Prevalence and Neonatal Factors Associated with Autism Spectrum Disorders in Preterm Infants

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Objectives To determine the prevalence of autism spectrum disorders (ASD) across gestational age, examine the risk of ASD by gestational age controlling for other risk factors, and identify potential risk factors in the neonatal intensive care unit.

Study design A retrospective cohort of infants born at ≥24 weeks between January 1, 2000, and December 31, 2007 at 11 Kaiser Permanente Northern California hospitals (n = 195 021). ASD cases were defined by a diagnosis made at a Kaiser Permanente ASD evaluation center, by a clinical specialist, or by a pediatrician. Cox proportional hazards regression models were used to evaluate the association between gestational age and ASD as well as potential risk factors in the neonatal intensive care unit and ASD.

Results The prevalence of ASD in infants <37 weeks was 1.78% compared with 1.22% in infants born ≥37 weeks ($P < .001$). Compared with term infants, infants born at 24-26 weeks had an adjusted hazard ratio (HR) for a diagnosis of ASD of 2.7 (95% CI 1.5-5.0). Infants born at 27-33 weeks (adjusted HR 1.4, 95% CI 1.1-1.8) and 34-36 weeks (adjusted HR 1.3, 95% CI 1.1-1.4) were also at increased risk. High frequency ventilation and intracranial hemorrhage were associated with ASD in infants < 34 weeks.

Conclusions ASD was ~3 times more prevalent in infants <27 weeks compared with term infants. Each week of shorter gestation was associated with an increased risk of ASD. High frequency ventilation and intracranial hemorrhage were associated with ASD among infants <34 weeks. *(J Pediatr 2014;164:20-5)*.

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Autism spectrum disorders (ASD) are a range of conditions characterized by impairments in communication, social interaction, and behavioral problems. These disorders include autism, pervasive developmental disorder not otherwise specified, and Asperger syndrome. The most recent Centers for Disease Control and Prevention estimate of prevalence of ASD in the US is 1 in 88 children,[1] a large increase since the first estimate of 4-5 per 10 000 was published in the mid-1960s.[2] However, the prevalence in infants born prematurely may be much higher. Both prematurity and low birth weight are associated with an increased risk of autism.[3-9] Prospective studies of surviving premature infants have shown high rates of positive screening results using the Modified Checklist for Autism in Toddlers at 2 years of age. Kuban et al found a 21% positive screen prevalence in infants <28 weeks gestation,[10] and Limperopoulos et al found a 26% positive screen prevalence in infants with a birth weight <1500 g, compared with 5.7% positive screen prevalence in unselected children.[11] Hack et al screened former extremely low birth weight infants with the Parent Child Symptom Inventory at 4 and 8 years of age and reported a 4% positive screening prevalence for ASD, compared with a 0.6% positive screening prevalence in normal birth weight controls.[12] Developmental impairments other than ASD that occur frequently in extremely low birth weight or extremely low gestational age infants may explain the high screening prevalence; however, Kuban et al found that after eliminating all children with impairments, the positive screen prevalence remained quite high (16% in infants <28 weeks).[10]

There is a limited literature on the prevalence of actual ASD diagnoses among infants born prematurely. Johnson et al studied children who were born at <26 weeks of gestation and compared them with term-born classmates at 11 years of age.[13] In this study, 16/201 (8%) of the preterm children were diagnosed with ASD using the Development and Well Being interview, and none of the classmates received an ASD diagnosis. Other studies of school-aged

ASD	Autism spectrum disorders	ICD-9-CM	ICD-9-clinical modification
CDER	Client Development and Evaluation Report	ICH	Intracranial hemorrhage
		KP	Kaiser Permanente
DDS	Developmental Services	KPNC	Kaiser Permanente Northern California
EDC	Estimated date of confinement		
HR	Hazard ratio	NICU	Neonatal intensive care unit
ICD-9	*International Classification of Diseases, 9th revision*	SGA	Small for gestational age

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outcomes in low birth weight and very low birth weight infants have found a prevalence of ASD of 1%-2%, based on the Asperger Syndrome Diagnostic Interview and the Autism Spectrum Screening Questionnaire.[6,14] Pinto-Martin estimated the prevalence of ASD in infants weighing <2000 g at birth to be 5% after evaluating a subgroup of 189 individuals from the National Brain Hemorrhage Study Cohort at 21 years of age with the Autism Diagnostic Observation Schedule or Autism Diagnostic Interview, revised.[15]

Research on the association between preterm delivery and ASD has thus far focused on all preterm infants as a group[9,16,17] or on the most severely premature infants.[13,18-20] Investigating risk across the entire gestational age spectrum and exploring the impact of illnesses and interventions during the birth hospitalization on risk may provide additional insight into the association between prematurity and ASD. The objectives of this study were to: (1) determine the prevalence of ASD across the spectrum of gestational age in a large, representative, population-based sample; (2) examine the risk of ASD associated with gestational age independent of other risk factors; and (3) identify factors in the neonatal intensive care unit (NICU) hospitalization that might explain the association between gestational age and ASD risk.

Methods

The study population was drawn from the cohort of infants born alive at a gestational age of ≥24 weeks between January 1, 2000, and December 31, 2007 at one of 11 Kaiser Permanente Northern California (KPNC) hospitals and who survived to discharge (n = 235 198). KPNC serves a population of 3.3 million members, which constitutes ~30% of the insured population in northern California. Except for the lowest and highest income earners, the KPNC membership is representative of the total population in the region.[21] Infants with missing data on gestational age (n = 368), sex (n = 1), missing maternal age (n = 135), and infants who transferred out of KPNC during their birth hospitalization (n = 253) were excluded. Children who did not remain in the health plan at 2 years of age were also excluded (n = 39 420) leaving 195 021 children for the primary analyses. Children who left the health plan were similar to children who remained in the health plan in regards to sex, rate of prematurity, and percentage of non-Hispanic whites. The mothers of children who left the health plan were more likely to be <30 years of age (55% vs 45%, $P < .001$). The KPNC Institutional Board for the Protection of Human Subjects and the State of California Institutional Review Board approved this study.

Predictor Variables for ASD

Gestational age was determined from the maternal record and defined according to the obstetrically assigned estimated date of confinement (EDC). For women with regular menstrual cycles, EDC was based on last menstrual period if in 7-day agreement with a first trimester ultrasound. For women with irregular menstrual cycles, EDC was determined from first trimester ultrasound results. Sex, maternal age, birth weight, maternal race/ethnicity, multiple gestation, and 5-minute Apgar score were from Kaiser Permanente (KP) administrative databases. Small/large for gestational age was determined by plotting the infant's weight and gestational age on the Fenton curves, using <5th percentile as a cut-off for small for gestational age (SGA) and >95th percentile for large for gestational age.[22] Chorioamnionitis, preeclampsia, and hypoglycemia were determined from the *International Classification of Diseases, 9th revision* (ICD-9) codes. Maternal education was from the infant's birth certificate.

Predictor Variables in Infants <34 Weeks

At KPNC, all infants delivered at <34 gestational weeks are admitted to a NICU. For these infants, we obtained detailed information on complications and interventions occurring during the NICU admission from the KPNC neonatal minimum data set.[23] Data in the neonatal minimum data set are captured through manual chart abstraction by medical record abstractors and through electronic collection from the electronic medical record. The following diagnoses and procedures were included for this analysis: necrotizing enterocolitis (Bell stage ≥II),[24] mechanical ventilation, intracranial hemorrhage (ICH), cystic periventricular leukomalacia, transfusion, inotropic support (dopamine/dobutamine/or epinephrine infusions), bacteremia, and difficult delivery room resuscitation (need for chest compressions or epinephrine). Standardized definitions of neonatal diagnoses are adapted from the Vermont Oxford Network data definitions.[25]

Outcome Variables

The birth cohort was linked to the KP Autism Registry.[26-29] The registry contains the location, provider, provider specialty, and date of any ASD diagnosis recorded in KP outpatient databases. Children with a diagnosis of autism (ICD-9 299.0), Asperger syndrome or pervasive developmental disorder not otherwise specified (ICD-9 299.8), were identified.[30] We retrieved all ASD diagnoses made through January 31, 2011. The minimum age of children in the cohort was 3 years of age at time we assessed the ASD registry.

For the primary analyses, KP ASD cases (n = 2462) were defined as children with at least 1 diagnosis of ASD made at a KP ASD evaluation center, or by a clinical specialist (psychiatrist, psychologist, developmental pediatrician) outside of the ASD evaluation center, or by a general pediatrician. The subgroup of children diagnosed at an ASD evaluation center were classified as KP definite ASD cases (n = 1418). They received a standardized assessment by a multidisciplinary clinical team including: child and adolescent psychiatrists and psychologists, general and developmental pediatricians, and social workers. The assessment protocol includes the Autism Diagnostic Observation Schedule,[31] a parent interview based on the Autism Diagnostic Interview, revised,[32] and evaluation of cognitive and adaptive functioning.

An additional group of children who had a diagnosis of "rule-out ASD" were classified as rule-out ASD cases (n = 454). These children had symptomatology suggestive of ASD but did not have a formal evaluation or there was insufficient information