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Coláiste na hOllscoile Corcaigh

1 **Association between Preeclampsia and Autism Spectrum Disorder:**

2 **A Population-Based Study**

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19 **Abbreviated Title:** Preeclampsia and Autism Spectrum Disorder

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21 **Word Count:** 6,912

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23 **Conflict of Interest Disclosures:** No conflicts of interest, including financial interest.

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25

26 **Abstract**

27 **Background:** The environmental contribution of autism spectrum disorder (ASD) is
28 approximately 17-50%, highlighting the importance of investigating factors potentially
29 contributing to the likelihood of its development, and of gaining a greater understanding of
30 the pathogenesis surrounding ASD. The objective of this study was to examine the
31 association between preeclampsia and ASD using a population-based cohort study.

32 **Methods:** All singleton live births in Sweden from 1982-2010 were included, using data
33 from Swedish National Registers. Exposures of interest included: 1. Preeclampsia (classified
34 according to ICD-8, ICD-9 and ICD-10) 2. Preeclampsia and small for gestational age (SGA)
35 combined, used as a proxy for preeclampsia with placental dysfunction. ASD status was
36 based on ICD-9 and ICD-10.

37 The cohort consisted of 2,842,230 children, with 54,071 cases of ASD. Follow-up began
38 from the child's first birthday and data were censored at first diagnosis of ASD, death,
39 migration or end of study period (31st December 2016). We conducted multivariate Cox
40 proportional hazards regression analysis, adjusting for several perinatal and
41 sociodemographic factors, selected *a priori*. We further controlled for shared genetic and
42 familial confounding using sibling-matched analysis.

43 **Results:** In the adjusted Cox proportional hazards regression analysis, preeclampsia was
44 associated with a 25% increase in the likelihood of ASD (Hazard Ratio (HR): 1.25, 95%
45 CI:1.19, 1.30) compared to those unexposed to preeclampsia, while in the sibling-matched
46 analysis the HR was 1.17 (95% CI:1.06, 1.28). The HR for preeclampsia and SGA combined
47 was 1.66 (95% CI:1.49, 1.85) in the adjusted Cox model and 1.95 (95% CI:1.53, 2.48) in the
48 sibling-matched analysis.

49 **Conclusions:** Exposure to preeclampsia or preeclampsia/SGA (i.e. SGA baby exposed to
50 preeclampsia) was associated with ASD. The stronger association with preeclampsia/SGA

51 than preeclampsia alone suggests that placental pathology may be a mechanism for the
52 increased likelihood of ASD.

53 **Keywords:** Autism Spectrum Disorder, Preeclampsia, Epidemiology

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76 **Introduction**

77 Autism spectrum disorder (ASD) is characterised by persistent impairments in interpersonal
78 interaction and restricted or repetitive patterns of behaviour (Lai et al., 2014). The prevalence
79 of ASD is approximately 1.5% (Idring et al., 2015, Lyall et al., 2017), and while genetics
80 play a major role in the development of ASD, the environmental contribution is estimated to
81 be between 17-50% (Sandin et al., 2017, Sandin et al., 2014). This highlights the importance
82 of investigating factors contributing to the likelihood of its onset, and potentially facilitate the
83 development of appropriate interventions (Jiang et al., 2018). Furthermore, while often
84 comorbid with intellectual disability, previous results indicate that risk factors for ASD with
85 and without intellectual disability may differ, and is therefore important to examine ASD
86 according to the presence or absence of intellectual disability (Langridge et al., 2013, Abel et
87 al., 2013).

88 Preeclampsia is one of the leading causes of maternal morbidity and mortality and has
89 recently been redefined by the International Society for the Study of Hypertension in
90 Pregnancy (ISSHP) as new-onset hypertension (blood pressure $\geq 140/90$ mmHg on/after 20
91 weeks' gestation) accompanied by proteinuria and/or other maternal organ dysfunction and/or
92 uteroplacental dysfunction (Brown et al., 2018). Preeclampsia is associated with maternal
93 inflammation, poor placentation and oxidative stress, which may also represent some of the
94 potential aetiological pathways in the development of ASD (Brown et al., 2014, Yui et al.,
95 2016, Nomura et al., 2017).

96 While there is conflicting evidence regarding a preeclampsia-ASD relationship, pooled
97 estimates from epidemiological research suggest preeclampsia is associated with a 50%
98 increase in odds of ASD (Maher et al., 2018b). However, several limitations of the existing
99 literature, including residual confounding (for example, family lifestyle factors such as diet),
100 small sample sizes, and poor phenotyping and use of definitions of hypertensive disorders of

101 pregnancy versus preeclampsia, need to be addressed before more definitive conclusions can
102 be reached.

103 Therefore, the objective of this study was to examine the association between preeclampsia
104 and ASD (overall, and stratified by ASD with and without intellectual disability), while
105 addressing the key limitations in the literature outlined above.

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126 **Methods**

127 **Study Population**

128 The study population consisted of all singleton live births in Sweden from 1982 to 2010 using
129 data from the Swedish Medical Birth Register. The Medical Birth Register was linked to the
130 National Patient Register, Multi-generation Register, Total Population Register and Register
131 of Education using personal identification numbers (PIN) assigned to each Swedish resident,
132 in order to conduct the study.

133 Similar to previous ASD-studies conducted on this population (Sandin et al., 2014, Curran et
134 al., 2015), follow-up began from the child's first birthday (or 1st January 1987, when the
135 ICD-code for ASD became available). Data were censored at first diagnosis of ASD, death,
136 migration or end of study period (i.e. 31st December 2016). This is in contrast to Sandin et al
137 (2014) and Curran et al (2015) who included follow-up data until the end of 2009 and 2011
138 respectively.

139 Ethical approval was previously obtained from the research ethics committee in Stockholm,
140 Sweden and informed consent was waived by the ethics committee.

141

142 **Exposures**

143 **Preeclampsia:** Data on preeclampsia was obtained from the Medical Birth Register. The
144 Medical Birth Register, established in 1973, contains data on over 97% of all births in
145 Sweden, and includes information on prenatal care, delivery, neonatal care and maternal
146 socio-demographic and lifestyle factors (The National Board of Health and Welfare
147 (Socialstyrelsen), 2018). However, since 1982, standardised copies of antenatal, obstetric and
148 pediatric records were used to collect data, while quality data on obesity and smoking status
149 during pregnancy also became available, marking the beginning of our study (Ros, 2001).

150 A doctor reviews discharge records and notes a diagnosis of preeclampsia at the time of
151 discharge from the hospital using a standard form, containing the definition of preeclampsia,
152 accompanied by an ICD-code and checkbox. These are forwarded to the National Board of
153 Health and Welfare for inclusion in the Birth Register. Preeclampsia is classified according to
154 the Swedish version of ICD-8 (through 1986), ICD-9 (1987-1996) and ICD-10 (from 1997
155 onwards) (Ros, 2001).

156 *1. Preeclampsia: ICD-8 [code 637]:* Gestational hypertension (blood pressure
157 $\geq 140/90$ mmHg on/after 20 weeks' gestation), accompanied by proteinuria (≥ 0.3 g/day or ≥ 1
158 on a urine dipstick) or edema (positive predictive value (PPV)=50%) (Ros, 2001).

159 *ICD-9 [code 642]:* Gestational hypertension accompanied by proteinuria (PPV=96%) (Ros,
160 2001).

161 *ICD-10 [code O14 or O15]:* Gestational hypertension accompanied by proteinuria.

162 *2. Preeclampsia with placental dysfunction:* We combined preeclampsia and small for
163 gestational age (SGA) as a proxy for preeclampsia with placental dysfunction, as SGA is
164 closely associated with uteroplacental dysfunction (Dalman et al., 1999). SGA was classified
165 according to the Swedish weight-based fetal growth standard (defined as birthweight < 2
166 standard deviations below the mean of the sex-specific and gestational age distributions)
167 (Khashan et al., 2015).

168

169 **Outcome**

170 Data on ASD and intellectual disability were obtained from the National Patient Register.
171 The National Patient Register contains information on inpatient psychiatric diagnoses from
172 1973 (obtaining complete national coverage in 1987) (Ludvigsson et al., 2011, Idring et al.,
173 2015). Outpatient data is available in the National Patient Register since 2001 (Idring et al.,
174 2015) (coverage of data from private caregivers is approximately 80%, and public caregivers

175 almost 100%) (Ludvigsson et al., 2011). ASD is classified according to ICD-9 [code 299],
176 available since 1987 and ICD-10 [code F84], available since 1997 (PPV=94.3%) (Curran et
177 al., 2015). Therefore, index persons (IP) who turned one year of age before 1987 began
178 follow-up on 1st January 1987, when an ICD-code for ASD first became available.
179 As risk factors for ASD with/without intellectual disability may differ (Langridge et al., 2013,
180 Abel et al., 2013), we examined ASD overall, and also stratified results by ASD with
181 intellectual disability (defined as IQ<70) (Idring et al., 2012, Idring et al., 2015) and ASD
182 without intellectual disability. For example, if cases of ASD did not receive a diagnosis of
183 intellectual disability throughout the study period, they were considered to have ASD without
184 intellectual disability. (Intellectual disability is classified according to ICD-9 [code 317-319]
185 and ICD-10 [code F70–F79]) (Abel et al., 2013).

186

187 **Confounding Variables**

188 Confounders were based on previous literature, and limited to the data available in the
189 National Registers. They were examined through the use of a directed acyclic graph to gain a
190 visual representation of the potential confounder pathways (FigureS1). We obtained year of
191 birth, infant sex, maternal age, maternal and paternal country of birth, birth order, maternal
192 smoking status, body mass index (BMI) at first antenatal visit, and gestational weight gain
193 from the Medical Birth Register. Similar to a previous ASD study conducted on this
194 population (Curran et al., 2015), we also controlled for maternal and paternal depression,
195 bipolar disorder, and non-affective psychiatric disorders, obtained from the National Patient
196 Register. Socioeconomic factors including family income and parental level of education
197 were obtained from the Total Population Register and Register of Education. Information on
198 all confounders was available for the entire study period with the exception of parental level
199 of education, available since 1990. (See MethodsS1 for description of confounders).

200 **Statistical Analysis**

201 Data were analysed using Stata/MP 14.2. Multivariate Cox proportional hazards regression
202 analysis was performed to estimate HR and 95% confidence intervals, for preeclampsia;
203 preeclampsia and SGA (i.e. SGA baby exposed to preeclampsia); and preeclampsia without
204 SGA, and likelihood of ASD (overall and with/without intellectual disability). The
205 proportional hazards assumption was assessed graphically and based on Schoenfeld residuals.
206 Partially adjusted models were stratified by year of birth in order to satisfy the proportional
207 hazard assumption (model 1). Fully adjusted models (model 2) controlled for year of birth,
208 infant sex, maternal age, maternal and paternal country of birth, birth order, parental
209 depression, bipolar disorder and non-affective psychiatric disorders, maternal smoking status,
210 BMI at first antenatal visit, gestational weight gain, family income and parental level of
211 education. To account for the possibility of increased diagnosis of ASD in recent years, and
212 due to a reliance on inpatient psychiatric diagnoses until 2001, we also stratified results by
213 decade of birth.

214 *Sibling-matched analysis:* To control for unmeasured confounding factors shared by siblings,
215 including family environment, lifestyle factors such as diet, maternal characteristics, and
216 genetic factors, we conducted a sibling-matched analysis (model 3) using stratified Cox
217 regression. This method is an extension of the paired binomial model, taking into account
218 different lengths of follow-up time. The analysis included full and half siblings on the
219 maternal side consisting of a separate stratum for each family, matched on maternal ID.
220 While each family has its own baseline probability of ASD, reflecting their shared genetic
221 and social factors, the exposure groups (i.e. preeclampsia v non-exposure to preeclampsia)
222 are made within the family, estimating the probability of ASD within the family (Obel et al.,
223 2011). We adjusted for the same potential confounders as model 2 with the exception of
224 maternal country of birth as this is the same across sibling pairs.

225 *Post-hoc analysis:* We examined the association between SGA-alone and ASD compared to
226 non-exposure to SGA/preeclampsia.

227 *Sensitivity analyses:* As the definition of preeclampsia from 1982-1986 does not correspond
228 to later years, and the National Patient Register obtained complete national coverage in 1987,
229 we performed a sensitivity analysis restricting the study population to 1987-2010. In addition,
230 we excluded births after 2006 to ensure each individual was followed-up for a minimum of
231 10 years.

232 Classifying preeclampsia into ‘mild’ or ‘severe’ is not recommended in clinical practice.
233 However, preeclampsia may present with or without severe features (Brown et al., 2018). As
234 delivery is the only effective cure for preeclampsia, gestational age is often used as a proxy
235 for severity. For example, preeclampsia could be considered severe if delivery occurred
236 before 34 weeks’ gestation (Hernández-Díaz et al., 2009). As a result, sensitivity analyses
237 were conducted examining the relationship between preeclampsia-ASD (in those born ≥ 34
238 weeks’ gestation) and preeclampsia-ASD (in those born < 34 weeks’ gestation) compared to
239 deliveries at ≥ 34 weeks’ gestation in mothers with no preeclampsia, using the full cohort.
240 Further sensitivity analyses included ‘preeclampsia without chronic hypertension’ as the
241 exposure, and ‘preeclampsia with chronic hypertension’ as the exposure. We examined the
242 association between preeclampsia-ASD excluding those with a family history of mental
243 illness, while we also included caesarean section in a multivariate model. Furthermore, we
244 analysed the relationship between preeclampsia with low/intermediate APGAR score at five
245 minutes. We examined a preeclampsia-ASD relationship by maternal age, in addition to
246 preeclampsia-ASD by BMI group at time of first antenatal visit. Finally, subgroup analyses
247 examined a preeclampsia-ASD relationship by gestational age and gender while controlling
248 for potential confounders. (Gestational age was defined according to ultrasound
249 measurements, or from information of the last menstrual period) (Ludvigsson et al., 2018).

250 **Results**

251 **Descriptive Statistics**

252 *Table 1:* There were 2,941,628 live births recorded in the Swedish Medical Birth Register
253 between 1st January 1982 and 31st December 2010. After exclusions, (figure 1) 2,842,230
254 children remained in the final cohort. Of these, 1,460,940 (51.4%) were male and 1,381,290
255 (48.6%) were female. There were 77,600 (2.7%) children exposed to preeclampsia. There
256 were 54,071 (1.9%) cases of ASD with a median age of diagnosis of 14 years. Of these, 2,024
257 were exposed to preeclampsia.

258

259 **Association between Preeclampsia and ASD**

260 *Table 2:* In the fully adjusted model (model 2) preeclampsia was associated with a 25%
261 increase in the likelihood of ASD (HR: 1.25, 95% CI: 1.19, 1.30) compared to those
262 unexposed to preeclampsia, and this association was reduced in the sibling-matched analysis
263 (model 3) (HR 1.17, 95% CI: 1.06, 1.28). The HR for preeclampsia and SGA combined was
264 1.66 (95% CI: 1.49, 1.85) in model 2 and 1.95 (95% CI: 1.53, 2.48) in model 3, and the HR
265 for preeclampsia without SGA was 1.20 (95% CI: 1.14, 1.26) in model 2 and 1.11 (95% CI:
266 1.01, 1.23) in model 3.

267 **Preeclampsia and ASD with intellectual disability**

268 *Table 2:* Preeclampsia was associated with a 56% increase in the likelihood of ASD with
269 intellectual disability (HR: 1.56, 95% CI: 1.41, 1.73) in model 2 and 32% increase in model 3
270 (HR: 1.32, 95% CI: 1.07, 1.62). Those exposed to preeclampsia and SGA were nearly 3 times
271 more likely to have ASD with intellectual disability in model 2 (HR: 2.95, 95% CI: 2.40,
272 3.64), with similar results observed in model 3 (HR: 3.07, 95% CI: 1.97, 4.79). The HR for
273 preeclampsia without SGA was 1.40 (95% CI: 1.24, 1.57) in model 2 and 1.15 (95% CI: 0.91,
274 1.45) in model 3.

275 **Preeclampsia and ASD without intellectual disability**

276 *Table 2:* The HR for preeclampsia was 1.19 (95% CI: 1.13, 1.25) in model 2, and 1.13 (95%
277 CI: 1.01, 1.26) in model 3. Preeclampsia and SGA were associated with a 42% increase in
278 likelihood of ASD without intellectual disability (HR: 1.42, 95% CI: 1.25, 1.62) in model 2,
279 and 63% in model 3 (HR: 1.63, 95% CI: 1.22, 2.19). The HR for preeclampsia without SGA
280 was 1.17 (95% CI: 1.10, 1.23) in model 2, and 1.10 (95% CI: 0.98, 1.23) in model 3.

281 Stratifying results by decade did not materially change results (Table 3).

282 **Post-Hoc Analysis**

283 The adjusted HR for an SGA only-ASD relationship was 1.60 (95% CI: 1.53, 1.67), while in
284 the sibling-matched analysis, the HR was 1.82 (95% CI: 1.65, 2.01) (Table 2).

285

286 **Sensitivity Analyses**

287 *Table S1:* When the study population was restricted to 1987-2010, an association between
288 preeclampsia and ASD was still observed. Similarly, excluding births after 2006 did not
289 materially change results. Fully adjusted results of the sensitivity analysis suggested that
290 preeclampsia exposure in those born at ≥ 34 weeks' gestational age was associated with an
291 18% increase in the likelihood of ASD (HR: 1.18, 95% CI: 1.13, 1.24) when compared to
292 those unexposed to preeclampsia, and born at a similar gestational age. The fully adjusted
293 result for preeclampsia in those born at < 34 weeks' gestational age (used as a proxy for
294 preeclampsia with severe features) was 2.04 (95% CI: 1.81, 2.30) when compared to non-
295 exposure to preeclampsia in those born at ≥ 34 weeks' gestation. The HR for a preeclampsia-
296 ASD relationship, excluding those with chronic hypertension, was 1.26; and including those
297 with both preeclampsia and chronic hypertension was a non-significant 0.91. The fully
298 adjusted HR for preeclampsia (excluding those with family history of mental illness) was
299 1.28, while including caesarean section in the multivariate model resulted in a HR of 1.21.

300 Preeclampsia with a low/intermediate APGAR score at five minutes increased the likelihood
301 of ASD by 30% compared to non-exposure to preeclampsia and low/intermediate score.
302 Finally, preeclampsia among mothers <20 years of age and mothers with a BMI of <20 was
303 associated with the highest odds of ASD (HR: 1.37 and 1.29 respectively) compared to those
304 of similar maternal age and BMI at first antenatal visit. (See ResultsS1 and TablesS1 for full
305 description of results).

306

307 **Subgroup Analyses**

308 *TableS2:* Adjusted subgroup analysis suggested a statistically significant increase in the
309 likelihood of ASD at all gestational ages when compared to non-exposure to preeclampsia in
310 those born at ≥ 37 weeks' gestation. When adjusted for potential confounders, exposure to
311 preeclampsia was associated with a 25% increase in the odds of ASD in both male and
312 female offspring. (ResultsS1 and TablesS2).

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325 **Discussion**

326 This study aimed to examine the association between preeclampsia and ASD (overall and
327 with/without intellectual disability) and has yielded two principal findings. First, exposure to
328 preeclampsia was associated with 25% increased odds of ASD when compared to those
329 unexposed, after controlling for known potential confounders. The sibling-matched analysis
330 allowed us to further control for shared genetic and familial factors and reduced the HR to
331 1.17. However, when results were stratified by ASD with and without intellectual disability,
332 the HRs were 1.32 and 1.13 respectively. These data are largely in line with a previous
333 systematic review, which suggested that preeclampsia was associated with a 50% increase in
334 the odds of ASD, with individual study estimates ranging from 0.90 to 2.36 (Maher et al.,
335 2018b).

336 Second, as SGA is closely associated with uteroplacental dysfunction (Dalman et al., 1999),
337 we combined preeclampsia and SGA as a crude proxy for preeclampsia with placental
338 dysfunction. This decision is also in line with the recent guidelines put forward by ISSHP to
339 include uteroplacental dysfunction in the definition of preeclampsia (Brown et al., 2018).
340 Being an SGA baby and exposed to preeclampsia was associated with a 95% increased odds
341 of ASD when compared to non-exposure to preeclampsia or SGA. This HR increased to 3.07,
342 when stratified by ASD with intellectual disability, and reduced to 1.63 when stratified by
343 ASD without intellectual disability (Jones et al., 2017). This observed preeclampsia and SGA
344 relationship with ASD suggests that impaired placentation may be a common factor
345 increasing the likelihood of ASD. Furthermore, the post-hoc analysis examining SGA-alone
346 and ASD further supports this hypothesised mechanism given the modest effect of
347 preeclampsia on likelihood of ASD compared to that of preeclampsia and SGA combined, or
348 SGA-alone.

349 The precise biological mechanisms contributing to a preeclampsia-ASD relationship are still
350 unknown however. In a previous study, we demonstrated that exposure of fetal neurons to
351 maternal serum from term preeclampsia altered fetal cortical neuronal growth and branching
352 (Curran et al., 2018), while treatment of fetal cortical neurons with conditioned media from
353 preeclamptic placentae also had similar effects, suggesting secreted factors may be important
354 (Scott et al., 2018). Such factors may include inflammatory cytokines given that preeclampsia
355 is associated with chronic immune activation, leading to a significant increase in the
356 circulation of pro-inflammatory cytokines. Thus, while uncomplicated pregnancies have a
357 normal systemic inflammatory response (Redman et al., 1999), preeclampsia results in a
358 state of exaggerated maternal inflammation (Redman et al., 1999, Maher et al., 2018a).
359 Therefore, maternal inflammation, a recognised risk factor for poor neurodevelopmental
360 outcome, could act as a mediator between preeclampsia and development of ASD, and the
361 pro-inflammatory cytokine interleukin (IL)-6 may be a leading candidate in this regard (Jiang
362 et al., 2018).

363 Straughen et al. (2017) demonstrated that placental inflammation of any type is associated
364 with an increased likelihood of ASD, while circulating levels of maternal IL-6 have been
365 shown to be inversely associated with brain connectivity and offspring cognition at 12
366 months of age, as well as short and long-term influences in offspring behaviour in separate
367 studies (Spann et al., 2018, Rasmussen et al., 2018). This may also partially explain the
368 increased HR when results were stratified by ASD with intellectual disability, as elevated
369 mid-gestational levels of numerous cytokines and chemokines such as GM-CSF, IFN- γ , IL-
370 1 α , and IL-6 are associated with ASD with intellectual disability, when compared to mothers
371 of children with either ASD without intellectual disability, developmental delay, or general
372 population controls (Jones et al., 2017).

373 In terms of mediation, while very little data exist in humans, a recent study has shown that
374 maternal depressive symptoms are associated with higher maternal inflammation, including
375 IL-6, and this mediated the effect on maternal report of infant negative affect (Gustafsson et
376 al., 2018), a known risk factor for later adverse neurological outcomes. This may also suggest
377 that preeclampsia-induced elevations in maternal IL-6 may act as a mediator of the
378 preeclampsia-ASD association.

379 Finally, the role of concurrent exposure to antihypertensive medication in the development of
380 ASD was beyond the scope of this paper, and needs to be explored in future research. This
381 research question could possibly be addressed using animal models such as the reduced
382 uterine perfusion pressure (RUPP) model in rats, which mimics many physiological features
383 of preeclampsia (Walsh et al., 2009), in order to study the impact of antihypertensive
384 medications administered using clinical relevant treatment protocols, on neurobehavioural
385 outcomes in offspring.

386

387 **Strengths and Limitations**

388 This study had several strengths. It is the largest epidemiological study to investigate the
389 association between preeclampsia and ASD, with data on over 2.8 million births. Information
390 on exposure and outcome status was classified according to ICD-coding, obtained from
391 national registers. Therefore, selection bias and recall bias were not likely an issue. The use
392 of registry data allowed us to control for a wide range of confounding variables, while
393 conducting a sibling-matched analysis allowed us to further control, at least in part, for shared
394 genetic and familial factors.

395 However, several limitations may also pose a threat to validity of findings. One, each
396 individual in the present study was followed-up until they reached a minimum of six years of
397 age (i.e. those born in 2010 followed-up until 2016). While it is possible that not enough time

398 had lapsed for a diagnosis of ASD to be received by some individuals, excluding births after
399 2006 to ensure everyone had at least 10 years of follow-up does not materially change results.
400 Two, the prevalence of ASD in the current study was 1.9%, compared to previous ASD
401 studies conducted on this population who had a ~1% prevalence of ASD (Sandin et al., 2014,
402 Curran et al., 2015). However, we included follow-up data until the end of 2016, whereas
403 Sandin et al. (2014) and Curran et al. (2015) included follow-up data until the end of 2009
404 and 2011 respectively. This means that each child in the present study was followed-up for 5-
405 7 additional years compared to the two previous studies. If we restrict our follow-up date to
406 2011, it results in a more comparable prevalence to that of previous studies (~1%). Given that
407 children are often not diagnosed with ASD until they are of school age, it is suspected that the
408 extended follow-up is the reason for the difference in ASD prevalence (Shattuck et al., 2009).
409 Three, severe cases may have been overrepresented in our data due to a reliance on inpatient
410 psychiatric diagnoses until 2001 (Ludvigsson et al., 2011). While results of a sensitivity
411 analysis by decade of birth (Table 3) were not significantly different from our main findings,
412 the HR of 4.39 for SGA babies exposed to preeclampsia in children with ASD and
413 intellectual disability born 2000-2010 warrants highlighting, and could possibly reflect an
414 increased awareness of ASD or increased diagnostic specificity in recent decades.
415 Four, a lack of robust data on gestational hypertension limited our analysis. Results of
416 existing studies suggest a non-significant gestational hypertension-ASD relationship (Maher
417 et al., 2018b). However, if a gestational hypertension-ASD association existed, this would
418 bias our results towards the null.
419 Finally, despite controlling for several potential confounders, residual confounding may still
420 be an issue. While this was reduced in the sibling-matched analysis, this method can only
421 adjust for factors constant between pregnancies, therefore we cannot rule out the possibility
422 of unmeasured confounding factors (Khashan et al., 2014).

423 **Conclusion**

424 The apparent preeclampsia/SGA-ASD relationship suggests that placental pathology may be
425 a common factor increasing the likelihood of ASD. Further research is needed to investigate
426 the role that maternal inflammation may play, as well as the potential impact of
427 pharmacological treatments used during pregnancy on likelihood of ASD.

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448 **Key points and relevance**

- 449 • There is conflicting evidence regarding a preeclampsia-ASD relationship, with several
450 limitations of the literature being identified
- 451 • Adjusted estimates from this population-based cohort study suggest that preeclampsia
452 is associated with an increase in the likelihood of ASD, while there is a stronger
453 association between preeclampsia and small for gestational age (SGA) combined (i.e.
454 SGA baby exposed to preeclampsia) and ASD.
- 455 • The stronger association between preeclampsia/SGA combined and ASD suggests
456 that placental pathology may be a common factor increasing the likelihood of ASD.
- 457 • Further research is needed to investigate the role that maternal inflammation may
458 play, as well as the potential impact of antihypertensive medication in the
459 development of ASD.

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461 **Supplementary Material**

462 Refer to Web version for supplementary material

463

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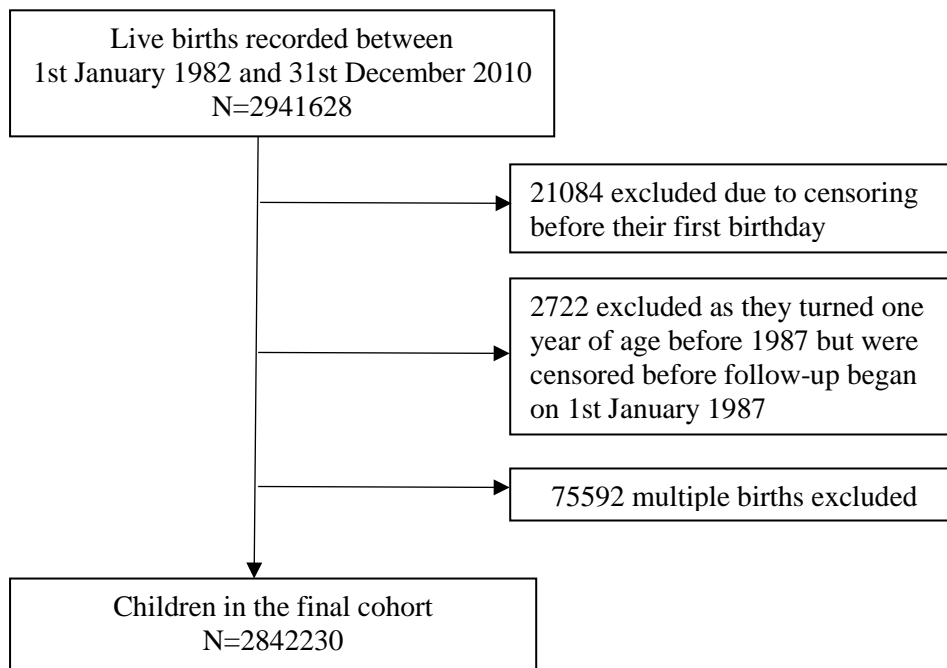
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630 **Figure 1**

631 **Flowchart of Study Participants**



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Table 1: Perinatal and Sociodemographic Characteristics Related to Preeclampsia and Autism Spectrum Disorder Among Singleton Live Births in Sweden between 1982 and 2010

Characteristic	No. (%) of Infants			
	Total Population		Preeclampsia	
Total Population	2842230		77600	(2.7)
ASD	54071	(1.9)	2024	(2.6)
ASD with intellectual disability	8981	(0.3)	388	(0.5)
ASD without intellectual disability	45090	(1.6)	1636	(2.1)
SGA	69355	(2.5)	9761	(12.7)
First-born child	1210413	(42.6)	49756	(64.1)
Sex (male)	1460940	(51.4)	40475	(52.2)
Decade of birth				
1982-1989	773489	(27.2)	19596	(25.3)
1990-1999	1006338	(35.4)	27635	(35.6)
2000-2010	1062403	(37.4)	30369	(39.1)
Maternal age, years				
<20	66946	(2.4)	2393	(3.1)
20-29	1495876	(52.6)	41463	(53.4)
30-39	1210467	(42.6)	31217	(40.2)
≥40	68941	(2.4)	2527	(3.3)
Gestational age, weeks				
<34	32,332	(1.1)	6375	(8.2)
34	17,162	(0.6)	2276	(2.9)
35	29,982	(1.1)	3080	(4.0)
36	60,016	(2.1)	5155	(6.7)
37	141036	(5.0)	8583	(11.1)
38	386963	(13.6)	12516	(16.1)
39	657765	(23.2)	14653	(18.9)

40	799752	(28.2)	13942	(18.0)
>40	712440	(25.1)	10894	(14.1)
5-Minute Apgar score				
0-3 (low)	5530	(0.2)	307	(0.4)
4-6 (intermediate)	20589	(0.7)	1599	(2.1)
7-10 (high)	2772613	(99.1)	74412	(97.5)
Delivery completed by caesarean section	260,650	(9.2)	19,574	(25.2)
Mother's country of birth				
Sweden	2272714	(80.0)	64024	(82.5)
Other Nordic country	85743	(3.0)	2309	(3.0)
Other country	336123	(11.8)	6602	(8.5)
Missing	147650	(5.2)	4665	(6.0)
Father's country of birth				
Sweden	2244697	(79.0)	63454	(81.2)
Other Nordic country	76280	(2.7)	2008	(2.6)
Other country	354182	(12.5)	6909	(8.9)
Missing	167071	(5.9)	5229	(6.7)
Maternal depression				
Never	2473216	(87.0)	66912	(86.3)
Before birth	44440	(1.6)	1355	(1.7)
After birth	177106	(6.2)	4676	(6.0)
Missing	147468	(5.2)	4657	(6.0)
Maternal bipolar disorder				
Never	2669867	(93.9)	72242	(93.1)
Before birth	3527	(0.1)	115	(0.1)
After birth	21368	(0.8)	586	(0.8)
Missing	147468	(5.2)	4657	(6.0)
Maternal nonaffective disorders				
Never	2674249	(94.1)	72359	(93.2)

Before birth	6898	(0.2)	207	(0.3)
After birth	13615	(0.5)	377	(0.5)
Missing	147468	(5.2)	4657	(6.0)
Paternal depression				
Never	2564110	(90.2)	69636	(89.7)
Before birth	24621	(0.9)	698	(0.9)
After birth	106031	(3.7)	2609	(3.4)
Missing	147468	(5.2)	4657	(6.0)
Paternal bipolar disorder				
Never	2679318	(94.3)	72562	(93.5)
Before birth	2661	(0.1)	75	(0.1)
After birth	12783	(0.4)	306	(0.4)
Missing	147468	(5.2)	4657	(6.0)
Paternal nonaffective disorders				
Never	2675845	(94.1)	72458	(93.4)
Before birth	7155	(0.3)	200	(0.2)
After birth	11762	(0.4)	285	(0.4)
Missing	147468	(5.2)	4657	(6.0)
Smoking at first antenatal visit				
No	2186399	(76.9)	63720	(82.1)
1-9 cigarettes/day	300389	(10.6)	5886	(7.6)
≥10 cigarettes/day	165015	(5.8)	2849	(3.7)
Missing	190427	(6.7)	5145	(6.6)
BMI at first antenatal visit				
<20	312520	(11.0)	5139	(6.6)
20-24.9	1200271	(42.2)	27112	(34.9)
25-29.9	441373	(15.5)	16118	(20.8)
≥30	167717	(6.0)	10300	(13.3)
Missing	720349	(25.3)	18931	(24.4)

Optimal gestational weight gain by BMI group at first antenatal visit (Cedergren, 2007)		
<20		
Optimum	45641 (1.6)	514 (0.7)
Inadequate/Excessive	158243 (5.5)	2656 (3.4)
20-24.9		
Optimum	141430 (5.0)	1958 (2.5)
Inadequate	2563 (0.1)	43 (0.06)
Excessive	512433 (18.0)	12424 (16.0)
25-29.9		
Optimum	36368 (1.3)	803 (1.0)
Excessive	172818 (6.1)	6,996 (9.0)
≥30		
Optimum	14994 (0.5)	606 (0.8)
Excessive	58340 (2.1)	3893 (5.0)
Missing	1699400 (59.8)	47,707 (61.5)
Income quintile		
First	513347 (18.1)	11098 (14.3)
Second	532669 (18.7)	12625 (16.3)
Third	537973 (18.9)	14611 (18.8)
Fourth	540823 (19.0)	16657 (21.5)
Fifth	536843 (18.9)	17281 (22.3)
Missing	180575 (6.4)	5328 (6.8)
Parental level of education at IP birthyear (available from 1990)		
Pre-high school	132,995 (4.7)	3,346 (4.3)
High school	891,979 (31.4)	26,755 (34.5)
Post high school	888,712 (31.3)	24,098 (31.0)

Missing	928544 (32.7)	23401 (30.2)
<p>Categories were collapsed if cell count <10, for example, inadequate/excessive weight gain in women categorised as BMI<20 were combined for the purpose of displaying data only.</p> <p>If missing data >5%, number (%) of missing data reported.</p> <p>Abbreviations: SGA, small for gestational age; BMI, body mass index; IP, index person</p>		

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Table 2: Association between Preeclampsia and Autism Spectrum Disorder With and Without Intellectual Disability Among Singleton Live Births in Sweden between 1982 and 2010

	Total population			Sibling pairs
	Exposed cases	Model 1 HR (95% CI) ^a	Model 2 HR (95% CI) ^b	Model 3 HR (95% CI) ^c
All ASD (n=54071)				
Preeclampsia	2,024	1.36 (1.31, 1.43)	1.25 (1.19, 1.30)	1.17 (1.06, 1.28)
Preeclampsia and SGA ^d	326	1.79 (1.61, 2.00)	1.66 (1.49, 1.85)	1.95 (1.53, 2.48)
Preeclampsia without SGA	1673	1.32 (1.26, 1.38)	1.20 (1.14, 1.26)	1.11 (1.01, 1.23)
SGA only	1884	1.77 (1.69, 1.85)	1.60 (1.53, 1.67)	1.82 (1.65, 2.01)
ASD with intellectual disability (n=8981)				
Preeclampsia	388	1.59 (1.44, 1.76)	1.56 (1.41, 1.73)	1.32 (1.07, 1.62)
Preeclampsia and SGA ^d	90	3.11 (2.52, 3.82)	2.95 (2.40, 3.64)	3.07 (1.97, 4.79)
Preeclampsia without SGA	287	1.42 (1.26, 1.60)	1.40 (1.24, 1.57)	1.15 (0.91, 1.45)
ASD without intellectual disability (n=45090)				
Preeclampsia	1636	1.32 (1.26, 1.39)	1.19 (1.13, 1.25)	1.13 (1.01, 1.26)
Preeclampsia and SGA ^d	236	1.54 (1.36, 1.76)	1.42 (1.25, 1.62)	1.63 (1.22, 2.19)
Preeclampsia without SGA	1386	1.30 (1.23, 1.37)	1.17 (1.10, 1.23)	1.10 (0.98, 1.23)

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval; SGA, small for gestational age.

^aAdjusted for year of birth.

^bAdjusted for year of birth, infant sex, maternal age, maternal and paternal country of birth, birth order, parental depression, bipolar disorder and non-affective psychiatric disorders, maternal smoking status, BMI at first antenatal visit, gestational weight gain, family income and parental level of education.

^cAdjusted for same potential confounders as above with the exception of maternal country of birth.

^dReference=no preeclampsia/no SGA.

Missing data on SGA for 25 cases of ASD (missing data on SGA for 11 cases of ASD with intellectual disability, and missing data on SGA for 14 cases of ASD without intellectual disability).

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Table 3: Association between Preeclampsia and Autism Spectrum Disorder With and Without Intellectual Disability Among Singleton

Live Births in Sweden by decade

	Children born 1982-1989		Children born 1990-1999		Children born 2000-2010	
	ASD (n=10938)		ASD (n= 24237)		ASD (n= 18896)	
All ASD (n=54071)	Exposed cases	Model 2 HR (95% CI) ^a	Exposed cases	Model 2 HR (95% CI) ^a	Exposed cases	Model 2 HR (95% CI) ^a
Preeclampsia	336	1.15 (1.03, 1.28)	898	1.23 (1.15, 1.32)	790	1.30 (1.21, 1.39)
Preeclampsia and SGA ^b	50	1.34 (1.01, 1.77)	124	1.39 (1.16, 1.65)	152	2.14 (1.83, 2.51)
Preeclampsia without SGA	281	1.14 (1.01, 1.28)	760	1.21 (1.13, 1.31)	632	1.20 (1.11, 1.30)
ASD with intellectual disability (n=8981)						
Preeclampsia	60	1.38 (1.07, 1.80)	176	1.53 (1.32, 1.79)	152	1.64 (1.39, 1.94)
Preeclampsia and SGA ^b	14	2.57 (1.51, 4.36)	26	1.87 (1.27, 2.76)	50	4.39 (3.31, 5.81)
Preeclampsia without SGA	44	1.25 (0.92, 1.69)	144	1.52 (1.28, 1.79)	99	1.29 (1.06, 1.58)
ASD without intellectual disability (n=45090)						
Preeclampsia	276	1.11 (0.98, 1.25)	722	1.17 (1.09, 1.27)	638	1.23 (1.14, 1.34)
Preeclampsia and SGA ^b	36	1.13 (0.81, 1.56)	98	1.30 (1.06, 1.58)	102	1.71 (1.41, 2.08)
Preeclampsia without SGA	237	1.12 (0.98, 1.28)	616	1.16 (1.07, 1.26)	533	1.18 (1.08, 1.29)
Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval; SGA, small for gestational age.						

^aAdjusted for year of birth, infant sex, maternal age, maternal and paternal country of birth, birth order, parental depression, bipolar disorder and non-affective psychiatric disorders, maternal smoking status, BMI at first antenatal visit, gestational weight gain, family income and parental level of education.

^bReference=no preeclampsia/no SGA

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