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Association between Preeclampsia and Autism Spectrum Disorder:

A Population-Based Study

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Abstract

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

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

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

Results: In the adjusted Cox proportional hazards regression analysis, preeclampsia was associated with a 25% increase in the likelihood of ASD (Hazard Ratio (HR): 1.25, 95% CI:1.19, 1.30) compared to those unexposed to preeclampsia, while in the sibling-matched analysis the HR was 1.17 (95% CI:1.06, 1.28). The HR for preeclampsia and SGA combined 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 sibling-matched analysis.

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

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

Keywords: Autism Spectrum Disorder, Preeclampsia, Epidemiology

Introduction

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

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

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

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

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

Methods

Study Population

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

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

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

Exposures

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

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

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

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

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

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

Outcome

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

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

Confounding Variables

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

Statistical Analysis

Data were analysed using Stata/MP 14.2. Multivariate Cox proportional hazards regression analysis was performed to estimate HR and 95% confidence intervals, for preeclampsia; preeclampsia and SGA (i.e. SGA baby exposed to preeclampsia); and preeclampsia without SGA, and likelihood of ASD (overall and with/without intellectual disability). The proportional hazards assumption was assessed graphically and based on Schoenfeld residuals. Partially adjusted models were stratified by year of birth in order to satisfy the proportional hazard assumption (model 1). Fully adjusted models (model 2) controlled 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. To account for the possibility of increased diagnosis of ASD in recent years, and due to a reliance on inpatient psychiatric diagnoses until 2001, we also stratified results by decade of birth.

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

Results

Descriptive Statistics

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

Association between Preeclampsia and ASD

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

Preeclampsia and ASD with intellectual disability

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

Preeclampsia and ASD without intellectual disability

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

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

Post-Hoc Analysis

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

Sensitivity Analyses

TableS1: When the study population was restricted to 1987-2010, as association between preeclampsia and ASD was still observed. Similarly, excluding births after 2006 did not materially change results. Fully adjusted results of the sensitivity analysis suggested that preeclampsia exposure in those born at ≥ 34 weeks' gestational age was associated with an 18% increase in the likelihood of ASD (HR: 1.18, 95% CI: 1.13, 1.24) when compared to those unexposed to preeclampsia, and born at a similar gestational age. The fully adjusted result for preeclampsia in those born at < 34 weeks' gestational age (used as a proxy for preeclampsia with severe features) was 2.04 (95% CI: 1.81, 2.30) when compared to non-exposure to preeclampsia in those born at ≥ 34 weeks' gestation. The HR for a preeclampsia-ASD relationship, excluding those with chronic hypertension, was 1.26; and including those with both preeclampsia and chronic hypertension was a non-significant 0.91. The fully adjusted HR for preeclampsia (excluding those with family history of mental illness) was 1.28, while including caesarean section in the multivariate model resulted in a HR of 1.21.

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

Subgroup Analyses

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

Discussion

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

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

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

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

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

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

Strengths and Limitations

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

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

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

Conclusion

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

Key points and relevance

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

Supplementary Material

Refer to Web version for supplementary material

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Figure 1

Flowchart of Study Participants

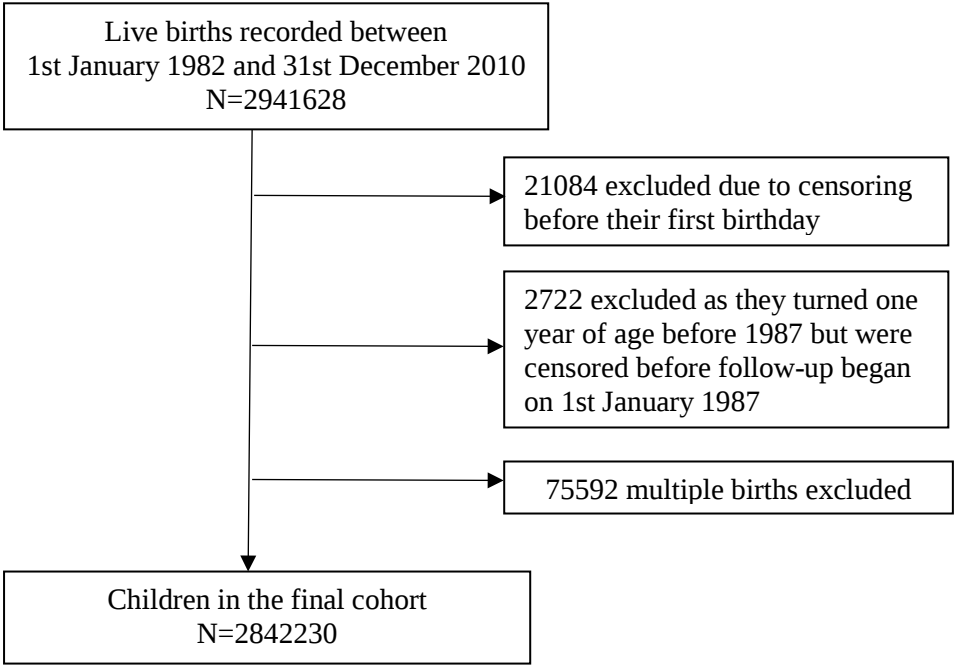


Table 1: Perinatal and Sociodemographic Characteristics Related to Preeclampsia and Autism Spectrum Disorder Among Singleton Live Births in Sweden between 1982 and 2010

	No. (%) of Infants		
Characteristic	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)
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. If missing data >5%, number (%) of missing data reported. Abbreviations: SGA, small for gestational age; BMI, body mass index; IP, index person		

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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)	
	Exposed cases	Model 2 HR (95% CI)^a	Exposed cases	Model 2 HR (95% CI)^a	Exposed cases	Model 2 HR (95% CI)^a
All ASD (n=54071)						
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