


# Association of Autism Spectrum Disorders With Neonatal Hyperbilirubinemia

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## Abstract

Autism spectrum disorders (ASD) are a common neurodevelopmental disorder of unknown etiology. Studies suggest a link between autism and neonatal jaundice. A 1:3 matched case-control study was conducted with children enrolled in the Military Health System born between October 2002 and September 2009. Diagnostic and procedure codes were used for identifying ASD and hyperbilirubinemia. Two definitions for hyperbilirubinemia were evaluated: an inpatient admission with a diagnosis of jaundice and treatment with phototherapy. A total of 2917 children with ASD and 8751 matched controls were included in the study. After adjustment, there remained an association between ASD in children and an admission with a diagnosis of jaundice (odds ratio = 1.18; 95% confidence interval = 1.06-1.31;  $P = .001$ ) and phototherapy treatment (odds ratio = 1.33; 95% confidence interval = 1.04-1.69;  $P = .008$ ). Children who develop ASD are more likely to have an admission with a diagnosis of jaundice in the neonatal period and more likely to require treatment for this jaundice.

## Keywords

autism, hyperbilirubinemia, neonatal jaundice, pervasive developmental disorders, autism spectrum disorders, phototherapy

## Introduction

Autism spectrum disorders (ASD) include a group of neurodevelopmental disorders characterized by impairments in 3 major domains: socialization, communication, and behavior. ASD is a common neurodevelopmental disorder in children and has an increasing incidence.<sup>1-7</sup> The causes of ASD are not well understood<sup>3,6</sup>; however, the etiology of ASD is likely a combination of genetic predisposition interacting with environmental factors in early life.<sup>1,2,5,8,9</sup> It is postulated that a risk factor of ASD should occur frequently enough to explain the high prevalence of ASD and have the potential for brain injury.<sup>10</sup>

Neonatal unconjugated hyperbilirubinemia (jaundice) is very common in the newborn period. Bilirubin is a product of heme catabolism and at low levels a beneficial antioxidant, but at higher levels is neurotoxic to the normal development of a neonatal brain. Bilirubin neurotoxicity has a spectrum of manifestations, with kernicterus being the most severe outcome among survivors.<sup>11,12</sup> A specific threshold-based relationship between serum bilirubin and neurotoxicity has been elusive.<sup>11</sup>

A recent meta-analysis of 13 studies has shown that ASD is associated with neonatal hyperbilirubinemia.<sup>10</sup> The majority of the studies included in the meta-analysis, however, were small (<400 subjects), did not account for confounding of factors such as prematurity, or used a variety of definitions for jaundice and ASD.<sup>10</sup> Utilizing a large US health care database representing a heterogeneous, demographically and socioeconomically diverse population, we sought to expand on previous smaller studies evaluating the risk of ASD among infants with a history of neonatal unconjugated hyperbilirubinemia (jaundice), while utilizing a more refined definition of both neonatal jaundice and ASD.

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**Table 1.** Characteristics of Children With Autism Spectrum Disorders and Matched Controls.

	ASD Cases (n = 2917)	Sex- and Age-Matched Controls (n = 8751)	P Value
Male, n (%)	2281 (78.2)	6843 (78.2)	1.0
Born during months April through September, n (%)	1475 (50.6)	4305 (49.2)	.20
Prematurity, n (%)	225 (7.7)	512 (5.9)	<.001
Firstborn, n (%)	980 (33.6)	2735 (31.3)	.02
Product of multiple gestation, n (%)	139 (4.8)	214 (2.5)	<.001

Abbreviation: ASD, autism spectrum disorders.

**Table 2.** Unadjusted and Adjusted Odds Ratios (Confidence Intervals) of the Diagnosis of Autism Spectrum Disorders Associated With Neonatal Jaundice.

	Admission With Jaundice as Surrogate for Exposure		Phototherapy as Surrogate for Exposure	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Jaundice	1.24 (1.12-1.38)	1.18 (1.06-1.31)	1.47 (1.16-1.86)	1.33 (1.04-1.69)
Prematurity <sup>a</sup>	1.35 (1.15-1.59)	1.10 (0.92-1.32)	13.6 (8.96-20.5)	1.12 (0.94-1.34)
Multiple gestation	2.00 (1.61-2.49)	1.87 (1.45-2.35)	4.07 (2.44-6.80)	1.90 (1.51-2.39)
Firstborn	1.13 (1.03-1.24)	1.15 (1.04-1.26)	1.27 (0.93-1.73)	1.15 (1.04-1.26)
April-September birth	1.07 (0.97-1.17)	1.07 (0.97-1.17)	0.97 (0.73-1.28)	1.06 (0.97-1.17)

<sup>a</sup>Prematurity defined as gestation <37 weeks.

## Patients and Methods

A matched case-control study was designed. All patient data were obtained from the TRICARE Management Activity's Military Health System (MHS) database, which oversees all health care delivery for the US military and their family members. Children born between October 1, 2000, and September 30, 2009, were eligible for inclusion. Children with ASD were identified as those with at least one outpatient visit to a pediatric specialist—neurologist, psychiatrist, or developmental behavioral pediatrician with an International Classification of Diseases, Ninth Edition Clinical Modification (ICD-9-CM) diagnostic code for ASD (299.0X, 299.8X, 299.9X) from October 1, 2002, through September 30, 2012. For each case, 3 controls without any outpatient diagnoses of ASD (given by a specialist or a generalist) were selected and matched on gender and age (birth date within 90-day period). The demographic information, enrollment date, birth order, and inpatient birth health claims records, including information on discharge diagnoses and procedures of each case and control, were extracted.

For the primary exposure of jaundice, 2 definitions were used and investigated. The first definition was a diagnosis of jaundice during the hospital stay associated with birth, or during an admission within the first month of life. The second definition was any phototherapy or

exchange transfusion procedure in the first month of life. Documentation of phototherapy or exchange transfusion was defined as an indication of more severe hyperbilirubinemia compared with an admission for jaundice without those procedures. ICD-9-CM diagnostic and procedure codes utilized for the definition of jaundice are listed in Supplemental Tables 1 and 2 (available online at <http://gph.sagepub.com/content/by/supplemental-data>).

Prematurity was defined as birth before 37 weeks gestational age and was identified using ICD-9-CM codes at the birth admission. Multiple gestation was similarly identified. Season of birth was categorized into birth in the colder months (October-March) versus birth in the warmer months (April-September).

McNeman's test determined the unadjusted odds ratio (OR) of the development of ASD with a history of neonatal jaundice, as previously defined. Multivariate conditional logistic regression determined ORs in adjusted analyses. Birth season, prematurity, multiple gestation, and birth order were considered as independent variables in multivariate models. *P* values <.05 were considered significant. Analyses were conducted using Stata Intercooled 10 (Stata Corp, College Station, TX). This study was reviewed and approved by the responsible institutional review boards.

## Results

There were 783 047 children who had a birth record available and 2917 of these were diagnosed with ASD by a specialist between 2002 and 2012 in the MHS database. The median age of ASD diagnosis was 5.3 years (interquartile range [IQR] = 3.8-7.2 years). Of children with ASD, 80% of cases were male, 7.7% were born premature, and 34% were firstborn. April to September births accounted for 51% of the cases. Characteristics of included cases are shown in Table 1. Controls included 8751 gender- and age-matched subjects without an ASD diagnosis.

Admissions for neonatal jaundice occurred in 19% of all subjects, and a procedure for treating hyperbilirubinemia was recorded in 2.8%. Of subjects who received a procedural treatment for jaundice, 100% had phototherapy and only one subject received an exchange transfusion for jaundice.

A history of admission with a diagnosis of neonatal jaundice was present in 640 (21.9%) of children with ASD compared with 1614 (18.4%) of controls ( $P < .001$ ). A procedural treatment for jaundice was documented in 107 (3.7%) of children with ASD and 221 (2.5%) of controls ( $P < .001$ ).

In unadjusted conditional logistic regression, there was a 24% increased odds of ASD in children who had an inpatient diagnosis of jaundice (OR = 1.24; 95% confidence interval [CI] = 1.22-1.38;  $P < .001$ ). There was a 47% increased odds of ASD in children who required phototherapy (OR = 1.47; 95% CI = 1.16-1.86;  $P = .001$ ). After adjusting for season of birth, birth order, multiple gestation, and prematurity, odds of ASD were increased in children with an admission for jaundice (OR = 1.18; 95% CI = 1.06-1.31;  $P = .001$ ). Using the procedure code for phototherapy as a more rigorous definition/confirmation of jaundice, the increased adjusted odds of ASD remained significant (OR = 1.33; 95% CI = 1.04-1.69;  $P = .008$ ). Point estimates and confidence intervals of odds ratios for covariates as determined by multivariate models are shown in Table 2.

A separate subgroup analysis of only preterm infants resulted in loss of the significant association between ASD and jaundice (unadjusted OR = 1.08; 95% CI = 0.78-1.49;  $P = .65$ ). After adjusting for season of birth, birth order, and multiple gestation, the association remained nonsignificant (OR = 1.06; 95% CI = 0.77-1.47;  $P = .71$ ). In preterm infants, phototherapy treatment was also not significantly associated with ASD (unadjusted OR = 0.98; 95% CI = 0.65-1.47;  $P = .91$ ; and adjusted OR = 0.99; 95% CI = 0.66-1.48;  $P = .94$ ).

## Discussion

Our study demonstrates an association between a diagnosis of ASD and previous hospitalization with a diagnosis of neonatal hyperbilirubinemia or treatment for hyperbilirubinemia in the neonatal period. The large number of cases of ASD and more rigorous definitions of clinically significant jaundice using inpatient admissions and treatments for jaundice strengthen the evidence for an association between hyperbilirubinemia and ASD.

There is biologic plausibility to suggest an association between bilirubin and ASD. Hyperbilirubinemia occurs frequently enough to explain the high prevalence of ASD and has the potential to cause brain injury. Bilirubin is a known neurotoxin. The globus pallidus, cerebellum, hippocampus, and subthalamic nuclear bodies have been identified as areas in the brain vulnerable to bilirubin toxicity.<sup>11,13</sup> There is evidence of lower gray matter volumes in the putamen and cerebellar hypoplasia in individuals with autism, creating a degree of overlap that may indicate shared mechanisms.<sup>14-16</sup> Additionally, there is overlap in the clinical features of bilirubin-induced neurologic dysfunction (BIND) and ASD. BIND may present with neuromotor abnormalities, muscle tone abnormalities, hyperexcitable neonatal reflexes, neurobehavior manifestations, speech and language abnormalities, and central processing abnormalities, such as sensorineural, audiological, and visuospatial dysfunctions.<sup>11</sup> Clinical features of ASD include social and communication impairment, rigid ritualistic interests, behavioral abnormalities, and can include intellectual disability.<sup>17</sup>

Our findings from a demographically and geographically diverse population are consistent with previous reports. The median age of ASD diagnosis (5.3 years) and male preponderance (80%) of children with ASD in our cohort are similar to other estimates.<sup>4,18,19</sup> The season of birth was not significantly associated with an increased risk for ASD in our cohort, contrary to other studies that found an association in children born in colder months (between October and March).<sup>20</sup> The geographically dispersed distribution of our cohort may explain this discrepancy.

As in the majority of other studies, we defined autism by ICD-9-CM codes.<sup>9,20,21</sup> However, we sought to use a more strict definition of ASD by restricting the cases to children with a diagnosis obtained from an outpatient visit with a pediatric subspecialist (neurologist, psychiatrist, developmental behavioral pediatrician). In the 7 previously published studies specifically addressing jaundice as a risk factor for ASD, 4 required specialist-diagnosed ASD or utilized the Autism Diagnostic

Interview–Revised criteria.<sup>9,20,22,23</sup> In all 4 of these studies, jaundice was significantly associated with ASD. The 2 studies showing no association did not specify whether a general pediatrician or a pediatric subspecialist assigned the ASD ICD codes.<sup>18,24</sup> Buchmayer et al defined ASD cases through utilization of an inpatient database, which may result in an overrepresentation of severe cases.<sup>24</sup> Additionally, their study used admission diagnoses, which raised the possibility that ASD may only have been a suspected diagnosis from the referring pediatrician, increasing the chance misclassification bias of noncases to be included in the ASD group resulting in an underestimate of the risk.

Of the infants included in our study, 19.3% met criteria for neonatal jaundice. Previous association studies have been criticized for the low prevalence of jaundice when it has been estimated that 60% to 80% of newborns experience jaundice.<sup>25</sup> In an attempt to capture only early jaundice and clinically significant jaundice, we included only ICD-9-CM codes linked to an inpatient admission. Our jaundice rate is the result of a more stringent definition of jaundice and is similar to previous association studies.<sup>26</sup> Furthermore, the only other study that limited classification of jaundice to the first 30 days of life found only 27.8% of their cases had a bilirubin level drawn.<sup>18</sup> Our study did not aim to capture all cases of jaundice but rather clinically significant jaundice warranting laboratory analysis or inpatient admission.

Only 2 previous studies investigating the association between neonatal jaundice and ASD have conducted separate analyses for preterm infants.<sup>24,27</sup> Similar to our findings neither study found a significant association in the preterm infant group. A meta-analysis combined these 2 studies, for fewer cases than our study, and found no significant association between neonatal jaundice and ASD in premature infants.<sup>10</sup> This finding may be due to differences in bilirubin metabolism and pathogenesis of neurotoxicity between term and preterm infants.

We were not able to control for gestational age but only prematurity as defined by gestational age <37 weeks. This may slightly overestimate the association between jaundice and ASD as clinical estimates of risk, which determine the need for admission and for treatment, are based on bilirubin levels in conjunction with gestational age, hours of life, and an infant's overall stability. A specific dose–response relationship and clinical signs of neurotoxicity have not been established. Our study did not have bilirubin levels available to investigate for a specific dose–response relationship with ASD. There is a chance that cases of ASD would not have been captured as subjects with

ASD diagnosis was only captured up until 2012, resulting in possible misclassification bias of children born in 2008–2009.

This study has several strengths that distinguish it from prior work on this topic. In contrast to prior studies, we report a large number of cases of ASD using more strict and validated definitions. Our population is geographically, demographically, and socioeconomically diverse and representative of the US population as a whole. We compensated for potential misclassifications by implementing strict definitions of hyperbilirubinemia (only those who were inpatient or who required treatment) and for ASD (diagnosis made by a pediatric subspecialist). We included all subjects with the diagnosis of ASD made by a subspecialist during the study period, making it unlikely to be affected by selection bias.

In conclusion, our study provides further evidence that neonatal unconjugated hyperbilirubinemia is associated with the development of ASD. The estimates are consistent with prior literature and there is biologic plausibility. Further prospective studies are needed to clarify specific serum levels of bilirubin in combination with other neonatal risk factors that mediate the association of jaundice and ASD.

### Authors' Note

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### Author Contributions

LEL contributed to conception and design, data interpretation and drafted the manuscript. CMN contributed to conception and design, acquisition and data analysis. DK contributed to design, analysis and interpretation of the data. GHG contributed to design, acquisition and data analysis. EHG and CREL contributed to data interpretation. CMN, DK, GHG, and EHG critically reviewed the manuscript. All authors approved the final manuscript as submitted.

### Declaration of Conflicting Interests

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## References

- Braunschweig D, Van de Water J. Maternal autoantibodies in autism. *Arch Neurol*. 2012;69:693-699. doi:10.1001/archneurol.2011.2506.
- Guinchat V, Thorsen P, Laurent C, Cans C, Bodeau N, Cohen D. Pre-, peri- and neonatal risk factors for autism. *Acta Obstet Gynecol Scand*. 2012;91:287-300. doi:10.1111/j.1600-0412.2011.01325.x.
- Gardener H, Spiegelman D, Buka SL. Prenatal risk factors for autism: comprehensive meta-analysis. *Br J Psychiatry*. 2009;195:7-14. doi:10.1192/bjp.bp.108.051672.
- Parner ET, Schendel DE, Thorsen P. Autism prevalence trends over time in Denmark: changes in prevalence and age at diagnosis. *Arch Pediatr Adolesc Med*. 2008;162:1150-1156. doi:10.1001/archpedi.162.12.1150.
- Kolevzon A, Gross R, Reichenberg A. Prenatal and perinatal risk factors for autism: a review and integration of findings. *Arch Pediatr Adolesc Med*. 2007;161:326-333. doi:10.1001/archpedi.161.4.326.
- Glasson EJ, Bower C, Petterson B, de Klerk N, Chaney G, Hallmayer JF. Perinatal factors and the development of autism: a population study. *Arch Gen Psychiatry*. 2004;61:618-627. doi:10.1001/archpsyc.61.6.618.
- Mazumdar S, Liu KY, Susser E, Bearman P. The disappearing seasonality of autism conceptions in California. *PLoS One*. 2012;7:e41265. doi:10.1371/journal.pone.0041265.
- Rosenberg RE, Law JK, Yenokyan G, McGready J, Kaufmann WE, Law PA. Characteristics and concordance of autism spectrum disorders among 277 twin pairs. *Arch Pediatr Adolesc Med*. 2009;163:907-914. doi:10.1001/archpediatrics.2009.98.
- Maimburg RD, Vaeth M. Perinatal risk factors and infantile autism. *Acta Psychiatr Scand*. 2006;114:257-264. doi:10.1111/j.1600-0447.2006.00805.x.
- Amin SB, Smith T, Wang H. Is neonatal jaundice associated with autism spectrum disorders: a systematic review. *J Autism Dev Disord*. 2011;41:1455-1463. doi:10.1007/s10803-010-1169-6.
- Bhutani VK, Johnson-Hammerman L. The clinical syndrome of bilirubin-induced neurologic dysfunction. *Semin Fetal Neonatal Med*. 2015;20:6-13. doi:10.1016/j.siny.2014.12.008.
- Shapiro SM. Definition of the clinical spectrum of kernicterus and bilirubin-induced neurologic dysfunction (BIND). *J Perinatol*. 2005;25:54-59. doi:10.1038/sj.jp.7211157.
- Bhutani VK, Wong R. Bilirubin-induced neurologic dysfunction (BIND). *Semin Fetal Neonatal Med*. 2015;20:1. doi:10.1016/j.siny.2014.12.010.
- Bauman ML, Kemper TL. Neuroanatomic observations of the brain in autism: a review and future directions. *Int J Dev Neurosci*. 2005;23:183-187. doi:10.1016/j.ijdevneu.2004.09.006.
- Palmen SJMC, van Engeland H, Hof PR, Schmitz C. Neuropathological findings in autism. *Brain*. 2004;127(pt 12):2572-2583. doi:10.1093/brain/awh287.
- Cheung C, Yu K, Fung G, et al. Autistic disorders and schizophrenia: related or remote? An anatomical likelihood estimation. *PLoS One*. 2010;5:e12233. doi:10.1371/journal.pone.0012233.
- Nazeer A, Ghaziuddin M. Autism spectrum disorders: clinical features and diagnosis. *Pediatr Clin North Am*. 2012;59:19-25. doi:10.1016/j.pcl.2011.10.007.
- Croen LA, Yoshida CK, Odouli R, Newman TB. Neonatal hyperbilirubinemia and risk of autism spectrum disorders. *Pediatrics*. 2005;115:e135-e138. doi:10.1542/peds.2004-1870.
- Developmental Disabilities Monitoring Network Surveillance Year 2010 Principal Investigators, Centers for Disease Control and Prevention (CDC). Prevalence of autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 sites, United States, 2010. *MMWR Surveill Summ*. 2014;63(2):1-21.
- Maimburg RD, Bech BH, Vaeth M, Møller-Madsen B, Olsen J. Neonatal jaundice, autism, and other disorders of psychological development. *Pediatrics*. 2010;126:872-878. doi:10.1542/peds.2010-0052.
- Chen WX, Wong VCN, Wong KY. Neurodevelopmental outcome of severe neonatal hemolytic hyperbilirubinemia. *J Child Neurol*. 2006;21:474-479.
- Juul-Dam N, Townsend J, Courchesne E. Prenatal, perinatal, and neonatal factors in autism, pervasive developmental disorder-not otherwise specified, and the general population. *Pediatrics*. 2001;107:E63.
- Sugie Y, Sugie H, Fukuda T, Ito M. Neonatal factors in infants with autistic disorder and typically developing infants. *Autism*. 2005;9:487-494. doi:10.1177/1362361305057877.
- Buchmayer S, Johansson S, Johansson A, Hultman CM, Sparén P, Cnattingius S. Can association between preterm birth and autism be explained by maternal or neonatal morbidity? *Pediatrics*. 2009;124:e817-e825. doi:10.1542/peds.2008-3582.
- Newman TB, Liljestrand P, Jeremy RJ, et al; Jaundice and Infant Feeding Study Team. Outcomes among newborns with total serum bilirubin levels of 25 mg per deciliter or more. *N Engl J Med*. 2006;354:1889-1900. doi:10.1056/NEJMoa054244.
- Wong F, Boo N, Othman A. Risk factors associated with unconjugated neonatal hyperbilirubinemia in Malaysian neonates. *J Trop Pediatr*. 2013;59:280-285. doi:10.1093/tropej/fmt023.
- Maimburg RD, Vaeth M, Schendel DE, Bech BH, Olsen J, Thorsen P. Neonatal jaundice: a risk factor for infantile autism? *Paediatr Perinat Epidemiol*. 2008;22:562-568. doi:10.1111/j.1365-3016.2008.00973.x.