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

Rachael J. Beer1 | Sven Cnattingius2 | Ezra S. Susser3 | Eduardo Villamor1

1Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor, Michigan, USA
2Division of Clinical Epidemiology, Department of Medicine (Söder), Karolinska Institutet, Stockholm, Sweden
3Department of Epidemiology, Mailman School of Public Health, Columbia University, and New York State Psychiatric Institute, New York, New York, USA

Correspondence
Eduardo Villamor, Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor, MI, United States.
Email: villamor@umich.edu

Funding information
The study was supported by the National Institutes of Health (R21MH120824), the Swedish Research Council for Health, Working Life and Welfare (2014-0073 and 2017-00134), and the Karolinska Institutet (Unrestricted Distinguished Professor Award 2368/10-221 to SC).

Role of the Funder/Sponsor:
The funding organisations for this study had no involvement in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; or the decision to submit the manuscript for publication.

Abstract
Aim: The aim of this study was 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 during 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 32–36 weeks, 28–31 weeks and 22–27 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, foetal growth restriction, placental abruption, preeclampsia, preterm birth

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; IPW, inverse probability weighting; IQR, interquartile range; SGA, small-for-gestational age.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made. © 2022 The Authors. Acta Paediatrica published by John Wiley & Sons Ltd on behalf of Foundation Acta Paediatrica.
1 | BACKGROUND

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

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; risk increases in a dose-response manner with decreasing gestational age. Foetal growth restriction (small-for-gestational age [SGA] birth size) is also associated with ADHD risk. 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, 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 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 aetiology.

2 | METHODS

2.1 | 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 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.

2.2 | 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), dexamfetamine (N06BA02), methylphenidate (N06BA04) or atomoxetine (N06BA09). Because the Prescribed Drugs Register became available in July 2005, we included births from July 2002 to 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.

2.3 | 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 (37–41 weeks), moderately preterm (32–36 weeks), very preterm...
(28–31 weeks) or extremely preterm (22–27 weeks). Preterm birth was further classified as spontaneous or medically indicated (i.e. induced). Spontaneous preterm birth was defined as labour with spontaneous onset, and medically indicated preterm birth was defined as induced labour or a caesarean section before onset of labour, 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 foetal growth, and SGA was defined as a birth weight for gestational age <3rd percentile. SGA was further classified by gestational age: ≥37 weeks, 34–36 weeks or <34 weeks. Secondary exposures were preeclampsia and placental abruption. Preeclampsia was further classified as term (≥37 weeks) or preterm (34–36 or <34 weeks). Information on obstetric complications was obtained from the Birth Register according to ICD-10 codes presented in Table S1.

2.4 | Covariates

Covariate information was primarily extracted not only 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 categorised 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/m²) 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%. 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. Parental ADHD was defined as codes ICD-9 314 or ICD-10 F90.

2.5 | Statistical analysis

2.5.1 | General cohort analyses

The general cohort comprised children born between July 2002 and December 2014. Children were followed starting at age 3 years until a first diagnosis or drug prescription for ADHD, emigration, death, or December 31, 2017, whichever came first.

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 the 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 (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.

2.5.2 | Sibling cohort analyses

We identified full siblings in the general cohort with the use of the Multi-generation 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 favourable 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 stabilised 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 the use of SAS version 9.4 (SAS Institute).

### 3 | RESULTS

From July 2002 to 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 pre-eclampsia. 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 (28–31 weeks) and extremely (22–27 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 (32–36 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). Risks 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 per cent 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).

### 4 | 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 or SGA 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, 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 or other indirect effects through different mediators such as neurological injury, structural brain changes, inflammation, oxidative...
### 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 (37–41)                           | 1,071,729 | 23,941 | 25.07 | 670,235 | 13,134 | 21.85 |
| Moderately preterm (32–36)            | 47,859 | 1422 | 32.87 | 27,295 | 755 | 29.70 |
| Very preterm (28–31)                  | 4529 | 204 | 49.63 | 2289 | 97 | 45.16 |
| Extremely preterm (22–27)             | 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–<10                                  | 56,698 | 1509 | 30.19 | 31,671 | 802 | 27.10 |
| 10–90                                  | 989,874 | 21,897 | 24.82 | 615,444 | 12,072 | 21.72 |
| >90–97                                 | 102,131 | 2324 | 25.19 | 66,124 | 1288 | 22.28 |
| >97                                    | 43,451 | 1182 | 29.97 | 27,785 | 622 | 25.93 |
| Missing                                | 2759 | 97 | 1580 | 46 |
| Small-for-gestational age (SGA) by gestational age |               |               |       |               |               |       |
| No SGA                                 | 1,192,154 | 26,912 | 25.29 | 741,024 | 14,412 | 22.16 |
| SGA at ≥37 weeks                       | 13,485 | 480 | 40.21 | 7078 | 229 | 34.21 |
| SGA at 34–36 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 34–36 weeks            | 4136 | 147 | 39.50 | 2150 | 71 | 34.62 |
| Preeclampsia at <34 weeks              | 2537 | 119 | 51.51 | 1151 | 57 | 51.10 |
stress and placental ischaemia. Further research could help elucidate these potential pathways. Placental abruption was not associated with ADHD in a study in the United States, 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. Because these comparisons are matched by gestational age, the findings suggest a causal effect of foetal growth on ADHD, which could be due to differential flow of nutrients or oxygen to the foetuses. 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 foetal health due to prenatal conditions such as preeclampsia, gestational diabetes, foetal 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.

Potential explanations for an effect of preterm birth on ADHD include brain injury from episodes of hypoxia and hypotension, which are common among children born preterm, as well as brain underdevelopment and hypothalamic-pituitary-adrenal axis dysregulation. Future research is warranted to investigate other events in the aetiological chain between spontaneous or medically indicated preterm birth and ADHD, including infection, cerebral 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. Sixteen per cent of children with ADHD were also diagnosed with autism in our study, similar to other populations (12%-13%). 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. 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, 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. In addition, the possibility of selection bias is minimised 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, standardised health care in Sweden and the relative sociodemographic homogeneity of the Swedish population. The validity of exposure variables from the Swedish Birth Register is excellent, and data were 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 generalisability 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

---

**TABLE 1 (Continued)**

| 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 |
| 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                    |

*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 | Sibling Cohort | Sibling comparison | IPW-adjusted hazard ratio (95% CI) |
|---------------------------|----------------|----------------|-------------------|-----------------------------------|
|                            | Adjusted hazard ratio (95% CI) | Adjusted hazard ratio (95% CI) | Adjusted hazard ratio (95% CI) | Adjusted hazard ratio (95% CI) |
| **Gestational age at birth (weeks)** | | | | |
| Term (≥37) | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| Moderately preterm (32–36) | 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 (28–31) | 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 (22–27) | 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<sup>h</sup> | <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<sup>i</sup> | <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) |
| 10–90 | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| >90–97 | 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<sup>j</sup> 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 34–36 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 |

<sup>a</sup>The cohort comprises 1,212,201 children with 27,665 cases of ADHD.

<sup>b</sup>The cohort comprises 751,464 full siblings distributed in 344,649 families. There were 15,138 cases of ADHD.

<sup>c</sup>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.

<sup>d</sup>Complete case analysis; n = 1,088,424 with 23,862 cases of ADHD.

<sup>e</sup>Complete case analysis; n = 633,319 with 12,113 cases of ADHD.

<sup>f</sup>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.

<sup>g</sup>Inverse probability weighting. Estimates are from weighted proportional hazards models. Stabilised 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.

<sup>h</sup>Wald chi-square test for a variable representing exposure categories introduced into the model as a continuous covariate.

<sup>i</sup>Wald chi-square test.

<sup>j</sup>Birth weight for gestational age percentile <3.
| Obstetric complication | General Cohort\(^a\) | Sibling Cohort\(^b\) | Sibling comparison | IPW-adjusted hazard ratio (95% CI)\(^g\) |
|------------------------|-----------------------|-----------------------|--------------------|------------------------------------------|
|                        | Adjusted hazard ratio (95% CI)\(^c,d\) | Adjusted hazard ratio (95% CI)\(^c,d\) | Adjusted hazard ratio (95% CI)\(^c,d\) | Adjusted hazard ratio (95% CI)\(^c,d\) |
| Preeclampsia           |                       |                       |                    |                                          |
| No                     | 1.00 (Reference)      | 1.00 (Reference)      | 1.00 (Reference)   | 1.00 (Reference)                        |
| Yes                    | 1.17 (1.09, 1.25)     | 1.19 (1.06, 1.33)     | 1.24 (0.97, 1.58)  | 1.20 (0.94, 1.52)                       |
| \(p\)                  | <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)   | 1.19 (0.97, 1.22)     | 1.18 (0.91, 1.54)  | 1.15 (0.88, 1.49)                       |
| Preeclampsia at 34–36 weeks | 1.50 (1.25, 1.79)  | 1.97 (1.72, 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. Stabilised 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 chi-square 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   | % Not mediated through preterm birth | \(p\) complication x preterm birth interaction |
| 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 the use of logistic regression.
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, even when adjustment is performed. Random measurement error in exposure and inherent adjustment for potential mediators shared within families 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. 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 makes 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.

5 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.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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, obtained funding, and contributed to administrative, technical or material support. Villamor, Beer, Cnattingius and Susser contributed to the concept and design. Cnattingius acquired the data. Beer drafted the manuscript and contributed to the statistical analysis. All authors critically revised the manuscript for important intellectual content. Villamor, Susser and Cnattingius supervised the study.

ORCID

Rachael J. Beer https://orcid.org/0000-0002-2940-7467
Eduardo Villamor https://orcid.org/0000-0003-3937-5574

REFERENCES

1. Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and meta-regression analysis. Am J Psychiatry. 2007;164:942-948.
2. Lara C, Fayyad J, de Graaf R, et al. Childhood predictors of adult attention-deficit/hyperactivity disorder: results from the world health organization world mental health survey initiative. Biol Psychi at. 2009;65(1):46-54.
3. Shaw M, Hodgkins P, Caci H, et al. A systematic review and analysis of long-term outcomes in attention deficit hyperactivity disorder: effects of treatment and non-treatment. BMC Med. 2012;10:99.
4. Faraone SV, Asherson P, Banaschewski T, et al. Attention-deficit/hyperactivity disorder. Nature Reviews Disease Primers. 2015;1:15020.
5. Franz AP, Bolat BU, Bolat H, et al. Attention-deficit/hyperactivity disorder and very preterm/very low birth weight: a meta-analysis. Pediatrics. 2018;141(1):e20171645.
6. Sucksdorff M, Lehtonen L, Chudal R, et al. Preterm birth and poor fetal growth as risk factors of attention-deficit/hyperactivity disorder. Pediatrics. 2015;136(3):e599-608.
7. Linnet KM, Wisborg K, Agerbo E, Secher NJ, Thomsen PH, Henriksen TB. Gestational age, birth weight, and the risk of hyperkinetic disorder. Arch Dis Child. 2006;91(8):655-660.
8. Halmøy A, Klungsøyr K, Skjærven R, Haavik J. Pre- and perinatal ischemic-hypoxic conditions and attention-deficit/hyperactivity disorder. JAMA. 2013;309(22):2362-2370.
9. VanderWeele TJ, Ding P. Sensitivity analysis in observational studies: introducing the E-value. Ann Intern Med. 2017;167(4):268-274.
18. Lindström K, Lindblad F, Hjern A. Preterm birth and attention-deficit/hyperactivity disorder in schoolchildren. Pediatrics. 2011;127(5):858-865.
19. Gumusoglu SB, Chilukuri AS, Santillan DA, Santillan MK, Stevens HE. Neurodevelopmental outcomes of prenatal preeclampsia exposure. Trends Neurosci. 2020;43(4):253-268.
20. Pettersson E, Sjolander A, Almqvist C, et al. Birth weight as an independent predictor of ADHD symptoms: a within-twin pair analysis. J Child Psychol Psychiatry. 2015;56(4):453-459.
21. Hultman CM, Torráng A, Tuvblad C, Cnattingius S, Larsson JO, Lichtenstein P. Birth weight and attention-deficit/hyperactivity symptoms in childhood and early adolescence: a prospective Swedish twin study. J Am Acad Child Adolesc Psychiatry. 2007;46(3):370-377.
22. Lehn H, Derks EM, Hudziak JJ, Heutink P, van Beijsterveldt TCEM, Boomsma DI. Attention problems and attention-deficit/hyperactivity disorder in discordant and concordant monozygotic twins: evidence of environmental mediators. J Am Acad Child Adolesc Psychiatry. 2007;46(1):83-91.
23. Blencowe H, Cousens S, Oestergaard MZ, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. The Lancet. 2012;379(9832):2162-2172.
24. Ment LR, Hertz D, Hüppi PS, Hüppi PS. Imaging biomarkers of outcome in the developing preterm brain. Lancet Neurol. 2009;8(11):1042-1055.
25. Antshel KM, Zhang-James Y, Wagner KE, Ledesma A, Faraone SV. An update on the comorbidity of ADHD and ASD: a focus on clinical management. Expert Rev Neurother. 2016;16(3):279-293.
26. Zablotsky B, Bramlett MD, Blumberg SJ. The co-occurrence of autism spectrum disorder in children with ADHD. J Atten Disord. 2020;24(1):94-103.
27. Gargaro BA, Rinehart NJ, Bradshaw JL, Tonge BJ, Sheppard DM. Autism and ADHD: how far have we come in the comorbidity debate? Neurosci Biobehav Rev. 2011;35(5):1081-1088.
28. Larsson H, Rydén E, Boman M, Långström N, Lichtenstein P, Landén M. Risk of bipolar disorder and schizophrenia in relatives of people with attention-deficit hyperactivity disorder. British J Psychiatry. 2013;203(2):103-106.
29. Frisell T, Oberg S, Kuja-Halkola R, Sjolander A. Sibling comparison designs: bias from non-shared confounders and measurement error. Epidemiology. 2012;23(5):713-720.
30. Saunders GRB, McGue M, Malone SM. Sibling comparison designs: addressing confounding bias with inclusion of measured confounders. Twin Res Hum Genet. 2019;22(5):290-296.
31. Sjolander A, Zetterqvist J. Confounders, mediators, or colliders: what types of shared covariates does a sibling comparison design control for? Epidemiology. 2017;28(4):540-547.
32. Sjolander A, Frisell T, Kuja-Halkola R, Oberg S, Zetterqvist J. Carryover effects in sibling comparison designs. Epidemiology. 2016;27(6):852-858.

SUPPORTING INFORMATION
Additional supporting information may be found in the online version of the article at the publisher’s website.

How to cite this article: Beer RJ, Cnattingius S, Susser ES, Villamor E. 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. Acta Paediatr. 2022;111:1546–1555. doi:10.1111/apa.16375