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Defective placantation syndromes and Autism Spectrum Disorder in the offspring: Population-based cohort and sibling-controlled studies

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Abstract

Defective placentation underlies diverse syndromic manifestations that could affect brain development including: 1) placental abruption, 2) term preeclampsia with a small-for-gestational age (SGA) infant, 3) preterm preeclampsia, and 4) spontaneous preterm birth. We investigated the relations between these defective placentation syndromes and the incidence of Autism Spectrum Disorder (ASD) in offspring. We conducted a population-based cohort study of 1,645,455 non-malformed singleton infants born in Sweden 2000–2016 who were followed for up to 17 years using national registers. We compared ASD rates for children prenatally exposed and unexposed to defective placentation syndromes with use of adjusted hazard ratios (HR) with 95% confidence intervals (CI) from Cox regression. We also conducted sibling-controlled analyses among 1,092,132 full siblings. The association of the syndromes with ASD independent of preterm birth was estimated in mediation analyses. There were 23,810 cases of ASD. In both general cohort and sibling analyses, adjusted HRs (95% CI) of ASD were increased in children of mothers with term preeclampsia combined with SGA (1.5 [1.3, 1.9] and 1.9 [1.1, 3.3], respectively), preterm preeclampsia <34 weeks (1.8 [1.4, 2.2] and 4.2 [2.1, 8.5], respectively), and spontaneous very or extremely preterm birth (≤31 weeks) (2.6 [2.2, 3.0] and 2.4 [1.5, 3.8], respectively). Placental abruption was associated with increased HR of ASD in general cohort analysis only. The association between preeclampsia and ASD was not fully explained by preterm

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Author contributions

All authors contributed to the study conception and design. Eduardo Villamor performed the analyses and wrote the first draft of the manuscript. Sven Cnattingius obtained the data. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors have no relevant financial or non-financial interests to disclose submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. None of the authors has conflicts of interest to disclose.

Ethics approval and consent to participate

This study was approved by the Regional Ethical Review Board in Stockholm, Sweden (No. 2018/5:2). In accordance with their decision, data linkage was allowed without informed consent from participants involved in the study. All individuals' information was anonymized and de-identified prior to analysis.

birth. In conclusion, syndromes linked to defective placentation are associated with increased incidence of ASD in the offspring.

Keywords

autism spectrum disorder; defective placentation; placental abruption; preeclampsia; preterm birth; small-for-gestational age

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition characterized by impaired social interactions and stereotypic, repetitive behaviors that affects up to 2% of children worldwide [1]. The etiology of ASD has a strong genetic component, including polygenic and rare heritable variants as well as de novo mutations in the offspring [2], which interact with the environment in complex ways [3].

Among environmental factors that have been related to ASD there are intrauterine and perinatal exposures. A monotonic inverse relation between gestational age at birth and ASD has been established [4] and some of the obstetric causes of preterm birth, including preeclampsia [5, 6] and small-for-gestational age (SGA) size at birth [7, 8] have also been related to ASD. These conditions may share a common etiology in defective placentation [9]. Normal placentation requires the exchange of cells in uterine spiral arteries with fetal trophoblast during early pregnancy, to secure an appropriate transfer of nutrients and oxygen to the fetus. Thus, defective placentation may result in hypoxemia, inflammation, undernutrition, and endocrine dysregulation, which could impair normal brain development [10] and increase risks of postnatal neurodevelopmental disorders, including ASD.

The characterization of defective placentation would require pathological examination of biopsy specimens, ultrasound techniques, or otherwise invasive procedures that are unwarranted or implausible in large epidemiologic studies. However, the role of placentation on the etiology of offspring's neurodevelopmental disorders, such as ASD, could be interrogated by studying the associations of these outcomes with perinatal syndromes that could be manifestations of defective placentation. Small-scale studies of placental histopathology, imaging, or perfusion indicate that defective placentation may be a contributing cause to placental abruption [11], early preeclampsia [12–15], and spontaneous preterm birth [16–18]. Population-based epidemiologic studies also support such a common defective placentation etiology. For example, placental abruption in first pregnancy is associated with preterm preeclampsia [19] or preterm delivery [20] in a subsequent pregnancy. In addition, late preeclampsia with a concurrent small-for-gestational age (SGA) infant predict early preeclampsia in the next pregnancy [21].

We conducted a nation-wide Swedish cohort study of ASD in relation to four syndromes whose origin has been linked in part to defective placentation: placental abruption, term preeclampsia with SGA, preterm preeclampsia, and spontaneous preterm birth. We hypothesized that each of these syndromes would be related to increased incidence of ASD. To account for potential confounding by familial (shared genetic and environmental) factors, we performed nested sibling-controlled comparisons. Finally, we considered ASD with and without comorbid neurodevelopmental disorders such as intellectual disability, attention-

deficit/hyperactivity disorder (ADHD), and epilepsy. Although some of the syndromes linked to defective placentation have been previously explored in isolation [22], no previous investigation has considered them together. Finding consistency in the associations between different syndromes of common origin and ASD in the same population would strengthen an argument for causation.

METHODS

Study design

We conducted a population-based retrospective cohort study among live singleton infants born at ≥22 completed gestational weeks who were recorded in the Swedish Medical Birth Register from 2000 through 2016. Information in the nation-wide Swedish Medical Birth Register [23] was cross-linked with other nation-wide registers kept by the National Board of Health and Welfare and Statistics Sweden: the National Patient- [24], Prescribed Drugs-, Total Population- [25], Education- [26], and Multi-generation [27] Registers. These linkages were performed using the person-unique national registration number that is assigned to all Sweden residents at birth or immigration [28]. The Birth Register includes information on prenatal, obstetric, and neonatal care on more than 98% of all births in Sweden. The National Patient Register includes discharge dates and diagnoses 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.

Outcome

ASD was defined among children born between 2000 and 2016 without congenital malformations as the presence of one or more ICD-10 diagnostic code F84 in the National Patient Register after 1 year of age. We included diagnoses that had been recorded either as the main reason for the visit or as an incidental diagnosis noted at a visit for a different reason. In supplemental analyses, we considered ASD with and without neurodevelopmental comorbidities, including intellectual disability, ADHD, and epilepsy. ICD-10 codes for all paediatric diagnoses used are presented in Supplementary Table 1.

Exposures

We considered four syndromes representing defective placentation: placental abruption, term preeclampsia with SGA, preterm preeclampsia, and spontaneous preterm birth. Exposure information was obtained from the Birth Register according to ICD-10 codes presented in Supplementary Table 1. Information on gestational age was obtained by early second trimester ultrasound, date of the last menstrual period, or a postnatal assessment in 90.0%, 5.6%, and 4.4%, respectively. Births were classified as term (≥37 completed weeks), moderately preterm (32 to 36 weeks), very preterm (28 to 31 weeks), or extremely preterm (22 to 27 weeks). Birthweight-for-gestational age was defined using the ultrasound-based Swedish reference for fetal growth [29], and SGA was defined as a birth weight for

gestational age <10th percentile. Placental abruption and preeclampsia were ICD-10 codes O45 and O14-O15, respectively. Preeclampsia was classified as term (≥37 weeks) without or with SGA, or preterm (34 to 36 weeks or <34 weeks). The type of preterm birth was classified as spontaneous or medically indicated, as recorded in the Birth Register.

Covariates

Covariate information was primarily extracted from the Birth, Total Population, and Education Registers. Maternal age at delivery (years) was the date of delivery minus the mother's birth date. Mothers' country of birth was categorized as Nordic (Sweden, Norway, Denmark, Finland, or Iceland) vs. non-Nordic (all other countries). Maternal education was defined as the highest level of schooling achieved. Information on whether or not the mother cohabited with the child's father, a socioeconomic indicator, was obtained at the first prenatal visit. Parity was characterized as 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 random error [30]. Early pregnancy body mass index (BMI, kg/m^2) was calculated from height and weight measured in light clothing at the first prenatal visit, which in Sweden occurs in 90% before 14 weeks of gestation [31]. 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) [32]. Smoking was determined by self-report at either the first prenatal visit or in the third trimester; this has been validated with cotinine markers [33]. Parental ASD was defined as the occurrence in the Patient Register of at least one ICD-10 code F84 or an ICD-9 code 299, since parents could have been diagnosed before the adoption of ICD-10.

Statistical Analysis

General cohort.—The general cohort consisted of children born 2000–2016, followed from 1 year of age until the first time an ASD diagnosis was entered in the Patient Register, age at emigration, age at death, or December 31st 2017; whichever occurred first. We estimated ASD rates as the number of cases divided by person-time of follow-up in the chronological age scale; these were compared 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. Models were adjusted for independent predictors of outcome that could be related to exposures without being their consequences per prior knowledge (Supplementary Figure 1), including maternal age, country of origin, cohabitation with the child's father, education level, parity, height, early-pregnancy BMI, smoking during pregnancy, parental ASD, maternal history of polycystic ovarian syndrome, sex of infant, and year of birth. All multivariable models were complete-case analyses. Preterm birth could be a cause of ASD [4, 5, 34] and a consequence of placental abruption or preeclampsia; hence, associations between these exposures and ASD could be mostly driven by preterm birth. We evaluated the contribution of placental abruption or preeclampsia to ASD independent of preterm birth by estimating the proportion of their associations with ASD that was not mediated through gestational age, with use of causal mediation analyses under the assumptions of a potential outcomes frame, detailed elsewhere [35, 36]. The

Swedish population is relatively homogenous with respect to ethnicity; hence, to explore the transportability of results to less homogeneous populations, we conducted supplemental analyses stratified by whether maternal country of origin was Nordic or non-Nordic.

Sibling cohort.—Sibling-controlled analyses have the potential to improve causal inference by 1) partly controlling for unmeasured genetic factors common to siblings, since they share up to one-half of autosomal DNA, and 2) completely controlling for genetic and all other time-invariant characteristics of the parents. We assembled a sibling cohort by identifying full siblings in the general cohort through the Multigeneration Register and conducted sibling-controlled comparisons by estimating HR with 95% CI through stratified Cox models in which each family was a stratum. These analyses were adjusted for time-changing characteristics including birth order, early pregnancy BMI, smoking during pregnancy, and the infant's sex. Children included in the sibling cohort differed from those excluded with respect to outcome rates, exposures prevalence, and sociodemographic characteristics. Compared with children in the sibling cohort, those excluded from the sibling cohort had higher rates of ASD, higher prevalence of exposures, less favourable sociodemographic conditions, more pregnancy complications, and increased rates of parental ASD (Supplementary Table 2). Because having a child with ASD could influence the parent's decision of having additional children, selection into the sibling cohort could bias the estimates of association. Thus, we corrected the stratified HR estimates for potential selection and confounding biases via inverse probability weighting (IPW). We computed stabilized weights as 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 [37]. All analyses were conducted with use of Statistical Analysis Software version 9.4 (SAS Institute, Cary, NC).

RESULTS

There were 1,752,268 live singleton births from 2000 to 2016 in the Birth Register. Exclusions were 28,505 and 837 births with missing maternal and child national registration numbers, respectively, 4800 infants who emigrated, 3978 infants who died before one year of age, and 68,693 infants with congenital malformations; thus, 1,645,455 (93.9%) infants were included in the general cohort. There were 23,810 cases of ASD (16.2 per 10,000 child-years) over a median 8.7 years of age (IQR 4.7, 13.0). Among them, the prevalence of intellectual disability, ADHD, and epilepsy was 14.4%, 40.3%, and 6.0%, respectively. The sibling cohort comprised 1,092,132 full siblings distributed in 490,737 families; among them, there were 14,483 cases of ASD (14.7 per 10,000 child-years) over a median 8.8 years of age (IQR 5.4, 12.6). There were 30,258 siblings discordant for ASD (n with ASD = 13,228), distributed in 12,862 families ranging in size from 2 to 10. In 8572 of the families (66.7%), the first born had ASD (Supplementary Table 3). The distribution of exposures is presented in Supplementary Figure 2.

In both general and sibling cohorts, unadjusted ASD rates (per 10,000 child-years) were increased in children of mothers with placental abruption (Table 1). Unadjusted rates of ASD were also increased in children of mothers with preeclampsia (Supplementary Table 4), especially term preeclampsia with SGA and preterm preeclampsia <34 weeks (Table 1).

Rates of ASD increased with decreasing gestational age (Supplementary Table 4), they were highest for very/extremely preterm birth, both spontaneous and medically indicated (Table 1).

In the general cohort, adjusted HR of ASD were increased for placental abruption, term preeclampsia with SGA, and preterm preeclampsia (Table 2). In sibling-controlled analyses, placental abruption was not related to ASD. Term preeclampsia with SGA was related to an adjusted 1.9-fold increased HR of ASD in IPW-adjusted sibling comparisons, whereas preterm preeclampsia <34 weeks was associated with a 4.2-fold increase (Table 2).

In both general cohort and sibling analyses ASD HRs increased with spontaneous very/extremely preterm birth (Table 2); the HR was 2.4-times higher in IPW-adjusted sibling comparisons. Medically indicated preterm birth of increasing severity was related to increasingly higher ASD HRs in cohort analyses; however, in IPW-adjusted sibling comparisons only medically indicated moderately preterm birth was significantly associated with ASD.

In the general cohort, the associations of placental abruption and preeclampsia with ASD were not completely explained by preterm birth. In mediation analyses 63% and 79% of these associations, respectively, were independent of preterm birth (Table 3).

Associations of defective placentation syndromes with ASD comorbid with other neurodevelopmental disorders were generally stronger for ASD with epilepsy or intellectual disability than they were for ASD with ADHD or for ASD without comorbidities (Table 4).

In supplemental cohort analyses stratified by maternal country of origin (Supplementary Table 5), placental abruption was only associated with ASD rates in Nordic mothers; whereas the association with preterm preeclampsia <34 weeks was stronger in non-Nordic than in Nordic mothers. The association of spontaneous very/extremely preterm birth with ASD was comparable between Nordic and non-Nordic mothers, whereas the associations with medically indicated preterm birth were somewhat stronger in the latter group.

DISCUSSION

In this nationwide investigation, defective placentation syndromes, including term preeclampsia with SGA, preterm preeclampsia, and very or extremely spontaneous preterm birth, were consistently associated with increased rates of ASD in cohort and sibling-controlled analyses. Medically indicated moderately preterm birth was also related to higher ASD rates. Because early-onset preeclampsia is one of its main causes, medically indicated preterm birth may also represent defective placentation.

Taken together, our findings support a role of defective placentation in the etiology of ASD. Very or extremely spontaneous preterm birth is likely to represent defective placentation, whereas moderately preterm birth is more related to chorioamnionitis [38]. Among very preterm infants, placental underperfusion may be more related to worse mental development than chorioamnionitis [39]. In a previous study, preeclampsia with SGA was more strongly related to ASD incidence than each condition alone [22]; late preeclampsia with SGA

in first pregnancy predicts early preeclampsia in second pregnancy [21], which suggests a common origin, possibly on defective placentation [12]. Although we found consistent associations between ASD and late preeclampsia with SGA or preterm preeclampsia, a substantial proportion of the association between preeclampsia and ASD was not mediated through preterm birth, which suggests a role of preeclampsia *per se*. While this association could represent an effect of defective placentation on brain development, it could also be due to brain injury from conditions that accompany the pathophysiology of preeclampsia, such as increased inflammatory response through dysregulated immune activation and oxidative stress [40].

Many studies have found a high prevalence of ASD among preterm-born children [41]. Among 3.5 million Scandinavian children, ASD risk increased with decreasing gestational age after adjustment for birth year and maternal age [4]. In the Stockholm Youth Cohort of >480,000 children, gestational age was inversely related to ASD risk after adjustment for maternal and perinatal characteristics [34]. Nevertheless, in a Swedish population-based case-control study of 1216 ASD cases [42] and in a cohort of 7876 US children followed through age 21 years [43], monotonic associations between preterm birth severity categories and ASD incidence were strongly attenuated after adjustment for maternal causes of preterm birth. This attenuation suggests that the relation between preterm birth *per se* and ASD may vary between medically indicated and spontaneous preterm birth. Prior sibling-controlled analyses of Swedish children suggested a positive association between preterm birth and ASD [5], but there was no stratification by preterm birth type. Our study extends previous findings by identifying associations between specific types of preterm birth and ASD. We found a consistent association between very or extremely spontaneous preterm birth and the incidence of ASD in cohort and sibling-controlled analyses. Spontaneous preterm birth has been associated with retained placenta [44]. It has also been related to altered placental blood flow resulting from defective placentation [18].

The consistency of findings between sibling-controlled and cohort analyses suggests that genetic confounding may not fully explain the associations between syndromes linked to defective placentation and ASD. Results in the sibling-controlled studies could suggest an effect of defective placentation independent of genetics [45].

We found that the associations of defective placentation syndromes and ASD were stronger for ASD comorbid with epilepsy or intellectual disability than they were with ASD comorbid with ADHD or non-comorbid ASD. One previous investigation suggested that the potential effect of SGA on ASD might be stronger on ASD comorbid with intellectual disability than on non-comorbid ASD [46]. It does not escape us that the strength of associations between the exposures under study and non-comorbid ASD were close to those of ASD comorbid with ADHD. Whether this may highlight shared etiologies between ASD and ADHD warrants further scrutiny.

This study has important strengths. The population-based design with over 1.5 million children linked to nation-wide registries reduces selection bias. Confounding by socioeconomic conditions is limited due to the relative homogeneity of the Swedish population and the existence of universal, high quality health care. Validity of exposure

variables from the Swedish Birth Register is excellent [47]; and data on gestational age at birth and birth weight-for-gestational age was virtually complete. Finally, the sibling comparisons offered a unique opportunity to enhance causal inference by partly ruling out confounding due to shared familial factors.

The study also has some limitations. The validity of ASD ICD-10 codes in the Patient Register has not been determined. Nevertheless, it is unlikely that any lack of sensitivity or specificity in outcome assessment would be differential with respect to the exposures. Non-differential misclassification could attenuate the associations with respect to their true values. While the sociodemographic homogeneity of the Swedish population improves internal validity, it may limit the generalizability of the findings to other populations. The associations between the syndromes studied and ASD were generally in agreement between mothers of Nordic and non-Nordic origin; still, there is a need to replicate the study in more heterogeneous populations. Statistical power limitations prevented us from examining the role of offspring's sex as a potential modifier of the associations between defective placentation syndromes and autism. Because male sex is a strong risk factor for both, future research on this possibility is warranted. Finally, despite the advantages of sibling-controlled analyses in adjusting for confounders shared within the family, they can produce biased estimates in some instances due to non-shared confounders [48, 49], random measurement error in exposure [48], or inherent adjustment for potential mediators shared within families [50].

We conclude that defective placentation syndromes, including term preeclampsia with SGA, preterm preeclampsia, and very or extremely spontaneous preterm birth, are related to increased rates of ASD. The association of preeclampsia with ASD is not fully explained by gestational age.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Incidence of Autism Spectrum Disorder starting at 1 year of age according to defective placentation syndromes. Live-born singleton non-malformed children in Sweden 2000–2016.

Defective placentation syndrome	General cohort			Sibling cohort		
	Number of children	No. with autism	Rate per 10,000 child-years	Number of children	No. with autism	Rate per 10,000 child-years
Total	1,645,455	23,810	16.17	1,092,132	14,483	14.66
Placental abruption						
No	1,640,167	23,684	16.14	1,088,931	14,411	14.64
Yes	5288	126	25.61	3201	72	24.35
Preeclampsia						
No preeclampsia	1,601,162	22,862	15.96	1,066,542	13,949	14.49
Preeclampsia at ≥37 weeks without SGA[1]	30,163	555	20.45	17,922	320	18.51
Preeclampsia at ≥37 weeks with SGA	4914	129	29.23	2674	79	30.10
Preeclampsia at 34 to 36 weeks	5660	140	26.88	3190	74	24.06
Preeclampsia at <34 weeks	3441	122	37.54	1739	61	35.31
Missing	115	2	15.84	65	0	
Gestational age[2]						
Term	1,571,286	22,204	15.81	1,047,369	13,590	14.38
Moderately preterm spontaneous	47,419	801	18.35	29,877	462	16.21
Very/extremely preterm spontaneous	5026	206	45.89	2784	115	44.69
Moderately preterm medically indicated	16,619	387	26.03	9429	211	24.87
Very/extremely preterm medically indicated	3281	137	45.92	1666	67	43.03
Missing	1824	75	33.45	1007	38	31.82

[1] Birth weight-for-gestational age <10th percentile.

[2] Term: ≥37 weeks. Moderately preterm: 32 to 36 weeks. Very/extremely preterm: 22 to 31 weeks.

Table 2.

Hazard ratios for Autism Spectrum Disorder (ASD) starting at 1 year of age according to defective placentation syndromes in general and sibling cohorts. Live-born singleton non-malformed children in Sweden 2000–2016.

Defective placentation syndrome	General Cohort[1]	Sibling Cohort[2]	
	Adjusted hazard ratio (95% CI)[3,4]	Adjusted hazard ratio (95% CI)[5]	IPW-adjusted hazard ratio (95% CI)[6]
Placental abruption			
No	1.00	1.00	1.00
Yes	1.43 (1.18, 1.73)	1.03 (0.62, 1.72)	1.11 (0.68, 1.81)
Preeclampsia			
No preeclampsia	1.00	1.00	1.00
Preeclampsia at ≥37 weeks without SGA[7]	1.07 (0.98, 1.18)	0.86 (0.66, 1.13)	0.86 (0.66, 1.13)
Preeclampsia at ≥37 weeks with SGA	1.53 (1.27, 1.86)	1.73 (1.00, 2.99)	1.93 (1.13, 3.28)
Preeclampsia at 34 to 36 weeks	1.50 (1.25, 1.79)	1.55 (0.91, 2.65)	1.45 (0.87, 2.43)
Preeclampsia at <34 weeks	1.75 (1.41, 2.16)	3.57 (1.73, 7.35)	4.22 (2.09, 8.53)
Gestational age[8]			
Term	1.00	1.00	1.00
Moderately preterm spontaneous	1.04 (0.96, 1.13)	1.16 (0.94, 1.43)	1.04 (0.85, 1.27)
Very/extremely preterm spontaneous	2.59 (2.21, 3.03)	2.53 (1.54, 4.17)	2.36 (1.47, 3.79)
Moderately preterm medically indicated	1.39 (1.24, 1.56)	1.49 (1.08, 2.05)	1.40 (1.01, 1.94)
Very/extremely preterm medically indicated	1.88 (1.52, 2.33)	2.50 (1.21, 5.15)	1.41 (0.53, 3.74)

[1]The cohort comprises 1,645,455 children with 23,810 cases of ASD.

[2]The cohort comprises 1,092,132 full siblings distributed in 490,737 families. There were 14,483 cases of ASD.

[3]From proportional hazards models with age at first diagnosis of ASD as the outcome and each defective placentation syndrome as the exposure, adjusted for maternal age, country of origin, cohabitation with the child's father, education level, parity, height, early-pregnancy body mass index, smoking during pregnancy, presence of a diagnosis of ASD in the mother or the father, maternal polycystic ovarian syndrome, and infant sex and year of birth. Estimates for type of preterm birth were further adjusted for preeclampsia and SGA. A robust estimate of the variance was specified in all models to account for siblings.

[4]Complete case analysis; n = 1,467,692 with 20,520 cases of ASD.

[5]From proportional hazards models with age at first diagnosis of ASD as the outcome, stratified by family. Models were adjusted for birth order, early-pregnancy body mass index, smoking during pregnancy, and infant sex. Estimates for type of preterm birth were further adjusted for preeclampsia and SGA. Complete case analyses; n = 940,475 with 11,880 cases of ASD.

[6]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.

[7]Birth weight-for-gestational age <10th percentile.

[8]Term: ≥37 weeks. Moderately preterm: 32 to 36 weeks. Very/extremely preterm: 22 to 31 weeks.

Table 3.

Proportion of the associations of placental abruption and preeclampsia with Autism Spectrum Disorder (ASD) that is independent of preterm birth (gestational age at birth <37 weeks)

	Hazard ratio (95% CI)[1]			% mediated through preterm birth	% independent of preterm birth	*P* for interaction complication x preterm birth
	Total	Indirect through preterm birth	Direct or indirect not through preterm birth			
Placental abruption	1.43 (1.18, 1.73)	1.12 (1.09, 1.15)	1.27 (1.04, 1.54)	37	63	0.94
Preeclampsia	1.23 (1.14, 1.32)	1.04 (1.03, 1.05)	1.18 (1.10, 1.27)	21	79	0.30

[1]From proportional hazards models with age at first diagnosis of ASD as the outcome adjusted for maternal age, country of origin, cohabitation with the child's father, education level, parity, height, early-pregnancy body mass index, smoking during pregnancy, presence of a diagnosis of ASD in the mother or the father, maternal polycystic ovarian syndrome, and infant sex and year of birth. The association between each complication and preterm birth was modeled with use of logistic regression.

Table 4.

Incidence of Autism Spectrum Disorder (ASD) with neurodevelopmental comorbidities starting at 1 year of age according to defective placentation syndromes. Live-born singleton non-malformed children in Sweden 2000–2016.

Defective placentation syndrome	ASD with intellectual disability n = 1,625,079			ASD with ADHD n = 1,631,233			ASD with epilepsy n = 1,623,077			ASD alone n = 1,621,645		
	No. with ASD	Rate per 10,000 child-y	Adjusted hazard ratio (95% CI)[1,2]	No. with ASD	Rate per 10,000 child-y	Adjusted hazard ratio (95% CI)[1,3]	No. with ASD	Rate per 10,000 child-y	Adjusted hazard ratio (95% CI)[1,4]	No. with ASD	Rate per 10,000 child-y	Adjusted hazard ratio (95% CI)[1,5]
Total	3434	2.36		9588	6.56		1432	0.99		11,357	7.77	
Placental abruption												
No	3413	2.36	1.00	9541	6.55	1.00	1425	0.98	1.00	11,298	7.76	1.00
Yes	21	4.35	1.74 (1.09, 2.77)	47	9.68	1.26 (0.92, 1.72)	7	1.45	1.71 (0.81, 3.60)	59	12.15	1.42 (1.07, 1.89)
Preeclampsia												
No preeclampsia	3281	2.32	1.00	9181	6.46	1.00	1380	0.98	1.00	10,937	7.69	1.00
Preeclampsia at ≥37 weeks without SGA[6]	72	2.70	1.05 (0.81, 1.36)	239	8.89	1.09 (0.95, 1.26)	23	0.86	0.68 (0.42, 1.09)	259	9.64	1.08 (0.94, 1.23)
Preeclampsia at ≥37 weeks with SGA	25	5.78	1.80 (1.13, 2.87)	51	11.70	1.55 (1.15, 2.07)	10	2.32	2.16 (1.12, 4.18)	56	12.89	1.43 (1.08, 1.89)
Preeclampsia at 34 to 36 weeks	24	4.70	1.96 (1.27, 3.01)	62	12.04	1.56 (1.19, 2.06)	6	1.18	1.30 (0.58, 2.90)	59	11.48	1.34 (1.02, 1.77)
Preeclampsia at <34 weeks	31	9.81	2.30 (1.40, 3.76)	54	16.92	1.69 (1.20, 2.38)	13	4.13	3.49 (1.86, 6.52)	45	14.15	1.66 (1.21, 2.28)
Missing	1	7.96		1	7.96		0			1	7.97	
Gestational age[7]												
Term	3107	2.24	1.00	8945	6.42	1.00	1305	0.94	1.00	10,648	7.64	1.00
Preterm spontaneous	195	4.11	1.57 (1.33, 1.85)	389	8.16	1.12 (1.00, 1.25)	81	1.71	1.59 (1.23, 2.05)	458	9.61	1.13 (1.02, 1.26)
Preterm medically indicated	117	6.69	2.06 (1.62, 2.62)	216	12.26	1.41 (1.20, 1.67)	40	2.29	2.13 (1.47, 3.08)	224	12.73	1.45 (1.24, 1.69)
Missing	15	6.91		38	17.23		6	2.77		27	12.34	

[1]Estimates are from proportional hazards models with age at first diagnosis of autism as the outcome and each placentation disorder as the exposure, adjusted for maternal age, country of origin, cohabitation with the child's father, education level, parity, height, early-pregnancy body mass index, smoking during pregnancy, presence of a diagnosis of ASD in the mother or the father, maternal

polycystic ovarian syndrome, and infant sex and year of birth. Estimates for type of preterm birth were further adjusted for preeclampsia and SGA. A robust estimate of the variance was specified in all models to account for siblings. The comparison group for each diagnosis comprises children without ASD.

[2]Complete case analysis; n = 1,447,172 with 2949 cases of ASD.

[3]Complete case analysis; n = 1,455,355 with 8183 cases of ASD.

[4]Complete case analysis; n = 1,447,172 with 1203 cases of ASD

[5]Complete case analysis; n = 1,457,042 with 9870 cases of ASD.

[6]Birth weight-for-gestational age <10th percentile.

[7]Term: ≥37 weeks. Preterm: ≤ 36 weeks.