Probability of an Autism Diagnosis by Gestational Age

Ashley Darcy Mahoney, *Emory University*
Bonnie L. Minter, *Emory University*
Melinda K Higgins, *Emory University*
Ying Guo, *Emory University*
Bryan L. Williams, *Emory University*
Lauren M. Head Zauche, *Emory University*
Katie Birth, *Children's Healthcare of Atlanta*

Copyright information:

Probability of an Autism Diagnosis by Gestational Age⋆,⋆⋆

Ashley Darcy-Mahoney, PhD, NNP, FAAN[a,b,*], **Bonnie Minter, MSN, CRNP**[c], **Melinda Higgins, PhD**[d], **Ying Guo, PhD**[e], **Bryan Williams**[d], **Lauren M. Head Zauche, RN, BSN**[d], and **Katie Birth, MSN, CRNP**[f]

[a]George Washington University School of Nursing, 2030 M St NW Suite 300, Washington, DC 20052

[b]George Washington University, Autism and Neurodevelopmental Institute, 2121 Eye Street NW Suite 601, Washington, DC 20052

[c]Marcus Autism Center, Children's Healthcare of Atlanta, 1920 Briarcliff Road, Atlanta, GA 30329, United States

[d]Emory University Nell Hodgson Woodruff School of Nursing, 1520 Clifton Rd., Atlanta, GA 30322, United States

[e]Emory University Rollins School of Public Health, 1518 Clifton Rd., Atlanta, GA 30322, United States

[f]Children's Healthcare of Atlanta, 1405 Clifton Rd., Atlanta, GA 30329, United States

Abstract

Early preterm infants (EPT) (<33 6/7 weeks) are at increased risk for autism spectrum disorders (ASDs) but prevalence estimates vary widely across studies. Furthermore, there are very few studies addressing the association between late preterm (LPT) births (34–36 6/7 weeks) and ASDs. To address the question of whether LPT infants carry the same risk for ASDs as full-term infants, this study aimed to estimate the relative probability of an ASD diagnosis using Bayes rule. A retrospective cohort analysis of 406 children was undertaken to look at gestational age, ASDs, and birth history. The application of Bayes rule was used, given that there is not sufficient information about the joint probabilities related to prematurity and autism. Using the estimated gestational age proportions within ASD diagnosis, plus national estimates of ASDs, probabilities for ASDs within a given gestational age were calculated. Among these 406 children with ASDs, 6.7% were EPT and 10.6% were LPT. In comparison to full term, EPT children are at 1.9 multiplicative increase in risk (95% CI [1.3, 2.5]). While the probability of ASDs for LPT children was higher than that for term, the estimated relative risk of the LPT infants was not statistically significant (95% CI [0.9, 1.5]). EPT infants were significantly more likely to be diagnosed with ASDs compared to their term peers. While the relative probability of ASD diagnosis among

children born LPT was not statistically significant in this limited sample, the results indicate a possible elevated risk. A larger cohort is needed to adequately estimate this risk.

Keywords

Autism spectrum disorders; Gestational age; Bayes rule

Autistic spectrum disorders (ASDs) are neurodevelopmental disorders characterized by impaired communication, social interaction, and behavior.[1] According to the Centers for Disease Control & Prevention (CDC), the prevalence of ASDs has increased over the past two decades and is estimated to affect one in 88 children in the United States.[2] Major advances in autism research have led to the development of validated autism screening tools that have facilitated early autism detection for children at risk for these disorders. Recent evidence suggests that early preterm birth (<32 weeks) is a risk factor for autism.[3–7] Like autism, the prevalence of preterm infants, particularly moderate (32–33 6/7 weeks gestation) to late preterm (34–36 6/7 weeks), has increased in the last two decades.[8,9] Moderate to late preterm infants make up 70% of all preterm births and are at risk for poor neurodevelopmental sequelae.[10] However, studies estimating the prevalence of ASDs in late preterm infants (34–36 6/7 weeks) are lacking.[8]

To address the gap in knowledge of whether late preterm infants are at higher risk for ASDs than full-term infants, this study estimated the relative probability of an ASD diagnosis by gestational age using Bayes rule in a cohort of patients screened at a large autism center in the southeastern United States between March 2009 and December 2010.

Background and Significance

Autism spectrum disorders (ASDs) are a group of complex developmental syndromes of the central nervous system that are characterized by restricted behaviors and deficits in communication and social interactions. Although neuropathology of ASDs varies across cases, the most consistent pathology includes curtailment of normal development of the limbic system and abnormal development of the cerebellum and associated nuclei.[11,12] While the pathogenesis of ASDs is not fully understood, evidence supports the hypothesis that ASDsdevelop in children with a genetic susceptibility who experience abnormal stressors during a critical period of brain development.[6]

Research points to the potential role of neurological insults in pre-term infants in the development of ASDs. Preterm birth is associated with high rates of perinatal brain injury and interrupts a critical period for brain growth and structural differentiation.[13,14] A significant proportion of brain growth and development, including that of cortical gray matter, white matter, and the cerebellum, occurs during the last six weeks of gestation.[15] Knowledge regarding brain development in pre-term infants derives primarily from the large body of literature surrounding infants born less than 32 weeks gestation and very low birth weight infants (<1500 g).[3–7] Neurodevelopmental abnormalities are well recognized among very low birth weight and very preterm infants (<32 weeks) and a growing line of evidence supports prematurity as a risk factor for ASDs.

Multiple prospective studies of very preterm or very low birth weight children screened for autism at less than 3 years of age demonstrate an elevated prevalence of autism in the preterm population compared to the general population. Estimated prevalence ranged from 12% to 41%.[3–7] Similarly, preterm toddlers born <30 weeks gestation scored higher on the Quantitative Checklist for Autism in Toddlers, indicating greater restrictive, stereotyped, and repetitive behavior as well as greater social communication difficulties.[16] These deficits seem to persist throughout childhood into adolescence as shown by Pinto-Martin et al.[17] In a regional and longitudinal cohort study, prevalence of autism in 623 adolescents with a history of birth weight <2000 g was 5%, approximately five times higher than the CDC reported prevalence for the general population.[17] The prevalence estimates of ASDs for early preterm infants vary widely, with estimates varying from 5% to 41% depending on the study referenced.

While much is known about the neurodevelopment of very preterm infants, less is known regarding brain development and cognitive outcomes of late preterm infants[18–20] despite the fact that late preterm infants comprise the largest and fastest growing segment of premature infants.[8,21] Typically, late preterm infants are perceived to be at similar risk for developmental issues as full-term infants and are often clinically treated in the same manner as their term counterparts. Emerging evidence suggests that neurologic morbidity and ASDs may also be a problem in late preterm infants.[22–25]

Few studies have examined ASD diagnosis across the spectrum of gestational age, however, there have been some studies that have shed light onto this subject using ASD screening tools. Pinto-Martin et al. found higher rates for autism screening and autism diagnosis in infants born less than two kilograms and Guy et al. found that late and moderately preterm infants are at increased risk for a positive autism screen at 2 years, but did not go on to discuss findings related to autism diagnosis. Kuzniewicz and colleagues demonstrated higher prevalence of ASDs in all preterm infants, including moderate and late preterm infants, relative to term infants at two years of age.[23,26] In a recent study, 4100 mothers with children with an already diagnosed ASD voluntarily completed two validated ASD questionnaires that screen for autistic characteristics.[25] Results indicated a higher degree of autism characteristics for preterm (<37 weeks) infants than for infants born at a normal gestational age.[25] These results suggest that normal gestational age at birth mitigates the severity of symptomology of ASDs. Further studies to confirm these findings are needed.

As described above, research estimating diagnosis of ASDs in late preterm infants is sparse and estimates of ASDs in all preterm children vary greatly. Identification of risk factors can lead to early diagnostic evaluations and referrals needed to receive support and interventions to minimize poor neurologic outcomes. Despite the need to better understand the relationship between prematurity and ASDs, estimation of this relationship is difficult. Direct estimation of the probability of ASDs in relation to gestational age is complicated by both the inherent variation in diagnosis and the relatively low joint prevalence of ASDs and prematurity. This issue is illustrated in a study by Kuban et al. who reported that prevalence of autism rates in extremely preterm children was reduced when children with sensory and cognitive impairments were excluded from analysis.[5] This highlights the need to develop alternative ways of estimating risk in preterm populations.

The application of Bayes Rule in estimating the probability of given conditions in a clinical sample using known population parameters has a long history.[27,28] The application of Bayes rule in this study is appropriate, given that there is not sufficient information about joint probabilities related to prematurity and autism. The rule of Bayes Rule calculates a posterior probability, or the probability of a diagnosis given knowledge of certain conditions, by taking into account empirical data from an experiment and known probabilities from other sources.

Using Bayes rule does not assume that the clinical information is completely accurate and thus accounts for the possibility of both false positive and false negative ascertainment of a disease status and may therefore provide a more robust assessment of the probability of ASDs given gestational age.[29] However, there is little evidence in the literature of its application toward estimation of risk factors associated with ASDs. In this study, we estimate the probability of an ASD diagnosis in preterm children across the range of gestational ages, including late pre-term infants, using Bayes rule.

Methods

Sample & Measures

This study involved a retrospective analysis of data ascertained from a cohort of children treated at the Pediatric Neurodevelopmental Clinic (PNC) at a large center for excellence in autism in the southeast portion of the United Sates. The center provides approximately 2500 diagnostic evaluations annually and served 4823 children during 2010, 28% of whom were African American and 70% of whom relied on Medicaid. For this study, IRB approval was obtained and data were abstracted from in-depth medical records to obtain ASD diagnosis and phenotype, gestational age, and timing of autism diagnosis. In addition, demographic information and birth history were also obtained from medical records. The inferences made in this study are on the population of referred children, a population with a higher proportion of ASDs than the general population.

ASD diagnosis was identified in the medical record based on multi-disciplinary assessments conducted by the PNC. The Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) describes five categories of disorders that collectively comprise the Pervasive Developmental Disorders (PDD). PDD is widely used by professionals to refer to children with autism spectrum disorders (ASDs). In the DSM-IV, the term "PDD" is not a specific diagnosis but an umbrella term under which these disorders are included: Autism, Childhood Disintegrative Disorder, Rett's Syndrome, Asperger's Disorder and Pervasive Developmental Disorder Not-Otherwise-Specified. According to Autism Speaks, "psychologists and psychiatrists sometimes use the term pervasive developmental disorders and autism spectrum disorders interchangeably".[30] While there are slight differences in the configuration of symptoms in each of these categories of PDD, diagnostic labels are used to indicate commonalities among individuals. The diagnosis of ASDs indicates qualitative impairments in social interaction and communication, and the presence of restricted, repetitive and stereotyped patterns of behavior, interests and activities. Most importantly, whether a child is diagnosed with a PDD, his/her treatment will be similar (Autism-

society.org). Children with any of the diagnoses noted above were included in our sample as having a diagnosis of autism spectrum disorders (ASDs).

All assessments were conducted by a pediatric psychologist and either a developmental pediatrician or pediatric nurse practitioner. In addition to a review of records, thorough medical and family history, and a physical exam, each child received a battery of psychological tests. The specific battery of tests was chosen by the psychologist based on the individual child's presenting concerns, age, and level of skill. Most assessments included a structured diagnostic play session (most commonly the Autism Diagnostic Observation Schedule-Generic), a standardized cognitive measure (e.g., Bayley Scales of Infant Development, Mullen Scales of Early Learning, Stanford Binet, Differential Ability Scales-II), an adaptive measure (e.g., Vineland Adaptive Measures Scales-Second Edition, Adaptive Behavior Assessment System-II), and parent/teacher report measures of social, emotional, and behavioral functioning (e.g., Social Responsiveness Scale-2, Social Communication Questionnaire, Childhood Autism Rating Scale, Autism Spectrum Rating Scale, Child Behavior Checklist, Caregiver-Teacher Report Form). The final diagnosis was made using the criteria outlined in the American Psychiatric Association's Diagnostic and Statistical Manual (DSM-IV TR). Given the timeframe of the study, the DSM V was not available and thus ASD diagnoses were made using the DSM IV criteria.[31] All sources of information were considered when making a formal diagnosis. Upon completion of the multidisciplinary assessment, a comprehensive medical and psychological report highlighting significant findings with recommendations for follow-up and intervention was provided to the parent and referral source.

Data Analysis

All data were checked for completeness and any discrepancies prior to analysis. SPSS v.20 (IBM Corp., Armonk, NY) and SAS® v.9.3 (SAS Institute Inc., Cary, NC) were used for all analyses. Descriptive statistics were compiled for all continuous, ordinal and categorical variables over all subjects and by ASD diagnosis. Because there is not sufficient information about joint probabilities related to prematurity and autism, we applied the Bayes rule. The unknown population parameter, which in this case is the posterior probability, was the prevalence of autism (ASD) given gestational age or birth term (BT) (P(ASD|BT)). This probability of ASD given BT (P(ASD|BT)) can be calculated using the prior knowledge of the probability (or proportion) of ASD (P(ASD)), the probability of BT (P(BT)) and the probability of BT within children diagnosed with ASD (P(BT|ASD)). In this context, autism represents (is assumed to be) an accurately diagnosed prior event. The probability of ASD (P(ASD)) was obtained from the CDC national estimate of 1 in 88 and was treated as a prior population (known) parameter.[2] The probability of birth terms (P(BT)) was obtained from the 2006 National Vital Statistics Report and also treated as prior population parameters.[9] The proportions of gestational age groups for children with an ASD diagnosis (P(BT|ASD)) were estimated from clinical records of the 406 ASD children within the center cohort. Bayes rule[27] was then used to estimate the probability of ASD diagnosis for each gestational age group as follows:

$$P(ASD|BT) = \frac{P(BT|ASD) * P(ASD)}{P(BT)}$$

where

- $P(ASD)$ is 1 in 88 or 0.0114 (CDC national estimate);

- $P(BT)$ is the population proportions for each birth term as provided in the 2006 National Vital Statistics Report;

- $P(BT|ASD)$ is the proportions of each birth term for children diagnosed with ASD (obtained from the 406 ASD children within the center cohort);

- $P(ASD|BT)$ is the proportion (or probability) estimate for ASD given knowledge of birth term.

To provide confidence intervals for these estimates, the SAS procedure CATMOD (categorical data modeling) was used (SAS code provided in Appendix). The formula provided was then used for the lower bound and upper bound of these estimates to calculate the subsequent confidence intervals for P(ASD|BT). Finally, the confidence intervals for the relative risk to term were calculated comparing each respective statistical estimate to its equivalent for the term category.

Results

A total of 406 records were obtained for children seen at the PNC diagnosed with ASDs at the autism center from March 1, 2009 through December 30, 2010. The mean birth weight in this cohort was 3197 grams (SD 768) and mean gestational age was 38.3 (SD 3.2) weeks (Table 1). The mean duration of hospital stay was nine days (SD 27). The cohort was predominantly male, with only 17% female. Mean maternal and paternal ages were 28 years (SD 6.1) and 32 years (SD 7.4), respectively. Forty-three percent were Caucasian and 35% were African American as determined by maternal race. Across the entire cohort, 6.65% were EPT, 10.59% were LPT, 78.08% were born at term and 4.68% were post-term compared to the 2006 Vital Statistics report of EPT, LPT, full-term, and post-term birth percentages of 3.64%, 9.09%, 81.03%, and 6.24% respectively (Table 2). These differences in relative percentages of gestational age between our sample of 406 ASD children and those reported in the 2006 Vital Statistics were statistically significant as evaluated by the chi-square goodness of fit ($\chi^2_{(3)} = 13.134$, $p = 0.004$).

Using these estimated gestational age proportions within ASD diagnosis, plus national estimates of ASDs from the CDC and gestational age from all children using the 2006 Vital Statistics,[9] probabilities for ASDs within a given gestational age were calculated using the Bayes rule (Table 2). In comparison to full term, EPT children are 1.9 multiplicative increase in risk (95% CI [1.3, 2.5]. While the probability of ASDs for LPT children (0.0132) was higher than that for term (0.0109), the estimated relative risk of LPT infants (1.2) was not statistically significant (95% CI [0.9, 1.5]).

Discussion

The purpose of this study was to estimate the relative probability of an ASD diagnosis by gestational age using Bayes rule applied to a cohort of children screened at a Neurodevelopmental Pediatric Interdisciplinary Diagnostic and Evaluation Clinic. These analyses estimated the probability of ASDs within birth term using Bayes Rule. The absence of population level data for children born preterm enabled us to use Bayes rule to estimate the probability of ASDs using knowledge of birth term. Future work to extend our findings to the general population will be important.

The technique yielded probability estimates of ASDs in a relatively small clinical sample that are comparable to population-based estimates. The early premature children (33 6/7 weeks) were significantly more likely to be diagnosed with ASDs as compared to their term counterparts. This is consistent with the literature; previous studies have found that prematurity is a significant risk factor for ASDs. A 2008 study found that as many as 26% of preterm infants had a positive screening for autism, and a 2012 study reported that the diagnostic prevalence of ASDs in infants with a birth weight<2000 g was higher than the prevalence in the general population reported by the CDC.[6,17]

Our study identified a two-fold greater risk among children born less than 33 weeks gestation. While we observed an elevated probability of ASDs among children born LPT, the magnitude of the elevation risk relative to term infants was not statistically significant. In a comparable study, Schendel and Bhasin[26] reported similar findings. They noted an approximately two-fold increased risk for ASDs among children born less than 33 weeks but found no statistically significant increased risk of ASDs in children born between 33 and 36 weeks.

There are several plausible physiologic explanations for why a statistically significant relationship between late prematurity and ASDs was not observed. First, white matter injuries have been associated with ASDs in the preterm population.[32] Rates of perinatal brain injury are much smaller in late preterm infants relative to very preterm infants.[14] Second, obstetrical complications that often lead to preterm birth have been suggested to play a role in the development of ASDs.[33] The brain of the late preterm infant is less immature than that of very preterm infants and thus may be less susceptible to birth insults. Third, research suggests that adverse environmental stimuli, such as stimuli in the intensive care unit, may mediate genetic susceptibility to ASDs.[34] However, late preterm infants often spend very little time in the neonatal intensive care unit and are therefore not subjected to this potential risk factor. Lastly, although significant disparities are present in cognitive performance between late preterm children and term children, late preterm children exhibit greater academic achievement and executive functioning relative to very preterm children and thus appear to be less cognitively impaired.[35]

Although Bayes rule has not been used previously to estimate the probability of ASDs given gestational age, this statistical approach has significant implications for clinical practice and has many strengths compared to the traditional approach to statistical analysis using hypothesis testing and regression models. Bayes rule reduces bias compared to traditional

statistical methods by including correlation between risk factor and outcome.[36] Previous ASD estimates reported are based on results of single studies[4–7]; Pinto-Martin, 2011; however, inferences in this study are based also on information from other sources. Incorporating evidence not only from a cohort of preterm children with an ASD diagnosis but also from the CDC and National Vital Statistics Report improves credibility of results and improves the overall strength of the study.

Limitations

A large number of preterm children are seen in developmental follow-up clinics and thus have a higher likelihood of being referred to the autism center and being diagnosed with ASDs. Early preterm infants have a referral bias within the autism center, since prematurity is a known risk factor for ASDs. Accordingly, this bias could produce an overestimate of the relative percentages of EPT and LPT in the center cohort compared to the general population. Our study was limited by the relatively small sample size of preterm infants. While our study looked at 43 late preterm children, this is a small number compared to the number in the general population in the United States (8.2%, 387,791).[21] Our future research will examine larger populations to see if the same conclusions hold true.

Additionally, the ASD probability estimates were only calculated given gestational age. Because other factors, such as race and gender, are known to have different prevalence in the general population and were not included, these estimates are only generalizable for gestational age groups, rather than for individuals.[37–41]

Implications and Future Research

Premature infants constitute a vulnerable population that requires specific and ongoing intervention to minimize poor neurologic outcomes. Early identification of risk factors through nursing assessment and intervention can trigger early diagnostic evaluation and referral. For this to occur, it is imperative that nurses, researchers, and pediatric providers improve our understanding of maturation and brain development in the later weeks of gestation and particularly understanding of how gestational age may contribute to the development of ASDs.

The application of Bayes rule in this context appears to provide a useful method for estimating the probability and characterizing the risk of autism in children born premature. We contend that estimating the joint probabilities related to prematurity and autism will continue to be difficult and that clinical samples such as these may provide generalizable estimations. The diagnosis of autism in this particular setting may be less subject to systematic bias that is likely present in population-based estimation of autism prevalence, thus making one more confident in the estimation. Future application of the Bayes rule should estimate the probability of ASDs based on maternal and social/demographic risk factors for preterm birth as well as for ASDs given gestational age using cohorts that have been diagnosed with the most recent criteria of ASDs in the DSM-V.

It is important to note that ASD estimates may change with the introduction of the DSM-V, with a recent meta-analysis demonstrating reduction rates between 25 and 68% when

applying the new criteria. This wide range may be a result of inconsistency of an operational diagnosis for ASDs including a variety of instruments and measures.[42] This did not change the results for this study, as the DSM IV was used for these children. Characterizing the change in ASD diagnosis when using the DSM-V will be important to follow, given the rise in ASDs over the past few decades.

Nursing and medical care for affected children and their families has become a topic for epidemiology and intervention research. Studies aimed at advancing nursing knowledge and practice in caring for this population are vital in improving community and provider awareness of ASDs and improving patient and parent access to comprehensive care. Interdisciplinary research provides a collaborative environment and resources to generate evidence-based nursing practice. By utilizing both retrospective database analysis and future prospective clinical studies to identify at-risk neonates, health care professionals will be able to identify therapeutic options that can optimize each child's outcome.

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4. 1994.

2. Baio J. Prevalence of autism spectrum disorders – Autism and Developmental Disabilities Monitoring Network, 14 sites, United States, 2008. MMWR Surveill Summ. 2012; 61:1–19.

3. Hack M, Taylor HG, Schluchter M, Andreias L, Drotar D, Klein N. Behavioral outcomes of extremely low birth weight children at age 8 years. J Dev Behav Pediatr. 2009; 30:122–30. [PubMed: 19322106]

4. Johnson S, Hollis C, Kochhar P, Hennessy E, Wolke D, Marlow N. Autism spectrum disorders in extremely preterm children. J Pediatr. 2010; 156:525–U527. http://dx.doi.org/10.1016/j.jpeds.2009.10.041. [PubMed: 20056232]

5. Kuban KCK, O'Shea TM, Allred EN, Tager-Flusberg H, Goldstein DJ, Leviton A. Positive screening on the Modified Checklist for Autism in Toddlers (M-CHAT) in extremely low gestational age newborns. J Pediatr. 2009; 154:535–40. http://dx.doi.org/10.1016/j.jpeds.2008.10.011. [PubMed: 19185317]

6. Limperopoulos C, Bassan H, Sullivan NR, et al. Positive screening for autism in ex-preterm infants: prevalence and risk factors. Pediatrics. 2008; 121:758–65. http://dx.doi.org/10.1542/peds.2007-2158. [PubMed: 18381541]

7. Moore T, Johnson S, Hennessy E, Marlow N. Screening for autism in extremely pre-term infants: problems in interpretation. Dev Med Child Neurol. 2012; 54:514–20. http://dx.doi.org/10.1111/j.1469-8749.2012.04265.x. [PubMed: 22458327]

8. [Accessed September 1, 2011] March of Dimes. PeriStats. 2006. Available at: http://www.marchofdimes.com/peristats/pdflib/195/99/pdf

9. Martin JA, Hamilton BE, Sutton PD, et al. Births: final data for 2006. Natl Vital Stat Rep. 2009; 57:1–102.

10. Engle W, Kay M, Tomasheck C. Late-preterm" infants : a population at risk. Pediatrics. 2007:126.

11. Kemper TL, Bauman M. Neuropathology of infantile autism. J Neuropathol Exp Neurol. 1998; 57:645–52. [PubMed: 9690668]

12. Sweeten TL, Posey DJ, Shekhar A, McDougle CJ. The amygdala and related structures in the pathophysiology of autism. Pharmacol Biochem Behav. 2002; 71:449–55. [PubMed: 11830179]

13. Adams-Chapman I. Neurodevelopmental outcome of the late preterm infant. Clin Perinatol. 2006; 33:947–64. http://dx.doi.org/10.1016/j.clp.2006.09.004. [abstract xi]. [PubMed: 17148014]

14. Volpe JJ. Perinatal brain injury: from pathogenesis to neuroprotection. Ment Retard Dev Disabil Res Rev. 2001; 7:56–64. http://dx.doi.org/10.1002/1098-2779(200102)7:1<56::aid-mrdd1008>3.0.co;2-a. [PubMed: 11241883]

15. Muhle R, Trentacoste SV, Rapin I. The genetics of autism. Pediatrics. 2004; 113:e472–86. [PubMed: 15121991]

16. Wong L, Wilkes J, Korgenski K, Varner M, Manuck T. Newly acquired social risk factors among women with a prior term delivery who subsequently deliver preterm. Am J Obstet Gynecol. 2014; 210:S404–S404.

17. Pinto-Martin JA, Levy SE, Feldman JF, Lorenz JM, Paneth N, Whitaker AH. Prevalence of autism spectrum disorder in adolescents born weighing <2000 grams. Pediatrics. 2011; 128:883–91. http://dx.doi.org/10.1542/peds.2010-2846. [PubMed: 22007018]

18. Gyamfi-Bannerman C. The scope of the problem: the epidemiology of late preterm and early-term birth. Semin Perinatol. 2011; 35:246–8. http://dx.doi.org/10.1053/j.semperi.2011.05.013. [PubMed: 21962621]

19. Kiechl-Kohlendorfer U, Ralser E, Pupp Peglow U, Reiter G, Trawoger R. Adverse neurodevelopmental outcome in preterm infants: risk factor profiles for different gestational ages. Acta Paediatr. 2009; 98:792–6. http://dx.doi.org/10.1111/j.1651-2227.2009.01219.x. [PubMed: 19191762]

20. McGowan JE, Alderdice FA, Holmes VA, Johnston L. Early childhood development of late-preterm infants: a systematic review. Pediatrics. 2011; 127:1111–24. http://dx.doi.org/10.1542/peds.2010-2257. [PubMed: 21624885]

21. Martin JA, Hamilton BE, Sutton PD, et al. Births: final data for 2009. Natl Vital Stat Rep. 2011; 60:1–72.

22. Guy A, Seaton SE, Boyle EM, et al. Infants born late/moderately preterm are at increased risk for a positive autism screen at 2 years of age. J Pediatr. 2015; 166:269–75. [PubMed: 25477165]

23. Kuzniewicz MW, Wi S, Qian YG, Walsh EM, Armstrong MA, Croen LA. Prevalence and neonatal factors asociated with autism spectrum disorders in preterm infants. J Pediatr. 2014; 164:20–5. http://dx.doi.org/10.1016/j.jpeds.2013.09.021. [PubMed: 24161222]

24. Morse SB, Zheng H, Tang Y, Roth J. Early school-age outcomes of late preterm infants. Pediatrics. 2009; 123:e622–9. http://dx.doi.org/10.1542/peds.2008-1405. [PubMed: 19336353]

25. Movsas TZ, Paneth N. The effect of gestational age on symptom severity in children with autism spectrum disorder. J Autism Dev Disord. 2012; 42:2431–9. http://dx.doi.org/10.1007/s10803-012-1501-4. [PubMed: 22422339]

26. Schendel D, Bhasin TK. Birth weight and gestational age characteristics of children with autism, including a comparison with other developmental disabilities. Pediatrics. 2008; 121:1155–64. http://dx.doi.org/10.1542/peds.2007-1049. [PubMed: 18519485]

27. Hall GH. The clinical application of Bayes' rule. Lancet. 1967; 2:555–7. [PubMed: 4166903]

28. Oskoui M, Joseph L, Dagenais L, Shevell M. Prevalence of cerebral palsy in Quebec: alternative approaches. Neuroepidemiology. 2013; 40:264–8. http://dx.doi.org/10.1159/000345120. [PubMed: 23363886]

29. Joseph L, Gyorkos TW, Coupal L. Bayesianestimation of disease prevalence and the parameters of diagnostic tests in the absence of a gold standard. J Epidemiol. 1995; 141:263–72.

30. Autism Speaks. What we've learns about autism. (Retrieved March 15, 2016)Retrieved from www.autismspeaks.org/what-autism/pdd-nos

31. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5. 2013.

32. Movsas TZ, Pinto-Martin JA, Whitaker AH, et al. Autism spectrum disorder is associated with ventricular enlargement in a low birth weight population. J Pediatr. 2013; 163:73–8. http://dx.doi.org/10.1016/j.jpeds.2012.12.084. [PubMed: 23410601]

33. Gardener H, Spiegelman D, Buka SL. Perinatal and neonatal risk factors for autism: a comprehensive meta-analysis. Pediatrics. 2011; 128:344–55. http://dx.doi.org/10.1542/peds.2010-1036. [PubMed: 21746727]

34. Limperopoulos C. Autism spectrum disorders in survivors of extreme prematurity. Clin Perinatol. 2009; 36:791. http://dx.doi.org/10.1016/j.clp.2009.07.010. [PubMed: 19944836]

35. Williams BL, Dunlop AL, Kramer M, Dever BV, Hogue C, Jain L. Perinatal origins of first-grade academic failure: role of prematurity and maternal factors. Pediatrics. 2013; 131:693–700. http://dx.doi.org/10.1542/peds.2012-1408. [PubMed: 23530177]

36. Burgess S, Thompson SG. Improving bias and coverage in instrumental variable analysis with weak instruments for continuous and binary outcomes. Stat Med. 2012; 31:1582–600. http://dx.doi.org/10.1002/sim.4498. [PubMed: 22374818]

37. Behrman, R., Butler, A. Institute of Medicine. Preterm birth: causes, consequences, and prevention. Washington, DC: The National Academies Press; 2006.

38. Darcy AE. Complications of the late preterm infant. J Perinat Neonatal Nurs. 2009; 23:78–86. http://dx.doi.org/10.1097/JPN.0b013e31819685b6. [PubMed: 19209064]

39. Knapp, M., Mandell, D. Abstract presented at investing in our future: the economic costs of autism; Hong Kong. 2012; Available at:http://www.autismspeaks.org/about-us/press-releases/annual-cost-of-autism-triples

40. Loftin RW, Habli M, Snyder CC, Cormier CM, Lewis DF, Defranco EA. Late preterm birth. Rev Obstet Gynecol. 2010; 3:10–9. [PubMed: 20508778]

41. World Health Organization. [Accessed September 1, 2011] 2009. Retrieved from www.who.int/reproductive-health

42. Kulage K, Smaldone A, Cohn E. How will DSM-5 affect autism diagnosis? A systematic literature review and meta-analysis. J Autism Dev Disord. 2014; 44:1918–32. [PubMed: 24531932]

Table 1

Descriptive statistics.

Birth history	n total	Mean (SD)
Birth weight (grams)	403	3197 (767.9)
Maternal age at delivery	405	28.7 (6.1)
Paternal age at delivery	392	31.8 (7.4)
Length of hospital stay (days)	403	8.6 (26.9)
Gestational age (weeks)	406	38.3 (3.2)
Age of ASD diagnosis (months)	406	49.9 (18.2)
Demographic data	n total	n (%)
Gender (% male)	406	338 (83.3%)
ASD (% yes)	406	406 (100%)
Maternal race	402	
Caucasian		173 (43.0%)
African American		142 (35.3%)
Other		87 (21.6%)
Gestational category	406	
Early preterm (EPT) 33 6/7 wks.		27 (6.7%)
Late preterm (LPT) 34 0/7–36 6/7 wks.		43 (10.6%)
Term 37 0/7–41 6/7 wks.		317 (78.1%)
Post term 42 0/7 wks.		19 (4.7%)

Notes: ASD, autism spectrum disorder; EPT, early preterm (<33 6/7); LPT, late preterm (34–36 6/7 weeks); SD, standard deviation.

Table 2

Bayes probabilities for estimating diagnosis of ASD based on birth term from 406 children diagnosed with ASD.

Birth term (BT)	n	P(BT|ASD) [95% CI]	P(ASD)[1]	P(BT)[1]	P(ASD|BT) [95% CI]	Relative risk to term [95% CI]
EPT	27	0.0665 [0.0423, 0.0907]	0.0114	0.0364	0.0208 [0.0132, 0.0283]	1.8981 *[1.2730, 2.4619]
LPT	43	0.1059 [0.0760, 0.1358]	0.0114	0.0909	0.0132 [0.0095, 0.0170]	1.2090 [0.9148, 1.4743]
Term	317	0.7808 [0.7405, 0.8210]	0.0114	0.8103	0.0109 [0.0104, 0.0115]	1.0000
Post Term	19	0.0468 [0.0263, 0.0673]	0.0114	0.0564	0.0094 [0.0053, 0.0136]	0.8611 [0.5102, 1.1777]

ASD,autism spectrum disorder; BT, birth term; EPT, early preterm (<33 6/7); LPT, Late Preterm (34–36 6/7 weeks); CI, confidence interval.

[1]P(ASD) from the CDC (Baio & CDC, 2012)[2] and P(BT) from 2006 Vital Statistics.[9]

*
$p < .05$.