Association of Perinatal Risk Factors with Autism Spectrum Disorder

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Abstract

Objective To examine the association between exposures to perinatal factors and autism spectrum disorders (ASD).

Study Design A retrospective cohort study of ASD among children born in Kaiser Permanente Southern California hospitals between 1991 and 2009 ($n = 594{,}638$). Medical records were used to determine exposure to perinatal (antepartum and intrapartum) complications. ASD was diagnosed using DSM-IV criteria. Multivariable Cox regression was used to estimate hazard ratios (HRs).

Result Children with ASD were more likely to be exposed to perinatal complications (HR = 1.15, 95% confidence interval [CI]: 1.09–1.21) than neurotypical children. Children exposed to antepartum (HR = 1.22, 95% CI: 1.10–1.36) and intrapartum (HR = 1.10, 95% CI: 1.04–1.17) complications were at increased risk of ASD. The risk was even greater when both antepartum and intrapartum conditions were present (HR = 1.44, 95% CI: 1.26–1.63).

Conclusion Exposure to antepartum or intrapartum complications increases the risk of ASD in the offspring. Therefore, pregnancy complications may help identify children who could benefit from early screening and intervention for this common neurodevelopmental condition.

Keywords
- perinatal
- antepartum
- intrapartum
- hypoxia
- autism
- pregnancy
- race

Autism spectrum disorders (ASDs) are a group of neurodevelopmental disorders characterized by impaired social interaction, communication deficits, and a range of restricted and repetitive patterns of behavior.[1] During the 30 years, the prevalence of ASD has been on the rise in most Western societies[2,3] and has become a major public health concern in the United States. According to the latest Centers for Disease Control and Prevention (CDC) estimate, approximately 1 in 68 (14.7 per 1,000) 8-year-old children meet the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) diagnostic criteria for ASD.[4] It ranks among the most common childhood chronic diseases that place a large

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burden on affected individuals, their families and the society. A recent study by Buescher et al,[5] it was estimated that the mean annual aggregate costs of autism-related medical expenditure and loss of family income and productivity are as high as $138 billion.

Despite extensive research, the underlying pathoetiologic mechanisms responsible for the development of ASD are unknown. It has been postulated that it is a multifactorial disease with genetic and environmental factors exerting their effects at a critical period of brain development.[6–8] Although fetal origin of childhood disease is a well-established phenomenon, studies investigating impact of conditions during fetal development on ASD are limited[9–11] and population-level data are scarce. Recent research in this area has shown that exposure to preeclampsia[12] and gestational diabetes[13] increases the risk of ASD. Our recent study demonstrates that exposure to ischemic-hypoxic condition in utero is associated with increased risk of attention deficit/hyperactivity disorder (ADHD), another neurodevelopmental disorder.[14] Although ASD and ADHD have distinct characteristics, both have overlapping etiology, neurologic features, symptoms, and comorbidities.[15–17]

We hypothesize that underperfusion of the placenta and obstetric complications that compromise blood flow to the fetus may induce oxygen and vital nutrient deprivation as well as generate toxic metabolites leading to damage and dysfunction of developing neurons.[18–20] Thus, the present study was undertaken to determine whether antepartum and intrapartum pregnancy complications are associated with increased risk of ASD independent of the gestational age at birth. Furthermore, we also examined whether the magnitude of any such association is modified by child's race/ethnicity.

Materials and Methods

This study used a retrospective cohort approach to examine the association between perinatal conditions and ASDs in singleton live-born children delivered in a large health maintenance organization (Kaiser Permanente Southern California [KPSC]). The KPSC system currently delivers approximately 36,000 babies annually at 14 Kaiser Permanente hospitals located throughout southern California. This study was approved by the KPSC Institutional Review Board.

The medical records used for this study include perinatal service system, maternal and child inpatient and outpatient medical care, along with laboratory and pharmacy records. Information extracted from the patient's electronic medical record include maternal medical and obstetric conditions and procedures, fetal and neonatal outcomes of all birth in KPSC hospitals, maternal sociodemographic and behavioral characteristics, parental age and race/ethnicity, child's age and sex, as well as child medical history. Parental demographic and maternal medical and obstetric health records were linked to child records using medical record numbers unique for each pregnancy. The validation of the linked data has been reported in detail elsewhere.[21–23]

The study population was drawn from a total of 594,638 births between 1991 and 2009. To become eligible for inclusion, children must have been born to KPSC-members in KPSC hospitals between January 1, 1991 and December 31, 2009 be a singleton birth with a gestational age of $28^{0/7}$ through $42^{6/7}$ weeks of gestation, born without congenital anomalies, and be KPSC health plan members at least for 3 months between 3 and 17 years of age during 1993 and 2013. Births at $< 28^{0/7}$ weeks of gestation were excluded because of their high incidence of morbidity. After applying these criteria, the final population consisted of 401,660 singleton, live born children (►**Fig. 1**).

Pregnancies were classified into three exposure groups based on exposure to (1) antepartum complications, (2) intrapartum complications, (3) or both antepartum and intrapartum complications (►**Table 1**). Pregnancies complicated by antepartum factors were defined by the presence of placental abruption (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 641.2x, 762.1) and preeclampsia (ICD-9-CM codes 642.x).[24,25] Intrapartum conditions consisted of one or more of the following pregnancy complications: breech/transverse presentation of the fetus (ICD-9-CM codes 652.2x, 652.3x, 669.6x, 763.0, 72.x), fetal dystocia (ICD-9-CM codes 660.4x), prolapsed/nuchal cord (ICD-9-CM codes 762.4, 762.5, 73.92), and birth asphyxia (ICD-9-CM codes 768.x, which included Apgar score <7 at 5 minute and neonatal resuscitation).[25–29] The validation of these clinical diagnosis codes has been reported in detail elsewhere.[21,22]

The outcome variable was physician-diagnosed ASD in children aged 3 to 17 years. The clinical diagnosis of ASD is based on confirmation of ASD case consistent with the diagnostic criteria listed in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) for any of the following conditions: autistic disorder, childhood disintegrative disorder, Rett disorder, Asperger disorder, or pervasive developmental disorder-not otherwise specified (PDD-NOS) during the follow-up period by a child/adolescent psychiatrist, developmental/behavioral pediatrician, child psychologist, or neurologist. The accuracy of ASD diagnosis has been validated by medical record review.[30]

Gestational age at delivery was based on a clinical estimate. Potential confounders and effect modifiers that were considered included child's sex (male/female), census tract's estimated annual median family household income for each year (< $29,999, $30,000–$49,000, $50,000–$69,999, $70,000–$89,999, ≥ $90,000), maternal age (< 20, 20–29, 30–34, ≥ 35 years) and education (< 12, 12, ≥ 13 years of completed schooling), parity, prenatal care (first trimester and none/late initiation), smoking (yes/no), year of diagnosis, and psychosocial disorders during pregnancy ascertained based on ICD-9-CM codes and medication use (yes/no). The child's race/ethnicity was based on maternal and paternal race/ethnicity information and classified as non-Hispanic white (white), non-Hispanic black (black), Hispanic, Asian/Pacific islander, and Other/mixed racial ethnic groups. Children of unknown/missing race were excluded from the study due to insufficient data (< 3.3%).

Follow-up for children started from the date of delivery and ended with an outcome (ASDs diagnosis) or when censoring occurred, on the earliest of the following dates: health plan disenrollment, 17th birthday, non-ASD–related death, or end of study (December 31, 2013).

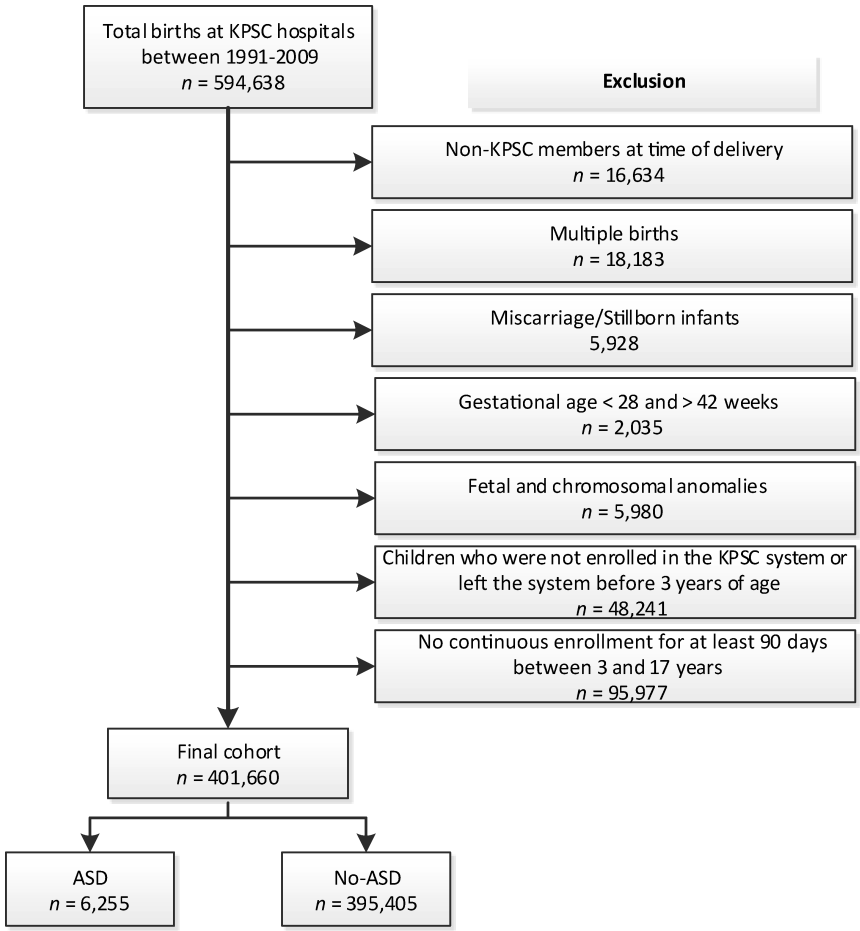

Fig. 1 Flow diagram of study cohort composition. ASD, autism spectrum disorder; KPSC, Kaiser Permanente Southern California.

Differences in maternal and child characteristics between children with and without ASDs were compared using χ^2 tests. Cumulative incidence rates (CIRs) were estimated by dividing the number of ASD cases by the person-years of follow-up. Cox proportional hazard models[31] were used to estimate hazard ratios (HRs) describing the association between perinatal risk factors and ASD before and after controlling for potential confounding variables. To investigate their independent effect, we examined the associations between individual antepartum and intrapartum conditions and ASD using hierarchical models that account for pregnancies with more than one complication. If a woman had more than one perinatal condition, only the first one in the hierarchical list was retained for the analysis. Therefore, perinatal conditions were examined both individually and as part of a cumulative risk index. Covariates included in the final model were chosen based on a potential a priori relationship with the exposure and outcome variables. Homogeneity of the HRs across gestational age of delivery and child race/ethnicity was evaluated by testing for significant interactions between perinatal conditions and each of the covariate in the model and stratified data analyses.

Table 1 Perinatal conditions that were considered for this study

1. Antepartum conditions
Preeclampsia
Placental abruption
2. Intrapartum conditions
Breech/transverse
Fetal dystocia
Prolapsed/nuchal cord
Birth asphyxia
With Apgar score of $<$ 7 at 5 min
Requiring neonatal resuscitation
$>$ 1 intrapartum conditions
3. Both antepartum and intrapartum conditions

In pregnancies complicated by preeclampsia, the placenta undergoes both histologic and morphologic changes impairing placental function leading to chronic oxidative stress and fetal hypoxemia.[32] Although the placenta adapts well to the hypoxic environment in preeclampsia, the compensatory changes that take place to meet fetal growth requirements are insufficient and generally persist throughout pregnancy. Therefore, its influence on risk by the gestational age and duration of in utero exposure (the number of days from first preeclampsia diagnosis to infant's date of birth) was

investigated. The diagnosis of ASD in children with accompanying developmental and emotional disorders (mental retardation, developmental dyslexia, deficits in language processing, conduct disorder, irritability, depressed mood, bipolar or anxiety disorders) is challenging, and including this group of children may, therefore, have affected our outcome. To verify whether our findings still hold, we performed a sensitivity analysis after excluding children with accompanying developmental and emotional disorders. In all analyses, children who were not exposed to any of listed perinatal conditions were the reference group. Stratum-specific and aggregated population-attributable risk fractions (PAF) were estimated by $PAF = pd_i$ ($[HR_i - 1]/HR_i$), where HR_i is the adjusted HR for the *i*th specific exposure and pd_i is the proportion of cases in the population from the *i*th exposure.[33] All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, SC).

Results

During the time period examined, there were 6,255 children born in KPSC hospitals that were diagnosed with ASDs between the age of 3 and 17 years. Those who were not diagnosed with ASD by 17 years formed the comparison group ($n = 395{,}405$; ►**Fig. 1**). The mean age at first diagnosis of ASDs was approximately 6.2 years (SD = 3.3). The median follow-up times for children with and without exposure to perinatal conditions were 4.9 and 10.6 years, respectively.

Characteristics of mothers and children by ASD status are summarized in ►**Table 2**. ASD children's mothers were more likely to be older, have ≥ 13 years of formal education, nulliparous, to initiate prenatal care earlier, and have psychosocial disorders during pregnancy. The rate of ASD diagnosis varied substantially by race/ethnicity, occurring most frequently in non-Hispanic white children and least frequently in Asian children. ASD was diagnosed approximately four times more frequently in boys (2.5%) as in girls (0.6%).

The incidence rate of ASD was significantly higher in children exposed to perinatal conditions (1.70%) than unexposed children (1.28%, HR 1.31, 95% CI: 1.25–1.38; ►**Table 3**). This association persisted after adjusting for potential confounding factors listed in ►**Table 2**. Further stratified analysis indicated that both antepartum (HR 1.22, 95% CI: 1.10, 1.36) and intrapartum (HR 1.10, 95% CI: 1.04, 1.17) conditions were significantly associated with increased risk of childhood ASD. The difference in the incidence rates of ASD were largely attributed to higher incidence fetal malpresentation, births asphyxia, and fetal dystocia from the intrapartum conditions and preeclampsia from the antepartum conditions and the coexisting of antepartum and intrapartum conditions in the ASD group, while the incidence rate of placental abruption was similar for ASD and non-ASD groups. The magnitude of association is particularly greater when both antepartum and intrapartum conditions occurred together in a pregnancy (HR 1.44, 95% CI: 1.26, 1.64). The association between prolapsed and nuchal cord and ASD became nonsignificant (HR 1.03, 95% CI: 0.95, 1.12) after adjustment for confounders, and we observed no association between placental abruption and ASD. A stratified analysis by the duration of exposure to preeclampsia revealed that children who were exposed to preeclampsia for 2 to 7 days (HR 1.56, 95% CI: 1.25, 1.95), and ≥ 8 days (HR 1.59, 95% CI: 1.25, 2.02) were at significantly increased risk of ASD compared with those children who were not exposed to any of listed perinatal conditions. By contrast, exposure to less than 24 hours had no detectible association with ASD risk (HR 1.12, 95% CI: 0.97, 1.30). The adjusted population fraction for ASD of having been exposed to perinatal conditions was 0.3% while the corresponding figures were 0.4% for exposure to antepartum conditions, 0.2% for exposure to intrapartum conditions, and 1.2% for exposure to both antepartum and intrapartum conditions. Preeclampsia confers an important risk factor for ASD regardless of the trimester in which diagnosis has been established (data not shown). Furthermore, we conducted a sensitivity analysis after excluding children with a history of accompanying developmental and emotional disorders. The exclusion of children with these comorbid factors did not produce any significant changes in the magnitude and direction of the associations (data not shown).

Significant differences in ASD incidence rate among preterm (1.76 per 1,000 person-years) and term (1.38 per 1,000 person-years) born children were found, regardless of exposure status to perinatal conditions (incidence rate ratio [IRR] 1.24, 95% CI: 1.13, 1.35). However, the incidence rates of ASD among preterm- and term-born children of pregnancies complicated by perinatal conditions were 1.93 per 1,000 person-years and 1.68 per 1,000 person-years, respectively (IRR 1.19, 95% CI: 1.09, 1.30). ►**Fig. 2** shows the association between exposures to perinatal conditions and the diagnosis of ASD at preterm (28–36 weeks) and term (37–42 weeks) born children after adjusting for several potential confounding factors, including maternal age, education, parity, smoking, prenatal care, year of diagnosis, psychosocial disorder during pregnancy, and child's sex and race/ethnicity. Children delivered at term gestation and exposed to perinatal conditions were significantly more likely to develop ASD later in life (HR 1.14, 95% CI: 1.08, 1.21) when compared with children who were not exposed to any of listed conditions. At a preterm birth, risk of ASD seemed to be elevated in children exposed to most of studied perinatal conditions. However, the increase in risk failed to reach statistical significance (►**Fig. 2**).

The race/ethnicity-specific incidence rates of ASD in exposed and unexposed children and HRs for the association of perinatal conditions with ASD, adjusted for potential confounders, are shown in ►**Table 4**. With non-Hispanic whites as the reference, the HRs for ASD were 0.89, 1.01, 0.90, and 1.03 for African Americans, Hispanics, Asian/Pacific islanders, and Others/mixed racial/ethnic groups, respectively. Exposure to antepartum and intrapartum or both perinatal conditions were associated with increased risk of ASD in white and black racial/ethnic groups. The magnitude of the associations differed considerably by race and ethnicity. Breech/transverse presentations, preeclampsia, and diagnoses with exposure to both antepartum and intrapartum conditions accounted for most of the ASD diagnoses in white and black racial/ethnic groups. Among Hispanics, significant associations were observed for birth asphyxia (HR 1.8, 95% CI: 1.2, 2.7)

Table 2 Distribution of maternal and child characteristics based on ASD status

	No ASD	ASD	*p* Values
Characteristics	***n* = 395,405 (%)**	***n* = 6,255 (%)**	
Maternal age (y)			< 0.001
< 20	26,722 (6.8)	243 (3.9)	
20–29	188,105 (47.6)	2,643 (42.3)	
30–34	110,264 (27.9)	1,891 (30.2)	
≥ 35	70,314 (17.8)	1,478 (23.6)	
Maternal education (y)			< 0.001
< 12	50,095 (12.7)	506 (8.1)	
12	122,002 (30.9)	1,670 (26.7)	
≥ 13	207,208 (52.4)	3,919 (62.7)	
Missing	16,100 (4.1)	160 (2.6)	
Household income[a]			0.242
< $30,000	24,165 (6.1)	371 (5.9)	
$30,000–$49,999	103,939 (26.3)	1,584 (25.3)	
$50,000–$69,999	115,928 (29.3)	1,838 (29.4)	
$70,000–$89,999	78,962 (20.0)	1,281 (20.5)	
≥ $90,000	72,411 (18.3)	1,181 (18.9)	
Parity			< 0.001
Parity 0	153,574 (38.8)	2,858 (45.7)	
Parity ≥1	141,821 (61.2)	3,397 (54.3)	
Gestational age at birth (wk)			< 0.001
28–36	27,425 (6.9)	524 (8.4)	
37–42	367,980 (93.1)	5,731 (91.6)	
Smoking during pregnancy	29,433 (7.4%)	441 (7.1)	0.239
Late/no initiation of prenatal care	57,440 (14.5)	786 (12.6)	< 0.001
Maternal psychosocial disorders	22,444 (5.7)	529 (8.5)	< 0.001
Child race/ethnicity			< 0.001
Non-Hispanic white	82,922 (21.0)	1,490 (23.8)	
Non-Hispanic black	37,468 (9.5)	593 (9.5)	
Hispanics	151,905 (38.4)	2,163 (34.6)	
Asian/Pacific islanders	31,515 (8.0)	523 (8.4)	
Others/mixed[b]	84,452 (21.4)	1,418 (22.7)	
Child sex			< 0.001
Female	194,998 (49.3)	1,131 (18.1)	
Male	200,407 (50.7)	5,124 (81.9)	

Abbreviation: ASD, autism spectrum disorder.
[a]Median household income based on census tract information.
[b]Others/mixed race/ethnicity category includes non-Hispanic children with multiple recorded races.

and for birth asphyxia with Apgar score < 7 at 5 minutes (HR 2.6, 95% CI: 1.4, 4.6). Among Asian/Pacific islanders, significant associations were observed for birth asphyxia requiring neonatal resuscitation (HR 2.4, 95% CI: 1.0, 5.8) and for having more than one intrapartum conditions (HR 2.1, 95% CI: 1.4, 3.1).

Discussion

The exact etiology of ASD remains uncertain. However, emerging evidence suggests that both genetic and environmental factors play a role in the pathogenesis of the disease. Twin

Table 3 Association between perinatal conditions and ASDs

	Total Birth	ASD N	Incidence rate[a]	Hazard ratio (95% CI)		PAF
				Crude	Adjusted[b]	
No perinatal condition	269,226	3,917	1.28	1.00 (Ref.)	1.00 (Ref.)	
Perinatal conditions	126,179	2,338	1.70	1.31 (1.25, 1.38)	1.15 (1.09, 1.21)	0.3
Antepartum conditions	18,757	354	1.89	1.34 (1.20, 1.49)	1.22 (1.10, 1.36)	0.4
Preeclampsia	16,693	325	1.78	1.38 (1.23, 1.54)	1.26 (1.13, 1.41)	0.4
Placental abruption	2,064	29	1.29	1.00 (0.69, 1.44)	0.91 (0.63, 1.32)	–
Intrapartum conditions	99,834	1,740	1.74	1.26 (1.20, 1.34)	1.10 (1.04, 1.17)	0.2
Breech/transverse	12,441	266	1.97	1.53 (1.35, 1.73)	1.39 (1.23, 1.58)	0.6
Fetal dystocia	38,993	734	1.75	1.36 (1.26, 1.47)	1.09 (1.01, 1.18)	0.2
Prolapsed/nuchal cord	45,877	686	1.43	1.10 (1.01, 1.19)	1.03 (0.95, 1.12)	0.1
Birth asphyxia	2,523	54	1.87	1.47 (1.13, 1.93)	1.29 (0.98, 1.69)	0.7
Apgar of $<$ 7 at 5 minute	948	23	2.06	1.65 (1.10, 2.49)	1.46 (0.97, 2.21)	1.0
Neonatal resuscitation	1,549	30	1.71	1.34 (0.94, 1.92)	1.16 (0.81, 1.66)	0.5
$>$ 1 intrapartum conditions	9,150	205	2.04	1.60 (1.39, 1.84)	1.34 (1.17, 1.55)	
Both conditions[c]	9,926	244	2.30	1.78 (1.56, 2.02)	1.44 (1.26, 1.64)	1.3

Abbreviation: ASD, autism spectrum disorder; CI, confidence interval; PAF, population attributable fraction.
[a]Incidence rate is shown per 1,000 person-years.
[b]Adjustments were made for maternal age, education, parity, smoking, prenatal care, year of diagnosis, psychosocial disorder during pregnancy, child's sex and race/ethnicity.
[c]Both conditions, the presence of antepartum and intrapartum conditions.

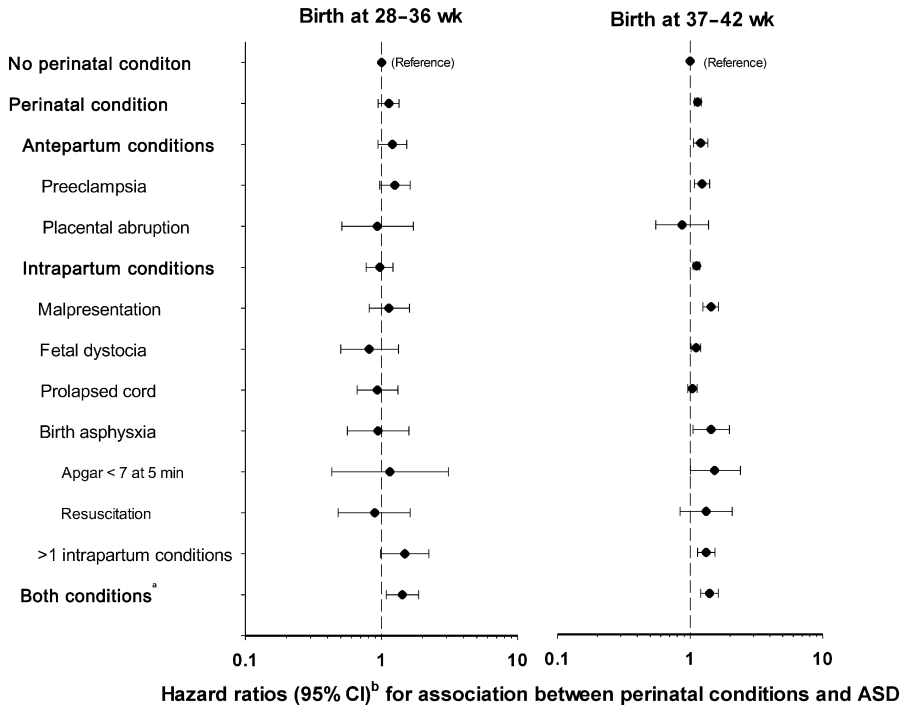

Fig. 2 Association between perinatal risk factors and autism spectrum disorders (ASDs) in children aged 3 to17 years by gestational age at delivery. CI, confidence interval. [a]Both conditions, the presence of antepartum and intrapartum conditions. [b]Adjustments were made for maternal age, education, parity, smoking, prenatal care, year of diagnosis, psychosocial disorder during pregnancy, child's sex and race/ethnicity.

Table 4 Association between perinatal conditions and ASD in children aged 3 to 17 years based on child's race/ethnicity

	Non-Hispanic white		Black		Hispanics		Asian/PIs		Others/Mixed[c]	
	Rate[a]	HR[b] (95% CI)	Rate[a]	HR[b] (95% CI)	Rate[a]	HR[b] (95% CI)	Rate[a]	HR[b] (95% CI)	Rate[a]	HR[b] (95% CI)
No perinatal condition	1.38	1.0 (Ref.)	1.12	1.0 (Ref.)	1.23	1.0 (Ref.)	1.40	1.0 (Ref.)	1.35	1.0 (Ref.)
Perinatal condition	1.94	1.2 (1.1, 1.3)	1.67	1.3 (1.1, 1.6)	1.51	1.1 (1.0, 1.2)	1.81	1.1 (1.0, 1.4)	1.85	1.2 (1.1, 1.3)
Antepartum conditions	2.30	1.5 (1.2, 1.8)	1.63	1.3 (1.0, 1.8)	1.56	1.2 (1.1, 1.4)	1.68	1.2 (0.8, 1.8)	1.59	1.1 (0.8, 1.3)
Preeclampsia	2.48	1.5 (1.2, 1.9)	1.71	1.4 (1.0, 1.9)	1.59	1.2 (1.1, 1.5)	1.77	1.3 (0.8, 2.0)	1.56	1.0 (0.8, 1.3)
Placental abruption	1.00	0.7 (0.3, 1.7)	0.81	0.7 (0.2, 2.8)	1.25	0.9 (0.5, 1.8)	1.24	0.8 (0.3, 2.4)	1.86	1.1 (0.6, 2.3)
Intrapartum conditions	1.80	1.1 (1.0, 1.3)	1.63	1.3 (1.1, 1.5)	1.47	1.0 (0.9, 1.2)	1.85	1.2 (1.0, 1.4)	1.77	1.1 (1.0, 1.3)
Breech/transverse	2.10	1.4 (1.1, 1.8)	2.48	1.9 (1.3, 2.8)	1.85	1.4 (1.1, 1.7)	1.87	1.3 (0.8, 2.0)	1.99	1.3 (1.0, 1.8)
Fetal dystocia	2.14	1.2 (1.1, 1.4)	1.57	1.2 (0.9, 1.5)	1.49	1.0 (0.8, 1.1)	2.01	1.2 (0.9, 1.5)	1.86	1.1 (0.9, 1.3)
Prolapsed/nuchal cord	1.42	1.0 (0.8, 1.2)	1.51	1.3 (1.0, 1.6)	1.31	1.0 (0.9, 1.1)	1.68	1.1 (0.9, 1.4)	1.61	1.1 (0.9, 1.3)
Birth asphyxia	1.65	1.1 (0.6, 1.9)	1.17	0.9 (0.4, 2.2)	2.48	1.8 (1.2, 2.7)	2.56	1.5 (0.6, 3.7)	1.70	1.2 (0.6, 2.1)
Apgar < 7 at 5 min	1.25	0.8 (0.3, 2.5)	2.17	1.7 (0.6, 4.5)	3.42	2.6 (1.4, 4.6)	0.00	–	1.90	1.3 (0.6, 3.2)
Neonatal resuscitation	1.89	1.2 (0.6, 2.4)	0.42	0.3 (0.1, 2.3)	1.79	1.2 (0.7, 2.3)	4.02	2.4 (1.0, 5.8)	1.60	1.1 (0.5, 2.3)
> 1 intrapartum conditions	2.27	1.4 (1.1, 1.8)	2.49	1.8 (1.2, 2.7)	1.62	1.1 (0.8, 1.5)	3.26	2.1 (1.4, 3.1)	1.91	1.2 (0.9, 1.6)
Both conditions[d]	2.78	1.6 (1.2, 2.0)	2.13	1.6 (1.1, 2.3)	1.79	1.2 (0.9, 1.5)	1.59	1.0 (0.6, 1.7)	3.10	1.8 (1.4, 2.3)

Abbreviations: ASD, autism spectrum disorders; CI, confidence interval; HR, hazard ratio; PI, Pacific islander.
[a]Incidence rate is shown per 1,000 person-years.
[b]Adjustments were made for maternal age, education, parity, smoking, prenatal care, year of diagnosis, psychosocial disorder during pregnancy, and child's sex.
[c]Others/mixed race/ethnicity category includes non-Hispanic children with multiple recorded races.
[d]Both conditions, the presence of antepartum and intrapartum conditions.

studies revealed that monozygotic twins are more strongly concordant than dizygotic twin for ASDs.[7,34,35] Furthermore, human and animal studies have shown that maternal psychosocial disorder,[36] influenza infection, fever,[37,38] environmental toxin exposure,[39] and diabetes[13] are associated with increased risk of neurodevelopmental disorders in the offspring. Previous studies have also suggested that maternal smoking, a known cause of fetal hypoxia, increases the risk of ASD. Therefore, we hypothesized that children exposed to perinatal conditions and obstetric complications that compromise blood flow to the fetal-placental unit would be at greater risk for ASD.[40,41]

In this retrospective cohort study, we found that children exposed to perinatal conditions were more likely to be diagnosed with ASD than those who were not exposed. These associations persisted after adjusting for potential confounding variables that include maternal demographic and behavioral characteristics, psychosocial disorder status, and child's sex and race/ethnicity. Furthermore, we found that exposure to intrapartum conditions (birth asphyxia, breech/transverse presentation, and fetal dystocia), preeclampsia, and exposure to both antepartum and intrapartum conditions simultaneously to be significant risk factors for ASD at term birth, but placental abruption was not associated with ASDs. Our results also suggest that the risk of an ASD diagnosis between 3 and 17 years of age was proportional to the duration of preeclampsia exposure. These findings support the hypothesis that longer exposure to preeclampsia during early fetal life may interfere with neurodevelopment at a critical stage of fetal brain development that results in later behavioral disorders. Most of the perinatal conditions-associated increase in ASDs risk is attributable to exposure to birth asphyxia with Apgar score < 7 at 5 minutes (46%), breech/transverse presentation (39%), and preeclampsia (26%). Although there is evidence that perinatal conditions may be associated with ASD, the population-attributable risk was small (PAF $= 0.3\%$), suggesting that a preventive strategy to reduce studied perinatal conditions would have minimal effects on reducing ASD rates in our population.

The use of Apgar score as a standalone measure for predicting future neurodevelopment outcomes is low. This is because it can be affected by many other factors, such as gestational age and maternal medications. However, the Apgar score provides important information on the success of a resuscitation effort. In the current study, we demonstrate that, in children who had birth asphyxia, Apgar score < 7 at 5 minutes and resuscitation clearly are at increased risk of ASD.

A properly functioning placenta is crucial for fetal development. Complications of the umbilical cord and a difficult birth process may also compromise fetal blood circulation and injure the developing brain in a manner that are not obvious at birth. Although the etiology of preeclampsia is not fully understood, it results in chronic oxidative stress and compromised fetal circulation via uteroplacental underperfusion.[32] Evidence from animal models and humans[42–46] and neuroimaging studies in humans[47–50] indicates that fetal exposure to hypoxia results in marked brain structural changes that are consistent with some of the neuroanatomical features of autism.[50,51] These include decreased arborization of the cerebellum and cortex, reduced numbers of Purkinje cells, strata oriens, and pyramidal layer in the dorsal hippocampal regions.[50,51]

Strengths of this study include use of a large cohort representing the diverse population of southern California and detailed medical records that enable us to control for many confounding factors. KPSC's integrated electronic medical record system contains updated and detailed diagnosis and treatment information on members receiving care in all KPSC hospitals and outpatient clinics. The validity of clinical diagnosis codes used for the exposure variables in this study has been established by reviewing medical records as the gold standard.[21,22] Exposure data were recorded before onset/diagnosis of ASD, avoiding potential differential selection and recall biases.

The diagnosis of ASD was ascertained based on confirmation of ASD case meeting DSM-IV-TR criteria for ASD during the follow-up period by a child/adolescent psychiatrists, developmental/behavioral pediatricians, child psychologists, or neurologists. In a preliminary analysis for related project, 96% of ADHD children were diagnosed by child/adolescent psychiatrists, developmental/behavioral pediatricians, child psychologists, or neurologists. Per KPSC guidelines (last revised in April 2013),[52] physicians perform behavioral and developmental surveillance at all preventive care and well-child checkup visits (as early as 4 months of life) to identify children who may have developmental delays. Checklist for ASD and developmental screening questionnaires are then completed (as early as 18 months of life) to confirm diagnosis by a specialist. This comprehensive approach limits the potential for patient misclassification.

Previous studies were likely underpowered to study the impact of fetal hypoxia on ASD and none looked at whether risks differ by the child's race/ethnicity, gestational age at birth, or duration of exposure. Using data from the Childhood Autism Risks from Genetics and the Environment study, Walker et al[12] found in their case-control study a 2.36-fold (95% CI: 1.18, 4.68) increased risk of ASD in children exposed in utero to preeclampsia. Although their finding is consistent with ours, women with an autistic child may report preeclampsia (a variable that was largely self-reported in their study) more often than women without an autistic child. This can bias results away from the null, a problem that was avoided for the present study.

One limitation of our study is the use of patient self-reported information on cigarette smoking during pregnancy. However, Buka et al[53] demonstrated significant agreement between self-reported smoking and serum levels of cotinine, a biomarker for exposure to tobacco smoke. The positive predictive value that was 66% for preeclampsia diagnosis in our validation study suggested possible misclassification of the variable.[21] Furthermore, some residual confounding is possible due to unaccounted factors such as maternal anthropometry[54] and in utero exposure to environmental agents such as polybrominated diphenyl ethers (PBDEs).[55,56] Unfortunately, these data were not available in the preelectronic medical record era for our institution (1991–2006). Another potential problem is surveillance bias related to the diagnosis of ASD. This nonrandom type of information bias is likely to occur if patients differ in likelihood of reporting a problem or explain or describe their symptoms to their doctors.[57]

Making a definite diagnosis of ASD in children with accompanying developmental and emotional disorders (mental retardation, developmental dyslexia, deficits in language processing, conduct disorder, irritability, depressed mood, bipolar or anxiety disorders) is challenging. Therefore, including children with these comorbidities may have affected our findings. However, when we limited the analysis to children with ASD but no other accompanying developmental and emotional disorders, we obtained similar results.

Our study suggests that perinatal conditions, especially birth asphyxia and preeclampsia, are associated with increased risk of childhood ASD even after accounting for gestational age at delivery and other potential confounding factors. This study raises the potential for early identification of at-risk children who could benefit from further surveillance and interventions. Early identification of at-risk children is critical, because early intervention with behavioral and developmental therapy in very young children with ASD can result in better long-term cognitive and behavioral function.[58,59]

Note

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Conflict of Interest

None.

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