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Association between Preeclampsia and Attention Deficit Hyperactivity Disorder: A Population-Based and Sibling-Matched Cohort Study

Running Title: Preeclampsia and ADHD

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Abstract

Objective: Examine the association between preeclampsia and attention deficit hyperactivity disorder (ADHD), using a large Swedish-based registry cohort.

Methods: This study comprised 2,047,619 children, with 114,934 (5.6%) cases of ADHD. Preeclampsia was based on two alternate definitions: 1.Preeclampsia (using ICD-9/ICD-10)

2.Preeclampsia and small for gestational age (SGA) combined. ADHD was determined in one of two ways: 1.If a diagnosis of ADHD was present in the National Patient Register or 2.If an individual was in receipt of ADHD medication in the Prescribed Drug Register. Multivariate Cox proportional hazards regression analysis allowed adjustment for several perinatal/sociodemographic factors. Sibling-matched analysis further controlled for shared genetic and familial confounding.

Results: In the adjusted Cox model, preeclampsia was associated with an increase in likelihood of ADHD (HR: 1.15, 95% CI: 1.12, 1.19). The HR for preeclampsia and those born SGA was 1.43 (95% CI: 1.31, 1.55) in the adjusted model, compared to those unexposed to preeclampsia/SGA. The sibling-matched analysis did not materially change these associations (HR: 1.13, 95% CI: 1.05, 1.22) and 1.55 (95% CI: 1.28, 1.88).

Conclusions: Exposure to preeclampsia or preeclampsia/SGA was associated with ADHD, independent of genetic/familial factors shared by siblings. However, it is important to note that sibling-matched analysis can only adjust for factors that are constant between pregnancies, therefore residual confounding cannot be ruled out. Further research is needed to explore modifiable risk factors and identify those most-at-risk babies following delivery.

Keywords: Preeclampsia, Obstetric complications, Attention Deficit Hyperactivity Disorder, Epidemiology.

Significant Outcomes

- This population-based cohort study suggests that preeclampsia, as well as preeclampsia and small for gestational age (SGA) combined (i.e. SGA baby exposed to preeclampsia), are associated with an increase in the likelihood of ADHD, independent of genetic/familial factors shared by siblings.
- Placental pathology may be a common mechanism increasing the likelihood of ADHD as a stronger association was observed for preeclampsia/SGA, rather than preeclampsia alone.
- Further research is needed to explore modifiable risk factors and identify those most-at-risk babies following delivery.

Limitations

- A lack of robust data on gestational hypertension limited the analysis to preeclampsia-ADHD only; therefore, the comparison group may contain women with a diagnosis of gestational hypertension. However, a gestational hypertension-ADHD association would more likely bias our results towards the null.
- Outpatient data only started becoming available in 2001, meaning more severe cases of ADHD may have been overrepresented due to a reliance on inpatient data. However, restricting the study population to 2001-2010 did not have a large impact on findings.
- While sibling-matched analysis may have reduced confounding due to shared genetic and familial factors, the possibility of residual confounding cannot be ruled out in observational studies.

Data availability statement

Authors are not permitted to share data due to GDPR restrictions.

Introduction

Preeclampsia, which affects approximately 5% of all pregnancies[1], is one of the leading causes of maternal morbidity and mortality, and was recently redefined by the International Society for the Study of Hypertension in Pregnancy (ISSHP) as gestational hypertension accompanied by at least two of the following: proteinuria and/or other maternal organ dysfunction and/or uteroplacental dysfunction[2].

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterised by inattention, hyperactivity and impulsivity. ADHD has a global pooled prevalence of over 5%, and while this estimate varies significantly worldwide, the variability can mostly be explained by methodological differences between studies[3, 4]. Despite high heritability estimates, gene environment interactions may also play a role[5].

Preeclampsia has been linked to adverse neurodevelopmental outcomes, including ADHD[6, 7]. Pooled results from a recent systematic review suggest that preeclampsia is associated with a 30% increase in odds of ADHD[6]. It is worth noting however, that while an apparent relationship exists in previous literature, residual confounding and quality of the studies may be a concern. For example, only one of ten studies included in the systematic review controlled for a combination of key potential confounders, such as maternal age, socioeconomic status, ethnicity, and maternal mental illness[6, 8].

Aim of the study

The aim of this study was to examine the association between preeclampsia and ADHD using a large population-based cohort study, controlling for a wide range of potential confounding factors, as well as shared genetic and familial confounding through sibling-matched analysis.

Materials and Methods

Study Population

All singleton live births in Sweden from 1990 to 2010, with a follow-up until December 2016, were included in the study. Data were obtained from Swedish National Registers. These included the Medical Birth Register, National Patient Register, Prescribed Drug Register, Multi-generation Register, Total Population Register and Register of Education, linked using personal identification numbers assigned to Swedish residents[9].

Ethical approval was previously obtained from the Stockholm Regional Ethical Review Board (number 2010/1185-31/5), and informed consent was waived by the ethics committee.

Exposures

Preeclampsia

Data on preeclampsia was obtained from the Medical Birth Register which contains data on over 97% of all births in Sweden[10]. We used two alternate definitions of preeclampsia:

1. Preeclampsia: Blood pressure ≥140/90 mmHg on or after 20 weeks' gestation combined with proteinuria (≥0.3 g/day or ≥1 on a urine dipstick on at least two occasions). Preeclampsia was classified using the Swedish version of the ICD, Ninth and Tenth Revision[11]: ICD-9 until 1996 (codes 642E-G) and ICD-10 from 1997 (codes O14-O15)[12, 13].

2. Preeclampsia and small for gestational age (SGA) combined: We combined preeclampsia (as above) and SGA as a proxy for preeclampsia with placental dysfunction[2]. SGA was defined as birthweight <2 standard deviations below the mean of the sex-specific and gestational age distributions[14].

Outcome

Data on ADHD were obtained from the National Patient Register and the Prescribed Drug Register. The National Patient Register was launched in 1964, contains inpatient psychiatric diagnoses from 1973, and outpatient data since 2001 (with increasingly better coverage until 2006)[15-17]. The Prescribed Drug Register was expanded on 1st July 2005 to include personal identification numbers allowing linkage to other registers[17, 18].

A diagnosis of ADHD was determined in one of two ways:

1. If a diagnosis of ADHD was present in the National Patient Register, using ICD-10 (code F90 and F98.8), available since 1997[17].

2. If the subject was in receipt of ADHD medication in the Prescribed Drug Register. ADHD medication data was classified according to Anatomical Therapeutic Chemical classification system, and included amphetamine (N06BA01), dexamphetamine (N06BA02), psychostimulants methyphenidate (N06BA04) and noradrenergic reuptake inhibitor atomoxetine (N06BA09).

Confounding Factors

Potential confounders were based on previous literature. Year of birth, infant sex, maternal age, parental country of birth, parity, maternal smoking status, body mass index (BMI) at first antenatal visit and gestational weight gain were obtained from the Medical Birth Register. Parental depression, bipolar disorder, and non-affective psychiatric disorders were obtained from the National Patient Register. Family income and parental level of education data were obtained from the Total Population Register and Register of Education. Information on all cofounders was available for the entire study period. Where a variable had missing data, the data were added as a separate category and included in the various Cox regression analyses by means of an indicator variable to ensure that all cases were included in the analyses[19]. (See eMethods for description of confounders).

Statistical Analysis

All data were analysed using Stata/MP 14.2. We conducted Cox proportional hazards regression analysis to calculate a hazard ratio (HR) and 95% confidence interval for a preeclampsia-ADHD relationship, preeclampsia/SGA-ADHD (i.e SGA baby exposed to preeclampsia) relationship and the relationship between preeclampsia without SGA and ADHD.

Similar to a previous ADHD study conducted on this population (and because a diagnosis of ADHD is less likely to occur before this time)[17], follow-up began from a child's third birthday, (or

1st January 1997 for children who turned three years of age before 1997). Children continued to be followed up until he/she received a diagnosis of ADHD, prescription for ADHD, death, emigration, or the study period had ended (31st December 2016).

Partially adjusted models were stratified for 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, parental country of birth, parity, parental depression, bipolar disorder, and non-affective psychiatric disorder, family income, maternal smoking status, BMI at first antenatal visit, gestational weight gain and parental level of education.

Sibling-matched analysis: We conducted a sibling-matched analysis (model 3) to control for shared genetic and familial confounding, using stratified Cox regression. This analysis was matched on maternal ID and consisted of a separate stratum for each family in order to estimate the probability of ADHD within family[20]. 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. Finally, we repeated these analyses, firstly, including only those with both an ICD code for ADHD and if the subject was in receipt of ADHD medication, and secondly, including only those with an ICD code for ADHD.

Post-hoc analysis: We examined the association between SGA only and ADHD compared to non-exposure to SGA/non-exposure to preeclampsia.

E-value: We calculated the E-value for the statistically significant primary effect estimates and lower limits of their 95% confidence interval (CI) to examine the extent of unmeasured confounding, using the publicly available online E-value calculator: (https://evalue.hmdc.harvard.edu/app/)[21, 22]. In summary, an E-value is a continuous measure that quantifies the minimum strength of association an unmeasured confounder would need to have with both preeclampsia and ADHD in order to explain away an effect estimate[22].

Sensitivity analyses: We conducted several sensitivity analyses, decided *a priori*. For example, while classifying preeclampsia into mild/severe is not recommended in clinical practice because it is a complex disorder that can deteriorate rapidly, gestational age is sometimes used as a proxy for preeclampsia with severe features. As a result, preeclampsia could be considered severe if delivery occurred before 34 weeks' gestation[23]. Therefore, we examined the association between preeclampsia and ADHD by gestational age. In addition, it is possible that a mother's lifestyle factors could change between pregnancies. As a result, we excluded women who had preeclampsia in her first pregnancy, and examined a preeclampsia-ADHD relationship in women who had a

diagnosis of preeclampsia in subsequent pregnancies only. Additional sensitivity analyses included restricting the study population to 2001-2010 (when outpatient data on ADHD started to become available), and restricting the study population to 1994-2010 to ensure every child begins follow-up at their third birthday. Furthermore, we included 'preeclampsia excluding chronic hypertension' as the exposure, and 'preeclampsia with chronic hypertension' as the exposure. We examined preeclampsia-ADHD excluding those with a family history of mental illness. We analysed the relationship between preeclampsia with low/intermediate APGAR score at five minutes, while we also examined a preeclampsia-ADHD relationship by maternal age, in addition to preeclampsia-ADHD by BMI group at time of first antenatal visit. Finally, we investigated a preeclampsia-ADHD association by gender.

Results

Descriptive Statistics

A total of 2,142,694 live births were recorded in the Swedish Medical Birth Register between 1990 and 2010. After excluding 61,172 multiple births, 30,636 children who were censored before their third birthday, and 3267 children who turned three years of age before 1997 but were censored before follow-up began on 1st January 1997, a total of 2,047,619 children remained in the final cohort (Table 1).

There were 57,493 (2.8%) children exposed to preeclampsia and 7191 (0.4%) exposed to preeclampsia and SGA combined. There were 114,934 (5.6%) cases of ADHD. Of these 101,075 (87.9%) cases were prescribed ADHD medication at some point, and 94,708 (82.4%) cases had an ICD diagnosis. A total of 80,849 (70.3%) cases were recorded with both an ICD code and medication, while there were 13,859 (12.1%) cases with an ICD code only, and 20,226 (17.6%) cases with medication only.

Association between preeclampsia, preeclampsia/SGA and ADHD

In the fully adjusted model (model 2), the results suggested an association between preeclampsia and ADHD (HR: 1.15, 95% CI: 1.12, 1.19) compared to those unexposed to preeclampsia. Result of the sibling-matched analysis (model 3) did not significantly change (HR: 1.13, 95% CI: 1.05, 1.22). The HR for those born SGA and exposed to preeclampsia was 1.43 (95% CI: 1.31, 1.55) in the adjusted model (model 2), and 1.55 (95% CI: 1.28, 1.88) in the sibling-match model (model 3), while the HR for those exposed to preeclampsia but not born SGA was 1.12 (95% CI: 1.08, 1.16) in model 2, and 1.09 (95% CI: 1.01, 1.18) in model 3. Limiting the data to those with both an ICD code and medication data did not materially change results, while including only those with an ICD code for ADHD produced similar results (Table 2).

Post-Hoc Analysis

The adjusted HR for SGA only (i.e. SGA without preeclampsia) and ADHD was 1.32 (95% CI: 1.27, 1.37), while the HR in the sibling-matched analysis was 1.29 (95% CI: 1.19, 1.39) compared to non-exposure to SGA/non-exposure to preeclampsia (Table 2).

E-Values

The E-values for significant primary effect estimates were 1.51 for preeclampsia, 2.47 for preeclampsia with SGA and 1.40 for preeclampsia without SGA, while the E-values for

corresponding lower limits of their 95% CI were 1.28, 1.88 and 1.11 respectively. (see eTable 1 in Supplement for worked example on preeclampsia-ADHD).

Sensitivity Analyses

Preeclampsia and ADHD by gestational age

When we restricted analysis to children born ≥39 weeks' gestational age, the HR for a preeclampsia-ADHD relationship was 1.07 (95% CI: 1.02, 1.12). Among children born at 37-38 weeks', the HR in those exposed to preeclampsia was 1.20 (95% CI: 1.13, 1.28), while the HR among those not exposed to preeclampsia was 1.09 (95% CI: 1.08, 1.11), when compared to non-exposure to preeclampsia in those born ≥39 weeks' gestational age. Exposure to preeclampsia (among children born 34-36 weeks') was associated with a 24% increase in likelihood of ADHD (HR: 1.24, 95% CI: 1.14, 1.35), while those unexposed to preeclampsia had a 14% increased likelihood of ADHD among those born at a similar gestational age (HR: 1.14, 95% CI: 1.11, 1.18). Finally, the HR among those exposed to preeclampsia (born <34 weeks' gestational age) was 1.74 (95% CI: 1.60, 1.91), while the HR among those not exposed to preeclampsia (born <34 weeks' gestational age) was 1.49 (95% CI: 1.42, 1.96) when compared to non-exposure to preeclampsia among those born ≥39 weeks' gestational age (Table 3).

Additional sensitivity analyses

Results of additional sensitivity analyses are outlined in eResults and eTable 2 in the Supplement and were not materially different from the primary analysis. In sum, when we excluded women who had preeclampsia in their first pregnancy, the adjusted HR was 1.21. When we restricted the study population to 2001-2010 and 1994-2010, the HR was 1.21 and 1.14 respectively. The fully adjusted HR for preeclampsia (excluding chronic hypertension) and preeclampsia (with chronic hypertension) were 1.15 and 1.18 respectively. The HR for preeclampsia (excluding those with a family history of mental illness was 1.16. Preeclampsia (with low/intermediate APGAR at 5 minutes) increased the likelihood of ADHD by 13% when compared to non-exposure to preeclampsia in those with a low/intermediate APGAR score. Results of the subgroup analysis suggested that preeclampsia was significantly associated with ADHD at each category of maternal age and at each category of BMI at first antenatal visit. The HR for preeclampsia-ADHD in males was 1.18 compared to non-exposure to preeclampsia in males, while the HR for preeclampsia-ADHD in females was 1.10 compared to non-exposure to preeclampsia in females. Finally,

exposure to preeclampsia in males was associated with a 9% increase in likelihood of ADHD when compared to exposure to preeclampsia in females.

Discussion

The aim of this study was to examine the association between preeclampsia and preeclampsia/SGA and ADHD, using a large population-based cohort study. We have yielded three principal findings. First, after controlling for known potential confounding factors, preeclampsia was associated with a 15% increase in likelihood of ADHD when compared to non-exposure to preeclampsia. This finding was similar in the sibling-matched analysis suggesting that this apparent preeclampsia-ADHD relationship was not due to shared genetics or familial environment. This result is in line with the pooled estimate from a systematic review, which suggested that preeclampsia was associated with a 30% increase in odds of ADHD, with individual study estimates ranging from 1.19 to 1.50[6].

Second, as SGA is associated with uteroplacental dysfunction[24], and due to recent guidelines put forward by ISSHP to include uteroplacental dysfunction in the definition of preeclampsia, we combined preeclampsia and SGA into a single exposure as a crude proxy for preeclampsia with placental dysfunction. Being an SGA baby and exposed to preeclampsia was associated with a 43% increase in likelihood of ADHD in the fully adjusted model, and a 55% increase in likelihood of ADHD in the sibling-matched analysis, when compared to non-exposure to preeclampsia or SGA. This may suggest that placental pathology may be a common factor increasing the likelihood of ADHD given the stronger association with preeclampsia/SGA than preeclampsia alone.

Three, while preeclampsia was associated with ADHD, independent of gestational age, the likelihood of ADHD increases with decreasing gestational age. For example, preeclampsia was associated with a 7% increase in likelihood of ADHD when we restricted the analysis to those born ≥39 weeks' gestation. However, the HR increases to 1.74 among those exposed to preeclampsia and born at <34 weeks' gestation.

This apparent preeclampsia-ADHD association may lack specificity however, as preeclampsia is associated with several neurodevelopmental outcomes such as autism spectrum disorder (ASD), cognitive impairment and intellectual disability (ID) in previous literature[6]. Therefore, preeclampsia could in fact be a risk factor for poor neurodevelopmental outcome in general, with the specificity of outcome (e.g. ADHD, ASD, ID etc.) being determined by underlying genetic risk factors[25].

Potential Mechanisms

The molecular basis of a preeclampsia-ADHD relationship remains unknown, and there are few studies that address the potential biological mechanisms of ADHD specifically. Animal models have shown that activation of interleukin-17a (IL-17a) in the fetal brain, in response to maternal immune activation, is associated with behavioural disturbances and an abnormal cortical phenotype in affected offspring[26, 27]. Therefore, we can speculate that maternal inflammation may be one such mechanism given the role of preeclampsia in chronic immune activation and elevated levels of inflammatory cytokines such as IL-17a[26, 28, 29]. In a separate study, maternal depressive symptoms throughout pregnancy were shown to be associated with ADHD in offspring[30]. As prenatal depression is linked to an increase in levels of pro-inflammatory cytokines[31], it is possible that the inflammatory response observed in preeclampsia may have a similar inflammatory mediated effect on ADHD-risk.

However, it may also be possible that lifestyle factors not available in the registers, such as maternal alcohol consumption may also play a role. Alcohol consumption during pregnancy has been shown to affect placentation, fetal growth, and likelihood of ADHD[32, 33]. As preeclampsia is, at least in part, a disease of placentation, leaving the fetus vulnerable to the effects of placental pathology, particularly fetal growth restriction[2], it is plausible that maternal alcohol consumption during pregnancy may contribute the observed preeclampsia-ADHD association.

Strengths and Limitations

There are several strengths in this study. To our knowledge, it is the largest epidemiological study to examine the association between preeclampsia-ADHD to date. Use of National Registers minimised recall bias, while also allowed us to control for a wide range of confounding factors. In addition, the sibling-matched analysis allowed us to adjust for unmeasured confounding factors

shared by siblings such as family environment, diet, lifestyle factors, maternal characteristics, and genetic factors[14]. Furthermore, use of the E-value allowed us to quantify Bradford-Hill's consideration of 'strength of association' in an attempt to investigate the robustness of our effect estimates to unmeasured confounding[22].

However, this study also contains several limitations. First, sibling-matched analysis may have reduced confounding due to shared genetic and familial factors. However, this method can only adjust for factors that are constant between pregnancies[34] and the possibility of residual confounding cannot be ruled out in observational studies. Taking preeclampsia-ADHD as an example: (E-value for effect estimate = 1.51), an unmeasured confounder associated with both preeclampsia and ADHD by a risk-ratio of 1.51 may potentially explain away our preeclampsia-ADHD effect estimate of 1.13. However, the effect-estimate for preeclampsia/SGA combined is less likely to be explained away by unmeasured confounding with an E-value of 2.47. Nonetheless, we cannot dismiss the potential effect of factors such as maternal alcohol consumption could have on findings. Second, a lack of robust data on gestational hypertension limited our analysis to preeclampsia-ADHD only. Therefore, our comparison groups may contain women with a diagnosis of gestational hypertension, and while previous literature suggests a positive gestational hypertension-ADHD association[35], this would likely bias our results towards to the null. Third, as outpatient data only started becoming available in 2001, more severe cases of ADHD may have been overrepresented in our data. However, when we restricted the study population to 2001-2010, results were not materially different from our main findings suggesting that the inclusion of less severe cases after 2001 may not have had a large impact on findings.

In conclusion, this population-based cohort suggests that preeclampsia as well as preeclampsia/SGA was associated with ADHD. Placental pathology may be a common mechanism increasing the likelihood of ADHD given the stronger association with preeclampsia/SGA, rather than preeclampsia alone. Further research is needed in order to clarify this association, explore modifiable risk factors and identify those most-at-risk babies following delivery.

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Table 1: Perinatal and Sociodemographic Characteristics Related to Preeclampsia and Attention Deficit Hyperactivity Disorder Among Singleton Live Births in Sweden between 1990 and 2010

	No. (%) of Infants	
Characteristic	**Total Population**	**Preeclampsia**
Total Population	2047619	57493 (2.8)
ADHD	114934 (5.6)	3941 (6.9)
SGA	46719 (2.3)	7191 (12.6)
First-born child	879954 (42.9)	37642 (65.5)
Sex (male)	1052095 (51.4)	29938 (52.1)
Maternal age, years		
<20	41285 (2.0)	1535 (2.7)
20-29	1015666 (49.6)	29354 (51.1)
30-39	935055 (45.7)	24569 (42.7)
≥40	55613 (2.7)	2035 (3.5)
Gestational age, weeks		
<34	23538 (1.1)	5048 (8.8)
34	12181 (0.6)	1702 (3.0)
35	20845 (1.0)	2337 (4.1)
36	41472 (2.0)	3868 (6.7)

37	98759 (4.8)	6385 (11.2)
38	277445 (13.6)	9153 (15.9)
39	472125 (23.1)	10632 (18.5)
40	580209 (28.4)	10128 (17.6)
>40	519037 (25.4)	8162 (14.2)
5-Minute Apgar score		
0-3 (low)	3419 (0.2)	228 (0.4)
4-6 (intermediate)	15330 (0.8)	1251 (2.2)
7-10 (high)	2013115 (99.0)	55464 (97.4)
Mother's country of birth		
Sweden	1597528 (78.0)	47286 (82.2)
Other Nordic country	44704 (2.2)	1301 (2.3)
Other country	278978 (13.6)	5709 (9.9)
Missing	126409 (6.2)	3197 (5.6)
Father's country of birth		
Sweden	1577672 (77.1)	46891 (81.6)
Other Nordic country	42429 (2.1)	1184 (2.0)
Other country	287522 (14.0)	5820 (10.1)
Missing	139996 (6.8)	3598 (6.3)
Maternal depression		
Never	1763485 (86.1)	49730 (86.5)
Previously diagnosed	157876 (7.7)	4574 (7.9)
Missing	126258 (6.2)	3189 (5.6)
Maternal bipolar disorder		
Never	1904427 (93.0)	53772 (93.5)
Previously diagnosed	16934 (0.8)	532 (0.9)
Missing	126258 (6.2)	3189 (5.6)
Maternal nonaffective disorder		
Never	1909156 (93.2)	53923 (93.8)
Previously diagnosed	12205 (0.6)	381 (0.6)
Missing	126258 (6.2)	3189 (5.6)
Paternal depression		
Never	1831285 (89.4)	51886 (90.2)
Previously diagnosed	90076 (4.4)	2418 (4.2)
Missing	126258 (6.2)	3189 (5.6)
Paternal bipolar disorder		
Never	1911454 (93.3)	54058 (94.0)

Previously diagnosed	9907 (0.5)	246 (0.4)
Missing	126258 (6.2)	3189 (5.6)
Paternal nonaffective disorder		
Never	1909156 (93.2)	53980 (93.9)
Previously diagnosed	12205 (0.6)	324 (0.5)
Missing	126258 (6.2)	3189 (5.6)
Income quintile		
First	362540 (17.7)	8168 (14.2)
Second	383691 (18.7)	9542 (16.6)
Third	388138 (19.0)	11044 (19.2)
Fourth	390219 (19.1)	12509 (21.8)
Fifth	384890 (18.8)	12772 (22.2)
Missing	138141 (6.7)	3458 (6.0)
Smoking at first antenatal visit		
No	1683882 (86.4)	49417 (90.7)
1-9 cigarettes/day	178176 (9.1)	3576 (6.5)
≥10 cigarettes/day	87699 (4.5)	1515 (2.8)
BMI at first antenatal visit		
<20	172519 (8.4)	3048 (5.3)
20-24.9	868599 (42.4)	19449 (33.8)
25-29.9	372026 (18.2)	13037 (22.7)
≥30	154136 (7.5)	9415 (16.4)
Missing	480339 (23.5)	12544 (21.8)
Optimal gestational weight gain by BMI group at first antenatal visit[36]		
<20		
Optimum	15910 (0.8)	211 (0.4)
Inadequate/Excessive	49130 (2.4)	891 (1.6)
20-24.9		
Optimum	75448 (3.7)	1003 (1.7)
Inadequate/Excessive	254217 (12.4)	5855 (10.2)
25-29.9		
Optimum	25752 (1.3)	527 (0.9)
Excessive	115893 (5.7)	4260 (7.4)
≥30		
Optimum	12147 (0.6)	461 (0.8)
Excessive	48240 (2.3)	3180 (5.5)

Missing	1450882 (70.8)	41105 (71.5)
Highest parental level of education at child's birthyear		
Pre-high school	131210 (6.4)	3304 (5.7)
High school	886656 (43.3)	26603 (46.3)
Post high school	877980 (42.9)	23844 (41.5)
Missing	151773 (7.4)	3742 (6.5)

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.

Table 2: Association between Preeclampsia and Attention Deficit Hyperactivity Disorder Among Singleton Live Births in Sweden between 1990 and 2010

	Total population			Sibling pairs
All ADHD (n=114934)	**Exposed cases**	**Model 1 HR (95% CI)†**	**Model 2 HR (95% CI)‡**	**Model 3 HR (95% CI)§**
Preeclampsia	3941	1.22 (1.18, 1.26)	1.15 (1.12, 1.19)	1.13 (1.05, 1.22)
Preeclampsia and SGA¶	582	1.49 (1.37, 1.61)	1.43 (1.31, 1.55)	1.55 (1.28, 1.88)
Preeclampsia without SGA	3322	1.19 (1.15, 1.23)	1.12 (1.08, 1.16)	1.09 (1.01, 1.18)
SGA without Preeclampsia	3205	1.51 (1.45, 1.56)	1.32 (1.27, 1.37)	1.29 (1.19, 1.39)
ADHD (ICD code and in receipt of medication) (n=80849)				
Preeclampsia	2795	1.23 (1.18, 1.27)	1.16 (1.11, 1.20)	1.11 (1.02, 1.21)
Preeclampsia and SGA¶	399	1.44 (1.31, 1.59)	1.37 (1.25, 1.52)	1.54 (1.23, 1.92)
Preeclampsia without SGA	2370	1.21 (1.16, 1.26)	1.13 (1.08, 1.18)	1.07 (0.98, 1.17)
ADHD (ICD code only) (n=94708)				
Preeclampsia	3267	1.23 (1.18, 1.27)	1.16 (1.12, 1.20)	1.11 (1.03, 1.20)
Preeclampsia and SGA¶	480	1.48 (1.35, 1.62)	1.41 (1.29, 1.55)	1.48 (1.21, 1.82)
Preeclampsia without SGA	2757	1.20 (1.16, 1.25)	1.13 (1.09, 1.18)	1.07 (0.99, 1.17)

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval; SGA, small for gestational age; ICD, International Classification of Disease;

†Adjusted for year of birth.

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

§Adjusted for same potential confounders as above with the exception of maternal country of birth.

¶Reference=no preeclampsia/no SGA.

Missing data on SGA for 37 cases of ADHD (full cohort). Missing data on SGA for 26 cases of ADHD (with both ICD code and medication data). Missing data on SGA for 30 cases of ADHD (with ICD code).

Table 3: Association between Preeclampsia and Attention Deficit Hyperactivity Disorder Among Singleton Live Births in Sweden between 1990 and 2010 by Gestational Age

	Total population		
All ADHD (n=114934)	**Exposed cases**	**Model 1 HR (95% CI)†**	**Model 2 HR (95% CI)‡**
No Preeclampsia, ≥39 weeks' gestational age (ref)	82844	1.00	1.00
Preeclampsia, ≥39 weeks' gestational age	1808	1.14 (1.09, 1.20)	1.07 (1.02, 1.12)
No Preeclampsia, 37-38 weeks' gestational age	21742	1.13 (1.12, 1.15)	1.09 (1.08, 1.11)
Preeclampsia, 37-38 weeks' gestational age	1066	1.28 (1.20, 1.36)	1.20 (1.13, 1.28)
No Preeclampsia, 34-36 weeks' gestational age	4545	1.28 (1.24, 1.32)	1.14 (1.11, 1.18)
Preeclampsia, 34-36 weeks' gestational age	568	1.32 (1.22, 1.44)	1.24 (1.14, 1.35)
No Preeclampsia, <34 weeks' gestational age	1703	1.78 (1.70, 1.87)	1.49 (1.42, 1.56)
Preeclampsia, <34 weeks' gestational age	491	1.85 (1.69, 2.02)	1.74 (1.60, 1.91)

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

†Adjusted for year of birth.

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

Missing data on gestational age for 167 cases of ADHD.