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TITLE: Risk Factors, Comorbid Conditions, and Epidemiology of Autism in Children

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CONTRACTING ORGANIZATION: HENRY M JACKSON FOUNDATION FOR THE
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14. ABSTRACT

Children with autism spectrum disorders (ASD) experience increased co-morbidities that affect their overall health and quality of life. Using a case:control cohort of children diagnosed with ASD in the Military Health System, the risk of having or developing specific conditions common to children or common to children with ASD was determined. Nutritional and gastrointestinal conditions were common. There was an increased risk of developing obesity and the components of metabolic syndrome (hypertension, hyperlipidemia, non-alcoholic steatoheapatitis). Despite that risk, children with ASD also were at risk of developing macronutrient and micronutrient deficiencies. There was no increased risk of eosinophilic esophagitis (EoE) in children with ASD, and the increased prevalence of EoE is mediated by the presence of a feeding disorder. In addition, children with ASD have an increased risk of developing complications from otitis media and appendicitis. This may be mediated by difficulties of inexperienced providers in examining children with ASD. Theses analyses have clarified the relative risk of co-morbidities that may be inherent to the behavioral issues of children with ASD.

15. SUBJECT TERMS
Autism, epidemiology

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INTRODUCTION:

This award funds the project entitled "Risk Factors, Comorbid Conditions, and Epidemiology of Autism in Children." The research team of pediatric specialists and researchers aims to understand contributing factors and associated condition with Autism Spectrum Disorders (ASD) using the military healthcare database. This medical system is unique in the United States in terms of the size of the population, its universal-coverage, open-access model, and its unified comprehensive electronic medical and demographic records. The researchers are examining the medical records of children diagnosed with ASDs and their mothers to determine if there are temporal associations between childhood ASD and pre-natal and post-natal conditions such as infections, pregnancy-related conditions, and perinatal conditions such as jaundice and infection. In addition, the researchers are examining records of children with ASD to determine the extent of co-morbid conditions and the use of medications.

KEYWORDS: Autism, epidemiology, risk factors

OVERALL PROJECT SUMMARY:

Task 1: Site: USUHS - Receive IRB approval of Military Autism Research Group project protocol (months 1-5)

1a.   Generate criteria for selection of control group for inclusion in submissions to IRB and Tricare Data Use Agreement (month 1)

Completed in FY13.

1b.   Complete IRB application and submit to USUHS IRB (month1)

Completed in FY13.

1c.   Complete Data Use Agreement (DUA) and submit to TriCare Management Authority (month 1)

Completed in FY13. Renewed in FY14.
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1d.   Coordinate with IRB, provide additional materials as needed and respond to questions (months 2-4)

Completed in FY13.

1e.   Receive IRB approval for Military Autism Research Group project (month4).

Completed in FY13. Continuing review submitted and approved in September 2014

1f.   Submit local USUHS IRB approval letter to Department of Defense, Health Research
        Protection Office (HRPO) for secondary protocol review and approval (month 4)

        Completed in FY13.

1g.   Finalize Data Use Agreement with TriCare Management Authority (month 5).

        Completed in FY13.

1h.   Receive HRPO IRB approval (month 5)

        Completed in FY13.

Task 2: Procure hardware and software equipment, and configure components for use in data
        downloads, cleaning and analysis. (months 1-5)

2a.   Purchase Computer Server (month 1-2)

        New hardware has been purchased.

2b.   Purchase Computer Software (month 1-2)

        Software has been obtained.

2c.   Link Computer Server with desktop computers used for data analysis and cleaning
        (months 2-5)

        Completed.

2d.   Load computer software onto computers for use in data analysis (months 2-5).

        Completed.

Task 3: Download data from the Military Health Services (MHS) Management Analysis and
        Reporting Tool (M2) (month 6-9)

3a.   Use established criteria to generate a list of control group members. (month 6-7)

        Completed in FY13. Cases and controls were identified using diagnostic code, dates of
        encounters, HIPAA Specialty codes for providers, dates of birth, and enrollment dates.
        Cases were identified by any individual who had (1) at least 2 outpatient visits on 2
        different dates with a diagnostic code for autism (299.X); or (2) one visit to a pediatric
        developmental behavioral pediatrician, child neurologist, or child psychologist. Controls
        then were identified using individuals born within the same month as a case, no
        outpatient visits with a diagnosis of autism, and equivalent enrollment duration.

3b.   Identify electronic data interchange patient number (EDIPN), a unique identifier common to Department of Defense databases for experimental and control groups. (month 6-7)

Completed in FY13.

3c.   Identify mothers of experimental and control group identified children, of appropriate age to accurately identify prenatal & perinatal risk factors. (month 6-7)

Mothers were identified as individuals with the same sponsor EDIPN as a case or control with the '30' family member prefix.

3d.   Download all health care visit and medication data for identified experimental and control group members. (month 7-9)

All outpatient and inpatient visit data and medication data has been extracted for cases and controls for the entire period of their enrollment time. Using this data, specific conditions including prevalence of otitis media, celiac disease, appendicitis, injuries, obesity and its complications (hypertension, hyperlipidemia), and sleep disorders were analyzed using conditional Poisson regression to determine incidence density. In an analysis of sleep disorders using this analytic technique, children with ASD had a 64% increase in the prevalence of sleep disorders [IRR 1.64 (95%CI 1.59, 1.69)] compared to controls.

Medication data was extracted and categorized using the American Hospital Formulary Services (AFHS) classification code. Since some medications have dual uses (e.g. clonidine is classified as an anti-hypertensive but also commonly used for behavior issues and insomnia in autism children), hand-review by the researchers and a child psychiatrist was performed to minimize classification bias. Specific medications analyzed to date include the prevalence of the use of psychotropic medications and antibiotics. Conditional logistic regression determined odds ratios of being prescribed a specific medication. Using this analytic technique, children with autism were determined to have an almost 11x increased odds of being prescribed a selective serotonin reuptake inhibitor (SSRI) compared to controls. Likewise, there was an almost 24x increased odds of being prescribed a psychotropic medication (OR 23.8 [95%CI 22.89-24.8]).

3e.   Download all health care visit and medication data for perinatal period for experimental and control group mothers. (month 7-9)

Using the date of birth of the case or control, the mother's outpatient, inpatient, laboratory, and prescription data were extracted for the period of time of 9 months prior to the birth and 6 months afterwards. Maternal medication use in the prenatal and perinatal period has not been downloaded.

Task 4: Cleaning & Organization of Data, and Data Analysis (months 10-17)

4a.   Convert downloaded data to format for use by Stata Statistical Software (month 10-11)

Completed in FY13.

4b.   Use established criteria to identify mothers with research indicated prenatal or perinatal risk factors, and create database flags (month 11-12)

Using extracted maternal perinatal data, methods to determine evidence of exposure to infectious agents were developed to guide later analyses. For perinatal infection exposure, laboratory data of commonly screened conditions during pregnancy were identified using LOINC codes. These include serological tests for Hepatitis B, HIV, and rubella. Antigen tests and urine culture results for Group B streptococcus were also identified. In the data cleaning stage, the need for an extra step of reviewing comments for the urine culture was identified to determine the result and the name of any recovered microorganism. A textual analysis algorithm is being developed to efficiently extract culture results.

Using AFHS codes, maternal medication data was categorized. The specific categories being prepared to analysis identify antibiotic exposure (multiple AFHS codes 0812XX).

4c.   Use established criteria to identify subjects with research indicated co-morbid conditions (months 11-12)

Co-morbid conditions of celiac disease, sleep-disordered breathing, obesity, hypertension, appendicitis, hyperlipidemia, non-alcoholic steatohepatitis, psychiatric conditions, tonsillectomy/adenoidectomy, and otitis media have been extracted and analyzed using conditional logistic or conditional Poisson regression. The criteria to identify these conditions include (1) two outpatient visits on two different dates with diagnostic codes for the condition, or (2) one visit with the diagnostic code by a provider with special training in diagnosing that condition.

In the analysis of complications of otitis media, the diagnosis of mastoiditis and cholesteatoma were primarily made by pediatric (HIPAA taxonomy 207YP0228X) or adult-trained otolaryngolists (207Y00000X). While the cumulative prevalence of acute otitis media was higher in children with autism compared to controls (62.1% vs 55.3%) with an IRR of 1.27 [95%CI 1.26-1.28], the odds of having a complication such as mastoiditis was more than doubled (OR 2.35 [95%CI 2.02-2.74] with similar odds of requiring a surgical procedure (OR 2.29 [95%CI 1.01-4.86]).

4d.   Merge Health Care utilization data with parental data provided to the research team by the Defense Manpower Data Center. Data will include: parental deployment history, rank, age, gender and other demographic characteristics. (months 11-13)

Deployment history has not yet been downloaded.

4e.   Write code for analysis of data. (months 13-15)

A full-time research assistant with SAS and UNIX programming skills was hired in April 2014. Code has been written for multiple analyses detailed and included in this report. A master extraction algorithm has been written that accounts for the variation of the same data field across fiscal years. Direct care data for 2001-2002, 2003-2004 and 2005-2014 are groups of data with different fields, field names, and data characteristics for the same data element.

4f.   Run statistical analysis, analyze results and refine analysis as appropriate (months 15-17)

Analyses have been completed for several aims. Using the case:control design, conditional analyses are used. Conditional Poisson regression determined incidence rate ratios of multiple count events such as otitis media. Conditional logistic regression determined odds ratio of single events such as developing mastoiditis or mastoidectomy following an otitis media diagnosis. The annotated bibliography (Appendix 1) details analyses for the following:

- OR of use of stimulants, psychotropic medications, and SSRIs
- IRR of otitis media and pressure equalization tube placement
- OR of mastoidectomy, mastoiditis, and tympanoplasty
- RR of a diagnosis of celiac disease (4.15 [95% CI, 3.21-5.36]).
- OR of obesity (1.74 [95%CI 1.68-1.64]), diabetes, hypertension, non-alcoholic steatohepatitis, and hyperlipidemia
- OR of malnutrition diagnoses such as failure to thrive, protein malnutrition, iron deficiency anemia (1.37 95%CI 1.30-1.44), vitamin B12 deficiency, Vitamin D deficiency, and other vitamin and mineral deficiencies.
- OR of concurrent ASD, feeding disorder and eosinophilic esophagitis (EoE) (16.6 [95%CI 10.9-25.5]), which was not significantly different than the OR of feeding disorder and EoE without ASD (20.2 [95%CI 11.5-35.6])
- Age-specific OR of appendicitis (higher in adolescent ASD patients compared to younger patients), and increased odds of perforation in ASD vs non-ASD patients (OR 12.8 [95%CI 4.37-37.39]).

4g.   Interpret results of data analysis in the clinical context of Autism care (months 15-17)

Interpretations have been completed for several aims. A general theme of the results of multiple analyses of co-morbidities is that complications of common and routinely managed conditions are increased, such as mastoiditis after acute otitis media and perforation after appendicitis. Our physician team hypothesizes that this is due to the difficulty for many providers to adequately examine children with ASD. However, an exception was the diagnosis of eosinophilic esophagitis, commonly thought to be increased in children with ASD. The presence of a feeding disorder was a confounding factor, with its presence mediating the association with EoE. The bibliography (Appendix 1) lists the research abstracts with each individual conclusion of the analyses.

4h.   As results emerge, create and submit abstracts for presentation at medical conferences (months 15-17)

See bibliography (Appendix 1).

Task 5: Present and Write up research results (months 18-24)

5a.   Create presentations and posters for presentation at medical conferences (months 18-20)

        See bibliography (Appendix 1).

5b.   Present findings at medical conferences (months 18-24)

        Peer-reviewed research has been presented in abstract form at the following medical
        conferences:

        - Pediatric Academic Society Annual Meeting, Vancouver, BC, May 2014
        - Society for Developmental and Behavioral Pediatrics, Nashville, TN, Sept 2014

5c.   Draft manuscripts for publication (months 18-24)

        One manuscript has been submitted for publication (Appendix 2).

5d.   Finalize papers and submit to pediatric medical journals (months 20-24)

        See 5d above.

KEY RESEARCH ACCOMPLISHMENTS:

- Confirmed association between ASD and neonatal jaundice using a more rigorous
  definition of exposure than that used in previous studies

- Documented increased risk of celiac disease in patients with ASD using procedurally and
  serological data

- Determined increased risk of complications from otitis media in patients with ASD

- Quantified psychotropic medication burden of children with ASD

- Determined increase in sleep-disorders in children with ASD

- Quantified the risk of macro- and micro-nutrient deficiencies in children with ASD

- Documented increased odds of obesity and components of metabolic syndrome in
  patients with ASD

- Identified increased risk of complications of appendicitis in children with ASD

- Identified no significant increase risk of eosinophilic esophagitis in children with ASD
  when the presence of feeding disorder is considered

CONCLUSION:

The research group has been able to quicken the pace of projects with the hiring of a full time research assistant, and development of algorithms to extract and analyze data. Analyses of relatively common co-morbid conditions, especially sleep-related diagnoses, ear infections, celiac disease, appendicitis, injury rates, and micronutrient deficiencies have been submitted for peer have progressed to peer-reviewed abstracts. These conditions were chosen for the first analyses of co-morbid conditions because they are relatively common, often go unnoticed due to the communication issues of ASD patients, or have a large impact on quality of patient and family life. The findings highlight the increased prevalence of these conditions which may be difficult to diagnose due to the communication difficulties in patients with ASD.

PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS:

Full abstracts are included in Appendix 1.

FY14 Abstracts

Marilisa G. Elrod, MD PhD, Cade M. Nylund, MD, Gregory H. Gorman, MD, Elizabeth Hisle-Gorman, PhD, Christine Erdie-Lalena, MD. Sleep Disorders and Sleep Related Procedures in Children with Autism Spectrum Disorder Diagnoses: A Retrospective Cohort Study Using the Military Health Systems Database. Society for Developmental and Behavioral Pediatrics, Nashville, TN, Sept 2014.

Marilisa G. Elrod, Cade M. Nylund, Gregory H. Gorman, Elizabeth J. Hisle-Gorman, Christine Erdie-Lalena. Sleep Disorders and Sleep Related Procedures in Children with Autism Spectrum Disorder Diagnoses. Society for Developmental and Behavioral Pediatrics, Nashville, TN, Sept 2014.

Daniel J. Adams, Apryl Susi, Elizabeth Hisle-Gorman, Christine Erdie-Lalena, Gregory Gorman, Michael Rajnik, Cade M. Nylund. Otitis Media and Related Complications among Children with Autism Spectrum Disorder Diagnoses. Pediatric Academic Society Annual Meeting, San Diego, CA, May 2015 [submitted]

Cade M Nylund, Apryl Susi, Elizabeth Hisle-Gorman, Christine Erdie-Lalena, Gregory Gorman. Children with Autism Spectrum Disorder are More Likely to be Diagnosed with Celiac Disease. NASPGHAN (North American Society of Pediatric Gastroenterology, Hepatology and Nutrition) Atlanta, GA Oct 2014

Cade M. Nylund, Apryl Susi, Elizabeth Hisle-Gorman, Christine Erdie-Lalena, Gregory Gorman. Macronutrient and Micronutrient Malnutrition in Children with Autism Spectrum Disorder Diagnoses. Digestive Diseases Week, Washington, DC, May 2015 [submitted]

Katie Shedlock, Apryl Susi, Elizabeth Hisle-Gorman, Christine Erdie-Lalena, Gregory Gorman, Cade M. Nylund. Children with Autism Spectrum Disorder Diagnoses Have Elevated Risk of

Obesity and Metabolic Comorbidities: A Retrospective Cohort Study Using the Military Healthcare Database. Pediatric Academic Society Annual Meeting, San Diego, CA, May 2015 [submitted]

Theresa Heifert, Apryl Susi, Gregory H Gorman, Elizabeth Hisle-Gorman, Christine Erdie-Lalena, Cade M Nylund. Feeding disorders in children with autism spectrum disorders are related to a diagnosis of eosinophilic esophagitis. Digestive Diseases Week 2015, Washington, DC, May 17-19, 2015. [submitted]

Apryl Susi, Elizabeth Hisle-Gorman, Gregory Gorman, Christine Erdie-Lalena, Cade M. Nylund. Perforated Appendix and Children with Autism Spectrum Disorder. Pediatric Academic Society Annual Meeting, San Diego, CA, May 2015 [submitted]

FY 13 Abstracts

Luis E. Lozada, Cade M. Nylund, Matthew D. Eberly, Elizabeth Hisle-Gorman, Anthony Goudie, Adam Huillet, Matilda Eide, Stephen L. Nelson, Christine Erdie-Lalena, Gregory H. Gorman, Devon Kuehn. Neonatal Hyperbilirubinemia as a Risk Factor for Autism Spectrum Disorder, a Retrospective Cohort Study. Pediatric Academic Society Annual Meeting, Washington D.C., May 6, 2013.

Society for Pediatric Research House Officer Research Award, Luis E. Lozada, M.D.

INVENTIONS, PATENTS AND LICENSES: None.

REPORTABLE OUTCOMES: None.

OTHER ACHIEVEMENTS: None.

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Daytime physical activity and sleep in pre-schoolers with developmental disorders. Tatsumi Y, Mohri I, Shimizu S, Tachibana M, Ohno Y, Taniike M. J Paediatr Child Health. 2014 Sep 3

Prevalence of overweight and obesity in a large clinical sample of children with autism. Broder-Fingert S, Brazauskas K, Lindgren K, Iannuzzi D, Van Cleave J. Acad Pediatr. 2014 Jul-Aug;14(4):408-14

Overweight and obesity: prevalence and correlates in a large clinical sample of children with autism spectrum disorder. Zuckerman KE, Hill AP, Guion K, Voltolina L, Fombonne E. J Autism Dev Disord. 2014 Jul;44(7):1708-19

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Pediatrics. 2010 Nov;126(5):872-8. Neonatal jaundice, autism, and other disorders of psychological development. Maimburg RD, Bech BH, Vaeth M, Møller-Madsen B, Olsen J.

APPENDICES:

Appendix 1: Abstracts

Appendix 2: Manuscript "Association of Autism Spectrum Disorder with Neonatal Hyperbilirubinemia"

1.

Sleep Disorders and Sleep Related Procedures in Children with Autism Spectrum Disorder Diagnoses

Marilisa G. Elrod, Cade M. Nylund, Gregory H. Gorman, Elizabeth J. Hisle-Gorman, Christine Erdie-Lalena

Purpose: Sleep disorders are common and important co-morbidities in children with autism spectrum disorder (ASD). Sleep problems are associated with intensified symptoms of autism or problems with day-time cognitive and adaptive functioning. The rate of diagnosis of sleep disorders and performance of sleep related procedures in children with ASD is unclear.

Methods: This retrospective matched cohort study included children aged 2-18 years old enrolled in the Military Health Systems Database (MHS) database between 2000 and 2013. The cohort was formed by matching children with ASD by birth date, gender, and enrollment time to 5 children without an ASD diagnosis. The MHS database was queried for the number of health care encounters with a sleep disorder ICD-9-CM diagnostic or procedure code during the specified period. We calculated incidence rate ratios (IRR) and 95% confidence Intervals (CI) for the encounters of sleep disorder related procedures and sleep diagnoses using conditional Poisson regression.

Results: See table

Table 1: Prevalence of Sleep Disorders in Autistic and Non-Autistic Children

	ASD (n= 48809)	No ASD (n= 244075)	IRR (95% CI)
Any Sleep Disorder	30.7%	13.9%	1.64 (1.59, 1.69)
Sleep Disordered Breathing	9.4%	4.1%	2.01 (1.90, 2.14)
Adenotonsillectomy	7.8%	5.6%	1.46 (1.41, 1.51)
Sleep Study	5.4%	1.4%	3.39 3.17, 3.63)

Conclusion: This database review is the first to show sleep disorder diagnosis rates that resemble the epidemiologic estimates of prevalence in both the ASD and control populations. Children with ASD have higher incidence rates of Sleep Disordered Breathing and undergo sleep related procedures more frequently than those without an ASD diagnosis.

2.

Psychotropic Medication Prescriptions in Children with Autism Spectrum Disorder

Daniel J. Tolson, Elizabeth Hisle-Gorman, Marilisa G. Elrod, Apryl Susi, Christine R. Erdie-Lalena, Cade M. Nylund.

Purpose: Previous studies describe polypharmacy among children with Autism Spectrum Disorder (ASD) without comparison to control groups. We studied the rates of psychotropic medication prescriptions in children with ASD using the Military Health System (MHS) database in relation to a matched cohort.

Methods: A retrospective matched cohort study was performed using prescription data for children aged 2-18 years old enrolled in the MHS database between 2000 and 2013. Five controls were matched without replacement to each child with ASD by age, gender, and enrollment time. Conditional logistic regression was performed with odds ratios (OR) with 95% confidence intervals calculated for having been prescribed the medication.

Results: Of the 48,810 individuals with ASD and 244,045 without ASD, our query showed that 48% with ASD had been prescribed a stimulant as opposed to 11.7% of children without ASD, OR of 8.5 (8.25, 8.67). Of children with ASD, 30.4% were prescribed an atypical antipsychotic while only 2.1% without ASD had the same medication prescribed, OR 23.8 (22.89, 24.8). For Selective Serotonin Reuptake Inhibitors (SSRI) the data showed that 27% of those with ASD were prescribed an SSRI and only 4.1% of children without an ASD were given an SSRI, OR 10.95 (10.59, 11.31).

Table 1: Percent of Children Prescribed Medication by Class

Class	With ASD (48,810)	Without ASD (244,045)	Odds Ratio
Stimulant	48%	11.7%	8.5 (8.25, 8.67)
Atypical Antipsychotic	30.4%	2.15	23.8 (22.89, 24.8)
SSRI	27%	4.1%	10.95 (10.59, 11.31)

Conclusion: Children with ASD in the MHS database are prescribed stimulants, atypical antipsychotics, and SSRIs more frequently than children who do not have an ASD diagnosis. This data may also indicate that they are given these medications at higher rates than expected compared to rates of comorbid conditions for which these medications are typically given.

3.

Otitis Media and Related Complications among Children with Autism Spectrum Disorder Diagnoses

Daniel J. Adams MD, Apryl Susi MS, Elizabeth Hisle-Gorman PhD, Christine Erdie-Lalena MD, Gregory Gorman MD, Michael Rajnik MD, Cade M. Nylund MD MS

Background: Autism spectrum disorder (ASD) encompasses a range of developmental disabilities that commonly affect speech and language skills. Acute otitis media (AOM) symptoms can be masked by behaviors common to children with ASD, leading to delayed or missed diagnoses. Using the Military Health System (MHS) database, we evaluated the risk of otitis media and its related complications in children with ASD.

Methods: Our retrospective matched case-cohort study includes children aged 2 to 18 years enrolled in the MHS database from Oct 2000 to Sept 2013. ASD cases were defined by having two encounters with a diagnosis code of ASD. We performed a 1:5 case:control match by age, gender, and enrollment timeframe. AOM, related diagnoses and complications were identified from inpatient and outpatient encounters utilizing diagnostic and procedure codes. Conditional Poisson and logistic regression were used to evaluate the association of ASD with AOM and its complications.

Results: The MHS dataset identified 48,809 children with ASD and 240,282 matched controls. Compared to controls, and after adjusting for the total number of outpatient visits, children with ASD had a significantly higher incidence of AOM, otitis media with effusion, otorrhea, and PE tube placement [Table 1]. Children with ASD were twice as likely to develop cholesteatoma, mastoiditis and to undergo mastoidectomy [Table 1].

Table 1. Risk of otitis media, related diagnoses, and complications among children with ASD compared to matched controls

	ASD (48,802)	Controls (240,282)	IRR (95% CI) or [a]OR (95% CI)
Acute otitis media	30,304 (62.1%)	132,982 (55.3%)	1.27 (1.26-1.28)
Otitis media with effusion	13,787 (28.3%)	50,568 (21.0%)	1.50 (1.48-1.52)
Otorrhea	3,043 (6.24%)	8,602 (3.58%)	1.77 (1.72-1.82)
PE tube placement	4,626 (9.48%)	11,083 (4.61%)	1.93 (1.87-1.99)
Cholesteatoma[a]	202 (0.41%)	547 (0.23%)	1.85 (1.57-2.17)
Mastoiditis[a]	239 (0.49%)	509 (0.21%)	2.35 (2.02-2.74)
Mastoidectomy[a]	11 (0.023%)	24 (0.01%)	2.29 (1.01-4.86)
Tympanoplasty[a]	9 (0.018%)	20 (0.008%)	2.25 (0.90-5.17)

Conclusion: Children with ASD are at increased risk for middle ear infections and otitis-related complications. These results highlight the importance of routine middle ear exams and close attention to hearing impairment in children with ASD in order to promote their full speech and language potential.

4.

Children with Autism Spectrum Disorder are more likely to Be Diagnosed with Celiac Disease

Cade M Nylund MD, Apryl Susi MS, Elizabeth Hisle-Gorman PhD,
Christine Erdie-Lalena MD, Gregory Gorman MD

Background: A Swedish nationwide study found that children with autism spectrum disorder (ASD) had 4.6 times the odds of having a positive celiac disease (CD) serologic test however in the same study ASD was not found to be associated with a diagnosis of CD. Other studies have not found a connection between ASD and CD. We sought to evaluate an association between ASD and the diagnosis of CD in a large US population.

Methods: A retrospective matched cohort study included children ages 2-18 years old enrolled in the Military Health System (MHS) database between Oct 2000 and 2013. The MHS database includes all military (minority) and civilian (majority) provider billing data for child beneficiaries of US uniformed service members. The cohort was created by matching children with ASD to children without ASD in a ratio of 1:5 by birthdate (within 45 days), sex, and period of enrollment time. ASD was defined as any patient with 2 or more International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnoses for ASD. A diagnosis of CD was defined by the combination of the ICD-9-CM diagnostic code "579.0" and any previous Current Procedural Terminology code for esophagogasgtroduodenoscopy (EGD). Conditional Poisson regression was utilized to calculate rate ratios for EGD and for CD.

Results: There were 48,810 subjects with ASD and 244,050 controls representing a total of 2,588,813 person-years. A total of 4,385 subjects had an EGD. Patients with ASD were more likely to have any EGD (1,884; 3.9 per 100) than controls (3,501; 1.4 per 100; Relative Risk [RR] 2.69; 95% confidence interval [CI], 2.54-2.86); $P <0.001$) and children with ASD also had slightly more absolute number of EGDs (Rate Ratio 1.13; 95% CI, 1.05-1.09; $P<0.001$). The rate of CD was higher among the ASD group (107; 22 per 10,000) than the controls (129; 5 per 10,000; RR 4.15, 95% CI, 3.21-5.36; P <0.001). After adjusting for the number of EGDs per subject, children with ASD continued to have a significantly increased rate of diagnosed CD (RR 1.53; 95% CI, 1.19-1.98).

Conclusions: Children with ASD are more likely to have a diagnosis of CD compared to sex and age adjusted controls. Children with ASD are also more likely to have an EGD performed. The increased rate of CD persists after adjusting for the increased rate of EGDs in the ASD population. Further studies are needed to evaluate the connected between ASD and celiac disease.

5.

Children with Autism Spectrum Disorder Diagnoses Have Elevated Risk of Obesity and Metabolic Comorbidities: A Retrospective Cohort Study Using the Military Healthcare Database

Background: Children with Autism Spectrum Disorders (ASD) often have an overly selective, energy-dense diet that can lead to obesity. The rate of obesity and its complications are unknown in children with ASD. We sought to determine and compare the rate of obesity, diabetes mellitus type II, hypertension, hyperlipidemia, and non-alcoholic fatty liver disease/steatohepatitis (NAFLD/NASH) between children with ASD and controls. For children with ASD, we evaluated the risk of obesity associated with psychotropic medications.

Methods: A retrospective case-cohort study over the time period of Oct 2000-Sept 2013 was performed using the military health system database, which is comprised of billing data for outpatient visits, inpatient admissions, and prescriptions of all military members and dependents treated in both military and civilian medical facilities. Children with two or more encounters with ICD-9 diagnostic codes for ASD were matched 1:5 with controls by age, gender, and enrollment timeframe. For both groups, ICD-9 diagnostic codes for obesity, diabetes mellitus type II, hypertension, hyperlipidemia, NAFLD/NASH, and prescriptions were obtained.

Results: There were 48,762 individuals with ASD and 243,810 controls. The percentage of children with ASD who also had a diagnosis of obesity was 11% compared to 7% of controls (See Table). Children with ASD had higher odds ratios of being diagnosed with diabetes mellitus type II, hypertension, hyperlipidemia, and NAFLD/NASH, to be treated for complications of obesity (OR, 2.78; 95% CI, 2.65-2.94). The administration of anti-psychotics, SSRIs, antiepileptics, and mood stabilizers were associated with obesity (*P*<0.001).

Diagnosis	ASD (n=48,762)	Control (n=243,810)	OR (95% CI)
Obesity	5,404 (11.08%)	17025 (6.98%)	1.74 (1.68-1.64)
Diabetes Mellitus Type II	513 (1.05%)	968 (0.4%)	2.68 (2.40-2.98)
Hypertension	1,125 (2.3%)	3,015 (1.24%)	1.90 (1.77-2.04)
Hyperlipidemia	1,606 (3.29%)	4,084 (1.68%)	2.01 (1.90-2.13)
NAFLD/NASH	88 (0.18%)	159 (0.07%)	2.77 (2.13-3.59)

Conclusion: Children with ASD have an increased risk of obesity and metabolic complications, and they are more likely to require prescriptions to treat these complications. The risk of becoming obese can be partially attributed to medications prescribed for ASD, such as anti-psychotics and anti-depressants suggesting that obesity in children with ASD may be partially iatrogenic.

6.

Macronutrient and Micronutrient Malnutrition in Children with Autism Spectrum Disorder Diagnoses

Cade M. Nylund MD, Apryl Susi MS, Elizabeth Hisle-Gorman PhD, Christine Erdie-Lalena MD, Gregory Gorman MD

Background: Autism spectrum disorder (ASD) represents a range of developmental disabilities which commonly affect behavior and sensory defensiveness related to eating and nutritional intake. Children with ASD have been shown to have self-selected, narrow dietary preferences and a preference for less nutritious snack foods. Feeding disorders and use of supplemental enteral nutrition are also common in children with ASD. Using the Military Health System (MHS) database, we sought to determine the prevalence of diagnosed malnutrition including specific micronutrient deficiencies in children with ASD relative to those children without an ASD diagnosis.

Methods: This retrospective case-cohort study included subjects enrolled in the MHS database comprised of data on outpatient visits and inpatient admissions of all military members and dependent children treated in military and civilian medical facilities. Children aged 2 to 18 years with ASD were classified by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for an ASD diagnosis from October 1, 2003 to Jun 30, 2012 at two separate clinical encounters. The cases were also enrolled in the MHS database 6 months prior to receiving the first ASD diagnosis code and 6 months following receipt of the diagnosis. Five controls were matched without replacement to each case by age, gender, and enrollment timeframe. The database was queried for a variety of malnutrition and nutrient deficiency diagnoses utilizing ICD-9-CM codes for each subject and control during the specified period. Conditional logistic regression was performed with odds ratios (OR) with 95% confidence intervals (95% CI).

Results: The MHS dataset yielded 48,809 individuals with ASD and 240,282 controls. The percentage of children receiving any diagnosis of malnutrition during enrollment within the study timeframe was 20.0% for the ASD group and 7.9% of controls. The frequencies and ORs are presented in Table 1. The most common diagnosis was Underweight/Loss of Weight (9.7% of children with ASD vs. 3.3% in controls). The most common micronutrient deficiency was iron deficiency anemia (3.6% of the children with ASD vs. 2.7% in controls). Consistent with a restrictive diet, the nutrient deficiencies most strongly associated with ASD were vitamin A deficiency (OR, 23.75; 95 % CI,15.29-36.88), calcium (OR, 7.53; 95% CI, 5.82-9.73) and folate (OR, 5.67; 95% CI, 2.83-11.35).

Conclusion: Diagnosed macro and micro nutrient deficiencies are very common in children with ASD with 1 in 5 having at least one malnutrition diagnosis. Diets deficient in vegetables or dairy correspond to the specific nutrient deficiencies found in children with ASD in this study. These results represent only diagnosed deficiencies and likely underrepresent the actual portion of malnourished children with ASD. Children with ASD are at nutritional risk and warrant nutrition focused health supervision.

Macronutrient and Micronutrient Malnutrition in Children with Autism Spectrum Disorder Diagnoses (abstract, continued)

Table 1: Odds Ratio of Macronutrient and Micronutrient Deficiencies in Children with Autistic Spectrum Disorders as Determined by Outpatient Diagnosis Codes

	ASD (n=48809)	Control (n=240282)	OR (95% CI)
Any Malnutrition Diagnosis	7279 (14.9%)	16106 (6.6%)	2.50 (2.43-2.58)
Failure to Thrive	4742 (9.7%)	8043 (3.3%)	3.19 (3.07-3.31)
Protein Malnutrition	269 (0.55%)	387 (0.16%)	3.50 (2.99-4.09)
Iron Deficiency Anemia	1778 (3.6%)	6563 (2.7%)	1.37 (1.30-1.44)
Vitamin B12 Deficiency Anemia	49 (0.10%)	119 (0.05%)	2.06 (1.48-2.87)
Folate Deficiency Anemia	17 (0.03%)	15 (0.01%)	5.67 (2.83-11.35)
Other Anemias	148 (0.30%)	438 (0.18%)	1.69 (1.40-2.04)
Vitamin D Deficiency	841 (1.7%)	1436 (0.59%)	2.98 (2.73-3.24)
Vitamin A Deficiency	114 (0.23%)	24 (0.01%)	23.75 (15.29-36.88)
Other Fat Soluble Vitamin Deficiency (E, K)	23 (0.05%)	22 (0.01%)	5.23 (2.91-9.38)
Vitamin B Deficiencies	143 (0.29%)	137 (0.06%)	5.22 (4.13-6.60)
Calcium Deficiency	146 (0.30%)	97 (0.04%)	7.53 (5.82-9.73)

OR=Odds Ratio; ASD= Autistic Spectrum Disorders. Ors determined by conditional logistic regression

7.

Feeding disorders in children with autism spectrum disorders are related to a diagnosis of eosinophilic esophagitis

Authors: Heifert, Theresa, Susi, Apryl, Gorman, Gregory H,Hisle-Gorman, Elizabeth, Erdie-Lalena, Christine, Nylund, Cade M

Background: Autism spectrum disorders (ASD) are characterized by difficulties with reciprocal social interactions and restricted patterns of behavior and interest. One of these behaviors is food selectivity in type and texture which often leads to the diagnosis of a feeding disorder. Children with ASD often can't communicate symptoms such as dysphagia or odynophagia. Eosinophilic esophagitis (EoE) can present as food selectivity or feeding disorders in children. The rate of EoE in autistic children with feeding disorders is unknown.

Objective: We sought to determine and compare the rate of EoE between children with ASD with and without feeding disorders and controls with and without feeding disorders. We also sought to investigate additional risk for EoE in children with ASD to help risk stratify the need for endoscopic evaluation. Methods: A retrospective case-cohort study was performed Oct 2009-Sept 2013 using the Military Health System database. This database is comprised of billing data for outpatient visits, inpatient admissions, and outpatient prescriptions of all military members and their family treated in both military and civilian medical facilities. Laboratory data is available for children cared for within military treatment facilities. Children with two or more encounters with ICD-9 diagnostic codes for ASD were matched 1:5 with controls by age, gender, and enrollment timeframe. Feeding disorders, EoE, and atopic disorders were identified from encounters utilizing diagnostic and procedure codes. Serum absolute eosinophil count was obtained when available. Conditional logistic regression was used to evaluate and compare the risk of EoE by ASD and feeding disorder and evaluate predictors of EoE with stratified models by ASD.

Results: There were 45,286 children with ASD and 226,430 matched controls. 3,567 (7.9%) of the children with ASD and 2,392 (1.1%) of the controls had a diagnosis of feeding disorder. EoE was more common in children with ASD; 189 (0.4%) with ASD and 322 (0.1%) of the controls. The rate and odds ratios of EoE by ASD and feeding disorder are presented in Table 1. Compared to control children with feeding disorder, children with ASD and feeding disorder had no statistically significant difference in the rate of the diagnosis of EoE (P=0.57). Feeding disorder is the strongest predictor of EoE compared to all other known risk factors among both children with ASD and controls (Table 2).

Conclusion: A diagnosis of feeding disorder is the strongest predictor of EoE among all children. Children with ASD are more likely to be diagnosed with EoE, although there is no difference in the risk of EoE among those with feeding disorder between children with ASD and controls. Feeding disorder in children with ASD should not be assumed to be behavioral and an esophagogastroduodenoscopy should be performed to evaluate for EoE.

Feeding disorders in children with autism spectrum disorders are related to a diagnosis of eosinophilic esophagitis (continued)

Table 1 Incidence and Odds Ratios of Eosinophilic Esophagitis by Autism Spectrum Disorder and Feeding Disorder

	Number with Eosinophilic Esophagitis	Total Number	Rate	Odds Ratio (95 % Confidence Interval)
ASD + Feeding Disorder	87	3,567	2.44%	16.6 (10.9-25.5)
ASD + No Feeding Disorder	102	41,719	0.24%	2.06 (1.63-2.59)
No ASD + Feeding Disorder	48	2,392	2.01%	20.2 (11.5-35.6)
No ASD + No Feeding Disorder	274	224,038	0.12%	Reference

Table 2. Predictors of a Diagnosis of Eosinophilic Esophagitis

	ASD Model Odds Ratios (95 % Confidence Interval)	No ASD Model (95% Confidence Interval)
Feeding Disorders	7.17 (4.87-10.5)	11.5 (7.57-17.5)
Asthma	2.71 (1.47-5.00)	2.15 (1.26-3.68)
Allergic Rhinitis	2.71 (1.68-4.38)	2.79 (1.88-4.14)
Eczema	1.94 (1.31-2.88)	1.26 (0.91-1.73)
Elevated Serum Absolute Eosinophil Count	2.71 (1.64-4.49)	4.43 (2.99-6.58)
Food Allergy	1.06 (0.61-1.82)	2.35 (1.55-3.55)

8.

Perforated Appendix and Children with Autism Spectrum Disorder

Background: Children with autism spectrum disorder (ASD) often exhibit impaired verbal and non-verbal communication, including inability in communicating discomfort. This can lead to diagnostic difficulty for the pediatrician in cases of surgical emergencies such as appendicitis. If appendicitis is not recognized early, the appendix can perforate, develop concurrent peritonitis, or lead to sepsis.

Objective: To determine if children with ASD have higher rates of appendiceal perforation, peritonitis, and appendicitis associated sepsis.

Methods: A retrospective matched case cohort study was performed. The cohort included children aged 2-18 years old enrolled in the Military Health Systems database between 2000 and 2013. Children with ASD were matched 1:5 to children without ASD by birthday, gender, and enrollment time. Participants were selected using the Agency for Healthcare Research and Quality pediatric quality indicators for perforated appendix admission rate and postoperative sepsis rate. Conditional logistic regression was used to calculate the odds of perforation and the odds of septicemia in children with appendicitis.

Results: Overall, 30% of children with ASD and appendicitis experienced perforation or peritonitis compared with 25% of controls (Table 1). Children with ASD 0-14 years of age did not have an increased rate of perforated appendix, however, children aged 15-17 did. Children with ASD were 5.43 times more likely to experience secondary sepsis following an appendicitis diagnosis (95% CI 2.00-14.76) after controlling for perforation/peritonitis and age (Table 2).

Conclusion: Adolescents with ASD have increased odds of perforation/peritonitis. This may be a result of poor communication of symptoms among children with ASD. Children with ASD also had an increased risk of sepsis after controlling for age and perforation/peritonitis.

Table 1: Odds of Perforated Appendix or Peritonitis

	ASD	No ASD	OR (95% CI)
All Ages	114 (29.5%)	463 (25.4%)	1.23 (0.96, 1.57)
0-4 Years	11 (44.0%)	72 (55.8%)	0.62 (0.26, 1.47)
5-9 Years	39 (27.1%)	169 (27.4%)	0.99 (0.66, 1.48)
10-14 Years	47 (29.2%)	181 (22.2%)	1.45 (0.99, 2.11)
15-17 Years	17 (30.4%)	41 (15.9%)	2.31 (1.19, 4.47)

Table 2: Adjusted Risk of Sepsis given ASD

Predictor	OR (95% CI)
ASD	5.43 (2.00, 14.76)
Age	0.84 (0.74, 0.96)
Perforation	12.79 (4.37, 37.39)

Association of Autism Spectrum Disorder with Neonatal Hyperbilirubinemia

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Short title: Neonatal Hyperbilirubinemia is a Risk Factor for Autism

Abbreviations: ASD - Autism Spectrum Disorder; DEERS - Defense Enrollment Eligibility Reporting System; EDIPN - Electronic Data Interchange Patient Number; FY - Fiscal Year; ICD-9 - International Classification of Disease, 9th Edition; IQR - Interquartile Range; MHS - Military Health System; OR - Odds Ratio; PDD-NOS - Pervasive Developmental Disorder- Not Otherwise Specified; SADR - Standard Ambulatory Data Record; TMA - TRICARE Management Authority

Key words: Autism, hyperbilirubinemia, neonatal jaundice, pervasive developmental disorders, Autism Spectrum Disorders, phototherapy

Disclaimer: The views expressed in this article are those of the authors and do not reflect the official policy or position of the United States Air Force, the United States Army, the United Sates Navy, the Department of Defense, or the U. S. Government.

What's Known on This Subject:
Neonatal hyperbilirubinemia is known to be neurotoxic at high levels. Several studies suggest that bilirubin levels at moderate levels may lead to increased risk of psychological disabilities. Parent-reported jaundice has been linked to autism.

What This Study Adds:
In a US pediatric population we confirm a link between clinically diagnosed or treated jaundice and specialist-diagnosed Autism Spectrum Disorder.

Contributor's Statement:

Luis E. Lozada: Dr Lozada assisted in design of the study, drafted the initial manuscript, and approved the final manuscript as submitted.

Cade M. Nylund: Dr Nylund conceptualized and designed the study, collected the data, reviewed the analyses, critically reviewed the manuscript, and approved the final manuscript as submitted.

Christine R. Erdie-Lalena: Dr. Erdie-Lalena contributed the study design, reviewed the manuscript, and approved the final manuscript as submitted.

Gregory H. Gorman, Elizabeth Hisle-Gorman, Devon Kuehn: Drs. Gorman, Hisle-Gorman and Kuehn contributed to the study design, carried out the initial analysis, critically revised the manuscript, and approved the final manuscript as submitted.

Abstract:

Objectives: Autism Spectrum Disorders (ASD) is a common neurodevelopmental disorder of unknown etiology. Studies suggested a link between autism and neonatal jaundice. We determined the risk of developing ASD in children who required inpatient admission or treatment for neonatal jaundice.

Methods: A 3:1 matched case-control study was conducted with children enrolled in the Military Health System (MHS) born between October 2000 and September 2009. Diagnostic and procedure codes were used for identifying ASD and hyperbilirubinemia. Two definitions for hyperbilirubinemia were evaluated: an inpatient admission for a diagnosis of jaundice and treatment with phototherapy or exchange transfusion for jaundice. Multivariable conditional logistic regression evaluated the odds ratio of ASD in children with neonatal jaundice.

Results: 2,917 children with ASD and 8,751 matched controls were included in the study. Neonatal jaundice was seen in 22% of cases and 18% of controls. Treatment for jaundice was used in 3.7% of children with ASD compared to 2.5% of controls. There was an increased unadjusted odds of developing ASD in children who had an inpatient diagnosis of jaundice (OR, 1.24; 95% confidence interval [CI], 1.12-1.38; p<0.001]) and in children who required treatment for jaundice (OR, 1.47; 95% CI, 1.16-1.86; p=0.001). After adjustment, there remained an increased risk of developing ASD in children with an admission for jaundice (OR, 1.18; 95% CI, 1.06-1.31; p=0.001) and in children who required phototherapy (OR, 1.33; 95% CI, 1.04-1.69; p=0.008).

Conclusions: Children who develop ASD are more likely to have a history of neonatal jaundice and admission for jaundice requiring treatment.

Introduction

Autism Spectrum Disorders (ASD) include a group of neurodevelopmental disorders

characterized by impairments in three major domains: socialization, communication, and

behavior. ASD is a common neurodevelopmental disorder in children and has an increasing

incidence.[1-7] The causes of autism are not well understood; [3,6] however, the etiology of ASD is

likely a combination of genetic predisposition interacting with environmental factors in early

life. [1,2,5,8,9] In two meta-analyses, over 60 neonatal and perinatal risk factors were compiled, [2,3]

including preterm birth, birth weight small for gestational age, fetal distress/low Apgar scores,

neonatal anemia, ABO or Rh incompatibility, and hyperbilirubinemia.

Neonatal unconjugated hyperbilirubinemia (jaundice) is very common; up to 65% of newborns

develop clinical jaundice in the first week of life.[10-15] Mildly elevated serum bilirubin, as a

product of heme catabolism, is non-pathological in most infants and has a number of causes.[16]

Unconjugated hyperbilirubinemia at high levels is neurotoxic with acute or chronic neurological

and developmental sequelae, such as kernicterus or death. The developmental effects of

kernicterus include intellectual disability, choreoathetoid cerebral palsy, sensorineural hearing

loss, and gaze abnormalities.[17]

It has been suggested that moderate levels of serum bilirubin could be associated with

neurodevelopmental disorders,[18] and many suggest an association with ASD.[9] A recent meta-

analysis of 13 studies has found that ASD likely is associated with neonatal

hyperbilirubinemia.[19] The majority of the studies performed, however, were small (< 400

subjects), did not account for confounding of factors such as prematurity, used a variety of

definitions for jaundice and ASD, or were not representative of the Unites States population.[19]

We hypothesized that there is an association between neonatal jaundice and development of

ASD as previous studies have suggested. Utilizing a large United States health care database

representing a heterogeneous, demographically- and socioeconomically-diverse population, we

sought to expand upon 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.

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 U. S. military and their family members domestically and abroad. Children born

between 01 October 2000 and 30 September 2009 were eligible for inclusion. Children with

ASD were identified as those with at least one outpatient visit to a 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 01 October 2000 through September 30, 2012. For each case, three controls without any outpatient diagnoses of ASD (specialist or generalist) were selected and matched by gender and 3-month birth cohort. 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, two 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 to 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.

Prematurity was defined as birth before 36 weeks post menstrual age and was identified using ICD-9-CM-codes at the birth admission. Multiple gestation was similarly identified. Since a prior study found an association between birth in the colder months (October-March), this study included a categorization for season of birth.

McNeman's Test determined the unadjusted odds ratio (OR) of the development of ASD with a history of neonatal jaundice, as previously defined. For adjusted analyses, multivariate conditional logistic regression determined ORs. Birth season, prematurity, multiple gestation, and birth order were considered as independent variables in multivariate models. P-values <0.05 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 2,917 children who had both a birth record available and who were diagnosed with ASD by a specialist between 2000 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 44% were firstborn. April-September births accounted for 51% of cases. Characteristics of included cases are shown in Table 1. Controls included 8,751 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 documented in 2.8%. Of subjects who received a procedural treatment for jaundice, 100% had documented 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 to 1614 (18.4%) if controls (p<0.001). A procedural treatment for jaundice was documented in 107 (3.7%) of children with ASD and 221 (2.5%) of controls (p<0.001).

In McNemar's Test and unadjusted conditional logistic regression, there was a 24% increased odds of developing ASD in children who had an inpatient diagnosis of jaundice (OR 1.24; 95% confidence interval [CI], 1.22-1.38; p<0.001). There was a 47% increased odds of ASD in children who required phototherapy (OR, 1.47; 95% CI, 1.16-1.86; p=0.001). After adjusting for season of birth, birth order, multiple gestation, and prematurity, there remained an increased odds of developing ASD in children with an admission for jaundice (OR 1.18; 95% CI, 1.06-1.31; p=0.001). Using the need for phototherapy as a more rigorous definition/confirmation of jaundice, the increased adjusted odds of ASD remained (OR 1.33; 95% CI, 1.04-1.69; p=0.008). Point estimates and confidence intervals of odds ratios for covariates as determined by multivariate models are shown in Table 2.

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, and the presumed mechanism that leads to kernicterus likely is the same mechanism that can explain our results. The pathological findings in the brain of bilirubin-induced neurotoxicity include cerebellar injury and decreased number of Purkinje cells.[20] Similar to the cerebellar injury in children with kernicterus, children with ASD also have evidence of cerebellar injury,[21] which includes cerebellar hypoplasia, likely a result from cerebellar injury early in life secondary to exposure to etiologic agents.[22]

Our demographically and geographically diverse population is similar to other populations. The median age (5.3 years) and male preponderance (80%) of children with ASD in our cohort are similar to other estimates.[4,23,24] The season of birth was not a significant factor that appeared to be associated with increased risk for ASD in our cohort, contrary with other studies that found increased incidence in children born in colder months (between October and March).[25] The worldwide geographic distribution of our cohort may explain this discrepancy.

As in the majority of other studies, we defined autism by ICD-9-CM codes. [9,12,25] We sought to have a 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 seven previously published studies specifically addressing the jaundice as a risk factor for ASD, four involved specialists in the diagnosis or utilized the Autism Diagnostic Interview-Revised (ADI-R) criteria.[9,25-27] In all four of these studies, jaundice was significantly associated with ASD. In the two studies showing no association, it was not specified as to whether a general pediatrician or a pediatric subspecialist assigned the ICD codes.[23,28] Buchmayer et al. defined ASD cases through utilization of an inpatient database, suggesting that with this method they may have an overrepresentation of severe cases.[28] This study used admission diagnoses, which raised the possibility that ASD was only a suspected diagnosis from the referring pediatrician.

Of the infants included in our study, 19.3% met criteria for neonatal jaundice. In 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 similar to previous association studies.[29] 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.[23] Previous association studies have been criticized for the low prevalence of jaundice when it has been estimated that 60-80% of newborns experience jaundice.[18] This study did not aim to capture all cases of jaundice, but rather clinically significant jaundice warranting laboratory analysis or inpatient admission. Previous studies have not shown a relationship between serum bilirubin levels and the development of ASD. Serum bilirubin level and neurologic risk, however, is time- and gestational-age dependent. Our study did not have bilirubin levels available, nor were we able to control for gestational age. 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.

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 stricter and validated definitions.

Our population is geographically, demographically, and socioeconomically diverse and representative of the U. S. population as a whole. We compensated for potential misclassifications by implementing strict definitions of hyperbilirubinemia (only those that 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 specialist during the study period, making it unlikely to be affected by selection bias.

Conclusion

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.

Table 1: Characteristics of children aged 0-12 years old with Autism Spectrum Disorders

	ASD cases (n=2917)	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)	0.20
Prematurity, n (%)	225 (7.7)	512 (5.9)	0.0003
First born, n (%)	980 (33.6)	2735 (31.3)	0.02
Product of multiple gestation, n (%)	139 (4.8)	214 (2.5)	<0.0001
Age of ASD diagnosis, median (IQR)	5.4 (3.9-7.4)		

ASD=Autism Spectrum Disorders; IQR=Interquartile Range

Table 2: Unadjusted and adjusted odds ratios of the diagnosis of Autism Spectrum Disorders associated with neonatal jaundice

	Jaundice Admission 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	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]

Prematurity defined as gestation < 36 weeks.

Supplemental Table 1 – International Classification of Diseases, Ninth Edition Clinical
Modification diagnostic codes used to define neonatal jaundice

ICD-9 Code	Definition
774.1	Perinatal jaundice from other excessive hemolysis. Fetal and neonatal jaundice from: bruising, drugs or toxins transmitted from mother, infection, polycytemia, swallowed maternal blood.
774.2	Neonatal jaundice associated with preterm delivery. Hyperbilirubinemia of prematurity.
774.6	Unspecified fetal and neonatal jaundice. Icterus neonatorum, neonatal hyperbilirubinemia (transient), physiologic jaundice NOS in newborn.
774.0	Perinatal jaundice from hereditary hemolytic anemias.
774.3	Neonatal jaundice due to delay conjugation from other causes.
774.30	Neonatal jaundice due to delay conjugation, cause unspecified.
774.31	Neonatal jaundice due to delay conjugation in diseases classified elsewhere.
774.39	Other neonatal jaundice due to delay conjugation from other causes (breast milk inhibitors, delay development of conjugating system).
774.5	Perinatal jaundice from other causes.
774.6	Unspecified fetal and neonatal jaundice.
774.7	Kernicterus of fetus or newborn not due to isoimmunization.

Supplemental Table 2 – International Classification of Diseases, Ninth Edition Clinical Modification procedure codes used to define jaundice treatment

Procedure	Definition
99.83	Other phototherapy (phototherapy of the newborn).
75.2	Intrauterine transfusion (exchange transfusion in utero).
99.01	Exchange transfusion.
S9008	Home visit, phototherapy services (bili-lite) including equipment rental, nursing services, blood draw, supplies, and other services, per diem.

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