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The associations of preterm birth, small-for-gestational age, preeclampsia, and placental abruption with attention-deficit/hyperactivity disorder in the offspring: Nationwide cohort and sibling-controlled studies

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ABSTRACT

Aim: To investigate preterm birth, small-for-gestational age (SGA), preeclampsia, and placental abruption in relation to attention-deficit/hyperactivity disorder (ADHD) in offspring.

Methods: We conducted a population-based cohort study among non-malformed live-born singleton children in Sweden born 2002-2014. Using national registries with recorded information, we followed 1,212,201 children for an ADHD diagnosis from 3 to 15 years. We compared ADHD rates between exposure categories using adjusted hazard ratios (HR) with 95% confidence intervals (CI) from Cox proportional hazards models. We also conducted sibling-controlled analyses among 751,464 full siblings.

Results: There were 27,665 ADHD diagnoses in the cohort. Compared with term birth (≥37 weeks), adjusted HR (95% CI) for ADHD increased with decreasing gestational age: 1.18 (1.11, 1.25), 1.61 (1.37, 1.89), and 2.79 (2.23, 3.49) for 32 to 36 weeks, 28 to 31 weeks, and 22 to 27 weeks. Both spontaneous and medically indicated preterm birth were associated with ADHD. SGA was related to 1.62 (1.49, 1.77) times higher ADHD incidence. Preeclampsia, but not placental abruption, was associated with ADHD. Sibling-controlled analyses showed similar results. Preterm birth did not fully explain the associations of SGA or preeclampsia with ADHD.

Conclusion: Preterm birth, SGA, and preeclampsia are related to ADHD incidence in offspring.

Keywords: Attention-deficit/hyperactivity disorder, fetal growth restriction, placental abruption, preeclampsia, preterm birth.

Key Notes:

In this nationwide investigation of over 1.2 million children, preterm birth, small-for-gestational age, and preeclampsia were each associated with increased rates of attention-deficit/hyperactivity disorder (ADHD) in the offspring in both cohort and sibling-controlled analyses. Both spontaneous and medically indicated preterm birth types were associated with ADHD incidence. These data also support the view that small-for-gestational age and preeclampsia influence the risk of ADHD in the offspring independent of preterm birth.

BACKGROUND

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder that affects about 5% of children and adolescents worldwide[1]; symptoms persist into adulthood in 33-84% of cases.[2] ADHD is characterized by inattention, hyperactivity, and impulsivity, and can have wide-ranging effects on quality of life.[3] Symptoms stem from abnormalities in the structural and functional capacity of brain networks, but the etiology of the disorder is not fully understood.[4] Risk factors predominantly include a combination of genetic and environmental characteristics.[4]

Prenatal and perinatal conditions are among the environmental factors associated with ADHD. Previous studies have suggested that preterm children are at increased risk of ADHD[5-9]; risk increases in a dose-response manner with decreasing gestational age. Fetal growth restriction (small-for-gestational age [SGA] birth size) is also associated with ADHD risk.[6,7] However, it is unclear whether there are independent effects of gestational age and SGA on risk of ADHD. Also, it is uncertain whether obstetric complications that may cause preterm birth or SGA, such as preeclampsia and placental abruption, are related to increased risk of ADHD. Some studies have found an increased ADHD risk associated with preeclampsia,[10-12] but few studies have examined placental abruption, and the role of gestational age and SGA on these associations is unclear. Preterm birth has been strongly related to incidence of ADHD[5-9] and could be a consequence of placental abruption, preeclampsia, or SGA; hence, associations between these exposures and ADHD could be mostly mediated by preterm birth.

We used data from Swedish population registers to examine whether gestational age or birth weight-for-gestational age are independently related to offspring ADHD risk in a nationwide cohort. We also assessed the contribution of preeclampsia or placental abruption to ADHD overall and independent of preterm birth or SGA. We performed nested sibling-controlled comparisons to account for potential confounding by stable (i.e. time-invariant) shared familial (genetic and environmental) factors. Finally, we considered the associations with ADHD alone vs. ADHD comorbid with autism since these conditions frequently co-occur, and this could contribute to understanding whether these disorders have a shared etiology.

METHODS

Study design

We conducted a population-based cohort study among live singleton children born at ≥22 completed gestational weeks between 2002 and 2014, who were recorded in the Swedish Medical Birth Register. The National Board of Health and Welfare and Statistics Sweden provided information from population-based registers. Information in the Birth Register[13] was cross-linked with the National Patient-, Prescribed Drugs-, Total Population-, Education-, and Multi-generation Registers using the person-unique national registration number assigned to all Sweden residents at birth or immigration. The Birth Register includes information on prenatal, obstetric, and neonatal care for more than 98% of all births in Sweden. The National Patient Register includes diagnoses at discharge from hospital admissions since 1987 and from outpatient hospital visits since 2001. Diagnoses are coded according to the Swedish version of the International Classification of Diseases (ICD), tenth revision (ICD-10) since 1997. The study was approved by the Regional Ethical Review Board in Stockholm, Sweden (No. 2018/5:2). Informed consent was not required.

Outcomes

ADHD among children born without congenital malformations was defined as the presence of at least one ICD-10 diagnostic code F90 starting at 3 years of age and at least one prescription of medication according to the Anatomical Therapeutic Chemical classification system that included amphetamine (N06BA01), dexamphetamine (N06BA02), methylphenidate (N06BA04), or atomoxetine (N06BA09). Because the Prescribed Drugs Register became available in July 2005, we included births from July 2002 through 2014. We included diagnoses that had been recorded either as the main or secondary diagnosis.

ADHD comorbid with autism was a secondary outcome. Autism was defined as the presence of one or more ICD-10 diagnostic codes F84.0 or F84.1 in the National Patient Register. ICD-10 codes for all diagnoses are presented in Table S1.

Exposures

The primary exposures of interest were preterm birth and SGA. Gestational age was obtained by using the following hierarchy: early second trimester ultrasound (90.3%), date of the last menstrual period (4.5%), or a postnatal assessment (5.2%). Births were classified as post-term

(≥42 completed weeks), term (37 to 41 weeks), moderately preterm (32 to 36 weeks), very preterm (28 to 31 weeks), or extremely preterm (22 to 27 weeks). Preterm birth was further classified as spontaneous or medically indicated (i.e. induced). Spontaneous preterm birth was defined as labor with spontaneous onset, and medically indicated preterm birth was defined as induced labor or a cesarean section before onset of labor, as recorded in the obstetric records, which are filled in by the midwife in charge at delivery. Birth weight-for-gestational age was defined using the ultrasound-based Swedish reference for fetal growth,[14] and SGA was defined as a birth weight for gestational age <3rd percentile. SGA was further classified by gestational age: ≥37 weeks, 34 to 36 weeks, or <34 weeks. Secondary exposures were preeclampsia and placental abruption. Preeclampsia was further classified as term (≥37 weeks) or preterm (34 to 36 or <34 weeks). Information on obstetric complications was obtained from the Birth Register according to ICD-10 codes presented in Table S1.

Covariates

Covariate information was primarily extracted from the Birth Register, but also from the Total Population and Education Registers. Maternal age at delivery was the date of delivery minus the mother's birth date. Mother's country of birth (from the Total Population Register) was categorized as Nordic vs. non-Nordic. Maternal education was the highest level of completed education. Information on whether the mother cohabited with the father-to-be was obtained at the first prenatal visit. Parity was the number of births of each mother. Maternal height was self-reported at the first prenatal visit; for multiparous women, we took the median height across pregnancies to decrease error. Early pregnancy body mass index (BMI, kg/m^2) was calculated from height and weight measured objectively in light clothing at the first prenatal visit, which in Sweden occurs before 14 weeks of gestation in 90%.[15] BMI was classified as underweight (BMI <18.5), normal weight (18.5-24.9), overweight (25.0-29.9), obesity grade 1 (30.0-34.9), obesity grade 2 (35.0-39.9), or obesity grade 3 (≥40.0). Smoking was determined by self-report at either the first prenatal visit or in the third trimester; this has been validated with cotinine markers.[16] Parental ADHD was defined as codes ICD-9 314 or ICD-10 F90.

Statistical Analysis

General cohort analyses. The general cohort comprised children born July 2002 through December 2014 who were followed starting at age 3 years until the earliest of a first diagnosis or drug prescription for ADHD, emigration, death, or December 31st, 2017.

We estimated ADHD rates as the number of cases divided by person-time of follow-up in the chronological age scale and compared them by categories of exposures with use of adjusted hazard ratios (HR) with 95% confidence intervals (CI) from Cox proportional hazards models. The robust sandwich estimate of the covariance matrix was used to compute 95% CI, to account for the correlation of measures among women with more than one pregnancy in the dataset. We adjusted models for independent predictors of ADHD that were associated with the exposures without being their consequence, based on prior knowledge. These included maternal age, country of origin, cohabitation with the child's parent, education level, parity, height, early-pregnancy BMI, smoking during pregnancy, presence of a diagnosis of ADHD in the mother or the father, sex of child, and year of birth. In supplemental analyses following an analogous approach, we also considered as secondary outcomes ADHD alone and ADHD comorbid with autism. In these analyses, the comparison group comprised children without ADHD. We evaluated the role of placental abruption, preeclampsia, or SGA independent of preterm birth by estimating the proportion of their associations with ADHD that was not mediated through gestational age, using natural direct effects from causal mediation analyses under the assumptions of a potential outcomes frame, detailed in the **Methodological Supplement** in **Supplemental Online Material**. In addition, to assess the impact of potential confounding by unmeasured mediator–outcome common causes, a violation of one of the assumptions, we conducted a sensitivity analysis using E-values[17] (**Methodological Supplement** in **Supplemental Online Material**). The E-value assesses the extent to which unmeasured confounders would need to affect the mediator and the outcome to account for the entire observed natural direct effect.

Sibling cohort analyses. We identified full siblings in the general cohort with use of the Multigeneration Register and assembled a sibling cohort for ADHD consisting of children with at least one full sibling in the general cohort. We noted, however, that children included in the sibling cohort differed from those who were excluded with respect to outcome rates, exposure

prevalences, and sociodemographic characteristics distributions. Compared with children in the sibling cohort, those excluded had higher rates of the outcome, higher prevalence of exposures, less favorable sociodemographic conditions, and higher parental prevalence of ADHD (**Table S2**). The reason for exclusion from the sibling cohort was lacking full siblings in the Birth Register during the birth years that defined the general cohort. This could be due to having older siblings born before systematic follow-up through the Patient and Prescribed Drugs Registers could be accomplished, or to not having any live siblings. Because the birth of a child with ADHD could influence the parent's decision of having additional children, selection into the sibling cohort could bias the estimates of association. To qualitatively assess bias in the sibling cohort, we first examined unstratified associations (ignoring sibship), in a manner analogous to the general cohort analyses. In the absence of substantial bias, the estimates of association should be similar in the sibling and general cohorts. Next, we conducted sibling comparisons by estimating HR with 95% CI through stratified Cox models in which each family was a stratum. Finally, we corrected the stratified estimates for potential selection and confounding biases via inverse probability weighting (IPW). We calculated HR with 95% CI from Cox regression models with stabilized weights, which were the product of the inverse of the probability of exposure as a function of measured covariates times the inverse of the probability of being selected into the sibling cohort as a function of covariates. All analyses were conducted with use of SAS version 9.4 (SAS Institute).

RESULTS

From July 2002 through December 2014, the Birth Register included 1,299,986 live singleton births. We excluded 18,387 and 393 with missing maternal and child national registration numbers, respectively. We additionally excluded 13,918 children who emigrated and 3313 who died before 3 years of age, and 51,774 children with congenital malformations. As a result, the general cohort comprised 1,212,201 children with 27,665 ADHD diagnoses (25.6 per 10,000 child-years) over a median 8.7 years of age (interquartile range [IQR] 5.9, 11.9). The risk of ADHD was 3.4% through 11 years of age. The sibling cohort involved 751,464 full siblings from 344,649 families with 15,138 ADHD cases (22.4 per 10,000 child-years) over a median 8.9 years of age (IQR 6.5, 11.5).

ADHD rates by prenatal and perinatal characteristics were similar in the general and sibling cohorts **(Table 1)**. In both cohorts, ADHD rates increased with decreasing gestational age. Children born post-term had similar rates of ADHD compared with those born at term. Although ADHD rates were increased for both medically indicated and spontaneous preterm births, rates were consistently higher for medically indicated preterm birth. Birth weight-for-gestational age <10th percentile, especially <3rd percentile, was related to increased rates of ADHD; among children born SGA, rates of ADHD increased with decreasing gestational age. ADHD rates were higher in offspring of mothers with preeclampsia, especially preterm preeclampsia. Rates of ADHD were also increased in offspring of mothers with placental abruption.

In the general cohort, adjusted HR of ADHD increased with decreasing gestational age in a dose-response manner **(Table 2)**. Estimates of association were in the same direction and of comparable magnitude in the sibling cohort analysis that ignored sibship, indicating that the effect of selection bias was not substantial. After accounting for sibship, adjusted HR for very (28 to 31 weeks) and extremely (22 to 27 weeks) preterm birth substantially increased. Children born very and extremely preterm had an adjusted 2.5 (95% CI 1.5, 4.2) and 8.6 (95% CI 3.0, 24.5) times higher HR of ADHD, respectively, compared with their full siblings born at term. Adjustment via IPW moderately attenuated the association. Both spontaneous and medically indicated preterm birth was associated with higher adjusted HR of ADHD. For moderately preterm birth (32 to 36 weeks), the HR was higher for the medically indicated type. Birth weight-for-gestational age <10th percentile was associated with higher ADHD incidence, and the rate increase was highest for children born ≤3rd percentile. The association of SGA and ADHD strengthened with decreasing gestational age. Conclusions for the sibling cohort were comparable.

Next, we examined the associations of obstetric complications that cause preterm birth or SGA. In the general cohort, preeclampsia increased adjusted ADHD HR; and the HR increased with decreasing gestational age **(Table 3)**. HRs were similar in the sibling cohort analysis that ignored sibship, indicating no substantial effect of selection bias. Adjusted HRs were of comparable magnitude after accounting for sibship, but were not statistically significant. Placental abruption

was not significantly associated with adjusted ADHD HR in general cohort analyses and estimates from the sibling cohort lacked statistical precision.

The association of SGA with ADHD was only to a little extent driven by preterm birth. In mediation analysis, the proportion of the association that was independent of preterm birth was high (95%) **(Table 4)**. A sensitivity analysis also showed that this result was robust to unmeasured mediator-outcome confounding (**Methodological Supplement** in **Supplemental Online Material**). The association of preeclampsia with ADHD was not completely driven by preterm birth or SGA; about half of the association was independent of preterm birth **(Table 4)** whereas 89% was independent of SGA **(Table S3)**.

Sixteen percent of ADHD cases were comorbid with autism. Associations of preterm birth with ADHD and autism were generally similar to those found in the overall ADHD analysis. However, for each association, the HR was higher for ADHD with autism compared with ADHD without autism **(Table S4)**.

DISCUSSION

In this nationwide investigation of over 1.2 million children, preterm birth, SGA, and preeclampsia were each associated with increased rates of ADHD. Both spontaneous and medically indicated preterm birth types were associated with ADHD incidence. Preterm SGA was more strongly associated with ADHD than was term SGA; this was also true for preeclampsia. Nonetheless, in mediation analyses preterm birth only partly explained the associations of SGA (5%) or preeclampsia (48%) with ADHD.

Although associations between preterm birth[5-9,18] or SGA[6,7] and ADHD had been reported before, we are unaware of studies exploring the possibility of a chain of events, from obstetric complications, like preeclampsia, to preterm birth or SGA, and increased risk of ADHD. Although prior investigations have found a relation between preeclampsia and ADHD,[10-12] none showed that this association could be partly independent of preterm birth or SGA. Lack of mediation by preterm birth or SGA suggests that there could be either a direct effect of preeclampsia on ADHD and/or other indirect effects through different mediators such as neurological injury, structural brain changes, inflammation, oxidative stress, and placental

ischemia.[19] Further research could help elucidate these potential pathways. Placental abruption was not associated with ADHD in a study in the United States,[10] in line with our results.

We found that the association between SGA and ADHD was apparent in both cohort and sibling-controlled analyses. The latter suggests that the relation is not fully explained by shared familial factors. Monozygotic twin pair comparisons have shown a relation between lower birth weight and increased ADHD symptoms.[20-22] Because these comparisons are matched by gestational age, the findings suggest a causal effect of fetal growth on ADHD, which could be due to differential flow of nutrients or oxygen to the fetuses.[20] Since we found that the association of SGA with ADHD was largely independent of preterm birth in mediation analyses, our results are consistent with the notion of an effect of intrauterine growth restriction; this result was robust to unmeasured confounding of the mediator-outcome relation (**Methodological Supplement** in **Supplemental Online Material**).

We found that both spontaneous and medically indicated preterm birth were associated with an increased risk of ADHD, and that risks were higher for medically indicated compared with spontaneous preterm birth. These are novel findings. Medically indicated preterm birth is often the result of concern for fetal health due to prenatal conditions such as preeclampsia, gestational diabetes, fetal growth restriction, or asphyxia. Thus, differences in the distribution of these conditions between medically indicated and spontaneous preterm birth may potentially explain the differences in risk of ADHD associated with each type. We also found that, for both spontaneous and medically indicated preterm birth, risk of ADHD increased with decreasing gestational age. However, we note that the relatively smaller increase in risk among moderately preterm children has important public health implications since this group represents the vast majority of preterm births.[23] Potential explanations for an effect of preterm birth on ADHD include brain injury from episodes of hypoxia and hypotension,[7] which are common among children born preterm, as well as brain underdevelopment[6,24] and hypothalamic–pituitary–adrenal axis dysregulation.[5] Future research is warranted to investigate other events in the etiologic chain between spontaneous or medically indicated preterm birth and ADHD, including infection, cervical insufficiency, asphyxia, and diabetes, among others.

Few studies have considered a combined diagnosis of ADHD with autism in relation to perinatal exposures, even though the disorders commonly co-occur and may share etiologies.[25] Sixteen percent of children with ADHD were also diagnosed with autism in our study, similar to other populations (12-13%).[26] We found that the HR of the associations of preterm birth and SGA with ADHD with autism were higher than those for ADHD alone. Some investigators have posited that a combined diagnosis of ADHD with autism may be a clinically distinct group.[27] This may be supported by the different strengths of associations in our study. However, since autism may be more strongly associated with preterm birth than ADHD,[9] another possible explanation is that the autism diagnosis is driving the higher HR we found for ADHD with autism compared with ADHD alone.

This study has several strengths. First, ADHD ICD-10 codes in the Patient Register have been validated. A Swedish register-based study of 20,000 twins found that about 70% of twins diagnosed with ADHD through ICD diagnoses or prescriptions of ADHD medication also screened positive for ADHD by their parents. In addition, the mean ADHD score from the Autism-Tics, ADHD, and Other Comorbidities Inventory was substantially higher among the twins with register-based diagnoses of ADHD than in the total sample.[28] In addition, the possibility of selection bias is minimized by the population-based design with over 1.2 million children linked through nationwide registries. Confounding by access to care and socioeconomic factors should be limited by the existence of universal, standardized healthcare in Sweden and the relative sociodemographic homogeneity of the Swedish population. The validity of exposure variables from the Swedish Birth Register is excellent;[13] and data was virtually complete for gestational age at birth and birth weight-for-gestational age. Finally, examining the associations of preterm birth, SGA, and obstetric complications with neurodevelopmental outcomes among siblings offers an opportunity to enhance causal inference by controlling for time-invariant shared confounding factors. Full siblings share up to one-half of autosomal DNA; thus, confounding by unmeasured genetic characteristics is less likely in studies comparing siblings with each other than in comparisons of unrelated children. Full sibling comparisons also control for environmental factors shared by siblings, and for genetic and all other time-invariant characteristics of the parents.

There are also some limitations. First, the relative sociodemographic homogeneity of the Swedish population may limit the generalizability of the study findings to populations with different sociodemographic structures. Second, the occurrence of ADHD in our cohort is relatively low. This is likely because the definition of ADHD required a prescription for medication, which we chose to include to increase the specificity of the diagnosis. Medication is recommended for individuals with severe ADHD or those who fail to respond to non-pharmacological therapy, per standard of care in Sweden. Therefore, the cases identified with this requirement may be relatively more severe. Third, although sibling-controlled analyses enhance adjustment for confounders shared within families, they can produce biased estimates when non-shared confounders differ more among siblings than the exposure does,[29] even when adjustment is performed.[30] Random measurement error in exposure[29] and inherent adjustment for potential mediators shared within families[31] could spuriously attenuate the sibling–controlled estimates. This approach also assumes that the exposure or outcome status of one child does not affect the exposure or outcome of a sibling.[32] Last, the sibling cohort differed from the general cohort on outcome and exposure distributions, which could lead to selection bias. Notwithstanding the limitations of sibling analyses, the consistency of results across different approaches in this study make them unlikely to explain the patterns observed. Third, we implemented causal mediation analyses to estimate the effect of prenatal exposures on ADHD independent of preterm birth. These analyses rely on assumptions that may not be consistently met; including lack of unmeasured confounding of the exposure-outcome, exposure-mediator, and mediator-outcome associations, and lack of effect of exposure on mediator-outcome common causes. Sensitivity analyses suggested that the estimated direct effect of preeclampsia on ADHD independent of preterm birth or SGA could be sensitive to unmeasured confounding of the mediator-outcome association (**Methodological Supplement** in **Supplemental Online Material**), and could be weaker than the unconfounded effect.

CONCLUSION

Preterm birth, SGA, and preeclampsia, but not placental abruption, were each associated with increased rates of ADHD in the offspring in both cohort and sibling-controlled analyses. These data also support the view that SGA and preeclampsia influence the risk of ADHD in the offspring independent of preterm birth. We found that associations with preterm birth and SGA had higher HR for ADHD comorbid with autism compared with ADHD without autism.

AUTHOR CONTRIBUTIONS

Drs Villamor and Cnattingius had full access to all of the data in the study and take full responsibility for the integrity of the data and the accuracy of the data analyses.

Concept and design: Villamor, Beer, Cnattingius, Susser.

Acquisition of data: Cnattingius.

Drafting of the manuscript: Beer.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Beer.

Obtained funding: Villamor, Cnattingius.

Administrative, technical, or material support: Cnattingius, Villamor.

Study supervision: Villamor, Susser, Cnattingius.

Conflict of Interest Disclosures

All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. None of the authors has conflicts of interest to disclose.

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ABBREVIATIONS

ADHD: Attention-deficit/hyperactivity disorder

BMI: Body mass index

CI: Confidence interval

HR: Hazard ratio

ICD: International Classification of Diseases

ICD-10: International Classification of Diseases, tenth revision

IQR: Interquartile range

IPW: Inverse probability weighting

SGA: Small-for-gestational age

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Table 1. Incidence of attention-deficit/hyperactivity disorder (ADHD) starting at 3 years of age according to gestational age, birth weight for gestational age, and obstetric complications. Live-born singleton non-malformed children in Sweden 2002-2014.

Perinatal and obstetric characteristics	General cohort			Sibling cohort		
	Number of children	No. with ADHD	Rate per 10,000 child-years	Number of children	No. with ADHD	Rate per 10,000 child-years
Total	1,212,201	27,665	25.57	751,464	15,138	22.36
Gestational age at birth (weeks)						
Post-term (≥42)	85,830	1967	25.28	50,528	1098	23.13
Term (37 to 41)	1,071,729	23,941	25.07	670,235	13,134	21.85
Moderately preterm (32 to 36)	47,859	1422	32.87	27,295	755	29.70
Very preterm (28 to 31)	4529	204	49.63	2289	97	45.16
Extremely preterm (22 to 27)	1776	110	70.32	843	45	58.42
Missing	478	21		274	9	
Type of preterm birth						
Term	1,157,559	25,908	25.09	720,763	14,232	21.95
Moderately preterm spontaneous	35,134	980	30.75	20,649	528	27.20
Very/extremely preterm spontaneous	3717	170	51.10	1925	82	46.04
Moderately preterm medically indicated	12,254	415	38.08	6405	217	37.66
Very/extremely preterm medically indicated	2424	132	60.58	1126	57	53.99
Missing	1113	60		596	22	
Birth weight for gestational age, Percentiles						
<3	17,288	656	42.74	8860	308	36.79
3 to <10	56,698	1509	30.19	31,671	802	27.10
10 to 90	989,874	21,897	24.82	615,444	12,072	21.72
>90 to 97	102,131	2324	25.19	66,124	1288	22.28

Perinatal and obstetric characteristics	General cohort			Sibling cohort		
	Number of children	No. with ADHD	Rate per 10,000 child-years	Number of children	No. with ADHD	Rate per 10,000 child-years
>97	43,451	1182	29.97	27,785	622	25.93
Missing	2759	97		1580	46	
Small-for-gestational age (SGA)[a] by gestational age						
No SGA	1,192,154	26,912	25.29	741,024	14,784	22.16
SGA at ≥37 weeks	13,485	480	40.21	7078	229	34.21
SGA at 34 to 36 weeks	1871	74	44.39	908	34	40.27
SGA at <34 weeks	1932	102	58.46	874	45	53.97
Missing	2759	97		1580	46	
Preeclampsia						
No	1,179,773	26,690	25.34	734,214	14,614	22.12
Yes	32,428	975	33.73	17,250	524	31.88
Preeclampsia by gestational age						
No preeclampsia	1,179,773	26,690	25.34	734,214	14,614	22.12
Preeclampsia at ≥37 weeks	25,741	709	31.02	13,942	396	29.86
Preeclampsia at 34 to 36 weeks	4136	147	39.50	2150	71	34.62
Preeclampsia at <34 weeks	2537	119	51.51	1151	57	51.10
Missing	14	0		7	0	
Placental abruption						
No	1,208,375	27,540	25.53	749,288	15,072	22.32
Yes	3826	125	35.91	2176	66	33.35

[a] Birth weight-for-gestational age percentile <3.

Table 2. Hazard ratios for attention-deficit/hyperactivity disorder (ADHD) starting at 3 years of age according to gestational age and birth weight for gestational age in general and sibling cohorts. Live-born singleton non-malformed children in Sweden 2002-2014.

Perinatal characteristics	General Cohort[a]	Sibling Cohort[b]		
		Unstratified analysis	Sibling comparison	
	Adjusted hazard ratio (95% CI)[c,d]	Adjusted hazard ratio (95% CI)[c, e]	Adjusted hazard ratio (95% CI)[f]	IPW-adjusted hazard ratio (95% CI)[g]
Gestational age at birth (weeks)				
Term (≥37)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Moderately preterm (32 to 36)	1.18 (1.11, 1.25)	1.23 (1.13, 1.34)	1.08 (0.91, 1.29)	1.12 (0.95, 1.32)
Very preterm (28 to 31)	1.61 (1.37, 1.89)	1.69 (1.32, 2.17)	2.47 (1.45, 4.20)	1.98 (1.19, 3.29)
Extremely preterm (22 to 27)	2.79 (2.23, 3.49)	2.66 (1.86, 3.82)	8.60 (3.02, 24.47)	5.63 (1.93, 16.5)
P, trend[h]	<0.0001	<0.0001	<0.0001	0.0005
Type of preterm birth				
Term	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Moderately preterm spontaneous	1.11 (1.03, 1.19)	1.13 (1.02, 1.25)	1.06 (0.86, 1.31)	1.06 (0.87, 1.28)
Very/extremely preterm spontaneous	1.84 (1.55, 2.20)	2.04 (1.58, 2.63)	4.08 (2.18, 7.62)	2.90 (1.63, 5.15)
Moderately preterm medically indicated	1.36 (1.22, 1.52)	1.61 (1.38, 1.88)	1.20 (0.88, 1.65)	1.38 (1.01, 1.88)
Very/extremely preterm medically indicated	1.99 (1.62, 2.45)	1.88 (1.33, 2.66)	2.61 (1.22, 5.57)	1.55 (0.70, 3.46)
P[i]	<0.0001	<0.0001	<0.0001	0.001
Birth weight for gestational age, percentiles				
<3	1.62 (1.49, 1.77)	1.56 (1.37, 1.77)	1.74 (1.29, 2.34)	1.53 (1.16, 2.00)
3 to <10	1.18 (1.11, 1.25)	1.23 (1.13, 1.34)	1.26 (1.06, 1.51)	1.22 (1.03, 1.43)
10 to 90	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
>90 to 97	0.95 (0.90, 1.00)	0.96 (0.90, 1.03)	0.84 (0.73, 0.96)	0.87 (0.76, 0.99)
>97	1.02 (0.96, 1.09)	1.03 (0.94, 1.13)	0.86 (0.70, 1.05)	0.82 (0.67, 1.01)
P, trend	<0.0001	<0.0001	<0.0001	<0.0001

SGA[j] by gestational age				
No SGA	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
SGA at ≥37 weeks	1.54 (1.40, 1.70)	1.44 (1.24, 1.67)	1.59 (1.14, 2.21)	1.37 (0.99, 1.89)
SGA at 34 to 36 weeks	1.61 (1.24, 2.09)	1.79 (1.24, 2.58)	1.81 (0.77, 4.27)	1.60 (0.72, 3.55)
SGA at <34 weeks	2.04 (1.63, 2.56)	2.08 (1.47, 2.95)	1.88 (0.83, 4.28)	1.80 (0.83, 3.93)
P	<0.0001	<0.0001	0.01	0.08

[a] The cohort comprises 1,212,201 children with 27,665 cases of ADHD.

[b] The cohort comprises 751,464 full siblings distributed in 344,649 families. There were 15,138 cases of ADHD.

[c] From proportional hazards models with age at first diagnosis of ADHD as the outcome and each perinatal characteristic as the exposure. Models were adjusted for maternal age, country of origin, cohabitation with the child's parent, education level, parity, height, early-pregnancy body mass index, smoking during pregnancy, presence of a diagnosis of ADHD in the mother or the father, and child sex and year of birth. A robust estimate of the variance was specified in all models to account for siblings.

[d] Complete case analysis; n = 1,088,424 with 23,862 cases of ADHD.

[e] Complete case analysis; n = 633,319 with 12,113 cases of ADHD.

[f] From proportional hazards models with age at first diagnosis of ADHD as the outcome, stratified by family. Models were adjusted for birth order, early-pregnancy body mass index, smoking during pregnancy, and child sex. Complete case analyses; n = 646,289 with 12,331 cases of ADHD.

[g] Inverse probability weighting. Estimates are from weighted proportional hazards models. Stabilized weights were computed as the product of the inverse of exposure probability given the covariates in footnote 3 times the inverse of the probability of inclusion into the sibling cohort given covariates.

[h] Wald χ^2 test for a variable representing exposure categories introduced into the model as a continuous covariate.

[i] Wald χ^2 test.

[j] Birth weight-for-gestational age percentile <3.

Table 3. Hazard ratios for attention-deficit/hyperactivity disorder (ADHD) starting at 3 years of age according to obstetric complications in general and sibling cohorts. Live-born singleton non-malformed children in Sweden 2002-2014.

	General Cohort[a]	**Sibling Cohort[b]**	
Obstetric complication		**Unstratified analysis**	**Sibling comparison**

	Adjusted hazard ratio (95% CI)[c, d]	Adjusted hazard ratio (95% CI)[c, e]	Adjusted hazard ratio (95% CI)[f]	IPW-adjusted hazard ratio (95% CI)[g]
Preeclampsia				
No	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Yes	1.17 (1.09, 1.25)	1.20 (1.08, 1.33)	1.24 (0.97, 1.58)	1.20 (0.94, 1.52)
P[h]	<0.0001	0.0005	0.09	0.15
Preeclampsia by gestational age				
No preeclampsia	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Preeclampsia at ≥37 weeks	1.06 (0.97, 1.15)	1.09 (0.97, 1.22)	1.18 (0.91, 1.54)	1.15 (0.88, 1.49)
Preeclampsia at 34 to 36 weeks	1.50 (1.25, 1.79)	1.57 (1.22, 2.02)	1.26 (0.73, 2.19)	1.25 (0.75, 2.07)
Preeclampsia at <34 weeks	1.77 (1.44, 2.17)	2.02 (1.48, 2.76)	1.81 (0.89, 3.71)	1.52 (0.74, 3.14)
P	<0.0001	<0.0001	0.24	0.48
Placental abruption				
No	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Yes	1.19 (0.96, 1.46)	1.40 (1.06, 1.86)	1.48 (0.80, 2.73)	1.44 (0.81, 2.56)
P	0.11	0.02	0.21	0.21

[a] The cohort comprises 1,212,201 children with 27,665 cases of ADHD.

[b] The cohort comprises 751,464 full siblings distributed in 344,649 families. There were 15,138 cases of ADHD.

[c] From proportional hazards models with age at first diagnosis of ADHD as the outcome and each obstetric complication as the exposure. Models were adjusted for maternal age, country of origin, cohabitation with the child's parent, education level, parity, height, early-pregnancy body mass index, smoking during pregnancy, presence of a diagnosis of ADHD in the mother or the father, and child sex and year of birth. A robust estimate of the variance was specified in all models to account for siblings.

[d] Complete case analysis; n = 1,088,575 with 23,866 cases of ADHD.

[e] Complete case analysis; n = 633,464 with 12,116 cases of ADHD.

[f] From proportional hazards models with age at first diagnosis of ADHD as the outcome, stratified by family. Models were adjusted for birth order, early-pregnancy body mass index, smoking during pregnancy, and child sex. Complete case analyses; n = 646,452 with 12,336 cases of ADHD.

[g] Inverse probability weighting. Estimates are from weighted proportional hazards models. Stabilized weights were computed as the product of the inverse of exposure probability given the covariates in footnote 3 times the inverse of the probability of inclusion into the sibling cohort given covariates.

[h] Wald χ^2 test.

Table 4. Proportion of the associations of small-for-gestational age (SGA) and preeclampsia with attention-deficit/hyperactivity disorder (ADHD) that is not mediated through preterm birth (gestational age at birth <37 weeks)

Complication	Hazard ratio (95% CI)a			% not mediated through preterm birth	*P* complication x preterm birth interaction
	Total	Indirect through preterm birth	Direct or indirect not through preterm birth		
SGA	1.57 (1.44, 1.70)	1.02 (1.01, 1.03)	1.54 (1.41, 1.67)	95	0.59
Preeclampsia	1.16 (1.08, 1.24)	1.07 (1.04, 1.10)	1.08 (1.00, 1.17)	52	0.007

[a] From proportional hazards models with age at first diagnosis of ADHD as the outcome adjusted for maternal age, country of origin, cohabitation with the child's parent, education level, parity, height, early-pregnancy body mass index, smoking during pregnancy, presence of a diagnosis of ADHD in the mother or the father, and child sex and year of birth. The model for SGA was additionally adjusted for preeclampsia, placental abruption, and pre-gestational or gestational diabetes. The association between each complication and preterm birth was modelled with use of logistic regression.