Article published online: 2021-07-05

The Effect of Neonatal Sepsis on Risk of Autism Diagnosis

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Am J Perinatol 2023;40:858–866.

Abstract

Objective The study aimed to examine the association between neonatal sepsis and autism risk among children and whether the risk varied with the timing of exposure, child's sex, and race/ethnicity.

Study Design We conducted a retrospective cohort study using electronic health records (EHR) extracted from Kaiser Permanente Southern California Health Care System. Mother–child dyads were constructed by linking records of children born to member mothers and continuing to receive care through the system during the follow-up period with those of their biological mothers ($n = 469{,}789$). Clinical health records were used to define neonatal sepsis. Diagnosis of autism was made by medical specialists. Potential confounders included maternal sociodemographic factors, obstetrical history, child's age, sex, race/ethnicity, and maternal and child medical history. Incident rates and adjusted hazard ratios (aHR) were used to estimate the associations.

Results Compared with children without the diagnosis of autism, children with the condition were more likely to be from Asian/Pacific Islander descent and male sex. Exposed children showed higher rates of autism as compared with unexposed children (3.43 vs. 1.73 per 1,000 person-years, aHR: 1.67–95% confidence interval [CI]: 1.39–2.00). Both preterm (aHR: 1.47; 95% CI: 1.09–1.98) and term (aHR: 1.63; 95% CI: 1.29–2.06) births were associated with increased risk for autism. Although the magnitude of the HRs and incidence ratios for neonatal sepsis to increase autism risk varied between race ethnicities, neonatal sepsis was associated with significantly increased likelihood of autism diagnosis for all race-ethic groups except for Asian/Pacific Islanders. Although neonatal sepsis was associated with significantly increased autism risk for both boys and girls, incident rates and HR point estimates suggested that the effect may be stronger in girls.

Conclusion Neonatal sepsis is associated with increased risk of autism diagnosis in preterm- and term-born children. The association was significant for both girls and boys and all race ethnicities except for Asian-Pacific Islanders.

Keywords

- neonatal sepsis
- autism
- autism spectrum disorder
- race
- ethnicity
- race/ethnicity

received
February 1, 2021
accepted after revision
May 12, 2021
article published online
July 5, 2021

DOI https://doi.org/10.1055/s-0041-1731648.
ISSN 0735-1631.

Key Points

- Neonatal sepsis is associated with increased risk of autism diagnosis.
- The association was significant in preterm- and term-born children.
- The association was significant for all race/ethnicities except for Asian-Pacific Islanders.

Autism spectrum disorders (ASD) affect 1 in 59 children in the United States according to the latest data from the Centers for Disease Control and Prevention (CDC).[1] Its prevalence has increased dramatically over the last two decades.[1] The condition persists into adulthood and poses a significant burden to families and healthcare systems.[2,3] In 2015, the annual direct healthcare expenditure associated with ASD and related costs were estimated at $268 billion.[1] This accounts for 0.9 to 2.0% of the nation's gross domestic product and exceeds the costs of hypertension and stroke combined.[4] Due to its fast-growing prevalence, the societal and healthcare costs will continue to rise in years to come.

The patho-etiology mechanism of ASD is largely unknown, but both genetic and environmental factors have been proposed.[5–7] These include a history of mood disorders in family members, having a sibling with autism, advanced parental age, white race/ethnicity, and male sex.[2,7–11] Medical and obstetrical factors including pregestational and gestational diabetes,[12,13] thyroid disorders,[14] hyperemesis gravidarum,[15] multiple births, preterm birth, small for gestational age birth, preeclampsia, and child medical history have also been linked with an increased risk of ASD.[16] Neonatal sepsis is a significant cause of infant morbidity and mortality, especially in neonates born preterm, at very low birth weight, or of black race. The incidence of the condition, especially for early onset (<72 hours) neonatal sepsis, has decreased since the implementation of guidelines[17–19] in the mid-1990s for intrapartum antibiotic prophylaxis to prevent group B streptococcus (GBS) infections.[20] However, infections still affect as many as 2 in 1,000 live births.[21,22] Neonatal sepsis is not only a major cause of hospitalization, but may also have profound effects on brain development that are not apparent until months and years later as the infant matures. Studies with animal models and human subjects have linked neonatal sepsis with adverse neurodevelopment.[23–27] However, all were limited either by sample size or that they only considered short-term adverse neurological outcomes. Although the neonatal sepsis-related mortality rate has dropped in recent years, the impact of neonatal sepsis on the long-term neurodevelopmental sequelae of these surviving children is largely unknown. Furthermore, the risk-modifying effects of timing of diagnosis, gestational age at birth, the child sex, and race/ethnicity on associations between neonatal sepsis and autism require further investigation. Therefore, we examined medical records from a large, sociodemographically diverse population to evaluate the extent to which neonatal sepsis is associated with ASD, and how it is modified by timing of sepsis diagnosis, the gestational age at birth, child's sex, and race/ethnicity.

Materials and Methods

Kaiser Permanente Southern California (KPSC) is a large integrated healthcare system that provides services to over 4.7 million members at 15 hospitals and 234 medical offices throughout Southern California. KPSC's member population is demographically diverse and broadly representative of the racial/ethnic groups living in Southern California. Services are provided through healthcare insurance with pharmaceutical benefits through group plans, individual plans, Medicare, Medicaid, and other low-income programs. On average, 40,000 pregnancies are delivered annually in the KPSC system, and the 5-year retention rate for these children is 75.4%.

We conducted a retrospective cohort study of singleton live born children delivered in all KPSC hospitals from January 1, 1991, to December 31, 2014 ($n = 469{,}789$; ►Appendix 1 [Fig. 1], available in the online version). Children were longitudinally linked to biological mothers by using unique maternal and infant medical record numbers. To be eligible for the study, children had to be born from a member mother and remain a member patient during the follow-up period (follow-up ended in December 31, 2018). The electronic health records (EHR) and pharmacy records contain detailed clinical information as well as drug-dispensing data on medications used to treat the mother and her baby for neonatal sepsis (antibiotics and immunoglobulin). Data on potential confounders and mediators that were extracted from EHRs included: maternal age (<20, 20–29, 30–34, and ≥35 years); educational attainment (<12, 12, and ≥13 years); median family household income based on census tract of residence; parity; smoking during pregnancy (yes/no); timing of prenatal care initiation (first trimester or late/no care); pre-pregnancy body mass index (BMI, kg/m^2) and gestational weight gain; child's characteristics (child's age, sex, and race/ethnicity); and obstetrical history (gestational diabetes [GDM], hyperemesis gravidarum, birth weight, gestational age at delivery based on clinical estimates, Apgar's score, and mode of delivery [cesarean vs. vaginal] and maternal and child medical history [chronic hypertension, pregestational diabetes, hypo/hyperthyroidism, neonatal respiratory distress syndrome [RDS], bronchopulmonary dysplasia [BPD], mechanical ventilation). The accuracy of variables utilized in this study has been previously validated.[28–30] Maternal and paternal race/ethnicity defined the child's race/ethnicity. A child was categorized non-Hispanic White (White) if born to non-Hispanic White mother and father. The same convention

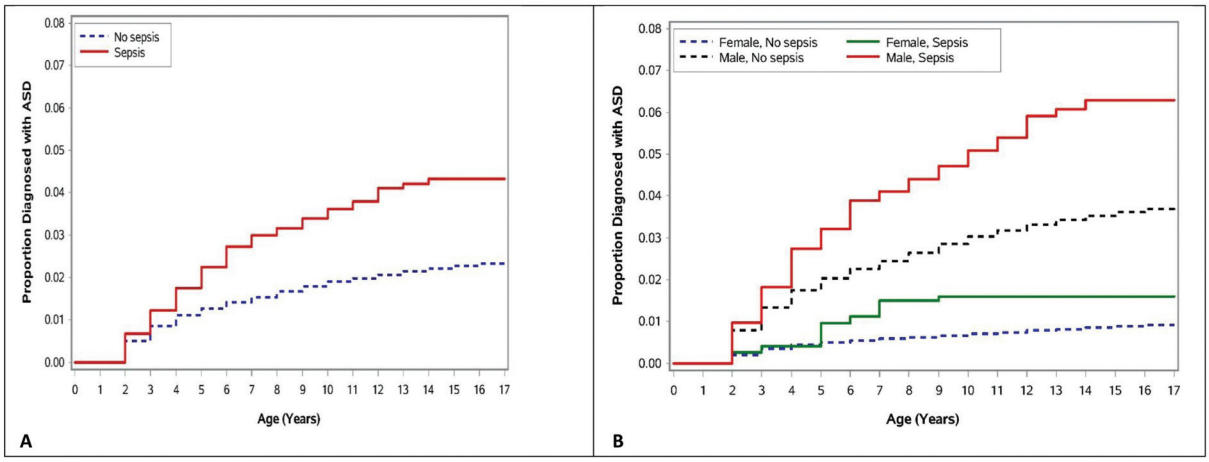

Fig. 1 Kaplan–Meier curves for the accumulation of autism spectrum disorder diagnosis in children with and without sepsis in general (**A**) and stratified by sex (**B**).

was applied to non-Hispanic Black (Black), Hispanic, and Asian/Pacific Islander race/ethnicity groups. The other/mixed race/ethnicity category includes children born from interracial/interethnic relationships. Institutional review board approval with exemption of informed consent was obtained for this study.

Exposure and Outcome

The primary exposure measure was clinical diagnosis of sepsis during the neonatal period ascertained from KPSC's EHRs, regional claim records, and laboratory records. Neonatal sepsis was defined as meeting the following criteria: ICD-9-CM codes for septicemia (038.x) and septic shock (785.5x).

To ascertain a clinical diagnosis of ASD, we used the diagnostic criteria of Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV-TR)[31] for ASD: autistic disorder, childhood disintegrative disorder, Rett's disorder, Asperger's disorder, or pervasive developmental disorder, not otherwise specified. Children, ages between 2 and 17 years, with at least one documented DSM-IV-TR code for ASD on any two separate visits during the follow-up period formed the ASD cases. Clinical experts validated the accuracy of ASD codes through medical record review.[32] As per KPSC guidelines, last revised April 2013,[33] ASD services are covered by healthcare providers (i.e., child/adolescent psychiatrist, developmental/behavioral pediatrician, and child psychologist, or neurologist) who are experts in taking care of children with neurodevelopmental conditions. The experts are required to perform a series of behavioral and developmental surveillance at all well-child visits, as early as 4 months of age. If there is a sufficient degree of suspicion, a modified version of the Checklist for Autism in Toddlers [M-CHAT][34] and developmental screening questionnaires for toddlers will be completed (as early as 18 months of life). For each diagnosed child, a treatment plan is developed and provided by a provider who is qualified in autism services. These criteria ensure that there is consistent testing and opportunity for diagnosis across all KPSC centers during the duration of the study.

Statistical Analysis

Perinatal and neonatal characteristics of children were compared by ASD status using Chi-square tests. Hazard ratios (HR) and their 95% confidence intervals (CI) derived from Cox's proportional hazard models were used to estimate the magnitude of associations before and after accounting for potential confounding factors. Follow-up of the children started from the delivery date until the first date of ASD diagnosis. Censoring occurred on the earliest of the following dates: health plan disenrollment, 17th birthday, non-ASD related death, or end of study (December 31, 2018).

Subgroup analyses for potential mediators: based on the timing of neonatal sepsis exposure, child's race/ethnicity, child's sex, and gestational age at birth were performed. Furthermore, to assess the relative influences of maternal and infant factors: periventricular leukomalacia, neonatal convulsion, other postnatal factors, maternal medical conditions (ischemic hypoxic conditions, endocrine abnormalities, hyperemesis gravidarum on the observed risk relationships, a sensitivity analysis was performed (►**Appendix 2 [Table 1]**, available in the online version) after (1) excluding children with only one ASD diagnosis; (2) excluding children with a history of congenital anomalies and developmental and emotional comorbidities (mental retardation, developmental dyslexia, deficits in language processing, conduct disorder, irritability, bipolar or anxiety disorders, and depression); (3) excluding pregnancies with a history of medical and/or perinatal adversities including gestational hypertension, diabetes, intrauterine growth restriction (IUGR) and low birth weight; (4) excluding children aged 2 to 3 years who may have had shorter follow-up period to capture events; (5) limiting the cohort to children without genetic predisposition; (6) accounting for maternal comorbidities (►**Appendix 2 [Table 2]**, available in the online version); (7) accounting for "year of birth"; (8) accounting for maternal pre-pregnancy BMI; and (9) examining the potential effects of residual confounders on the observed association using a range of E-values for the overall result and the lower limits of their 95% CI observed in Cox's regression

Table 1 Distribution of maternal and infant characteristics based on autism spectrum disorders status

Characteristics	No ASD $n = 461,342$	ASD $n = 8,447$	*p*-Value
Maternal age (%)			<0.001
<20 y	27,632 (98.9)	299 (1.1)	
20–29 y	200,884 (98.4)	3,212 (1.6)	
30–34 y	140,057 (98.1)	2,729 (1.9)	
≥35 y	92,769 (97.7)	2,207 (2.3)	
Maternal education (%)			<0.001
<12 y	47,188 (98.9)	530 (1.1)	
12 y	130,869 (98.4)	2,127 (1.6)	
≥13 y	268,056 (97.9)	5,629 (2.1)	
Median family household income[a] (%)			<0.001
<$29,999	45,589 (98.4)	744 (1.6)	
$30,000–$49,999	158,634 (98.3)	2,768 (1.7)	
$50,000–$69,999	137,170 (98.1)	2,658 (1.9)	
$70,000–$89,999	70,288 (98.1)	1,344 (1.9)	
≥$90,000	46,807 (98.1)	889 (1.9)	
Parity (%)			<0.001
Parity 0	177,881 (97.9)	3,857 (2.1)	
Parity 1	156,302 (98.2)	2,808 (1.8)	
Parity ≥2	127,146 (98.6)	1,782 (1.4)	
Smoking during pregnancy (%)	31,433 (98.4)	527 (1.6)	0.038
Late initiation of prenatal care (%)	42,166 (98.5)	649 (1.5)	<0.001
Mode of delivery (%)			<0.001
Cesarean	109,624 (97.6)	2,643 (2.4)	
Vaginal	351,120 (98.4)	5,794 (1.6)	
Child race/ethnicity (%)			<0.001
Non-Hispanic White	98,821 (98.2)	1,843 (1.8)	
Non-Hispanic Black	39,940 (98.2)	741 (1.8)	
Hispanic	172,994 (98.3)	2,948 (1.7)	
Asian/Pacific Islander	39,927 (97.9)	844 (2.1)	
Other/mixed[b]	103,461 (98.1)	2,010 (1.9)	
Child's sex (%)			<0.001
Female	227,859 (99.3)	1,589 (0.7)	
Male	233,483 (97.1)	6,858 (2.9)	
Gestational age at birth (%)			<0.001
28–36 wk	33,536 (97.6)	820 (2.4)	
37–42 wk	427,806 (98.2)	7,627 (1.8)	
Birth weight (%)			<0.001
<1,500 g	2,469 (97.0)	77 (3.0)	
1,500–2,499 g	19,162 (97.6)	469 (2.4)	
≥2,500 g	439,709 (98.2)	7,901 (1.8)	
SGA birth at <10th percentile (%)	41,529 (98.0)	853 (2.0)	0.002
Apgar's score <7 at 1 min (%)	23,181 (97.7)	549 (2.3)	<0.001
Apgar's score <7 at 5 min (%)	2,689 (97.2)	77 (2.8)	<0.001
Neonatal RDS (%)	9,336 (96.9)	298 (3.1)	<0.001

(*Continued*)

Table 1 (*Continued*)

Characteristics	No ASD $n = 461,342$	ASD $n = 8,447$	*p*-Value
Bronchopulmonary dysplasia (%)	199 (91.3)	19 (8.7)	<0.001
Bilirubin >15 mg/dL (%)	26,845 (97.6)	658 (2.4)	<0.001
Mechanical ventilation (%)	5,659 (96.7)	195 (3.3)	<0.001
NICU admission (1999–2014)[c] (%)	36,242 (97.1)	1,100 (2.9)	<0.001

Abbreviations: ASD, autism spectrum disorder; SGA, small for gestational age at <10th percentile; RDS, respiratory distress syndrome; NICU, neonatal intensive care unit.
[a]Median household income based on census tract information, values in U.S. dollars.
[b]Other/mixed racial/ethnic category includes non-Hispanic children with multiple recorded races.
[c]NICU admission (1999–2014), data on NICU admission was available starting from 1999.
Note: Row percentages in the table are with respect to the total number of observations in each row.

models.[35] The E-values were estimated by using the online calculator for HR with an outcome prevalence of <15%. All analyses were performed by using SAS version 9.4 (SAS institute, Cary, NC).

Results

Mothers of children with ASD were more likely to be older, have ≥13 years of formal education, have a high median family household income, have a history of smoking during pregnancy, and to be nulliparous (►Table 1) than mothers of children without the condition. Compared with children without ASD diagnosis, children with the condition were more likely to have been delivered by cesarean section, have birth weight <2,500 g and shorter gestational ages, have an Apgar's score <7 at 1 and 5 minutes, be from Asian/Pacific Islander racial/ethnic group, be male sex (4:1 male to female ratio), and have the diagnosis of BPD and RDS and require mechanical ventilation during neonatal period (►Table 1).

Between 1991 and 2014, a total of 3,582 (0.8%) neonates were diagnosed with neonatal sepsis and were admitted to KPSC hospitals with NICU facilities (►Table 2). Of those children who met the diagnostic criteria for neonatal sepsis: 2,817 (79%) had the diagnosis made within 24 hours of birth, 162 (4.5%) had the diagnosis between 25 and 72 hours, and 603 (16.8%) had the diagnosis made after 72 hours. Distribution of mean child's age at ASD diagnosis in those with (mean ± standard deviation [SD] = 5.13 ± 3.55 years) and

Table 2 Associations between neonatal sepsis and autism spectrum disorders

Conditions	Total births $n = 469,789$	ASD *n* (IR)[a]	Hazard Ratio (95% CI)	
			Unadjusted	Adjusted[b]
No sepsis	466,207	8,330 (1.73)	1.00 (reference)	1.00 (reference)
Sepsis	3,582	117 (3.43)	1.88 (1.57–2.26)	1.67 (1.39–2.00)
Diagnosis timing				
≤3 d of age	2,979	105 (3.77)	2.05 (1.69–2.48)	1.79 (1.47–2.17)
<1 d of age	2,817	100 (3.80)	2.06 (1.69–2.51)	1.80 (1.43–2.19)
2–3 d of age	162	5 (3.25)	1.81 (0.75–4.35)	1.59 (0.66–3.82)
>3 d of age	603	12 (1.92)	1.10 (0.62–1.93)	1.04 (0.59–1.84)
Gestational age at birth				
28–33 wk	665	27 (4.29)	1.60 (1.06–2.40)	1.61 (1.07–2.42)
34–36 wk	586	18 (3.21)	1.37 (0.86–2.19)	1.23 (0.77–1.97)
37–42 wk	2,331	72 (3.24)	1.83 (1.45–2.30)	1.63 (1.29–2.06)
Birth weight				
<1,500 g	346	17 (5.26)	1.25 (0.80–1.95)	1.79 (1.04–3.08)
1,500–2,499 g	678	20 (3.07)	1.88 (1.10–3.23)	1.13 (0.72–1.77)
≥2,500 g	2,558	80 (3.29)	1.84 (1.47–2.29)	1.63 (1.30–2.03)

Abbreviations: ASD, autism spectrum disorder; CI, confidence interval.
[a]Incidence rate per 1,000 person-years.
[b]Hazard ratios were adjusted for maternal age, education, smoking during pregnancy, parity, prenatal care, household income, child race/ethnicity, and sex.

without (mean ± SD = 5.10 ± 3.55 years) neonatal sepsis were comparable. The number of neonates with neonatal sepsis differed based on gestational age at delivery: 820 (2.4%) at early preterm (28–36 weeks) and 7,627 (1.8%) at term gestation.

Compared with other children, neonates with the diagnosis of sepsis were more likely to have the diagnosis of ASD (1.73/1,000 person-years vs. 3.43/1,000 person-years; adjusted odds ratio [aHR]: 1.67; 95% CI: 1.39–2.00; ►Table 2; ►Fig. 1A). Early neonatal sepsis was associated with a 2.06-fold increased risk of ASD (95% CI: 1.69–2.51). The observed associations of neonatal sepsis with ASD persisted after controlling for several potential confounding factors.

The incidence of ASD diagnosis varied based on child's sex and racial/ethnic background (►Table 3). Neonatal sepsis significantly increased the risk of ASD diagnoses starting at the age of 4 years in boys and 5 years in girls (►Fig. 1B). Although HR for neonatal sepsis was significant for boys and girls, the IR differences and HR were slightly higher for girls (►Table 3), suggesting a stronger relationship. However, tests for heterogeneity of regression analysis of the Kaplan–Meier plots did not detect an interaction between sepsis and child's sex ($p = 0.573$), suggesting similar impact on male and female children. We also did not detect significant interaction between race/ethnicity and neonatal sepsis on the risk of ASD ($p = 0.445$). Neonatal sepsis does seem to influence the incidence (►Appendix 3 [Fig. 1], available in the online version) and risk of ASD in both preterm (aHR: 1.47; 95% CI: 1.09–1.98) and term (aHR: 1.63; 95% CI: 1.29–2.06) gestation.

In a series of sensitivity analyses, we evaluated how different factors such as only one ASD diagnosis, a history of developmental and emotional comorbidities, congenital malformation, excluding children diagnosis prior to age 4 years not confirmed at later age, year of birth, familial predisposition to ASD, maternal BMI, and maternal medical and obstetrical comorbidities may have affected the observed associations. The finding of the overall analysis persisted after accounting for these factors (►Appendix 2 [Table 1], available in the online version). Furthermore, we computed an E-value to assess bias due to potential unmeasured confounders[35] and estimated it at 2.73 (95% CI: 2.66–2.80) for the overall adjusted

Table 3 Rates of neonatal sepsis and its associations with autism spectrum disorders by child's sex and race/ethnicity

Child's characteristics	Total births *n*	ASD, *n* (IR)[a]	Hazard ratios (95% CI)[b]	
			Crude	Adjusted
Female sex				
No sepsis	227,927	1,569 (0.66)	1.00 (reference)	1.00 (reference)
Sepsis	1,521	20 (1.37)	1.98 (1.27–3.08)	1.90 (1.22–2.95)
Male sex				
No sepsis	238,280	6,761 (2.76)	1.00 (reference)	1.00 (reference)
Sepsis	2,061	97 (4.98)	1.70 (1.39–2.08)	1.63 (1.33–1.98)
Non-Hispanic White				
No sepsis	100,117	1,821 (1.75)	1.00 (reference)	1.00 (reference)
Sepsis	547	22 (4.22)	2.31 (1.52–3.52)	2.01 (1.32–3.06)
Non-Hispanic Black				
No sepsis	40,294	728 (1.56)	1.00 (reference)	1.00 (reference)
Sepsis	387	13 (3.30)	1.98 (1.15–3.43)	1.96 (1.13–3.38)
Hispanic				
No sepsis	174,419	2,903 (1.63)	1.00 (reference)	1.00 (reference)
Sepsis	1,523	45 (3.12)	1.80 (1.34–2.42)	1.56 (1.16–2.10)
Asian/Pacific Islander				
No sepsis	40,476	839 (2.10)	1.00 (reference)	1.00 (reference)
Sepsis	295	5 (1.79)	0.82 (0.34–1.98)	0.75 (0.31–1.80)
Other/mixed[c]				
No sepsis	104,653	1,978 (1.89)	1.00 (reference)	1.00 (reference)
Sepsis	818	32 (4.24)	2.13 (1.50–3.02)	1.91 (1.34–2.70)

Abbreviations: ASD, autism spectrum disorder; CI, confidence interval.
[a]Incidence rate per 1,000 person-years.
[b]Hazard ratios were adjusted for maternal age, education, smoking during pregnancy, perinatal care, parity, household income, child's sex, and year of diagnosis.
[c]Others, non-Hispanic children with multiple recorded races.

HR of 1.67 (95% CI: 1.39–2.00). Therefore, a minimum risk ratio of 2.66 would be required between unmeasured confounders and neonatal sepsis exposure, and between unmeasured confounders and ASD to account for the significant association we found between neonatal sepsis and child ASD.

Discussion

Using a large socioeconomically and racially/ethnically diverse sample of children, we demonstrated that neonatal sepsis is associated with increased risk of ASD. This association could not be explained by potential confounding factors, and any unknown, unmeasured, confounders would have to be unusually strong to impact the validity of our findings. The magnitude of association differed by the timing of exposure and was strongest when the exposure occurred during the first 24 hours of life. Neonatal sepsis is associated with increased ASD risk, regardless of the gestational age at birth. We detected an effect of neonatal sepsis for all racial/ethnic groups studied except for Asian/Pacific Islanders. This and the variability in the strength of the association as measured by IRs and HRs suggest that race/ethnicity may be a risk modifying factor. Although both girls and boys with sepsis were at increased risk for ASD, both the IRR (107 vs. 80%) and the HR (1.90 vs. 1.63) were higher for girls suggesting a stronger relationship; however, we did not detect a significant interaction. Therefore, further studies are needed to explore the possibility that different levels of ASD risk associated with neonatal sepsis.

Neonates, especially those born at a very preterm gestation, are at increased risk for developing severe inflammation. In the United States, the incidence of neonatal sepsis has decreased since the mid-1990s[20] due in part to the CDC,[17] the American College of Obstetricians and Gynecologists,[18] and the American Academy of Pediatrics[19] recommendation for intrapartum antibiotic prophylaxis against GBS infection. Despite the implementation of this recommendation and other advancements in neonate care since then, neonatal sepsis remains a significant cause of infant morbidity and mortality. Immaturity or underdevelopment of the immune system has been previously proposed to increase the infants vulnerability to microorganism invasions and systemic infection during the neonatal period.[36] However, a different view on the patho-etiology of neonatal susceptibility to infections has emerged in recent years. Using animal models, Elahi et al[37] demonstrated that CD71+ cell-mediated immune suppression during neonatal period, as opposed to the immaturity of immune cells, make neonates vulnerable to developing infections.[37] Sepsis-induced inflammation and oxidative stress on neurons have often been reported for immuno-compromised patients. The same mechanism may be at work in neonates whose brain cellular components are especially susceptible to oxidative damage from infections resulting in adverse neurodevelopment.

Our findings are consistent with a previous study performed in Denmark that also reported an association between neonatal sepsis and ASD that appeared to be dependent on gestational age at birth.[38] However, we also found significant race/ethnicity differences as well as timing of neonatal sepsis diagnosis that modify the observed associations.

Neonatal sepsis at a vulnerable period in brain development increases the risk for long-term adverse outcomes that impact the child's behavior and achievement. This is most clear when it occurs in the first 24 hours of life, as it has been shown in our study. This association has been supported by previous animal model and human epidemiological studies demonstrating an increase in the white matter injury and periventricular leukomalacia in early-onset neonatal sepsis.[39–43] Furthermore, changes in synapse formation that may be affected by inflammation that could also be associated with ASD has been suggested.[44] Moreover, adjusting for potential pre- and postnatal factors did not affect the magnitude of association, suggesting an independent effect of neonatal sepsis on ASD risk.

Consistent with recent studies, we found substantial sex-related variation in the associations between perinatal factors and ASD diagnosis rates.[7,14,15] After controlling for several confounding factors, ASD diagnosis rates were higher in males. However, the ASD risk in relation to neonatal sepsis was similar in both boys and girls (no interaction between sepsis and child's sex) suggesting that there are no neuroprotective effects of estrogens on sepsis-mediated neurodevelopmental changes in these very young age children as there is in older women with Parkinson's disease[45,46] and Alzheimer's disease.[47,48] Our study also shows important race/ethnic variation in ASD diagnosis and its relation to a history of neonatal sepsis. Using a stratified analysis, we found that the risk of ASD later in life was significantly higher in White, Black, Hispanic, and other racial/ethnic groups but not in Asian/Pacific Islander children with a history of neonatal sepsis compared with children from respective racial/ethnic background without a history of neonatal sepsis. These variations in the incidence rates of neonatal sepsis and the heterogeneity in ASD risk across racial/ethnic groups observed in our study may stem from differences in the rate of intrapartum antibiotic prophylaxis utilization and the known racial/ethnic differences in the rates of neonatal sepsis, preterm birth and low birth weight,[21,49,50] but genetic polymorphism variation and socioeconomic deprivation may also contribute.[51] Although we adjusted for gestational age, birth weight, maternal education and median family income in the race/ethnicity-specific analysis, we lack data on genetic polymorphisms that may account for these differences. The use of older siblings and mothers with ASD diagnosis as a proxy for genetic predisposition did not alter our findings (►**Appendix 2 [Table 1]**, available in the online version), however.

Strengths of this study include health information extracted from a large integrated health care system's EHRs, use of a sociodemographically diverse population that is representative of the Southern California population, and controlling for several potential confounding factors. Other key strengths of this study are ASD diagnosis by medical specialists, maternal-child medical history extracted from virtually complete and already validated EHRs,[28–30] and a follow-up period from birth until 17 years

of age. This ensures that all children in the study had the same baseline probability of being diagnosed with ASD by medical professionals.

Like all epidemiologic observational studies, this one also has some imitations. First, causality cannot be established because of the retrospective nature of this study design. Second, data on history of maternal smoking during pregnancy, a known risk factor for childhood behavioral and cognitive impairments,[52] was self-reported by mothers at prenatal visits. The validity of self-reported tobacco use is often questioned because of pressure women feel to not smoke during pregnancy may result in underreporting of this common habit. However, Buka et al[53] found strong agreement between self-reported smoking and serum cotinine levels suggesting that self-report is a valid tool for quantifying tobacco use in pregnancy. Third, surveillance bias can occur when exposed and unexposed children differ in measurement (the intensity and diagnostic process) of health outcome during the follow-up period leading to unequal ascertainment of ASD events. We minimized this possibility by including only clinically diagnosed and validated ASD cases.[32,33]

Conclusion

Our findings of this study suggest that neonatal sepsis is a predictor of ASD risk later in life. Therefore, preventive measures for early neonatal sepsis may be crucial to preventing adverse neurodevelopmental sequalae that do not become apparent until later in life. The strong association observed between neonatal sepsis within 24 hours of life and ASD risk suggest that early inflammatory processes may have profound effects. The association between neonatal sepsis and ASD risk is higher for White, Black, and Hispanic children, but not for Asian/Pacific Islanders. The drivers of these disparities are not clear and need to be investigated further.

Note

The opinions expressed are solely the responsibility of the authors and do not necessarily reflect the official views of the Kaiser Permanente Community Benefit Funds.

Authors' Contributions

D.G. obtained funding, conceptualized and designed the study, acquired data, analyzed and interpreted data, drafted the initial manuscript, and reviewed and revised the manuscript for important intellectual content. M.J.F., A.H.X., S.F.S., M.R.P., and H.S.T. conceptualized and designed the study and critically reviewed the manuscript for important intellectual content. V.Y.C. designed the study, acquired data, performed analyses, and reviewed and revised the manuscript.

Funding

This study was supported in part by Kaiser Permanente Direct Community Benefit Funds.

Conflict of Interest

None declared.

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