motor, problem solving and personal/social issues. The child's mother
183 completed the ASQ when the infants were 9-months old by selecting 'yes', 'sometimes', or
184 'not yet' for items in each domain, with each of these responses assigned a score of ten, five or
185 zero, respectively(Al Khalaf et al., 2015). Scores for each domain range from 0-60, with higher
186 scores indicating more positive outcomes. A total ASQ score for each domain was calculated,
187 in addition to a pass/fail cut-off for each domain defined as follows: communication \leq 25, gross
188 motor \leq 15, fine motor \leq 35, problem solving \leq 30, and personal/social issues \leq 30(Al Khalaf et al.,
189 2015).

190

191 **Strengths and Difficulties Questionnaire (SDQ)**

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

202 scored (i.e. higher scores indicate more positive outcomes). Similar to other childhood
203 behavioural outcome studies conducted in Ireland and the United Kingdom(Al Khalaf et al.,
204 2015; Heikkilä, Sacker, Kelly, Renfrew, & Quigley, 2011; Kelly et al., 2009), abnormal SDQ
205 cut-off points were defined as follows: total SDQ \geq 17, emotional \geq 5, conduct \geq 4,
206 hyperactivity \geq 7, peer problems \geq 4 and prosocial behaviour \leq 4 (see eTable 1 in the Supplement
207 for a summary of the data collection process).

208

209 **Confounding Variables**

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

219

220 **Statistical Analysis**

221 Data were analysed using Stata/MP 14.2. All data were weighted to represent the national
222 sample of infants aged less than one year, and who were on the Child Benefit Register in the
223 2008 calendar year (n=73,662)(Quail et al., 2011a). The weighting was constructed by
224 adjusting the distribution of the sample to known population figures using Irish Census data
225 and the Child Benefit Register.

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

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

233 *Repeated Measures Analysis:* As the SDQ was measured at three time points (ages 3, 5 and 7-
234 8 years), we conducted linear spline multilevel modelling (placing 'knot points' at age 5 and
235 7-8 years). Multilevel models take non-independence of repeated measures on the same
236 individual into account, therefore addressing the issue of correlations between measurements
237 from the same individual over time (Howe et al., 2016; O'Keeffe et al., 2018). Furthermore,
238 the multilevel approach can estimate the SDQ trajectory for all participants regardless of the
239 number and timing of their measurements, while also taking non-linearity in the trajectory into
240 account (Tilling et al., 2011). We modelled trajectories for preeclampsia-SDQ score and
241 preeclampsia+SGA-SDQ score, with random effects at two levels: measurement occasion and
242 individual. (Preeclampsia+SGA could be combined in this linear spline analysis only due to
243 small numbers). We conducted sex-specific analyses but as there was no evidence of sex-
244 specific effects, all results were sex-combined. We also modelled trajectories for preeclampsia-
245 SDQ domains. In all models, the starting point was centred at age 3 (when SDQ was first
246 measured). Similar to above, model 1 represented the crude model and model 2 represented the
247 fully adjusted model. Finally, we assessed model fit by comparing mean SDQ scores predicted
248 by the multilevel model to mean observed scores.

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

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

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

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276 **Results**

277 The GUI study contained a total of 11,134 children, representing a weighted national sample
278 of 73,662 children who were aged less than one year, and who were on the Child Benefit
279 Register in the 2008 calendar year. We excluded 45 children from the study because their
280 primary caregiver was not their biological mother. In addition, we excluded 397 non-singleton
281 children. Therefore, a total of 10,692 children were included in the study at baseline,
282 representing a weighted total of 70,791. Mother and child characteristics are outlined in Table
283 1, and are based on weighted data. Of the study cohort, over 6% (n=709, [weighted sample
284 n=4,899]) had preeclampsia. Among women with preeclampsia, over 11% (n=84, [weighted
285 sample=548]) had preeclampsia+SGA. The vast majority of respondents were white, had a
286 secondary level of education, were of normal weight, with a mean maternal age of 31 years,
287 while the majority of infants in the study were born at term.

288

289 **Preeclampsia and ASQ (age 9-months)**

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

292

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

294 *Logistic regression:* Adjusted results in Table 3 suggested that preeclampsia was not associated
295 with abnormal SDQ score in any of the domains at age 3 years and age 7-8 years. At age 5
296 years, adjusted results from parent-reported data suggested that preeclampsia was associated
297 with a 50% increase in odds of having an abnormal SDQ score in the Emotional domain (OR:
298 1.50, 95% CI: 1.04, 2.17). When stratified by infant sex, results spanned the null for males
299 (OR: 1.21, 95% CI: 0.69, 2.14), however the OR for females increased to 1.83, 95% CI: 1.13,
300 2.97. In addition, exposure to preeclampsia was associated with increased odds of abnormal

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

306

307 **Repeated Measures Analysis**

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

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

327

328 **Sensitivity Analysis**

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

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350 **Discussion**

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

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

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

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

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

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

397 With regards to potential mechanisms, the association between preeclampsia exposure and a
398 failure in specific SDQ domains may result from neuroanatomical alterations in the brains of
399 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.

406

407 **Strengths and Limitations**

408 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

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

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

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

451

452 **Conclusion**

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

458

459 **Supplementary Material**

460 Refer to Web version for supplementary material

461 **Conflicts of interest:** none

462

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470 Irish Social Science Data Archive - www.ucd.ie/issda. The Growing Up in Ireland Study team
471 composed of Economic and Social Research Institute (ESRI), and Trinity College Dublin
472 (TCD) staff designed and implements the project.

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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)
<i>Infant Sex, n (%)</i>		
Male	36,406 (51.43)	2438 (49.86)
Female	34,385 (48.57)	2,461 (50.14)
<i>Gestational age, n (%)</i>		
<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
<i>Maternal age, years, mean (SD)</i>	31.6 (5.49)	30.6 (5.79)
<i>SGA</i>		
Yes	7,015 (10.03)	548 (11.34)
No	62,950 (89.97)	4,283 (88.66)
<i>Maternal Ethnicity, n (%)</i>		
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)
<i>Maternal Education completed, n (%)</i>		
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)
<i>Maternal BMI, n (%)</i>		
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)
<i>Failure of ASQ domain, n (%)</i>		
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)
<i>Total SDQ: Maternal-reported (age 3 years), mean (SD)</i>	7.77 (4.53)	8.25 (4.62)
<i>Total SDQ: Maternal-reported (age 5 years), mean (SD)</i>	7.18 (4.75)	8.34 (5.07)
<i>Total SDQ: Maternal-reported (age 7-8 years), mean (SD)</i>	7.10 (5.30)	7.73 (5.49)
<i>Total SDQ: Teacher-reported (age 5 years), mean (SD)</i>	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.		

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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
<i>Failure of ASQ domains</i>					
<i>Communication</i>					
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)
<i>Gross Motor</i>					
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)
<i>Fine Motor</i>					
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)
<i>Problem Solving</i>					
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)
<i>Personal Social</i>					
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
<i>Abnormal SDQ (age 3 years) Maternal-reported</i>					
<i>Emotional</i>					
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)
<i>Conduct</i>					
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)
<i>Hyperactivity</i>					
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)
<i>Peer Problems</i>					
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)
<i>Prosocial Behaviour</i>					
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)
<i>Abnormal SDQ (age 5 years) Maternal-reported</i>					
<i>Emotional</i>					
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)
<i>Conduct</i>					
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)
<i>Hyperactivity</i>					
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)
<i>Peer Problems</i>					
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)
<i>Prosocial Behaviour</i>					
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)
<i>Abnormal SDQ (age 7-8 years) Maternal-reported</i>					
<i>Emotional</i>					
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)
<i>Conduct</i>					
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)
<i>Hyperactivity</i>					
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)
<i>Peer Problems</i>					
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)
<i>Prosocial Behaviour</i>					
Preeclampsia	36	0.61 (0.23, 1.65)	0.58 (0.21, 1.59)	0.74 (0.26, 2.05)	-

^aCrude analysis.

^bAdjusted 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.

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
<i>Age 3 SDQ</i>	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)
<i>Age 7-8 SDQ</i>	7.39 (7.25, 7.53)	8.06 (7.51, 8.60)	-0.67 (-0.10, -1.22)
Model 2^b			
<i>Age SDQ3</i>	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)
<i>Age 7-8 SDQ</i>	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
<i>Age 3 SDQ</i>	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)
<i>Age 7-8 SDQ</i>	7.28 (7.13, 7.43)	8.28 (6.72, 9.85)	-1.00 (-2.58, 0.57)
Model 2^b			
<i>Age 3 SDQ</i>	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)
<i>Age 7-8 SDQ</i>	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.			

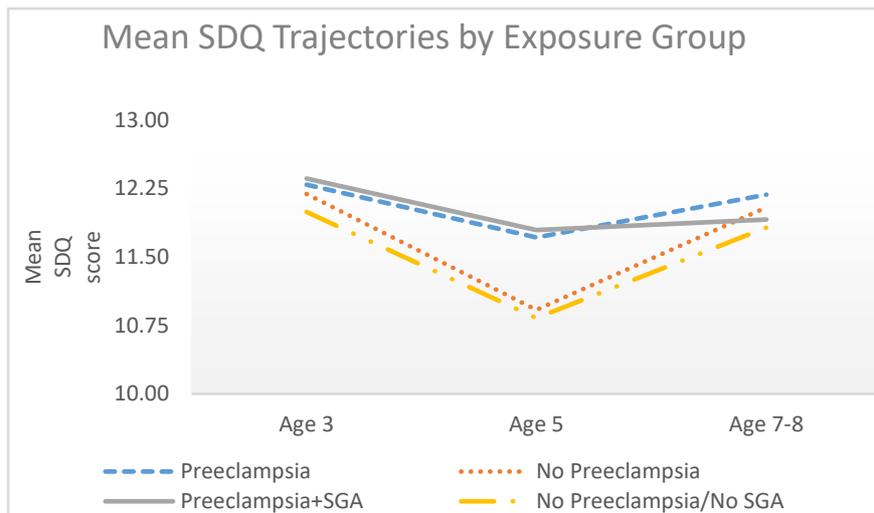


Fig. 1 Predicted trajectory of mean SDQ scores in waves 2-4 (adjusted model)

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