# Autism Spectrum Disorder:
# Comorbidity and Etiology

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## Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social interaction and communication and the presence of restricted and repetitive behavior. These core characteristics are frequently accompanied by impairments in cognition, learning, attention, and sensory processing. Males are affected with ASD more frequently than females with an average male-to-female ratio of 4:1 (Fombonne, 2005). ASD includes various conditions, including Autistic Disorder (or Autism), classified as Pervasive Developmental Disorders in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Revised* (DSM-IV-TR) (APA, 2000). ASD is typically diagnosed in early childhood and remains a lifelong condition. It is currently estimated that as many as 1 in 88 children in the United States has ASD (Baio, 2012). The prevalence has increased steadily over the past decades, and while we know there has been an increase in the diagnosis of ASD, it is not known whether this is due to a true increase in incidence.

Healthcare expenditures are three to ten times greater for children with ASD than typically developing children (Croen, Najjar, Ray, Lotspeich, & Bernal, 2006; Leslie & Martin, 2007). Furthermore, compared to costs of other childhood health conditions, the healthcare costs associated with ASD are disproportionately borne by families (Jarbrink, 2007). The lifetime per capita incremental societal cost of ASD is estimated at $3.2 million (Ganz, 2007). The substantial increase in ASD prevalence in recent years, combined with the high cost of care for persons with ASD, make it an important public health concern.

# INTRODUCTION

A condition that frequently co-occurs with ASD is intellectual disability (ID). ID is defined in the DSM-IV as IQ at or below 70 and impairment in adaptive functioning. ID is characterized by cognitive and social deficits, and is often accompanied by stereotypies and challenging behaviors (Matson & Shoemaker, 2009). In the past, ASD was considered to be highly associated with ID. The long-established view was that up to 75% of individuals with ASD had co-occurring ID (Fombonne, Du Mazaubrun, Cans, & Grandjean, 1997; Newschaffer, 2007; Ritvo et al., 1989). More recent epidemiological surveys have reported rates of ID in ASD closer to 40-50% (Baio, 2012; Bertrand et al., 2001; Chakrabarti & Fombonne, 2001; Charman, 2011; Yeargin-Allsopp et al., 2003). As the prevalence of ASD has increased, there has been a particularly large increase in children with ASD without ID (Baio, 2012). Much of the reduction in the proportion of individuals with ASD and ID over time is likely due to the expansion of diagnostic criteria. Furthermore, increased awareness has resulted in better identification of children with milder forms of ASD of higher cognitive ability.

Epilepsy, a neurologic condition characterized by recurrent, unprovoked seizures (Commission on Epidemiology and Prognosis, 1993), is another condition that frequently co-occurs with ASD. Epilepsy is commonly reported to occur in 30% of individuals with ASD (Canitano, 2007; Maski, Jeste, & Spence, 2011; Rapin I, 1998; Tuchman, 2010), which far exceeds the rate of approximately 1% in the general population (Forsgren, 2005). It has been suggested that the most common reason for the co-occurrence of ASD and epilepsy is that the same brain pathology causes both disorders (Deonna & Roulet, 2006); however, further research is needed to determine the cause of both disorders. Turk and colleagues (Turk, 2009) found that children with ASD and epilepsy had more

comorbid medical disorders, motor difficulties, developmental delays, and challenging behaviors, compared to children with ASD only. Perhaps most striking, persons with ASD and epilepsy have higher mortality rates than persons with ASD alone (Danielsson, 2005; Pickett, Xiu, Tuchman, Dawson, & Lajonchere, 2011).

Epilepsy prevalence estimates in ASD populations have varied widely, ranging from 5% to 46% (Spence, 2009). Many previous studies of epilepsy in ASD have had small sample sizes (Spence, 2009; Turk, 2009) and have been limited to lower-functioning autistic individuals (Danielsson, 2005). While the co-occurrence of ASD and epilepsy is well established, the characteristics of children with both conditions have not been studied in large, contemporary datasets.

The first two papers of this three-paper dissertation examine comorbid epilepsy in children with ASD. The first paper, titled "*Clinical Characteristics of Children with Autism Spectrum Disorder and Co-Occurring Epilepsy*," estimates the prevalence of epilepsy in a large, population-based sample of children with ASD, as well as in other diverse samples that include a substantial number of children with high-functioning ASD. At present, there is insufficient information to make strong predictions as to which individuals with ASD are at greatest risk for epilepsy and what the associated clinical characteristics may be. While prior studies have found associations between epilepsy in ASD and female gender (Amiet, 2008; Bolton, 2011; Danielsson, 2005; Turk, 2009), lower cognitive ability (Amiet, 2008; Bolton, 2011; Danielsson, 2005; Hara, 2007; Volkmar, 1990) and adaptive functioning (Danielsson, 2005), and a history of developmental regression (Hishinuma et al., 2000; Hrdlicka, 2004), findings have been inconsistent and often contradictory. The first paper of this dissertation addresses this gap

in the literature by examining the association between epilepsy and several clinical characteristics. The first chapter details the methods and results of this study.

Little is known about differences in the autism phenotype between children with and without epilepsy. The occurrence of seizures may lead to changes in brain function that impact core autism symptoms and associated maladaptive behaviors. There is initial evidence to suggest that individuals with comorbid ASD and epilepsy demonstrate higher levels of certain autism symptoms, however, further research is needed. A better understanding of the effect of seizures on autism symptoms and behaviors in persons with ASD can help guide clinical care for patients. The second paper of this dissertation, titled "*The Association between Epilepsy and Autism Symptoms and Behaviors in Children with Autism Spectrum Disorder*," examines the relationship between epilepsy and autism symptoms and maladaptive behaviors in children with ASD. The second chapter details the methods and results of this study.

The cause or causes of autism remain unknown but there is strong evidence for the role of genetic factors in the etiology of ASD. The risk of ASD is greater in individuals who have an affected sibling (Lauritsen, Pedersen, & Mortensen, 2005; Ozonoff et al., 2011) and there is a higher concordance rate in monozygotic (MZ) than dizygotic (DZ) twins (Lichtenstein, Carlstrom, Rastam, Gillberg, & Anckarsater, 2010). However, concordance in MZ twins is incomplete, suggesting that nonheritable factors also contribute to risk. Furthermore, while prior studies showed very low concordance rates in DZ twins (Bailey et al., 1995; Steffenburg et al., 1989), more recent studies have provided evidence of a greater role for environmental factors. Rosenberg (Rosenberg et al., 2009) and Hallmayer (Hallmayer, 2011) reported concordance rates of ASD in DZ

twins over 30%, leading Hallmayer to conclude that environmental factors explain about 55% of the liability to autism. This provides support for the role of environmental risk factors in ASD, particularly those occurring during the prenatal period.

Prenatal risk factors and autism have been the subject of ample research. Most studies have shown that prenatal factors are associated with an increase in risk, but results have been inconsistent. Discrepancies in findings from prior studies are likely due to methodological differences in exposure assessment, selection of control group, model covariates, and other study design choices. And most previous studies have not accounted for potential confounding by IQ (Dodds et al., 2011; Hultman, Sparen, & Cnattingius, 2002; Larsson, 2005; Lauritsen, et al., 2005). To address inconsistencies in results from prior studies, attempts to replicate findings in well designed studies are essential. The third paper of this dissertation, titled "*Prenatal Risk Factors for Autism: Findings from the Collaborative Perinatal Project*," examines the association between autism and prenatal risk factors using a prospective cohort design. The study focuses in particular on prenatal risk factors that have been examined in multiple prior studies, as well as a meta-analysis. The study is unique because of the available data on IQ, as well as the large sample size and prospectively collected exposure data. The third chapter describes the methods and results of this study.

The three studies in this dissertation address important epidemiologic questions in the autism field regarding comorbidities and etiology. These studies utilize large samples in order to investigate current topics in autism and to account for the potential impact of confounding, in particular by cognitive ability.

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# Chapter 1: Clinical Characteristics of Children with Autism Spectrum Disorder and Co-Occurring Epilepsy


## ABSTRACT

**Objectives:** To estimate the prevalence of epilepsy in children with Autism Spectrum Disorder (ASD) and to determine the demographic and clinical characteristics of children with ASD and epilepsy in a large patient population.

**Methods:** Cross-sectional study using four samples of children with ASD for a total of 5,815 participants with ASD. The prevalence of epilepsy was estimated from a population-based sample. Children with and without epilepsy were compared on demographic and clinical characteristics. Multivariate logistic regression was used to examine the association between demographic and clinical characteristics and epilepsy.

**Results:** The average prevalence of epilepsy in children with ASD 2-17 years was 12.5%; among children aged 13 years and older, 26% had epilepsy. Epilepsy was associated with older age, lower cognitive ability, poorer adaptive and language functioning, a history of developmental regression and more severe ASD symptoms. The association between epilepsy and the majority of these characteristics appears to be driven by the lower IQ of participants with epilepsy. In a multivariate regression model, only age and cognitive ability were independently associated with epilepsy. Children age 10 or older had 2.35 times the odds of being diagnosed with epilepsy ($p < .001$) and for a one standard deviation increase in IQ, the odds of having epilepsy decreased by 47% ($p < .001$).

**Conclusion:** This is among the largest studies to date of patients with ASD and co-occurring epilepsy. Based on a representative sample of children with ASD, the average

prevalence of epilepsy is approximately 12% and reaches 26% by adolescence. Independent associations were found between epilepsy and older age and lower cognitive ability. Other risk factors, such as poor language and developmental regression, are not associated with epilepsy after controlling for IQ. These findings can help guide prognosis and alert clinicians to patients with ASD who are at increased risk for epilepsy.

## INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social interaction and communication and the presence of restricted and repetitive behavior. Epilepsy is a neurologic condition characterized by recurrent, unprovoked seizures (Commission on Epidemiology and Prognosis, 1993). The co-occurrence of ASD and epilepsy is well established among clinicians and researchers (R. Canitano, 2007; R. Tuchman, Rapin I, 2002) but the characteristics of children with both conditions have not been studied in large, contemporary datasets. Epilepsy is commonly reported to occur in 30% of individuals with ASD (R. Canitano, 2007; Danielsson, 2005; Maski, Jeste, & Spence, 2011; Rapin I, 1998; R. Tuchman, Cuccaro, M., Alessandri, M. , 2010), which exceeds that of the general population (0.7-1%) (Forsgren, 2005) but prevalence estimates have varied widely, ranging from 5% to 46% (Bolton, 2011; R. Canitano, 2007; R. Canitano, Luchetti A, Zappella M, 2005; Danielsson, 2005; Hara, 2007; Kielinen, Rantala, Timonen, Linna, & Moilanen, 2004; Mouridsen, 1999; Olsson, 1988; Pavone et al., 2004; Spence, 2009; R. Tuchman, Rapin I, 2002; Volkmar, 1990; Wong, 1993). This variation is likely due to differences between prior studies in the age and cognitive level of participants and in the sampling and diagnostic methods used.

Many previous studies of epilepsy in ASD have had small sample sizes that are unlikely to be representative of the general ASD population and insufficiently powered to make rigorous conclusions about risk factors (Spence, 2009; Turk, 2009). In addition, some prior studies were based on previous diagnostic criteria for ASD (Mouridsen, 1999; Rossi, Parmeggiani, Bach, Santucci, & Visconti, 1995).

Prior studies have reported that epilepsy in ASD is associated with female gender (Amiet, 2008; Bolton, 2011; Danielsson, 2005; Turk, 2009), lower cognitive ability (Amiet, 2008; Bolton, 2011; Danielsson, 2005; Hara, 2007; Volkmar, 1990) and adaptive functioning (Danielsson, 2005), and a history of developmental regression (Hishinuma et al., 2000; Hrdlicka, 2004). However, findings have been inconsistent and often contradictory, which is likely due to small sample sizes. At present, there is insufficient information to make strong predictions as to which individuals with ASD are at greatest risk for epilepsy and what the associated clinical characteristics may be.

We conducted among the largest studies to date on the co-occurrence of ASD and epilepsy. The aim was to compare children with ASD and epilepsy to children with ASD alone on demographic and clinical characteristics. Participants were drawn from four samples; an epidemiologic population-based sample (the 2007 National Survey of Children's Health) and three genetic collaborative samples (the Autism Genetic Resource Exchange, the Simons Simplex Collection, and the Autism Consortium). Combining all samples, a total of 5,815 individuals with ASD were studied. Using this large sample we provide important insights regarding the prevalence and clinical correlates of epilepsy in this subgroup of patients with ASD.

## METHODS

### SUBJECTS

Subjects were enrolled in one of the four studies described below. See **Table 1** for a summary of the study populations.

#### *2007 NATIONAL SURVEY OF CHILDREN'S HEALTH (NSCH)*

The NSCH is a nationally representative random-digit-dial telephone-based survey sponsored by the U.S. Department of Health and Human Services Administration Maternal and Child Health Bureau and conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention. A parent/guardian was asked questions regarding the child's health during a telephone interview. A sampling weight was provided by the NSCH with the data record for each child. This weight is based on the probability of selection of the child's telephone number, with adjustments for known survey response biases and further adjustments to ensure that weighted estimates match demographic control totals from the U.S. Census Bureau's American Community Survey. Weighted results represent the population of non-institutionalized children ages 0-17 at the national and state level. Substantive and methodological details of the survey have been previously described (Blumberg, 2009). Out of 81,176 children aged 2 to 17 years in the sample, there were 921 children with a current diagnosis of ASD used in the present study.

#### *AUTISM GENETIC RESOURCE EXCHANGE (AGRE)*

The AGRE is a collection of genetic and phenotypic data on families with ASD from across the United States. The majority of families have more than one child affected with ASD (multiplex families) (Geschwind, 2001; Lajonchere, 2010). Detailed information on

the study methodology has been previously described (Lajonchere, 2010). The AGRE sample used in the present study includes 2,524 individuals with ASD.

### *SIMONS SIMPLEX COLLECTION (SSC)*

The SSC is a collection of genetic and phenotypic data on simplex families (one child affected with ASD) across the United States. Families were recruited from clinics serving children with ASD and were included if the family had only one child aged 4-18 years who met criteria for ASD. Detailed information on inclusion and exclusion criteria can be found in the SFARI Base/SSC Researcher Welcome Packet (Simons, 2010) and additional information on the study methodology has been previously described (Fischbach, 2010). The SSC sample used in the present study includes 1,891 children with ASD from version 9 (released 8/2/2010).

### *AUTISM CONSORTIUM (AC)*

The AC is a collection of genetic and phenotypic data on simplex and multiplex families of individuals with ASD in the Massachusetts area. Families were recruited from Boston area hospitals. There were no specific inclusion or exclusion criteria. The AC sample used in the present study includes 479 individuals with ASD.

## MEASURES

***Autism Spectrum Disorder (ASD)***. All of the subjects in the study had been diagnosed, or were reported to be diagnosed, with ASD. In the genetic collaborative samples, diagnosis of ASD was based on standardized diagnostic assessments including the Autism Diagnostic Interview–Revised (ADI-R) (Rutter, Le Couteur, & Lord, 2003) and the Autism Diagnostic Observation Schedule (ADOS) (C. Lord et al., 2000). The SSC and AC samples used in the present study included individuals meeting criteria for a less

severe diagnostic classification of 'ASD' on the ADI-R (equivalent to DSM-IV PDD-NOS (APA, 2000)) based on modified cut-off scores widely used in ASD research (Risi et al., 2006). In the AGRE sample, only individuals who met ADI-R criteria for autism were included because information on the 'ASD' classification was not available.

In the NSCH, diagnosis of ASD was based on parent-report. During the phone interview, parents of children aged 2-17 years were asked if they had ever been told by a doctor or other health care provider that their child had "autism, Asperger disorder, pervasive developmental disorder, or other autism spectrum disorder." If parents responded affirmatively, they were then asked if their child currently had ASD. All 2-17 year old children reported to be currently diagnosed with ASD were included in the present study (n = 921).

***Epilepsy***. Diagnosis of epilepsy was based on parent report in all of the samples. In the genetic collaborative samples, epilepsy was measured by parent response to an ADI-R question asking if the child "has ever fainted or had a fit or seizure or convulsion?" The child was classified as having been diagnosed with epilepsy if the parent reported that the child had a definite diagnosis of epilepsy. The child was classified as having never been diagnosed with epilepsy if the parent reported the child had had no attacks or febrile convulsions only. Sixty-three children from AGRE and one child from SSC were missing data on epilepsy and were therefore excluded from the analyses. Children reported to have a "history of attacks that might be epileptic, but diagnosis not established" were excluded from the analyses to prevent misclassification (n=323 participants total from AGRE, SSC, and AC). Table 2 presents demographic characteristics of the entire sample, including these 323 participants. Tables 3-6 and Tables S1-S9 present analyses excluding

these participants. In the NSCH, during the phone-based interview, parents were asked if they had ever been told by a doctor or other health care provider that their child had "epilepsy or seizure disorder." Children reported to be currently or ever diagnosed with epilepsy were classified as having epilepsy.

## CLINICAL CHARACTERISTICS

Clinical characteristics were available for subjects in the genetic collaborative samples (Table 1).

***Cognitive Ability***. Cognitive ability was measured via standardized intelligence tests, each of which provided an intelligence quotient (IQ). IQ data were available for a subset of AGRE participants (n=469) who completed the *Stanford Binet Intelligence Scales, 5th Edition* (Roid, 2003a). IQ data were available for all SSC participants, the majority (n=1632) of whom completed the *Differential Ability Scales, 2nd Edition (DAS-II)* (Elliott, 2007a); a minority completed other cognitive assessments. IQ data were available for a subset of AC participants (n=273) derived from a variety of intelligence tests including the *Mullen Scales of Early Learning* (Mullen & American Guidance Service., 1995), the *Wechsler Abbreviated Scale of Intelligence (WASI)* (David Wechsler, 1999), the *Wechsler Preschool and Primary Scale of Intelligence, Third Edition (WPPSI-III)* (D. Wechsler, 1967), and the *DAS-II*. Full-scale IQ scores were used to create a dichotomous Intellectual Disability (ID) variable defined as IQ at or below 70 (ID) versus above 70 (not ID).

***Adaptive Functioning***. Adaptive functioning was measured by the Vineland Adaptive Behavior Scales, Second Edition (Vineland-II) (Sparrow, Balla, & Cicchetti, 2005), a

valid and reliable measure of adaptive functioning. The Adaptive Behavior Composite score is a summary score derived by adding the standard scores for each domain (communication, daily living skills, socialization, and motor skills). The Motor Skills standard score is derived from the motor skills domain, which is comprised of two subdomains: gross and fine motor skills. This score was available for subjects less than seven years of age.

***Developmental Regression***. A history of developmental regression was measured by parent response to various questions on the ADI-R. Detailed descriptions of the items can be found in the ADI-R manual (Rutter, et al., 2003). We created a composite variable for any regression, defined as a loss of any previously acquired communication or social skill. This was based on all items from the ADI-R pertaining to loss of language or other skills. We also examined two specific items, "loss of any language" and "loss of any skills."

***Language***. Language was measured by parent report response to an ADI-R question regarding the child's current overall use of language and by the *Peabody Picture Vocabulary Test (PPVT)* (Dunn, 1997), which measures receptive one-word vocabulary. PPVT data were available for 1,277 AGRE, 1,748 SSC, and 337 AC participants.

***ASD Severity***. ASD severity was measured by the ADOS Calibrated Severity score, a severity metric created by Gotham, Pickles, and Lord (Gotham, Pickles, & Lord, 2009) that takes into account age and language level and is based on raw total scores of the Autism Diagnostic Observation Schedule (ADOS) (Catherine Lord et al., 2000). The Calibrated Severity score was available for genetic collaborative participants administered ADOS modules 1-3, as it has not been devised for module 4.

## STATISTICAL METHODS

Statistical analyses were conducted using SAS software, version 9.3. Bivariate analyses were conducted to compare individuals with and without epilepsy on demographic and clinical characteristics. Chi-square and t-test p-values were calculated when appropriate. Statistical significance was evaluated using 2-sided tests at a 0.05 alpha-level. For the NSCH, we computed the weighted prevalence of epilepsy in the entire sample of children with ASD and in subgroups. Using proc survey weights in SAS, the survey weights adjust the survey responses to reflect characteristics of the non-institutionalized population of children in the US. We report unweighted sample sizes, weighted percentages, and weighted 95% confidence intervals for estimated rates.

Logistic regression was used to examine the association between epilepsy and demographic and clinical characteristics among genetic collaborative study participants. We report odds ratios and 95% confidence intervals. Cases with missing values were excluded. We fit separate models for each variable (model 1), separate models for each variable adjusted for IQ score (model 2), and a model with all of the predictors entered simultaneously (model 3). Model diagnostics performed on the final multivariate model (model 3) included the removal of outliers, checking for normal distribution of continuous predictors, checking for over-dispersion, and testing model fit using the Hosmer-Lemeshow Test. The Vineland Motor Skills standard score and ADOS Calibrated Severity score were not included in the regression models because of the small sample size for these measures.

# RESULTS

## SAMPLE CHARACTERISTICS

The total sample size from all four studies combined was 5,815 participants with ASD, of whom 289 had co-occurring epilepsy. The majority of total participants were male, ranging from 80.3% male in AGRE to 86.4% male in SSC, and the majority were between the ages of 4 and 12 years (**Table 2**). Most participants were White, ranging from 66.9% White in the NSCH to 85.9% White in the AC. Among genetic collaborative study total participants for whom IQ data were available, 33.3% of AGRE, 28.8% of SSC, and 15.3% of AC participants had intellectual disability (ID).

## OCCURRENCE OF EPILEPSY

The distribution of epilepsy in the AGRE, SSC, and AC studies was 5.3% (n = 120), 2.9% (n = 51), and 6.7% (n = 30), respectively with a combined frequency of 4.5% (n = 201) (**Table 3**). In the population-based sample, the NSCH, the prevalence of epilepsy was 12.5% (n = 88).

## CLINICAL CHARACTERISTICS OF INDIVIDUALS WITH ASD AND EPILEPSY

Findings comparing individuals with ASD with and without epilepsy are presented. Individual-level data from the genetic collaborative samples were combined. Results from each of the genetic collaborative samples can be found in supplemental Tables 1-9. As shown in **Table 4** and **Figure 1**, epilepsy was more prevalent in older children. Among children aged 13 or older, 10.3% had epilepsy in the combined genetic

collaborative sample and 26.2% had epilepsy in the NSCH. Epilepsy was more prevalent in females in the combined genetic collaborative sample; 7% of females had epilepsy as compared to 3.9% of males ($p<.001$). In all of the genetic collaborative samples the prevalence of epilepsy was greater in females, but this difference was only statistically significant in the AGRE study (Table S2). In the NSCH, there were no gender differences in epilepsy prevalence. We also found that among both males and females epilepsy rates increased significantly with age.

**Table 5** presents comparisons of clinical characteristics in children with ASD with and without epilepsy from the combined genetic collaborative sample. Children with a history of developmental regression were significantly more likely to have epilepsy (6.7% of children with definite loss of language or skills had epilepsy, as compared to 3.6% without loss, $p <.001$). With regard to language, epilepsy was more prevalent in children with fewer than 5 words and children with epilepsy had a significantly lower mean PPVT score (67.8 vs. 85.9, $p <.001$). Epilepsy was associated with significantly lower cognitive ability, as evidenced by a lower mean IQ score in the epilepsy group (66.2 vs. 84.9, $p <.001$) and a greater prevalence of epilepsy in children with ID (6.2% vs. 1.9%, $p <.001$). Individuals with epilepsy also had poorer adaptive functioning, as evidenced by significantly lower mean Adaptive Behavior Composite score and Motor Skills standard score. Children with epilepsy also had a significantly higher mean ADOS Calibrated Severity score (7.4 vs. 7.1, $p = 0.04$), indicating more severe ASD symptoms.

**Table 6** presents logistic regression analyses modeling the odds of epilepsy by demographic and clinical characteristics for participants from the genetic collaborative samples. In the unadjusted models (model 1), all of the characteristics were significantly

associated with epilepsy. In the models adjusted for IQ (model 2), age was the only variable that remained associated with epilepsy. In the multivariate model that adjusted for all of the variables (model 3), age and full scale IQ score were the only variables that significantly increased risk of epilepsy. Controlling for all other variables in the model, individuals age 10 or older had 2.35 times the odds of being diagnosed with epilepsy ($p < .001$) and for a one standard deviation increase in full scale IQ, the odds of having epilepsy decreased by 47% ($p < .001$).

## DISCUSSION

This is among the largest studies to date of children with ASD and co-occurring epilepsy. Our sample includes 5,815 participants with ASD, 289 of whom had comorbid epilepsy. Using statistical modeling in this well-powered sample of patients we have made several important observations about a contemporary group of individuals with ASD and epilepsy. We identified several correlates of epilepsy in children with ASD including older age, lower cognitive and adaptive functioning, poorer language skills, a history of developmental regression, and more severe ASD symptoms. Through multivariate logistic regression we found that only age and cognitive ability were independent predictors of epilepsy.

The average prevalence of epilepsy among children aged 2 to 17 years in our population-based sample, the NSCH, was 12.5%. This estimate is comparable to a recent report of a 15.5% rate of epilepsy in another population-based sample of children with ASD (Levy, 2010). While the prevalence was 10% or lower in children under 13 years of age, by adolescence it reached 26.2%. Therefore, the best estimate of the cumulative

prevalence of epilepsy in ASD through 17 years of age is 26%. Our study replicates findings from prior studies that have followed children with ASD into adolescence/early adulthood and reported epilepsy prevalence rates from 22% to 38% (Bolton, 2011; Danielsson, 2005; Hara, 2007).

Population-based samples like the NSCH can provide accurate estimates of the prevalence of epilepsy in the general population of children with ASD by random sampling, which reduces sampling bias and improves generalizability. However, these samples often have smaller numbers of ASD cases and lack detailed phenotypic information on study participants. In contrast, samples from genetic collaboratives are less likely to be representative of the greater ASD population due to specific inclusion and exclusion criteria; however, these datasets are often large, include carefully confirmed cases of ASD, and provide rich phenotypic information collected with modern assessment tools. In the present study, we make use of both a population-based sample and several genetic collaborative samples allowing for an estimate of the prevalence of epilepsy in ASD and an examination of important clinical correlates of ASD and epilepsy. The average prevalence of epilepsy found in the combined genetic collaborative sample of 4.5% and the cumulative estimate of 10.3% in children aged 13 and older was considerably lower than the prevalence in the NSCH. This likely reflects the specific inclusion and exclusion criteria of these samples, in particular, the tendency to recruit children with higher-functioning ASD and to exclude children with certain disorders and other conditions (i.e. some known genetic syndromes) associated with epilepsy.

Additional strengths of our study are the large sample size and detailed and standardized assessments of clinical correlates using modern, reliable measures. The

large sample size allowed us to use regression modeling to examine the association between epilepsy and various characteristics in a multivariate model. Because of their small sample size, most prior studies have been unable to control for confounders in the examination of risk factors for epilepsy in ASD. In particular, there has been a need for an examination of gender and epilepsy controlling for confounding by cognitive ability (Amiet, 2008).

As reported in previous studies (Amiet, 2008; Bolton, 2011; Danielsson, 2005; Hara, 2007), individuals with epilepsy in our study had lower cognitive ability and were more likely to have ID. Over half of children with epilepsy in the genetic collaborative samples had ID and the mean IQ score for individuals with ASD and comorbid epilepsy was 66.2. Although our findings with regard to IQ and epilepsy replicate those reported in prior studies, our results are important given that the IQ distribution of children with ASD has shifted considerably in the last few years, as many more children with ASD without ID are being identified (Baio, 2012). The relationship between ASD, epilepsy and IQ is complex, and some investigators believe that the association between autism and epilepsy is primarily driven by the presence of ID (Berg & Plioplys, 2012). van Eeghen et al. (van Eeghen et al., 2013) found a strong inverse association between autistic traits and IQ in persons with epilepsy. They concluded that autistic features appear to be part of the neurocognitive construct of disorders like epilepsy. They also found associations between autistic traits and epilepsy in patients with Tuberous Sclerosis. In addition to IQ, the present study examined other related measures such as adaptive functioning and language skills, which have not been extensively studied.

Our findings with regard to gender were mixed. Females were significantly more likely to have epilepsy in the combined genetic collaborative sample, but males were more likely to have epilepsy in the NSCH (although this difference was not statistically significant). We also found variation in the association between gender and epilepsy in the individual genetic collaborative samples; while all of the samples showed a higher proportion of females with epilepsy, this difference was only statistically significant in the multiplex sample (AGRE). Tuchman (R. Tuchman, Rapin I, Shinnar S, 1991) found that female gender was not a risk factor for epilepsy after controlling for ID and motor deficit. In contrast, Bolton (Bolton, 2011) found that female gender was significantly associated with epilepsy even after adjusting for verbal ability and non-verbal IQ. In the present study, female gender was associated with epilepsy among subjects of the genetic collaborative samples only in the unadjusted logistic regression model; gender was not an independent risk factor for epilepsy after adjusting for IQ. The association between gender and epilepsy is theorized to be due to a greater proportion of females with ASD having low cognitive ability (Newschaffer, 2007), as low IQ is associated with epilepsy. This is supported by our finding that female gender was not associated with increased risk of epilepsy after controlling for IQ. However, this theory cannot be confirmed based on our statistical observations alone. It is also possible that there is a biological mechanism by which females with ASD are at increased risk for both lower IQ and epilepsy. Further research is needed to better understand the association between gender and epilepsy in ASD and to determine if the association differs in multiplex versus simplex families.

Epilepsy onset in persons without autism has been shown to be highest in the first year of life (Ellenberg, Hirtz, & Nelson, 1984; Hauser, 1994) and generally shows a bi-modal curve with higher rates in early and later life (Hauser, Annegers, & Kurland, 1993). In persons with ASD, two peaks of seizure onset have been reported, one in early childhood (Volkmar, 1990) and one in adolescence and continuing through adulthood (R. Tuchman & Cuccaro, 2011). This pattern may be unique to individuals with ASD (R. Tuchman, Cuccaro, M., Alessandri, M. , 2010). We found a higher prevalence of epilepsy in children with ASD of older age, which is expected given that older children have had a longer amount of time to develop epilepsy. The pattern was evident in both males and females with ASD showing that it is independent of gender. This finding is in line with other studies that report the highest epilepsy rates in samples that include adolescents and adults. It is also consistent with studies showing a peak in epilepsy onset in adolescence (Deykin & MacMahon, 1979). A limitation of our study is that the sample included a large number of young participants, and given that this is a cross-sectional study, we cannot be certain that some of the participants will not develop epilepsy at a later time.

Additional limitations should be considered when interpreting the results of this study. First, we relied exclusively on parent report for the diagnosis of epilepsy, which may have resulted in misclassification. For a subset of participants from the genetic collaborative samples (n=2,525) we were able to cross-validate parent report of epilepsy diagnosis on the ADI-R with assessment of non-febrile seizures based on a medical history interview or questionnaire. We found that children reported by their parent to have epilepsy on the ADI-R were highly likely (95%) to also have a history of non-febrile seizures based on medical history (Table S10). This provides support for the

reliability of the parent-report epilepsy measure. Furthermore, previous studies have used the ADI-R to identify cases of epilepsy in children with ASD (Bolton, 2011; Cuccaro et al., 2011). In addition, we relied on parent-report of ASD diagnosis in the NSCH. However, a number of studies have utilized maternally-reported diagnosis of ASD and other child health conditions and shown the reliability of these reports (Faraone, Biederman, & Milberger, 1995). In addition, parent report of medical conditions in the NSCH were consistent with those expected by clinical assessment (U.S. Department of Health and Human Services 2009) and the NSCH has been used to estimate the prevalence of ASD in the United States (Kogan et al., 2009).

Another limitation is that the genetic collaborative samples were ascertained based on the nature of the pedigrees sought, specific inclusion and exclusion criteria, and the ability of the affected participants to complete the extensive phenotyping batteries. A smaller percentage of participants in the genetic collaborative samples had cognitive abilities in the ID range, as compared to the rate in the general ASD population, recently reported to be 38% (Baio, 2012). This may in part explain the lower occurrence of epilepsy found in these samples as compared to the NSCH. We did not use the genetic collaborative samples for estimates of epilepsy prevalence given that they are not population-based samples. Instead, we used these samples to examine clinical characteristics that are less likely to be affected by this sampling bias.

There was also some heterogeneity across the genetic collaborative samples in the occurrence and clinical correlates of epilepsy due to differences between the samples. We combined data from the genetic collaborative samples in our main analyses, which may not reflect the findings from the individual samples (see Tables S1-S9 for results from the

individual samples). However, these differences were minor and in general, the results were similar across samples, suggesting that combining individual level data from each of the samples was appropriate.

An additional caveat to our study is missing data. In particular, IQ data were available for only a subset of participants. Genetic study participants for whom we had IQ data had somewhat higher IQ than would be expected in a representative sample of children with ASD (as mentioned above). The subjects used in the multivariate regression models were more likely to be from the SSC sample due to missing IQ data among AC and AGRE participants. As such, the findings may be more applicable to children with ASD from simplex families who meet the specific inclusion criteria of the SSC study. We conducted sensitivity analyses to determine if the results would differ if more participants from the AC and AGRE samples were included in the regression model. When we ran the analyses using PPVT score as a measure cognitive ability (which was available for the majority of genetic collaborative participants), instead of IQ score, the results were the same. Furthermore, when fully adjusted regression models were run separately in each of the genetic collaborative study samples the results were similar to the results from the combined sample (Table S9). The effect sizes (odds ratios) from the individual studies were similar to the combined sample; however in the AGRE sample gender was a significant predictor of epilepsy and IQ was a non-significant predictor. This is likely to be explained by the small number of AGRE participants with IQ data.

Individuals with ASD and epilepsy are an important subgroup of patients who require specialized medical care and may be of etiological significance to understanding the neurobiology of ASD. It has been suggested that the most common reason for the co-

occurrence of ASD and epilepsy is that the same brain pathology causes both disorders (Deonna & Roulet, 2006). Turk et al. (Turk, 2009) found that children with ASD and epilepsy were more likely to receive a later ASD diagnosis and have additional medical disorders, motor difficulties, developmental delays, and challenging behaviors, compared to children with ASD only. Perhaps most striking, persons with ASD and epilepsy have higher mortality rates (Danielsson, 2005; Pickett, Xiu, Tuchman, Dawson, & Lajonchere, 2011). The ASD-epilepsy subgroup may also be helpful to genetic research into ASD etiology. Duplications of the 15q11-13 locus or 15q13 copy number variants are frequently associated with ASD and epilepsy, and several key candidate genes are located in these intervals (R. Canitano, 2007). Recent sequencing studies in autism have identified *de novo* variants in a variety of epilepsy-related genes (Neale et al., 2012; O'Roak et al., 2012; Sanders et al., 2012; Veeramah et al., 2012).

## CONCLUSIONS

Our findings suggest that epilepsy is a common comorbid condition in individuals with ASD, occurring in approximately 12% of children with ASD and reaching 26% by adolescence. In a large, contemporary sample of children with ASD, we identified several risk factors for epilepsy including older age, low IQ and adaptive functioning, poor language skills, a history of developmental regression, and more severe ASD symptoms. Through statistical modeling we demonstrated that the most-widely reported factors associated with epilepsy are not predictive after adjusting for IQ. Low IQ is the best clinical predictor of epilepsy in children with ASD. These findings can help guide prognosis and alert clinicians to patients who are at increased risk for epilepsy.

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## TABLES

Table 1. Summary of Samples and Measures

| Sample | The Autism Genetic Resource Exchange (AGRE) | The Simons Simplex Collection (SSC) | The Autism Consortium (AC) | The 2007 National Survey of Children's Health (NSCH) |
|---|---|---|---|---|
| Total ASD Sample Size | 2,524 | 1,891 | 479 | 921 |
| Description of Sample | Majority multiplex families (more than one child with ASD) in U.S. | Simplex families (only one child with ASD) in U.S. | Simplex and multiplex families in New England. | Population-based survey of children in U.S. |
| ASD Diagnosis | Standardized diagnostic assessments | Standardized diagnostic assessments | Standardized diagnostic assessments | NSCH survey |
| Epilepsy Diagnosis | ADI-R | ADI-R | ADI-R | NSCH survey |
| Cognitive Ability | Available | Available | Available | Not available |
| Adaptive Functioning | Available | Available | Available | Not available |
| Language | Available | Available | Available | Not available |
| Developmental Regression | Available | Available | Available | Not available |
| ASD Severity | Available | Available | Available | Not available |

Abbreviations: ASD, Autism Spectrum Disorder; ADI-R, Autism Diagnostic Interview–Revised.

Table 2. Demographic Characteristics of Individuals with Autism Spectrum Disorder by Study Sample

| | **AGRE** (n = 2524) | **SSC** (n = 1891) | **AC** (n = 479) | | **NSCH** (n = 921) |
|---|---|---|---|---|---|
| **Characteristic** | | **No. (%)** | | **Characteristic** | **No.[b] (Wt. %)** |
| Gender | | | | Gender | |
| Male | 2026 (80.3) | 1633 (86.4) | 388 (81.0) | Male | 753 (81.0) |
| Female | 498 (19.7) | 258 (13.6) | 91 (19.0) | Female | 168 (19.0) |
| Age (years) | | | | Age (years) | |
| Under 4 | 295 (11.7) | 0 (0.0) | 40 (8.4) | 2-3 | 46 (3.1) |
| 4-6 | 861 (34.1) | 682 (36.1) | 171 (35.7) | 4-7 | 253 (27.4) |
| 7-9 | 693 (27.5) | 548 (29.0) | 117 (24.4) | 8-11 | 236 (33.4) |
| 10-12 | 338 (13.4) | 368 (19.5) | 72 (15.0) | 12-14 | 200 (22.2) |
| 13-18 | 264 (10.5) | 293 (15.5) | 73 (15.2) | 15-17 | 186 (14.0) |
| Over 18 | 73 (2.9) | 0 (0.0) | 6 (1.3) | Over 18 | N/A |
| Race | | | | Race | |
| White | 1781 (70.6) | 1492 (78.9) | 401 (85.9) | White, Non-Hispanic | 664 (66.9) |
| African-American | 49 (1.9) | 69 (3.6) | 10 (2.1) | Black, Non-Hispanic | 57 (8.3) |
| Asian | 62 (2.5) | 70 (3.7) | 11 (2.4) | Hispanic | 94 (19.1) |
| More Than One Race | 170 (6.7) | 157 (8.3) | 30 (6.4) | Other, Non-Hispanic | 86 (5.6) |
| Other | 12 (0.5) | 83 (4.4) | 2 (0.4) | | - |
| Not Specified | 450 (17.8) | 20 (1.1) | 13 (2.8) | | - |
| Type of ASD[a] | | | | | |
| Autism | 2524 (100.0) | 1700 (89.9) | 428 (89.4) | | N/A |
| ASD | N/A | 191 (10.1) | 51 (10.7) | | N/A |
| Intellectual Disability (ID) | | | | | |
| No | 344 (66.7) | 1345 (71.2) | 238 (84.7) | | N/A |
| Yes | 172 (33.3) | 545 (28.8) | 43 (15.3) | | N/A |

Abbreviations: ASD, Autism Spectrum Disorder; AGRE, the Autism Genetic Resource Exchange; SSC, the Simons Simplex Collection; AC, the Autism Consortium; NSCH, the 2007 National Survey of Children's Health; Wt. %, weighted percentage; N/A: not applicable or data not unavailable.

[a]Diagnosis based on the Autism Diagnostic Interview, Revised (ADI-R) cut-off scores for autism and ASD (Risi et al. 2006).

[b]Unweighted number of children.

Values may not add up to total due to missing data.

ID defined as IQ $\leq$ 70.

Table 3. Distribution of Epilepsy among Individuals with Autism Spectrum Disorder by Study Sample

| | **Distribution of Epilepsy** | | | | **Prevalence of Epilepsy** | |
|---|---|---|---|---|---|---|
| | **AGRE** (n = 2273) | **SSC** (n = 1786) | **AC** (n = 450) | **Combined**[a] (n = 4509) | **NSCH** (n = 918) | |
| | **No. (%)** | | | | **No.**[b] **(Wt. %)** | **(Wt. 95% CI)** |
| Never Diagnosed with Epilepsy | 2153 (94.7) | 1735 (97.1) | 420 (93.3) | 4308 (95.5) | 830 (87.5) | |
| Diagnosed with Epilepsy | 120 (5.3) | 51 (2.9) | 30 (6.7) | 201 (4.5) | 88 (12.5) | (10.4 – 14.7) |

Abbreviations: AGRE, the Autism Genetic Resource Exchange; SSC, the Simons Simplex Collection; AC, the Autism Consortium; NSCH, the 2007 National Survey of Children's Health; Wt. %, weighted percentage; CI, confidence interval.

[a]Genetic Collaborative Samples (AGRE, SSC, and AC) combined.

[b]Unweighted number of children.

Table 4. Epilepsy Diagnosis by Gender and Age among Individuals with Autism Spectrum Disorder

| | **Combined Genetic Collaborative Sample[a]** (n = 4509) | | | **NSCH** (n = 921) | | | |
|---|---|---|---|---|---|---|---|
| | **Never Diagnosed with Epilepsy** | **Diagnosed with Epilepsy** | | **Never Diagnosed with Epilepsy** | **Diagnosed with Epilepsy** | | |
| | **No. (%)** | | **p-value** | **No.[b] (Wt. %)** | | **(Wt. 95% CI)** | **p-value** |
| Age (years) | | | <.001 | | | | 0.009 |
| 6 or under | 1824 (97.8) | 41 (2.2) | | 209 (94.6) | 15 (5.4) | (2.4 – 8.4) | |
| 7-9 | 1218 (96.2) | 48 (3.8) | | 179 (92.9) | 18 (7.1) | (3.5 – 10.7) | |
| 10-12 | 682 (93.8) | 45 (6.2) | | 172 (89.6) | 17 (10.4) | (6.0 – 14.8) | |
| 13 or older | 574 (89.6) | 67 (10.5) | | 270 (73.8) | 38 (26.2) | (21.2 – 31.1) | |
| Gender | | | <.001 | | | | 0.81 |
| Male | 3586 (96.1) | 147 (3.9) | | 688 (87.3) | 62 (12.7) | (10.3 - 15.1) | |
| Female | 719 (93.0) | 54 (7.0) | | 142 (88.5) | 26 (11.5) | (6.7 – 16.4) | |
| Gender by Age | | | | | | | |
| Male | | | <.001 | | | | <.001 |
| 6 or under | 1496 (98.1) | 29 (1.9) | | 175 (95.7) | 10 (4.3) | | |
| 7-9 | 1020 (96.4) | 38 (3.6) | | 148 (91.2) | 14 (8.8) | | |
| 10-12 | 581 (95.1) | 30 (4.9) | | 144 (89.7) | 11 (10.3) | | |
| 13 or older | 484 (90.6) | 50 (9.4) | | 221 (70.8) | 27 (29.2) | | |
| Female | | | <.001 | | | | <.001 |
| 6 or under | 328 (96.5) | 12 (3.5) | | 34 (87.8) | 5 (12.2) | | |
| 7-9 | 198 (95.2) | 10 (4.8) | | 31 (98.8) | 4 (1.2) | | |
| 10-12 | 101 (87.1) | 15 (12.9) | | 28 (88.6) | 6 (11.4) | | |
| 13 or older | 90 (84.1) | 17 (15.9) | | 49 (81.2) | 11 (18.8) | | |

Abbreviations: NSCH, 2007 National Survey of Children's Health; Wt. %, weighted percentage; CI, confidence interval.
[a]Genetic Collaborative Samples (AGRE, SSC, and AC) combined. [b]Unweighted number of children.

Table 5. Epilepsy Diagnosis by Clinical Characteristics among Individuals with Autism Spectrum Disorder, Genetic Collaborative Samples

| | Combined Genetic Collaborative Sample[a] (n = 4509) | | |
|---|---|---|---|
| | **Never Diagnosed with Epilepsy** | **Diagnosed with Epilepsy** | |
| | **No. (%)** | | **p-value** |
| **Regression** | | | |
| Any Regression | | | <.001 |
| No Definite Loss | 3095 (96.4) | 114 (3.6) | |
| Definite Loss | 1210 (93.3) | 87 (6.7) | |
| Loss of Any Language | | | .001 |
| No | 2911 (96.8) | 96 (3.2) | |
| Yes | 615 (94.2) | 38 (5.8) | |
| Loss of Skills | | | <.001 |
| No Consistent Loss | 2680 (97.0) | 82 (3.0) | |
| Probable Loss | 127 (92.0) | 11 (8.0) | |
| Definite Loss | 712 (94.7) | 40 (5.3) | |
| **Language** | | | <.001 |
| Overall Level of Language | | | |
| Meaningful Use of Phrases | 3366 (96.5) | 123 (3.5) | |
| Fewer than 5 Words | 463 (92.2) | 39 (7.8) | |
| PPVT Score | 3251 (85.9, 27.9) | 110 (67.8, 31.3) | <.001 |
| **Cognitive Ability** | | | |

| Table 5. Epilepsy Diagnosis by Clinical Characteristics among Individuals with Autism Spectrum Disorder, Genetic Collaborative Samples | | | |
|---|---|---|---|
| Intellectual Disability (ID) | | | <.001 |
| No | 1797 (98.1) | 34 (1.9) | |
| Yes | 653 (93.8) | 43 (6.2) | |
| | **No. (Mean, SD)** | | |
| Full Scale IQ Score | 2450 (84.9, 25.7) | 77 (66.2, 26.8) | <.001 |
| **Adaptive Functioning** | | | |
| Adaptive Behavior Composite Score | 3531 (68.1, 17.5) | 151 (55.3, 20.7) | <.001 |
| Motor Skills Standard Score | 2171 (82.3, 18.4) | 94 (73.0, 21.5) | <.001 |
| **ASD Severity** | | | |
| ADOS Calibrated Severity Score | 3153 (7.1, 1.9) | 119 (7.4, 1.8) | 0.04 |

Abbreviations: SD, standard deviation, PPVT, Peabody Picture Vocabulary Test; ADOS, Autism Diagnostic Observation Schedule.
[a]Genetic Collaborative Samples (AGRE, SSC, and AC) combined.
Values may not add up to total due to missing data.
ID defined as IQ $\leq$ 70.

Table 6. Logistic Regression Modeling the Odds of an Epilepsy Diagnosis by Demographic and Clinical Characteristics, Combined Genetic Collaborative Sample[a]

| | Model 1: Unadjusted | | Model 2: Adjusted for FSIQ | | Model 3: Fully Adjusted | |
|---|---|---|---|---|---|---|
| **Characteristic** | **OR (95% CI)** | **p-value** | **OR (95% CI)** | **p-value** | **OR (95% CI)** | **p-value** |
| Age | | | | | | |
| 9 years and younger | 1.00 [Reference] | | 1.00 [Reference] | | 1.00 [Reference] | |
| 10 years and older | 3.05 (2.29 – 4.06) | <.001 | 2.40 (1.51 - 3.82) | <.001 | 2.35 (1.42 – 3.88) | <.001 |
| Gender | | | | | | |
| Male | 1.00 [Reference] | | 1.00 [Reference] | | 1.00 [Reference] | |
| Female | 1.86 (1.35 - 2.56) | <.001 | 1.43 (0.82 - 2.49) | 0.21 | 1.36 (0.77 - 2.43) | 0.29 |
| Cognitive Ability | | | | | | |
| Full Scale IQ Score | 0.51 (0.4 1 -0.63) | <.001 | 0.51 (0.41 - 0.63) | <.001 | 0.53 (0.39 - 0.73) | <.001 |
| Adaptive Functioning | | | | | | |
| Adaptive Behavior Composite Score | 0.52 (0.45 - 0.61) | <.001 | 0.80 (0.58 - 1.10) | 0.17 | 0.98 (0.70 - 1.37) | 0.89 |
| Language | | | | | | |
| Meaningful Use of Single Words, Two-Word Phrases, or Three-Word Phrases | 1.00 [Reference] | | 1.00 [Reference] | | 1.00 [Reference] | |
| Fewer than 5 Words | 2.00 (1.39 – 2.87) | <.001 | 0.75 (0.27 – 2.05) | 0.57 | 0.75 (0.27 - 2.13) | 0.59 |
| Developmental Regression | | | | | | |
| No Loss of Language or Skills | 1.00 [Reference] | | 1.00 [Reference] | | 1.00 [Reference] | |
| Loss of any Language or Skills | 1.93 (1.45 - 2.57) | <.001 | 1.05 (0.64 - 1.72) | 0.86 | 1.14 (0.69 - 1.89) | 0.60 |

Abbreviations: OR, odds ratio; CI, confidence interval; FSIQ, full scale IQ score.
[a]Genetic Collaborative Samples (AGRE, SSC, and AC) combined.
Model 1: Individual models for each variable.
Model 2: Individual models for each variable, adjusted for full scale IQ score only.

Model 3: Single model adjusted for all variables.
Odds ratios for full scale IQ score and adaptive behavior composite score represent the odds of epilepsy for a one standard deviation increase.

## SUPPLEMENTAL TABLES

Table S1. Epilepsy Diagnosis by Age among Individuals with Autism Spectrum Disorder, Genetic Collaborative Samples

| | AGRE | | | SSC | | | AC | | |
|---|---|---|---|---|---|---|---|---|---|
| | Never Diagnosed with Epilepsy | Diagnosed with Epilepsy | | Never Diagnosed with Epilepsy | Diagnosed with Epilepsy | | Never Diagnosed with Epilepsy | Diagnosed with Epilepsy | |
| | No. (%) | | p-value | No. (%) | | p-value | No. (%) | | p-value |
| Age (years) | | | <.001 | | | <.001 | | | 0.006 |
| 6 or under | 1039 (97.7) | 25 (2.4) | | 632 (98.0) | 13 (2.0) | | 190 (96.0) | 8 (4.0) | |
| 7-9 | 586 (94.8) | 32 (5.2) | | 514 (98.5) | 8 (1.5) | | 102 (96.2) | 4 (3.8) | |
| 10-12 | 280 (91.2) | 27 (8.8) | | 337 (96.8) | 11 (3.2) | | 59 (86.8) | 9 (13.2) | |
| 13 or older | 248 (87.3) | 36 (12.7) | | 252 (93.0) | 19 (7.0) | | 60 (87.0) | 9 (13.0) | |

Abbreviations: AGRE, the Autism Genetic Resource Exchange; SSC, the Simons Simplex Collection; AC, the Autism Consortium.

Table S2. Epilepsy Diagnosis by Gender among Individuals with Autism Spectrum Disorder, Genetic Collaborative Samples

| | AGRE | | | SSC | | | AC | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Never Diagnosed with Epilepsy** | **Diagnosed with Epilepsy** | | **Never Diagnosed With Epilepsy** | **Diagnosed with Epilepsy** | | **Never Diagnosed With Epilepsy** | **Diagnosed with Epilepsy** | |
| | **No. (%)** | | **p-value** | **No. (%)** | | **p-value** | **No. (%)** | | **p-value** |
| Gender | | | | | | | | | |
| Male | 1745 (95.5) | 83 (4.5) | .001 | 1500 (97.3) | 42 (2.7) | 0.40 | 343 (94.0) | 22 (6.0) | 0.26 |
| Female | 408 (91.7) | 37 (8.3) | | 235 (96.3) | 9 (3.7) | | 77 (90.6) | 8 (9.4) | |

Abbreviations: AGRE, the Autism Genetic Resource Exchange; SSC, the Simons Simplex Collection; AC, the Autism Consortium.

Table S3. Epilepsy Diagnosis by History of Developmental Regression among Individuals with Autism Spectrum Disorder, Genetic Collaborative Samples

| | AGRE | | | SSC | | | AC | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Never Diagnosed with Epilepsy** | **Diagnosed with Epilepsy** | | **Never Diagnosed with Epilepsy** | **Diagnosed with Epilepsy** | | **Never Diagnosed with Epilepsy** | **Diagnosed with Epilepsy** | |
| | **No. (%)** | | **p-value** | **No. (%)** | | **p-value** | **No. (%)** | | **p-value** |
| Any Regression | | | <.001 | | | 0.25 | | | <.001 |
| No Definite Loss | 1517 (95.8) | 66 (4.2) | | 1251 (97.4) | 33 (2.6) | | 330 (95.7) | 15 (4.3) | |
| Definite Loss | 636 (92.2) | 54 (7.8) | | 484 (96.4) | 18 (3.6) | | 90 (85.7) | 15 (14.3) | |
| Loss of Any Language | | | 0.11 | | | 0.03 | | | 0.04 |
| No | 1128 (96.6) | 40 (3.4) | | 1432 (97.6) | 35 (2.4) | | 354 (94.4) | 21 (5.6) | |
| Yes | 260 (94.6) | 15 (5.5) | | 290 (95.4) | 14 (4.6) | | 65 (87.8) | 9 (12.2) | |
| Loss of Skills | | | 0.05 | | | 0.47 | | | <.001 |
| No Consistent Loss | 1007 (96.9) | 32 (3.1) | | 1325 (97.4) | 36 (2.6) | | 351 (96.2) | 14 (3.8) | |
| Probable Loss | 42 (97.7) | 1 (2.3) | | 64 (94.1) | 4 (5.9) | | 21 (77.8) | 6 (22.2) | |
| Definite Loss | 333 (94.1) | 21 (5.9) | | 341 (97.2) | 10 (2.8) | | 38 (80.8) | 9 (19.2) | |

Abbreviations: AGRE, the Autism Genetic Resource Exchange; SSC, the Simons Simplex Collection; AC, the Autism Consortium.

Table S4. Epilepsy Diagnosis by Language among Individuals with Autism Spectrum Disorder, Genetic Collaborative Samples

| | AGRE | | | SSC | | | AC | | |
|---|---|---|---|---|---|---|---|---|---|
| | Never Diagnosed with Epilepsy | Diagnosed with Epilepsy | | Never Diagnosed with Epilepsy | Diagnosed with Epilepsy | | Never Diagnosed with Epilepsy | Diagnosed with Epilepsy | |
| | No. (%) | | p-value | No. (%) | | p-value | No. (%) | | p-value |
| Overall Level of Language | | | 0.03 | | | 0.02 | | | 0.007 |
| Meaningful Use of Phrases | 1453 (95.7) | 66 (4.3) | | 1574 (97.5) | 40 (2.5) | | 339 (95.2) | 17 (4.8) | |
| Fewer than 5 Words | 374 (93.0) | 28 (7.0) | | 48 (92.3) | 4 (7.7) | | 41 (85.4) | 7 (14.6) | |

Abbreviations: AGRE, the Autism Genetic Resource Exchange; SSC, the Simons Simplex Collection; AC, the Autism Consortium.

Table S5. Epilepsy Diagnosis by Cognitive Ability among Individuals with Autism Spectrum Disorder, Genetic Collaborative Samples

| | Never Diagnosed with Epilepsy | Diagnosed with Epilepsy | |
|---|---|---|---|
| | No. (Mean, SD) | | p-value |
| **AGRE** | | | |
| Full Scale IQ (n = 469) | 456 (82.6, 23.6) | 13 (75.2, 30.4) | 0.27 |
| PPVT Standard Score (n = 1277) | 1233 (83.7, 26.7) | 44 (73.1, 32.9) | 0.04 |
| **SSC** | | | |
| Full Scale IQ (n = 1785) | 1734 (84.1, 26.5) | 51 (61.3, 26.5) | <.001 |
| PPVT Standard Score (n = 1748) | 1699 (86.8, 28.4) | 49 (64.7, 30.6) | <.001 |
| **AC** | | | |
| Full Scale IQ (n = 273) | 260 (94.3, 21.1) | 13 (76.7, 16.2) | 0.003 |
| PPVT Standard Score (n = 337) | 320 (89.6, 28.9) | 17 (63.1, 27.4) | <.001 |

Abbreviations: SD, standard deviation; AGRE, the Autism Genetic Resource Exchange; SSC, the Simons Simplex Collection; PPVT, Peabody Picture Vocabulary Test.

Table S6. Epilepsy Diagnosis by Intellectual Disability among Individuals with Autism Spectrum Disorder, Genetic Collaborative Samples

| | AGRE | | | SSC | | | AC | | |
|---|---|---|---|---|---|---|---|---|---|
| | Never Diagnosed with Epilepsy | Diagnosed with Epilepsy | | Never Diagnosed with Epilepsy | Diagnosed with Epilepsy | | Never Diagnosed with Epilepsy | Diagnosed with Epilepsy | |
| | No (%) | | p-value | No (%) | | p-value | No (%) | | p-value |
| Intellectual Disability (ID) | | | 0.08 | | | <.001 | | | 0.02 |
| No | 314 (98.1) | 6 (1.9) | | 1259 (98.4) | 20 (1.6) | | 224 (96.6) | 8 (3.4) | |
| Yes | 143 (95.3) | 7 (4.7) | | 475 (93.9) | 31 (6.1) | | 36 (87.8) | 5 (12.2) | |

Abbreviations: AGRE, the Autism Genetic Resource Exchange; SSC, the Simons Simplex Collection; AC, the Autism Consortium.
ID defined as IQ $\leq$ 70.

Table S7. Epilepsy Diagnosis by Adaptive Functioning among Individuals with Autism Spectrum Disorder, Genetic Collaborative Samples

| | AGRE | | | SSC | | | AC | | |
|---|---|---|---|---|---|---|---|---|---|
| | Never Diagnosed with Epilepsy | Diagnosed with Epilepsy | | Never Diagnosed with Epilepsy | Diagnosed with Epilepsy | | Never Diagnosed with Epilepsy | Diagnosed with Epilepsy | |
| | No. (Mean, SD) | | p-value | No. (Mean, SD) | | p-value | No. (Mean, SD) | | p-value |
| Adaptive Behavior Composite Score | 1439 (58.9, 19.0) | 74 (45.9, 19.9) | <.001 | 1735 (74.5, 11.5) | 51 (65.9, 12.0) | <.001 | 357 (74.5, 19.2) | 26 (61.3, 23.8) | 0.001 |
| Motor Skills Standard Score | 1369 (82.2, 20.9) | 70 (72.6, 23.6) | <.001 | 631 (82.8, 12.6) | 14 (76.5, 11.0) | 0.06 | 171 (80.7, 14.0) | 10 (70.8, 17.8) | 0.03 |

Abbreviations: SD, standard deviation; AGRE, the Autism Genetic Resource Exchange; SSC, the Simons Simplex Collection; AC, the Autism Consortium.

Table S8. Epilepsy Diagnosis by Autism Severity among Individuals with Autism Spectrum Disorder, Genetic Collaborative Samples

| | AGRE | | | SSC | | | AC | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Never Diagnosed with Epilepsy** | **Diagnosed with Epilepsy** | | **Never Diagnosed with Epilepsy** | **Diagnosed with Epilepsy** | | **Never Diagnosed with Epilepsy** | **Diagnosed with Epilepsy** | |
| | **No. (Mean, SD)** | | **p-value** | **No. (Mean, SD)** | | **p-value** | **No. (Mean, SD)** | | **p-value** |
| ADOS Calibrated Severity Score | 1200 (6.8, 1.8) | 58 (7.2, 1.8) | 0.07 | 1679 (7.4, 1.7) | 50 (7.8, 1.7) | 0.08 | 274 (6.8, 2.6) | 11 (7.1, 2.3) | 0.70 |

Abbreviations: SD, standard deviation; AGRE, the Autism Genetic Resource Exchange; SSC, the Simons Simplex Collection; AC, the Autism Consortium; ADOS, Autism Diagnostic Observation Schedule.

Table S9. Logistic Regression Modeling the Odds of an Epilepsy Diagnosis by Demographic and Clinical Characteristics, Individual Genetic Collaborative Samples

| | AGRE (n = 430) | | SSC (n = 1785) | | AC (n = 260) | |
|---|---|---|---|---|---|---|
| **Characteristic** | **OR (95% CI)** | **p-value** | **OR (95% CI)** | **p-value** | **OR (95% CI)** | **p-value** |
| Age | | | | | | |
| 9 years and younger | 1.00 [Reference] | | 1.00 [Reference] | | 1.00 [Reference] | |
| 10 years and older | 1.70 (1.02-2.86) | 0.04 | 1.52 (1.15-2.02) | 0.004 | 2.07 (1.14-3.77) | 0.02 |
| Gender | | | | | | |
| Male | 1.00 [Reference] | | 1.00 [Reference] | | 1.00 [Reference] | |
| Female | 3.52 (1.05-11.78) | 0.04 | 1.05 (0.49-2.23) | 0.91 | 0.75 (0.15-3.82) | 0.73 |
| Cognitive Ability | | | | | | |
| Full Scale IQ Score | 0.80 (0.41-1.57) | 0.53 | 0.47 (0.31-0.71) | 0.004 | 0.35 (0.16-0.74) | 0.01 |
| Adaptive Functioning | | | | | | |
| Adaptive Behavior Composite Score | 0.87 (0.43-1.77) | 0.70 | 0.96 (0.61-1.53) | 0.88 | 0.87 (0.40-1.90) | 0.72 |
| Language | | | | | | |
| Meaningful Use of Single Words, Two-Word Phrases, or Three-Word Phrases | 1.00 [Reference] | | 1.00 [Reference] | | 1.00 [Reference] | |
| Fewer than 5 Words | 2.24 (0.21-24.12) | 0.51 | 0.72 (0.21-2.42) | 0.59 | *Not estimated* | 0.98 |
| Developmental Regression | | | | | | |
| No Loss of Language or Skills | 1.00 [Reference] | | 1.00 [Reference] | | 1.00 [Reference] | |
| Loss of any Language or Skills | 1.52 (0.46-5.04) | 0.49 | 0.92 (0.49-1.71) | 0.78 | 2.39 (0.64-8.86) | 0.19 |

Abbreviations: OR, odds ratio; CI, confidence interval; FSIQ, full scale IQ score; AGRE, the Autism Genetic Resource Exchange; SSC, the Simons Simplex Collection; AC, the Autism Consortium.

Model is adjusted for all variables.
Odds ratios for full scale IQ score and adaptive behavior composite score represent the odds of epilepsy for a one standard deviation increase.

Table S10. Cross-Validation of Parent Report Epilepsy Diagnosis on the ADI-R with Report of Non-Febrile Seizures based on Medical History, Subset of Genetic Collaborative Study Participants (n=2,525)

| **Parent Report of Non-Febrile Seizures on Medical History** | **Parent Report of Epilepsy Diagnosis on ADI-R** | |
|---|---|---|
| | Never Diagnosed with Epilepsy | Diagnosed with Epilepsy |
| | **No. (%)** | |
| No Non-Febrile Seizures | 2372 (97.8) | 5 (5.0) |
| One or More Non-Febrile Seizures | 53 (2.2) | 95 (95.0) |

Abbreviations: ADI-R, Autism Diagnostic Interview- Revised (ADI-R

# Chapter 2: The Association between Epilepsy and Autism Symptoms and Maladaptive Behaviors in Children with Autism Spectrum Disorder


## Abstract

Background: Epilepsy is common in children with Autism Spectrum Disorder (ASD) but little is known about how seizures impact the autism phenotype.

Objectives: To examine the association between epilepsy and autism symptoms and associated maladaptive behaviors in children with ASD.

Methods: Cross-sectional study of 2,645 children with ASD, of whom 139 had epilepsy, from the Simons Simplex Collection. The relationship between epilepsy and parent-reported autism symptoms and maladaptive behaviors was examined using Poisson regression.

Results: Children with ASD and epilepsy had significantly more autism symptoms and maladaptive behaviors than children without epilepsy. However only hyperactivity symptoms remained significantly increased (13% higher) after adjusting for IQ. Among children with ASD without intellectual disability, children with epilepsy had significantly more irritability (20% higher) and hyperactivity (24% higher) symptoms.

Conclusions: This is the largest study to date comparing the autism phenotype in children with ASD with and without epilepsy. Children with ASD and epilepsy showed greater impairment than children without epilepsy, which was mostly explained by the lower IQ of the epilepsy group. However, children with ASD and epilepsy had significantly more

hyperactivity symptoms even after accounting for differences in IQ. These findings have important clinical implications for patients with ASD.

## Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social interaction and communication and the presence of restricted and repetitive behavior, which affects an estimated 1 in 88 children (Baio, 2012). Epilepsy is a condition defined by unprovoked, recurrent seizures. The co-occurrence of ASD and epilepsy is well established (Canitano, 2007; Spence, 2009; R. Tuchman, Rapin I, 2002). Epilepsy prevalence estimates in persons with ASD have ranged from 5% to 46% (Spence, 2009) and studies that have followed children with ASD into adolescence/early adulthood have reported rates between 22% and 38% (Bolton, 2011; Danielsson, 2005; Hara, 2007).

Much of the prior research on epilepsy and ASD has focused on clinical features of seizures, as well as IQ and gender differences. Lower cognitive ability in persons with ASD and epilepsy as compared to persons with ASD only has been consistently shown. Intellectual disability (ID) is known to co-occur with both ASD and epilepsy, and many studies have found higher rates of epilepsy among children with ASD and comorbid ID than in children with ASD without ID (Amiet, 2008; Bolton, 2011; Danielsson, 2005; Hara, 2007; Hrdlicka, 2004; Rossi, Parmeggiani, Bach, Santucci, & Visconti, 1995; R. Tuchman, Rapin I, Shinnar S, 1991; F. R. Volkmar & Nelson, 1990; F. R. Volkmar, Nelson DS, 1990). Prior studies have also reported higher rates of epilepsy in females than males with ASD (Amiet, 2008; Bolton, 2011; Danielsson, 2005; Turk, 2009). In

addition, there is evidence that individuals with ASD and epilepsy have worse behavioral and social outcomes than those with ASD only (Danielsson, 2005; Hara, 2007; Turk, 2009).

The core symptoms of autism include impaired social interaction, communication and imaginative play, and restrictive and repetitive activities and interests. Maladaptive behaviors frequently associated with autism include hyperactivity/inattention, aggression, and motor stereotypies. At present, little is known about differences in the autism phenotype between children with and without epilepsy. The occurrence of seizures may lead to changes in brain function that impact core autism symptoms and associated maladaptive behaviors in children with comorbid ASD and epilepsy. A better understanding of the effect of seizures on autism symptoms and behaviors in persons with ASD can help guide clinical care for patients. This research can also aid in our understanding of the co-occurrence of ASD and epilepsy and in the identification, assessment, and treatment of patients. Furthermore, increasing our knowledge of the behavioral features of the ASD-epilepsy phenotype may shed light on the biological underpinnings of these co-occurring disorders. For example, evidence of specific symptoms or behaviors that are more frequent in individuals with epilepsy and ASD may indicate particular areas of the brain that are impacted by seizures.

In a sample of 60 children with ASD and epilepsy and 60 children with ASD only, Turk and colleagues (Turk, 2009) found that children with epilepsy had more motor difficulties, impaired daily living skills, and challenging behaviors than children with ASD alone. But no differences were observed in social functioning. Cuccaro and colleagues (Cuccaro et al., 2011) examined 577 children with ASD, of whom 64 had

epilepsy. Using latent class cluster analysis, they found that the cluster with the highest rate of epilepsy was also characterized by repetitive object use and unusual sensory interests.

These studies provide initial evidence to suggest that individuals with comorbid ASD and epilepsy may demonstrate higher levels of certain autism symptoms and associated impairment. However, further research is needed. A large study is required with reliable, quantitative measures of autism symptoms and maladaptive behaviors in order to better investigate the association between epilepsy and autism symptoms. Furthermore, it is important to account for IQ as a confounder because IQ is associated with both autism symptoms (Matson & Shoemaker, 2009; Poustka & Lisch, 1993) and epilepsy (Amiet, 2008; Berg et al., 2008; Ellenberg, Hirtz, & Nelson, 1984) and some investigators believe that the association between autism and epilepsy is primarily driven by the presence of ID (Berg & Plioplys, 2012).

In the present study we examined autism symptomatology and associated maladaptive behaviors in children with ASD from the Simons Simplex Collection (SSC), a large, well-phenotyped sample of simplex families with ASD (those with only one affected child). The aim of the study was to determine whether autism symptomology and maladaptive behaviors varied by epilepsy status. We hypothesized that children with ASD and epilepsy would have more autism symptoms and maladaptive behaviors than children without epilepsy. We examined the association between epilepsy and parent-reported autism symptoms and behaviors on the Social Responsiveness Scale (SRS), Repetitive Behavior Scale-Revised (RBS-R), and Aberrant Behavior Checklist (ABC).

## Methods

### *Participants*

2,645 children with ASD from the Simons Simplex Collection (SSC), a collection of phenotypic and genetic information on simplex families recruited from 12 university-based sites across the United States. Families were recruited from clinics serving children with ASD and were included in the study if the family had only one child aged 4 to 18 years who met criteria for ASD according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth edition Revised* (DSM-IV-TR) (APA, 2000) and had a nonverbal mental age of at least 18 months. The majority of the families (75%) had at least one unaffected sibling. Probands with Fragile X Syndrome and Down Syndrome (Trisomy 21) were excluded; other genetic diagnoses were not excluded. Probands with prematurity (fewer than 36 weeks gestation and less than 2000 grams at birth) and extensive pregnancy or birth complications were also excluded. Further information on inclusion and exclusion criteria for probands and other family members can be found in the SFARI Base/SSC Researcher Welcome Packet (Simons, 2010) and additional information on the study methodology has been previously described (Fischbach, 2010). Parents gave informed consent and the study was approved by Institutional Review Boards at each university involved in the study. The SSC sample used in the present study includes the 2,648 probands from version 13 (released 8/10/2011) (of these participants, 3 subjects were not used in our analyses because they were missing data on epilepsy).

### *Measures*

***Autism Spectrum Disorder (ASD).*** Study subjects were required to have a clinical "Best Estimate Diagnosis" of Autistic Disorder, Asperger's Disorder, or PDD-NOS, according to the DSM-IV-TR. The Best Estimate Diagnosis was made by a psychologist or physician with appropriate training and experience requisite for making diagnoses. Diagnosis was based on observation, chart review, and Autism Diagnostic Interview–Revised (ADI-R) (Lord, 1994) and Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 2000) findings. Both the ADOS and the ADI-R have excellent established reliability and validity for diagnosis of ASD.

***Epilepsy*.** Epilepsy was assessed through use of the medical section of the ADI-R and a medical history interview administered by SSC clinical staff to parents. On the ADI-R, the parent was asked if their child "has ever fainted or had a fit or seizure or convulsion?" Responses were classified as "no attacks," "history of attacks that might be epileptic, but diagnosis not established," "definite diagnosis of epilepsy," and "febrile convulsions only, with no continuing daily medication outside the period of fever." During the medical history interview the parent was asked if the child had ever had non-febrile seizures. A composite variable was created by SSC researchers that combined information from the ADI-R and medical history interview. Children were classified as having: a diagnosis of epilepsy (code 3); likely presence of non-febrile seizures (code 2); possible presence of non-febrile seizures or caregiver report that they were "not sure" if the child had experienced non-febrile seizures (code 1); or no evidence for presence of non-febrile seizures (code 0). The variable was coded conservatively so that if there was inconsistency, a lower score was assigned. In the present study, children with epilepsy

were defined as children who were classified as having a diagnosis of epilepsy (code 3) or the likely presence of non-febrile seizures (code 2). Children without epilepsy were those who were reported as possible presence of non-febrile seizures (code 1) or no evidence for presence of non-febrile seizures (code 0).

***Cognitive ability.*** Cognitive ability was measured via standardized intelligence tests administered based on the child's age, each of which provided an intelligence quotient (IQ) or equivalent score. The majority of participants completed the *Differential Ability Scales, Second edition* (DAS-II) (Elliott, 2007a) (administered to participants ages 4-17 years 11 months). A minority of participants completed the *Wechsler Intelligence Scale for Children, Fourth edition* (WISC-IV) (D. Wechsler, 2003a) (administered to participants ages 9-17 years), the *Wechsler Abbreviated Scale of Intelligence* (WASI) (David Wechsler, 1999) (administered to participants ages 9-17 years), or the *Mullen Scales of Early Learning* (Mullen & American Guidance Service., 1995) (administered to participants ages 4-5 years). An IQ score was derived from each of the cognitive assessments using either deviation IQs (derived from standard scores) or ratio IQs (derived by dividing the child's averaged mental age by chronological age for individuals who were not able to obtain a full-scale deviation IQ due to the type of test administered). Intellectual Disability (ID) was defined as full scale IQ score less than or equal to 70.

***Autism symptoms and associated behaviors.*** The following assessments were used to measure core autism symptoms and associated maladaptive behaviors. These measures have been used to assess a range of behavioral symptoms in persons with ASD (Brinkley et al., 2007; J. N. Constantino et al., 2003; J. N. Constantino et al., 2004) and have

demonstrated associations with functional outcomes among children with ASD (Aman et al., 2004; Arnold et al., 2006; Belsito, Law, Kirk, Landa, & Zimmerman, 2001).

***Social Responsiveness Scale (SRS).*** The SRS is a reliable and validated psychometric, quantitative measure of autistic behaviors in 4 to 18 year olds (J.N. Constantino, 2002). The SRS is commonly used as a screening tool for identifying children with ASD. The scale is completed by caregivers or companions and contains 65 items spanning five domains: (1) social awareness; (2) social cognition, including information processing and interpretation; (3) social and reciprocal communication; (4) social motivation, including questions on social anxiety and avoidance; and (5) autistic preoccupations and mannerisms such as stereotyped behavior. In the present study we used raw scores, which have been recommended for research use (J.N. Constantino, 2002). Higher scores on the SRS indicate greater severity of social impairment. In the present study, we used SRS scores based on the parent-completed questionnaire. The SRS has strong reliability and acceptable internal consistency (J. N. Constantino, et al., 2003).

***Repetitive Behavior Scales-Revised (RBS-R).*** The RBS-R is an empirically derived clinical rating scale for measuring the presence and severity of repetitive behaviors, which are a key feature of ASD (J. Bodfish, Symons F., Lewis M, 1999; J. W. Bodfish, Symons, Parker, & Lewis, 2000). The items have been conceptually grouped into six subscales: stereotyped behavior; self-injurious behavior; compulsive behavior; ritualistic behavior; sameness behavior; and restricted behavior. Higher scores indicate more symptoms. The RBS-R is frequently used in ASD research and has been shown to have high inter-rater reliability (Lam & Aman, 2007).

***Aberrant Behavior Checklist (ABC).*** The ABC (Aman, Singh, Stewart, & Field, 1985a) is a 58-item checklist that assesses maladaptive behaviors in individuals with developmental disabilities using a four-point rating scale (0–3, with higher scores reflecting more problems). The ABC is made up of five subscales; Irritability, agitation, crying; Lethargy, social withdrawal; Stereotypy; Hyperactivity, non-compliance; and Inappropriate speech. Higher scores indicate more symptoms. The ABC has good reliability, as evidenced by very good internal consistency, acceptable inter-rater reliability and very good test–retest reliability (Aman, Singh, Stewart, & Field, 1985b).

### *Statistical Analyses*

Statistical analyses were conducted using SAS software, version 9.3. Statistical significance was evaluated using 2-sided tests at a 0.05 alpha-level. The association between epilepsy and autism symptoms and maladaptive behaviors (as measured by symptom counts on the SRS, RBS-R, and ABC) was estimated with Poisson regression models using the log link function for generalized linear models (GLM). Rate ratios (RR) and 95% confidence intervals (CI) were computed using the GENMOD procedure in SAS. Over-dispersion was addressed by using the p-scale option for all of the Poisson models, which provides a scale parameter estimated by the square root of Pearson's Chi-Square/degrees of freedom. Cases with missing values were excluded.

We constructed separate models for total score and subdomain score for each of the three assessments. In the first set of models, unadjusted RRs were estimated. In the second set of models, RRs were adjusted for age; in the third, for age and gender, and in the final, RRs were adjusted for age, gender, and full scale IQ score. We stratified the sample by

intellectual disability and examined the association between epilepsy and autism symptoms and maladaptive behaviors using Poisson regression models adjusted for age and gender.

**Results**

Based on the special criteria established by the SSC, out of 2,645 children with ASD, 59 had a confirmed diagnosis of epilepsy (2.2%) (code 3) and 80 were classified as likely to have had non-febrile seizures (3.0%) (code 2). For the purposes of our study, we combined these two groups, which resulted in 139 participants (5.2%) who we refer to as the epilepsy group. The mean age of the entire sample was 9 years (standard deviation (SD) 3.6 years) and the mean age of the epilepsy group was 10.1 years (SD 3.8 years).

A comparison of the demographic characteristics of children with and without epilepsy is presented in **Table 1**. There were no differences in the prevalence of epilepsy by gender, race, or ethnicity. Older children were more likely to have epilepsy; 10% of 13 to 15 year olds and 7.8% of 16 to 18 year olds had epilepsy, as compared to 3.9% of 4 to 6 year olds ($p < 0.01$). Epilepsy was more prevalent in children with ID; 9.6% of children with ID had epilepsy, as compared to 3.4% of children without ID ($p < 0.01$). Among children with epilepsy, 55.4% ($n = 77$) had ID, while 44.6% ($n = 62$) did not have ID. The mean IQ of children with epilepsy was 60.8 (SD 28.7), as compared to mean IQ of 82.3 (SD 27.4) in children without epilepsy ($p < 0.01$) (data not shown).

**Table 2** presents the association between autism symptoms and maladaptive behaviors and potential confounders (gender, ID, and age) among all subjects. All of these characteristics were significantly related to autism symptoms and behaviors in

children with ASD. There were no gender differences on the SRS, but females had significantly more self-injurious behavior and less restricted behavior on the RBS-R. Females also had significantly more irritability and lethargy symptoms, but fewer hyperactivity symptoms, on the ABC. Children with ID had significantly more symptoms in the majority of domains on the SRS, RBS-R, and ABC. Age was also highly associated with symptoms; children over age 10 had significantly more symptoms on the SRS, but in general fewer symptoms on the RBS-R and ABC.

The unadjusted and adjusted associations between epilepsy and autism symptoms and maladaptive behaviors in children with ASD are presented in **Table 3**. In the unadjusted models, children with epilepsy had significantly higher scores on the SRS, RBS-R, and ABC. Children with epilepsy had 9% more total SRS symptoms ($p < 0.01$), 15% more total RBS-R symptoms ($p = 0.01$), and 12% more total ABC score symptoms ($p = 0.02$), as compared to children without epilepsy. Significantly higher scores were also seen on all sub-domains of the SRS and most sub-domains of the RBS-R and ABC. Adjusting for age (model 1) had little effect on the estimates; and further adjusting for gender (model 2) also did not change the results. However, additionally adjusting for full scale IQ score attenuated the effect estimates. In the fully adjusted models, there were no significant differences in SRS or RBS-R scores between children with and without epilepsy. The only score that remained significant was the ABC hyperactivity score; children with epilepsy had 13% more hyperactivity symptoms ($p = 0.01$) than children without epilepsy.

Because of the large effect of IQ overall on the association between autism symptoms and behaviors and epilepsy, we wanted to determine if there was an effect of epilepsy on

the autism phenotype even in the absence of intellectual disability (ID). **Table 4** shows the association between epilepsy and autism symptoms and maladaptive behaviors stratified by ID and adjusted for age and gender. Among children with ASD *without* ID, there were still no differences in core autism symptoms as measured by the SRS and RBS-R, but children with epilepsy had significantly more irritability (20% higher, $p = 0.05$) and hyperactivity (24% higher, $p < 0.01$) symptoms. Among children with ASD *with* ID, children with epilepsy had significantly more autistic mannerisms (8% higher, $p = 0.05$).

**Discussion**

Among children with ASD from simplex families, we found significant differences in autism symptoms and associated maladaptive behaviors between children with and without epilepsy. Children with epilepsy had more symptoms and maladaptive behaviors, indicating greater impairment. Adjusting for age and gender did not change the results, but adjusting for IQ had a large effect on symptom rates. After adjusting for IQ, there were no significant differences between the groups, with the exception of hyperactivity symptoms, which were higher in children with epilepsy. When stratified by ID, hyperactivity and irritability symptoms were significantly higher among children with ASD and comorbid epilepsy who did not have ID.

Our findings indicate that epilepsy is not *independently* associated with more severe autism symptoms and maladaptive behaviors, as we failed to find an association after controlling for IQ. Instead, the evidence suggests that children with ASD and epilepsy are at risk for elevated autism symptoms and behaviors due to the increased likelihood of

these children having low IQ. In our sample, ID was associated with epilepsy (Table 1) and with increased autism symptoms and maladaptive behaviors (Table 2). Prior studies have also shown that ID is a strong predictor of greater severity in ASD (Matson & Shoemaker, 2009) and is associated with various maladaptive behaviors (Emerson et al., 2001). Based on our statistical models, much of the association between epilepsy and autism symptoms and maladaptive behaviors in children with ASD is explained by the association between epilepsy and low IQ/ID. However, we did find higher rates of hyperactivity behavior in the epilepsy group even after adjusting for IQ.

Our finding that epilepsy is associated with increased hyperactivity is consistent with prior epidemiologic studies that have reported more inattention, hyperactivity, and impulsivity in children with epilepsy, compared with controls (Carlton-Ford, Miller, Brown, Nealeigh, & Jennings, 1995). It is possible that seizures impact specific parts of the brain that regulate behavior control, but further research is needed. While hyperactivity is not one of the core symptoms of ASD, hyperactivity, short attention span, and impulsivity are common associated features of ASD. Studies show that a large proportion of children with ASD meet diagnostic criteria for attention ADHD (Leyfer et al., 2006) or have been diagnosed with both disorders (Kogan et al., 2009). Hyperactivity is therefore an important behavioral feature in ASD, which has been linked to problems with executive function, autistic traits, adaptive function, and externalizing behaviors (Yerys et al., 2009). In the present study, hyperactivity symptoms were 13% higher in the epilepsy group. The mean hyperactivity score in children with epilepsy was 19, as compared to a mean of 16 in children without epilepsy. This is an average difference of 3 points, which may be clinically meaningful.

Intellectual disability in persons with ASD has clinical relevance and patients with comorbid ID may represent a distinct subgroup of ASD patients. In addition, it has been proposed that the association between ASD and epilepsy is driven by comorbid ID (Berg & Plioplys, 2012). Therefore, we wanted to determine if there was an effect of epilepsy on the autism phenotype in the absence of ID. We found differences in the association between epilepsy and autism symptoms and maladaptive behaviors by intellectual disability. Specifically, among children with ASD *without* ID, the epilepsy group had significantly higher irritability (20% higher) and hyperactivity (24% higher) symptoms. In contrast, among children with ID, no differences emerged except for a moderately increased rate of autistic mannerisms (8% higher) in the epilepsy group. These findings suggest that there are differences in the association of epilepsy with the autism phenotype in patients with and without comorbid ID, but further research is needed.

The present study somewhat contrasts the findings by Turk and colleagues (Turk, 2009) comparing 60 children with ASD and epilepsy matched on verbal IQ to 60 children with ASD alone. Using the *Diagnostic Interview for Social and Communication Disorders (DISCO)*, they found significant differences between children with ASD with and without epilepsy, even after matching on cognitive level. In their study, children with ASD and epilepsy were significantly more likely to have abnormal fascination with objects and inappropriate eye contact, but there were no significant differences in social interaction. The study by Turk and colleagues had several limitations. In addition to a small sample size, the participants were very low functioning with over half of the children having IQ in the severe ID range. Thus, the study findings may not be applicable

to all children with ASD. In contrast, our study is larger and includes many participants with high-functioning ASD.

Children with epilepsy in our study had lower cognitive functioning, which is in line with prior studies in the general population (Steffenburg, Hagberg, Viggedal, & Kyllerman, 1995; van Blarikom, Tan, Aldenkamp, & van Gennep, 2006) and in ASD populations. In a meta-analysis of studies of ASD and epilepsy, Amiet and colleagues (Amiet, 2008) reported a pooled prevalence of epilepsy of 21% in subjects with ASD and ID, as compared to 8% in subjects with ASD without ID. Evidence suggests that the occurrence of seizures do not cause lower IQ or cognitive decline, instead, lower IQ is more frequent in children with epilepsy due to neurological abnormalities present before seizures develop (Ellenberg, Hirtz, & Nelson, 1986). This implies a shared underlying pathology increasing risk of both epilepsy and ID. The relationship between autistic traits, epilepsy, and cognitive functioning is complex. In a recent study, van Eeghen and colleagues (van Eeghen et al., 2013) found a strong inverse association between autistic traits and IQ in persons with epilepsy. They concluded that autistic features appear to be part of the neurocognitive construct of disorders like epilepsy

Evidence also suggests that there may be underlying etiologies and pathologies responsible for both seizures and the deficits and behaviors that define ASD (Bernard et al., 2013; R. Tuchman, Moshe, & Rapin, 2009). There may be shared susceptibility factors, such as genetic mutations or environmental insults that concurrently lead to both epilepsy and ASD. There is biological evidence that a common cause of both disorders is disruptions in neural networks (Minshew & Williams, 2007; Spencer, 2002). Another area of research is abnormalities in synaptic structure and function (Sutcliffe, 2008). One

hypothesis currently being pursued is that abnormalities in synaptic plasticity early in development, either as the result of early seizures or genetic variants, may be a common cause of ASD and epilepsy (R. Tuchman & Cuccaro, 2011). Finally, there is overlap in copy number variants (CNVs) associated with ASD, epilepsy, and ID (Morrow, 2010; Owen, 2012; R. Tuchman & Cuccaro, 2011) suggesting a shared genetic etiology to all three of these disorders.

In the present study, 44% of children with ASD and comorbid epilepsy did not have ID, which may simply reflect the ascertainment strategies of the SSC and an intrinsic bias towards recruitment of children with higher-functioning ASD. Alternatively, this high proportion of epilepsy in ASD participants without ID may reflect the simplex pedigree structure. Further study will be necessary to explore this aspect further; however, the SSC represents an opportunity to study the association between epilepsy and ASD in a relatively high functioning sample. Prior studies on epilepsy and the autism phenotype have been limited to participants with comorbid ASD and epilepsy of low IQ (Hara, 2007; Turk, 2009). We believe that the identification and characterization of a large group of high-functioning patients makes our study fairly unique, as this population of higher-functioning ASD requires state-of-art methods to phenotypically characterize and is often missed in ASD/epilepsy studies.

The prevalence of epilepsy in our sample was 5.2%. This is somewhat lower than would be expected in a representative sample of children with ASD, which is closer to 15% (Levy, 2010; Suren et al., 2012; R. Tuchman, et al., 2009). The low prevalence of epilepsy in our study is likely explained by the specific inclusion and exclusion criteria of the SSC study. In particular, the SSC recruited more children with high-functioning ASD

and required a minimum nonverbal mental age for inclusion in the study. Among all SSC participants in the current study, 30% had ID, which is lower than current estimates in representative ASD samples of approximately 40% (Baio, 2012). Higher IQ is associated with lower rates of epilepsy in children with ASD (Amiet, 2008; Viscidi, 2013), which could explain the relatively low prevalence of epilepsy in the SSC sample. In addition, the age of the sample was young; 35% of children were 4-6 years while only 5% were 16-18 years. The prevalence of epilepsy in ASD increases with age (Hara, 2007; R. Tuchman & Cuccaro, 2011; Viscidi, 2013) and as such, lower prevalence rates are expected in younger samples. In studies that include preadolescent children the reported rate of epilepsy is less than 10% (R. Tuchman, et al., 2009).

The present study is the largest to date examining the autism phenotype in children with ASD with and without epilepsy. The large sample size allowed us to use multivariate modeling to control for confounders, most importantly IQ, and to stratify our sample by ID. Another strength of the study is the SSC sample, which is a cohort of well-characterized children with ASD. It includes carefully confirmed cases of ASD who were administered detailed and standardized assessments using modern, reliable measures. Our autism symptom and behavior assessments are valid and reliable quantitative measures of autism symptomology.

Despite these strengths, a few limitations should be considered in interpreting the results of the study. Epilepsy diagnosis was based on parent report, which is subject to misclassification. However, two different parent report assessments (the ADI-R and medical history interview) were used to improve reliability. The composite measure developed by SSC staff is conservative and takes into account both assessments. The

epilepsy group includes both children with an epilepsy diagnosis and those considered likely to have a history of non-febrile seizures. We combined these groups because the number of participants with a strict epilepsy diagnosis (n = 59) was small and likely an overly conservative cut-off for epilepsy. In a sensitivity analysis we included only the 59 children with a confirmed epilepsy diagnosis. The effect estimates were in the same direction but not statistically significant (data available upon request). This suggests that the results would be similar if we restricted our sample to only children with an SSC category 3 epilepsy diagnosis but we would not have had sufficient power to detect statistically significant differences. We also conducted a sensitivity analysis excluding children classified as having 'possible seizures' or 'the parent was unsure of whether the child had seizures' (code 1) from the non-epilepsy group and this did not change the results (data available upon request). Together these findings suggest that our results were not greatly affected by our classification of epilepsy.

Another limitation is that the SSC sample may not be representative of all children with ASD because participants were recruited from families with only one child with ASD, and other specific inclusion/exclusion criteria were applied. The SSC recruited a large number of high-functioning children with ASD. Approximately 30% of children in the sample have ID, which is somewhat lower than the 40% expected in a representative ASD sample (Baio, 2012). However, the IQ distribution of the SSC sample is also a strength of the present study because we were able to examine the autism phenotype in a large number of children with epilepsy without ID.

A final limitation is that the sample included a large number of young participants, and as such, we cannot be certain that some of the participants without epilepsy will not

develop epilepsy at a later time, as there is evidence that epilepsy onset in ASD often occurs after 10 years of age (Bolton, 2011). However, this misclassification is unlikely to have biased the study findings given the overall low prevalence of epilepsy in the sample. In sub-analyses we compared all children with epilepsy to children without epilepsy aged 13 years and older (n=399). The effect estimates were larger, which indicates that the inclusion of younger children in our study somewhat attenuated the results (data available upon request). Future research might address this issue by designing a longitudinal study of children with ASD that follows participants through young adulthood to ensure sufficient time for epilepsy to develop.

Finally, we conducted several statistical tests to examine the association between autism symptoms and behaviors and epilepsy. We ran 19 separate models for each symptom/behavior scale. It is therefore important to consider the issue of multiple comparisons. When conducting multiple statistical tests there is a greater probability of declaring a significant result when in fact there is not one. If we use a Bonferonni adjustment and consider only p-values less than or equal to 0.002 as statistically significant, then none of the effect estimates in the models adjusted for IQ are statistically significant. It is therefore possible that our results are due to chance or that our sample size is insufficient to address the study question. Our methods should be replicated in a sample with a larger number of participants with epilepsy to confirm the findings.

### *Conclusions*

Children with ASD and epilepsy had more autism symptoms and associated maladaptive behaviors than children without epilepsy, but this difference was largely explained by the

lower IQ of children with epilepsy. However, even after adjusting for IQ, children with epilepsy had significantly more hyperactivity symptoms. When stratified by ID, hyperactivity and irritability symptoms were elevated among children with comorbid ASD and epilepsy without ID. These findings have important clinical implications for patients with ASD and highlight the important role of cognitive ability in the relationship between epilepsy and the autism phenotype. Further research on the biological mechanisms explaining these associations is needed and the results should be replicated in other ASD populations, including predominantly multiplex samples.

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## Tables

Table 1: Demographic Characteristics by Epilepsy among Children with Autism Spectrum Disorder

| | No Epilepsy (n=2,506) N (%) | Epilepsy (n=139) N (%) | p value |
|---|---|---|---|
| **Gender** | | | 0.15 |
| Male | 2181 (95.0) | 115 (5.0) | |
| Female | 325 (93.1) | 24 (6.9) | |
| **Age** | | | <.01* |
| 4-6 years | 886 (96.1) | 36 (3.9) | |
| 7-9 years | 754 (95.7) | 34 (4.3) | |
| 10-12 years | 467 (94.3) | 28 (5.7) | |
| 13-15 years | 269 (90.0) | 30 (10.0) | |
| 16-18 years | 130 (92.2) | 11 (7.8) | |
| **Race** | | | 0.57 |
| White | 1962 (94.6) | 113 (5.5) | |
| African-American | 95 (93.1) | 7 (6.9) | |
| Asian | 109 (98.2) | 2 (1.8) | |
| More than one Race | 200 (95.7) | 9 (4.3) | |
| Other | 120 (93.3) | 8 (6.7) | |
| **Ethnicity** | | | 0.48 |
| Hispanic | 282 (95.6) | 13 (4.4) | |
| Non-Hispanic | 2220 (94.6) | 126 (5.4) | |
| **Intellectual Disability** | | | <.01* |
| No | 1776 (96.6) | 62 (3.4) | |
| Yes | 725 (90.4) | 77 (9.6) | |

*$p \leq 0.05$.
Intellectual disability defined as full scale IQ score of less than or equal to 70.

Table 2: Unadjusted Relative Risks for the Association between Gender, Intellectual Disability, and Age and Autism Symptoms/Behaviors in Children with Autism Spectrum Disorder

| | Gender[a] | | | Intellectual Disability[b] | | | Age[c] | | |
|---|---|---|---|---|---|---|---|---|---|
| | **RR** | **(95% CI)** | **p value** | **RR** | **95% CI** | **p value** | **RR** | **95% CI** | **p value** |
| **SRS** | | | | | | | | | |
| Total | 1.02 | (0.99 - 1.06) | 0.14 | 1.14 | (1.11 - 1.16) | <.01* | 1.05 | (1.03 - 1.07) | <.01* |
| Autistic Mannerisms | 1.00 | (0.96 - 1.05) | 0.89 | 1.14 | (1.11 - 1.17) | <.01* | 1.07 | (1.04 - 1.11) | <.01* |
| Social Awareness | 1.02 | (0.99 - 1.05) | 0.29 | 1.12 | (1.09 - 1.14) | <.01* | 0.98 | (0.96 - 1.00) | 0.07 |
| Social Cognition | 1.03 | (1.00 - 1.07) | 0.07 | 1.15 | (1.13 - 1.18) | <.01* | 1.03 | (1.00 - 1.05) | 0.03* |
| Social Communication | 1.03 | (1.00 - 1.06) | 0.09 | 1.14 | (1.11 - 1.17) | <.01* | 1.05 | (1.03 - 1.07) | <.01* |
| Social Motivation | 1.03 | (0.99 - 1.08) | 0.18 | 1.12 | (1.08 - 1.15) | <.01* | 1.10 | (1.07 - 1.13) | <.01* |
| **RBS-R** | | | | | | | | | |
| Total | 0.99 | (0.92 - 1.07) | 0.83 | 1.19 | (1.13 - 1.25) | <.01* | 0.94 | (0.89 - 0.99) | 0.01* |
| Stereotyped behavior | 0.94 | (0.86 – 1.02) | 0.15 | 1.55 | (1.46 - 1.64) | <.01* | 0.80 | (0.75 - 0.85) | <.01* |
| Self-injurious behavior | 1.17 | (1.01 - 1.36) | 0.03* | 1.50 | (1.35 - 1.66) | <.01* | 1.11 | (1.00 - 1.24) | 0.05* |
| Compulsive behavior | 1.03 | (0.92 - 1.14) | 0.62 | 1.32 | (1.23 - 1.43) | <.01* | 0.96 | (0.89 - 1.04) | 0.29 |
| Ritualistic behavior | 1.02 | (0.93 - 1.11) | 0.74 | 0.97 | (0.91 - 1.04) | 0.44 | 0.92 | (0.86 - 0.98) | 0.01* |
| Sameness behavior | 1.03 | (0.95 - 1.12) | 0.49 | 1.04 | (0.98 - 1.11) | 0.23 | 1.03 | (0.97 - 1.09) | 0.41 |
| Restricted Behavior | 0.82 | (0.74 - 0.90) | <.01* | 1.12 | (1.06 - 1.20) | <.01* | 0.84 | (0.79 - 0.89) | <.01* |
| **ABC** | | | | | | | | | |
| Total | 1.03 | (0.97 - 1.10) | 0.29 | 1.21 | (1.15 - 1.26) | <.01* | 0.88 | (0.84 - 0.92) | <.01* |
| Irritability | 1.14 | (1.05 - 1.24) | <.01* | 1.13 | (1.06 - 1.20) | <.01* | 0.84 | (0.78 - 0.89) | <.01* |
| Lethargy | 1.13 | (1.04 - 1.22) | <.01* | 1.22 | (1.15 - 1.30) | <.01* | 1.16 | (1.09 - 1.23) | <.01* |
| Stereotypy | 1.00 | (0.91 - 1.10) | 1.00 | 1.64 | (1.53 - 1.75) | <.01* | 0.96 | (0.90 - 1.03) | 0.29 |
| Hyperactivity | 0.92 | (0.86 - 0.99) | 0.03* | 1.15 | (1.09 - 1.21) | <.01* | 0.74 | (0.70 - 0.78) | <.01* |
| Inappropriate Speech | 1.01 | (0.92 - 1.11) | 0.78 | 1.16 | (1.08 - 1.23) | <.01* | 0.97 | (0.91 - 1.04) | 0.39 |

Abbreviations: SRS, Social Responsiveness Scale; RBS-R, Repetitive Behavior Scale Revised; ABC, Aberrant Behavior Checklist.

[a]Unadjusted model of the RR of autism symptoms in females vs. males (referent group).
[b]Unadjusted model of the RR of autism symptoms in children with intellectual disability vs. children without intellectual disability (referent group).
[c]Unadjusted model of the RR of autism symptoms in children aged 10 years or older vs. aged 4 to 9 years (referent group).
*$p \leq 0.05$.

Table 3: Relative Risks for the Association between Epilepsy and Autism Symptoms/Behaviors in Children with Autism Spectrum Disorder

| | Unadjusted | | | Model 1: Adjusted for Age | | | Model 2: Adjusted for Age and Gender | | | Model 3: Adjusted for Age, Gender, and IQ | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **RR** | **95% CI** | **p value** | **RR** | **95% CI** | **p value** | **RR** | **95% CI** | **p value** | **RR** | **95% CI** | **p value** |
| **SRS** | | | | | | | | | | | | |
| Total | 1.09 | (1.04 - 1.14) | <.01* | 1.08 | (1.04 - 1.13) | <.01* | 1.08 | (1.03 - 1.13) | <.01* | 1.03 | (0.98 - 1.08) | 0.21 |
| Autistic Mannerisms | 1.12 | (1.06 - 1.19) | <.01* | 1.11 | (1.04 - 1.17) | <.01* | 1.11 | (1.04 - 1.17) | <.01* | 1.05 | (0.99 - 1.12) | 0.09 |
| Social Awareness | 1.06 | (1.02 - 1.12) | 0.01* | 1.07 | (1.02 - 1.12) | 0.01* | 1.07 | (1.02 - 1.12) | 0.01* | 1.02 | (0.98 – 1.07) | 0.34 |
| Social Cognition | 1.10 | (1.05 - 1.15) | <.01* | 1.09 | (1.04 - 1.15) | <.01* | 1.09 | (1.04 - 1.15) | <.01* | 1.03 | (0.99 - 1.07) | 0.19 |
| Social Communication | 1.09 | (1.04 - 1.15) | <.01* | 1.08 | (1.03 - 1.14) | <.01* | 1.08 | (1.03 - 1.14) | <.01* | 1.03 | (0.98 - 1.08) | 0.23 |
| Social Motivation | 1.07 | (1.00 - 1.14) | 0.04* | 1.05 | (0.99 - 1.12) | 0.12 | 1.05 | (0.99 - 1.12) | 0.12 | 1.01 | (0.94 - 1.07) | 0.86 |
| **RBS-R** | | | | | | | | | | | | |
| Total | 1.15 | (1.04 - 1.27) | 0.01* | 1.16 | (1.05 - 1.28) | <.01* | 1.16 | (1.05 - 1.28) | <.01* | 1.08 | (0.97 - 1.19) | 0.17 |
| Stereotyped behavior | 1.12 | (0.99 - 1.27) | 0.07 | 1.16 | (1.03 - 1.31) | 0.02* | 1.16 | (1.03 - 1.31) | 0.01* | 0.97 | (0.86 - 1.09) | 0.60 |
| Self-injurious behavior | 1.37 | (1.12 - 1.68) | <.01* | 1.35 | (1.10 - 1.66) | <.01* | 1.34 | (1.10 - 1.65) | <.01* | 1.14 | (0.93 - 1.40) | 0.21 |
| Compulsive behavior | 1.26 | (1.08 - 1.46) | <.01* | 1.27 | (1.09 - 1.47) | <.01* | 1.26 | (1.09 - 1.46) | <.01* | 1.12 | (0.97 - 1.30) | 0.13 |
| Ritualistic behavior | 1.05 | (0.92 - 1.19) | 0.51 | 1.05 | (0.92 - 1.20) | 0.43 | 1.05 | (0.92 - 1.20) | 0.44 | 1.07 | (0.93 - 1.22) | 0.35 |
| Sameness behavior | 1.15 | (1.02 - 1.30) | 0.02* | 1.14 | (1.01 - 1.29) | 0.04* | 1.14 | (1.01 - 1.29) | 0.04* | 1.11 | (0.98- 1.26) | 0.10 |
| Restricted Behavior | 1.09 | (0.96 - 1.24) | 0.19 | 1.11 | (0.98 - 1.26) | 0.10 | 1.12 | (0.99 - 1.27) | 0.08 | 1.05 | (0.93 - 1.20) | 0.42 |
| **ABC** | | | | | | | | | | | | |
| Total | 1.12 | (1.02 - 1.22) | 0.02* | 1.14 | (1.04 - 1.24) | 0.01* | 1.13 | (1.04 - 1.24) | 0.01* | 1.04 | (0.95 - 1.14) | 0.38 |
| Irritability | 1.11 | (0.98 - 1.26) | 0.10 | 1.14 | (1.01 - 1.29) | 0.04* | 1.13 | (1.00 - 1.28) | 0.05* | 1.07 | (0.94 - 1.21) | 0.32 |
| Lethargy | 1.06 | (0.94 - 1.20) | 0.33 | 1.03 | (0.92 - 1.17) | 0.59 | 1.03 | (0.91 - 1.16) | 0.66 | 0.95 | (0.84 - 1.07) | 0.38 |
| Stereotypy | 1.19 | (1.04 - 1.37) | 0.01* | 1.20 | (1.05 - 1.38) | 0.01* | 1.20 | (1.05 - 1.38) | 0.01* | 0.97 | (0.85 - 1.11) | 0.63 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Hyperactivity | 1.15 | (1.04 - 1.27) | 0.01* | 1.21 | (1.10 - 1.34) | <.01* | 1.21 | (1.10 - 1.34) | <.01* | 1.13 | (1.02 - 1.25) | 0.01* |
| Inappropriate Speech | 1.00 | (0.87 - 1.15) | 0.98 | 1.00 | (0.87 - 1.15) | 0.97 | 1.00 | (0.87 - 1.15) | 0.98 | 0.94 | (0.81 - 1.08) | 0.35 |

Abbreviations: SRS, Social Responsiveness Scale; RBS-R, Repetitive Behavior Scale Revised; ABC, Aberrant Behavior Checklist.
Relative Risk (RR) comparing children with epilepsy to children without epilepsy (referent group).
*$p \leq 0.05$.

Table 4: Relative Risks for the Association between Epilepsy and Autism Symptoms/Behaviors in Children with Autism Spectrum Disorder, By Intellectual Disability

| | Adjusted for Age and Gender | | | | | |
|---|---|---|---|---|---|---|
| | Children without ID | | | Children with ID | | |
| | RR | 95% CI | p value | RR | 95% CI | p value |
| **SRS** | | | | | | |
| Total | 1.05 | (0.98 - 1.13) | 0.16 | 1.05 | (0.99 - 1.11) | 0.08 |
| Autistic Mannerisms | 1.06 | (0.97 - 1.16) | 0.22 | 1.08 | (1.00 - 1.16) | 0.05* |
| Social Awareness | 1.04 | (0.96 - 1.12) | 0.33 | 1.04 | (0.98 - 1.11) | 0.22 |
| Social Cognition | 1.08 | (1.00 - 1.17) | 0.06 | 1.03 | (0.98 - 1.09) | 0.26 |
| Social Communication | 1.06 | (0.98 - 1.14) | 0.13 | 1.05 | (0.99 - 1.11) | 0.14 |
| Social Motivation | 1.00 | (0.91 - 1.11) | 1.00 | 1.05 | (0.97 - 1.14) | 0.22 |
| **RBS-R** | | | | | | |
| Total | 1.09 | (0.92 - 1.28) | 0.31 | 1.11 | (0.98 - 1.26) | 0.11 |
| Stereotyped behavior | 1.00 | (0.82 - 1.23) | 0.99 | 1.04 | (0.91 - 1.20) | 0.54 |
| Self-injurious behavior | 1.16 | (0.82 - 1.64) | 0.39 | 1.25 | (0.97 - 1.62) | 0.08 |
| Compulsive behavior | 1.16 | (0.92 - 1.48) | 0.21 | 1.16 | (0.97 - 1.40) | 0.11 |
| Ritualistic behavior | 1.04 | (0.86 - 1.26) | 0.69 | 1.04 | (0.87 - 1.26) | 0.66 |
| Sameness behavior | 1.12 | (0.93 - 1.35) | 0.24 | 1.12 | (0.95 - 1.33) | 0.17 |
| Restricted Behavior | 1.07 | (0.89 - 1.30) | 0.47 | 1.08 | (0.91 - 1.28) | 0.36 |
| **ABC** | | | | | | |
| Total | 1.14 | (0.99 - 1.30) | 0.06 | 1.04 | (0.92 - 1.17) | 0.52 |
| Irritability | 1.20 | (1.00 - 1.44) | 0.05* | 1.02 | (0.86 - 1.21) | 0.84 |
| Lethargy | 0.98 | (0.81 - 1.18) | 0.83 | 1.00 | (0.86 - 1.17) | 0.98 |
| Stereotypy | 1.06 | (0.84 - 1.34) | 0.64 | 1.05 | (0.90 - 1.24) | 0.53 |
| Hyperactivity | 1.24 | (1.07 - 1.44) | <.01* | 1.11 | (0.97 - 1.26) | 0.12 |
| Inappropriate Speech | 1.02 | (0.83 - 1.26) | 0.85 | 0.89 | (0.74 - 1.07) | 0.21 |

Abbreviations: ID, intellectual disability; SRS, Social Responsiveness Scale; RBS-R, Repetitive Behavior Scale Revised; ABC, Aberrant Behavior Checklist.
Relative Risk (RR) comparing children with epilepsy to children without epilepsy (referent group).
Intellectual disability defined as full scale IQ score of less than or equal to 70.
*$p \leq 0.05$.

# Chapter 3: Prenatal Risk Factors for Autism: Findings from the Collaborative Perinatal Project


## ABSTRACT

Background: Autism is a neurodevelopmental disorder that is estimated to affect as many as 1 in 88 children. Many studies have reported associations between prenatal risk factors and autism, but results have been inconsistent. Prospective cohort studies of autism are rare but are the ideal means to investigate prenatal risk factors for autism.

Objectives: To apply current diagnostic criteria to identify children with autism in the Collaborative Perinatal Project (CPP) and to examine prenatal risk factors for autism.

Methods: The CPP was a population-based longitudinal cohort study of approximately 55,000 pregnant women and their offspring. Multivariate logistic regression was used to examine the association between prenatal risk factors and autism.

Results: The prevalence of autism was 6.8 per 1,000. In a multivariate model, autism was associated with maternal age 35 years or older (OR = 1.62; CI = 1.10 - 2.38), paternal age 30 years or older (OR = 1.42; CI = 1.05 – 1.91), bleeding during pregnancy (OR = 1.33; CI = 1.01 – 1.75), and edema during pregnancy (OR = 1.33; CI = 1.02 – 1.74).

Conclusion: Prenatal risk factors are more common in children with autism, specifically, older maternal and paternal age, bleeding, and edema.

# CHAPTER 3

## INTRODUCTION

Autism Spectrum Disorder refers broadly to a group of neurodevelopmental disorders that are characterized by deficits in social interaction and communication and the presence of restricted and repetitive behavior (APA, 2000). Autism is typically diagnosed in early childhood and remains a lifelong condition. The disorder was first described in the U.S. and European medical literature in the 1940s and believed to be rare. Since then prevalence estimates have increased steadily and it is currently estimated that 1 in 88 children in the US has an ASD (Baio, 2012).

There is strong evidence for the role of genetic factors in the etiology of autism. Twin studies show a higher concordance rate in monozygotic (MZ) than dizygotic (DZ) twins (Lichtenstein, Carlstrom, Rastam, Gillberg, & Anckarsater, 2010). However, concordance in MZ twins is incomplete, suggesting that nonheritable factors also contribute to autism risk. Furthermore, while prior twin studies showed very low concordance rates in DZ twins of 0% to 10% (Bailey et al., 1995; Steffenburg et al., 1989), more recent studies with larger sample sizes have reported concordance rates from 25% to 31% (Hallmayer, 2011; Rosenberg et al., 2009). It is likely that the mechanism underlying autism etiology is polygenic and that genetic and environmental factors interact to produce the disease. It is hypothesized that some of the environmental factors impacting susceptibility to autism exert their effect during the fetal development period. Although the neuropathology of autism is currently unknown, studies have shown brain abnormalities that suggest pathogenesis may begin during the prenatal period (Courchesne, Yeung-Courchesne, Press, Hesselink, & Jernigan, 1988).

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Prenatal risk factors and autism has been the subject of ample research. In addition to individual risk factors identified in several prior studies, autism has been associated with poorer overall optimality score (Bolton et al., 1994; Bolton et al., 1997; Bryson, Smith, & Eastwood, 1988; Gillberg & Gillberg, 1983; Stein, Weizman, Ring, & Barak, 2006). While most studies have shown that obstetrical complications and prenatal factors are associated with an increase in risk, results have been inconsistent. Discrepancies in findings from prior studies are likely due to methodological differences in exposure assessment, selection of control group, model covariates, and other study design choices. Gardener and colleagues (Gardener, 2009) conducted the first quantitative review and meta-analysis of the association between pregnancy-related factors and autism. They examined over 50 prenatal risk factors from 40 epidemiological studies and identified several factors that significantly increase risk of autism, as well as factors with weak evidence for a role in autism. In the present study, we examined these risk factors to determine if the findings could be replicated in a large, prospective cohort study.

The Collaborative Perinatal Project (CPP) was a population-based cohort study of approximately 55,000 pregnant women and their offspring born in the US in the 1960s. The objectives of the study were to: 1) apply current diagnostic criteria to identify children in the CPP with autism; and 2) examine prenatal risk factors for autism.

## METHODS

***Participants.*** The Collaborative Perinatal Project (CPP) was a multi-site, population-based, cohort study of approximately 55,000 pregnant women and their offspring born between 1960 and 1966 (Niswander, Gordon, & National Institute of Neurological

Diseases and Stroke., 1972). Pregnant women were enrolled when they presented for prenatal care at clinics throughout the United States. Children were followed through 7 years of age. The sample used in the present study includes 51,235 children for whom post-delivery data were available (**Figure 1)**. Based on the diagnostic criteria for autism (described below), children were required to have been seen at age 4 or 7 years to be considered for an autism diagnosis. The analytic sample used for all analyses includes 44,976 children with records at age 4 or age 7 and available IQ data.

***Exposures: Prenatal risk factors.*** Information on prenatal risk factors was drawn from medical records obtained by CPP staff on study participant mothers during pregnancy using standardized assessment procedures. Data on numerous prenatal risk factors were collected. To narrow our focus, we selected risk factors that have been studied in multiple prior studies, in particular, factors identified in the 2009 meta-analysis by Gardener and colleagues (Gardener, 2009) (Table S1). For a detailed description of the prenatal risk factors see Supplemental Section S1.

***Outcome: Autistic Disorder.*** Information on autism symptoms was drawn from standardized assessments conducted on study participant children from 8 months to 7 years. A diagnostic algorithm was developed based on DSM-IV-TR criteria for Autistic Disorder, which consists of three domains required for diagnosis: (A) impairment in social interaction; (B) impairment in communication; and (C) restricted, repetitive, and stereotyped patterns of behavior, interest, and activities (APA, 2000). Within each domain there are four subdomains. We categorized CPP variables into the DSM domains and subdomains. As per the DSM, to meet criteria for autism children were required to

have two symptoms in the social domain and one each in the communication and restricted and repetitive behavior domains. See tables S2 and S3 for more information.

***Covariates.*** Covariates included child's race, gender, study site, and family socioeconomic status (SES). A composite index of socioeconomic status was used that reflects education and occupation of the head of household and household income (Myrianthopoulos & French, 1968). Information on the child's intellectual ability was derived from IQ tests administered at ages 4 and 7 years. At age 4, children were administered the *Stanford-Binet Intelligence Scales* (completed by 38,673 children) and at age 7, the *Wechsler Intelligence Scale for Children* (completed by 40,540 children). Age 7 IQ was used when available; when unavailable, age 4 IQ was used instead. We created a dichotomous Intellectual Disability (ID) variable defined as IQ $\leq$ 70 (ID) vs. IQ > 70 (not ID).

***Statistical Analyses.*** All analyses were completed using SAS version 9.3. Bivariate analyses used chi-square and t-tests, as appropriate. Statistical significance was evaluated using 2-sided tests at a 0.05 alpha-level. Logistic regression was used to examine the association between prenatal risk factors and autism. Correlation between siblings nested within a family was adjusted in the analyses using the repeated subject statement based on mother's ID number. Cases with missing values were excluded, with the exception of paternal age at birth, for which a missing indicator variable was used due to a large amount of missing data (n = 11,024 observations). Unadjusted and adjusted odds ratios and 95% confidence intervals were reported. Crude models with each risk factor entered individually were run, as well as individual models adjusted for demographic characteristics (gender, race, SES, and study site), and adjusted for demographic

characteristics and intellectual disability. In the final fully adjusted model all of the predictors were simultaneously entered, as well as demographic characteristics and intellectual disability.

## RESULTS

Of the 45,122 children in the CPP cohort assessed for autism, 308 children (0.68%) met diagnostic criteria for a prevalence of 6.8 per 1,000. Of the 44,976 participants in the analytic sample, 275 (0.61%) had autism. Tables 1 through 3 compare children with and without autism from the analytic sample. **Table 1** shows the distribution of sociodemographic characteristics by autism status. Males were significantly more likely to have autism than females (0.8% vs. 0.4%, $p<.0001$) for an approximate male-to-female ratio of 2:1. Children from New Orleans and Virginia were more likely to have autism than children from other study sites and the autism group had significantly lower socioeconomic status. **Table 2** presents bivariate analyses comparing children with and without autism. Autism was significantly associated with intellectual disability (ID). Among children with autism, 61.1% had ID, while 4.1% of children without autism had ID ($p<.0001$). As compared to children without autism, children with autism were significantly more likely to have an older mother and father at birth, a mother with diabetes during pregnancy, and a mother with hypertension during pregnancy.

**Table 3** presents logistic regression models of the association between prenatal risk factors and autism, accounting for correlation within families. In the unadjusted analyses, maternal and paternal age at birth, bleeding, and hypertension were associated with significantly increased risk of autism. After adjusting for demographic characteristics, maternal and paternal age at birth, bleeding, and hypertension remained associated with

significantly increased odds of autism. Adjusting for ID attenuated some of the effect estimates; diabetes and hypertension were no longer significant risk factors after adjusting for ID, although they remained associated with higher risk of autism. Several prenatal predictors were relatively unchanged after adjusting for ID (maternal age, paternal age, bleeding, and proteinuria). Adjusting for ID had a strong impact on edema, which became a significant risk factor after adjustment (ORa = 1.33, CI = 1.02 – 1.74).

The final model included all of the prenatal predictors entered simultaneously, as well as demographic characteristics and ID. Maternal age of 35 or older (ORa = 1.51, CI = 0.97 - 2.37), bleeding during pregnancy (ORa = 1.32, CI = 0.99 - 1.75), and edema (ORa = 1.35, CI = 1.02 - 1.79) were associated with increased risk of autism, although only the effect estimate for edema fully reached statistical significance. Older father's age at birth was no longer a significant risk factor in the fully adjusted model. Previous fetal loss was a protective factor for autism, although it was not statistically significant (ORa = 0.70, CI = 0.49 - 1.02).

## DISCUSSION

We identified 308 children with autism for a prevalence of 6.8 per 1,000. This is somewhat higher than current prevalence estimates for Autistic Disorder around 4 per 1,000 (Baird et al., 2006; Bertrand et al., 2001; Fombonne, 2009), but within the range of estimates for the prevalence of all ASDs, which is estimated at 11 per 1,000 (Baio, 2012). In the 1960's and 1970's clinicians had much less awareness of autism and there was no standard diagnostic criteria. Autism was thought to be a very rare disorder; prevalence estimates from the 1960s were approximately 0.5 per 1,000 (Lotter, 1966). It is, therefore, not surprising that autism was not formally diagnosed at the time of the CPP.

Over time the prevalence has increased and ASD is now estimated to affect over 1% of children (Baio, 2012).

In the present study the prevalence of autism in a cohort born in the 1960s was similar to current prevalence estimates. This suggests that studies conducted in the past may have under-estimated prevalence (as defined by contemporary diagnostic criteria) and provides support for the argument that changes in diagnostic criteria explain at least part of the increase in autism prevalence. Heussler and colleagues (Heussler et al., 2001) re-examined autism in the British cohort 1970 study. In 1970, the estimated prevalence of autism was 0.45 per 1,000. In 2001, the authors re-examined questionnaire data and estimated the prevalence at 3.76 per 1,000. These findings are similar to those from the CPP: in 1974 Torrey and colleagues identified 14 cases of autism in the CPP for a prevalence of 0.5 per 1,000 (Torrey, Hersh, & McCabe, 1975), which is considerably lower than the prevalence found in the present study. Further information on the case definition used by Torrey and colleagues, and a comparison with the criteria used in the present study, can be found in Section S2 of the appendix.

Children with autism in our study had significantly lower cognitive ability than children without autism. Among children with autism, 61% had ID, which is similar to current estimates for children with Autistic Disorder (Bertrand, et al., 2001; Chakrabarti & Fombonne, 2001; Charman, 2011). Mean IQ scores were also significantly lower in children with autism (Table S4) and females with autism had lower IQ than males. These findings provide support for our measure of autism as they are consistent with contemporary autism samples with regard to cognitive functioning (Newschaffer, 2007).

Several prenatal factors were significantly associated with autism in this study. After controlling for demographic characteristics and ID, maternal age, paternal age, bleeding, and edema were significant predictors of autism. In the fully adjusted model, edema remained a significant risk factor for autism and maternal age and bleeding were also associated with increased risk (although they did not reach statistical significance). Given that the symptoms of preeclampsia include hypertension and proteinuria, preeclampsia/eclampsia was not included in the fully adjusted model.

A specific aim of our study was to compare our findings to the Gardener et al. meta-analysis (Gardener, 2009). Among the factors significantly associated with autism in the meta-analysis, several of the risk factors (maternal and paternal age, bleeding, and diabetes) were associated with increased risk of autism in our study. However, we did not find evidence of increased risk associated with birth order or mother born abroad. Of the risk factors that Gardener and colleagues concluded were *least* likely to be associated with autism, we also found no association between autism and previous fetal loss, proteinuria, and preeclampsia. However, we did find that hypertension and edema were associated with increased risk.

ID was a mild confounder of the association between prenatal factors and autism. In general, there was only a small change in the effect estimates after controlling for ID, suggesting that the association between several of the prenatal risk factors and autism is not explained by differences in IQ in children with and without autism. However, maternal diabetes and hypertension were no longer statistically significant risk factors for autism after adjusting for ID. In contrast, edema became a significant risk factor after adjusting for ID.

Older maternal age was a significant predictor of autism in our study, which is consistent with the meta-analysis and many prior studies. Paternal age at birth was also associated with increased risk of autism but was not statistically significant in the fully adjusted model. Thus, we found that maternal age was a stronger risk factor than paternal age. Results from prior studies have been inconsistent with some studies reporting associations with maternal age only (Glasson et al., 2004) and others paternal age only (Lauritsen, Pedersen, & Mortensen, 2005; Reichenberg et al., 2006). Two recent meta-analyses found that both maternal and paternal age were independent risk factors for autism (Hultman, Sandin, Levine, Lichtenstein, & Reichenberg, 2011; Sandin et al., 2012). Although several adverse birth outcomes including autism have been associated with advanced age, the specific biological mechanisms are not well understood.

We replicated findings from the meta-analysis and several prior studies (Finegan & Quarrington, 1979; Hultman, Sparen, & Cnattingius, 2002; Torrey, et al., 1975) of an association between autism and maternal bleeding. Bleeding during pregnancy may be an indicator of abnormalities in fetal development indicative of autism. It has also been proposed that the relationship between maternal bleeding during pregnancy and autism is due to fetal hypoxia, as bleeding is one of several complications believed to be associated with hypoxia (Kolevzon, Gross, & Reichenberg, 2007) and hypoxia may disrupt brain development leading to neurodevelopmental problems including autism. First trimester bleeding, or threatened abortion, is also associated with low birth weight (van Oppenraaij et al., 2009), which is a risk factor for autism (Gardener, 2011).

In contrast to findings from the meta-analysis, we did not find an association between birth order and autism. Higher risk of autism in first born children is theorized to be due

to stoppage, when parents of an affected child decide not to have more children or to restrict to only one more child (Jones & Szatmari, 1988; Szatmari, Jones, Zwaigenbaum, & MacLean, 1998). This results in affected children being more likely to be first born, as has been shown in the autism literature (P. Bolton, Murphy M, Macdonald H, Whitlock B, Pickles A, Rutter M, 1997; Deykin & MacMahon, 1980). Given that in the 1960's little was known about autism, in particular that it may have genetic causes, parents of children with autism in the CPP may have been less likely to stop having children after having a child with autism. This may explain why we did not find a higher risk of autism in first born children.

We also did not find a significant association between having a mother born abroad and autism. The studies in the meta-analysis that reported associations were from Nordic countries, while our study was conducted in the US. Our findings are consistent with a California study, which did not find increased risk of autism in mothers born outside the US (Croen, Grether, & Selvin, 2002).

Consistent with the meta-analysis, previous fetal loss was not associated with autism in our study. However, we did find a somewhat protective effect after adjusting for ID. Previous fetal loss was associated with 30% lower odds of autism in the fully adjusted model (although it was not statistically significant). Prior fetal loss has been shown to be protective against preeclampsia (Saftlas et al., 2003) which is hypothesized to be due to immune tolerance whereby exposure to fetal antigens through prior pregnancy enhances development of maternal-fetal immunologic tolerance in a subsequent pregnancy. A similar mechanism may occur in relation to autism. Our findings warrants further research.

Hypertension was associated with increased risk of autism; however, after adjusting for ID the effect was attenuated and no longer statistically significant. Langridge et al. (Langridge et al., 2013) found that hypertension was associated with autism in children with ASD with ID, but not in children with ASD without ID. Hultman et al. (Hultman, et al., 2002) found that hypertensive diseases was associated with higher odds of autism in univariate analyses but did not remain statistically significant in a multivariate model.

In contrast to findings from the meta-analysis, edema was a significant risk factor for autism in our study. This is a somewhat novel finding as only one prior study reported a statistically significant association between autism and edema (Zhang et al., 2010). In our sample, edema was protective against ID (Table S6), but a risk factor for autism, indicative of negative confounding. Prior studies may not have found an association between edema and autism because these studies did not control for ID. Therefore, replication of our findings is needed in other studies that control for IQ. Edema is common during pregnancy and occurred in approximately 30% of women in the CPP. Edema in pregnant women may cause poor placental perfusion and function, and could damage fetal development through hypoxia (Zhang, et al., 2010). However, further research is needed to determine the biological mechanisms behind the association.

This study has a number of strengths. We used prospectively collected data on prenatal exposures, which prevents recall bias. The exposure data in our study were obtained for the purposes of research on perinatal health and collected by doctors and other health care professionals using standardized assessment procedures, as opposed to medical records or registry data. Previous population-based cohort studies have used national registries for information on autism diagnoses and pregnancy-related exposures

(Dodds et al., 2011; Glasson, et al., 2004; Larsson, 2005), which may be subject to misclassification. Pregnancy and maternal data may be incomplete or based on maternal report on birth certificates, and the diagnosis of autism from administrative databases comes solely from diagnostic codes.

Administrative datasets also do not control well for confounding because there are limited available data on covariates. In addition to well collected exposure data, we had information on important covariates, including cognitive ability. As summarized by Guinchat et al. (Guinchat et al., 2012) in a review of studies on pregnancy-related risk factors for autism, many prior studies have not controlled for IQ (Dodds, et al., 2011; Hultman, et al., 2002; Larsson, 2005; Lauritsen, et al., 2005). The present study is one of few to adjust for ID as a confounder. A final strength of the study is the large population-based cohort. The diverse sample includes many African-American children and children of lower SES, which has been lacking in previous studies, and enhances generalizability.

The main limitation of the present study is the diagnosis of autism. The CPP data were not collected for the purposes of diagnosing autism and we, therefore, lacked some of the necessary criteria for a diagnosis as outlined in the DSM (noted in Tables S2 and S3). This is primarily because of a lack of information on the child's behavior outside of the examination. The lack of information on certain autism symptoms could have resulted in false negatives. However, this is unlikely to bias the study findings given the large number of children without autism in the sample.

There may also be false positives as it is possible that some of the children in our study do not have autism but a condition with similar symptoms, the most likely being intellectual disability. Symptoms of ID can overlap with autism (Matson & Shoemaker,

2009) and making a clear distinction between symptoms of ASD and ID can be difficult. A potential distinction is in social interaction, which is more often impaired in children with ASD (Jackson et al., 2003). Our diagnostic criteria for social interaction deficits were strict, which should reduce the number of children with ID only meeting criteria for autism. Furthermore, we found that 61% of children with autism in our study had ID, which is in line with current estimates for AD. We conducted several sensitivity analyses with regard to our autism case definition and found that the results were generally consistent with the main findings (see appendix tables S7 and S8 and section S3).

Another limitation of our study is missing data. A little less than half of the sample was missing data for the age 3 assessment. Children who were missing at age 3 may be more likely to be false negatives. In a sensitivity analysis we restricted the sample to children who were not missing at age 3 and the findings were similar to the main analyses (Table S9). One hundred and forty-six children were excluded from the analyses because they were missing IQ data. In a sensitivity analysis we classified children missing IQ data as having ID and the findings were similar to the main analyses. See section S3 for a description of the sensitivity analyses.

There is also the issue of multiple comparisons as we conducted several statistical tests on the association between prenatal risk factors and autism. If we use a Bonferonni adjustment then the majority of the risk factors do not meet statistical significance. It is therefore possible that our results are due to chance or that our sample size is insufficient to address the study question. A final potential limitation of our study is lack of power. Although the overall sample size was large, the number of cases of autism was small. For

rare prenatal risks, such as diabetes and preeclampsia, we may not have had sufficient power to detect differences.

## CONCLUSION

Using contemporary diagnostic criteria the prevalence of autism in CPP was 6.8 per 1,000, which is comparable to current estimates for ASD and suggests that the prevalence of autism in the 1960's was similar to today. We identified several prenatal characteristics that increase risk of autism including older maternal and paternal age at birth, bleeding, diabetes, hypertension, and edema. In this study we adjusted for ID, which has not been done in most prior studies of prenatal risk factors and autism.

Future studies should further explore the risk factors identified in our study to better understand the biological mechanisms by which these characteristics increase autism risk. In particular, further research on the role of edema in the etiology of autism is needed as this is a newer finding. Both causal and non-causal hypotheses for the association between prenatal complications and autism have been proposed. Prenatal factors may influence fetal development, resulting in brain abnormalities that cause autism. Alternatively, obstetrical complications may occur as a result of autism in the child, or as a consequence of other factors (e.g. genetic factors) that are the true causal determinants of autism (Bolton, et al., 1997). In the present study we identified factors that are predictive of autism, but more research is needed to determine if the relationship is causal.

We plan to conduct a follow-up study of CPP participants in adulthood. Offspring from the CPP study are now in their 50's and have been successfully followed-up in other studies (Klebanoff, Zemel, Buka, & Zierler, 1998). After locating study participants who

were diagnosed with autism in our study, we can administer standardized diagnostic assessments to confirm diagnosis. Long term follow-up studies of persons with autism from birth to adulthood are rare. Given the large sample size and detailed information on pregnancy and early life, the CPP provides a unique opportunity to study the life course of persons with autism from the fetal period through adulthood.

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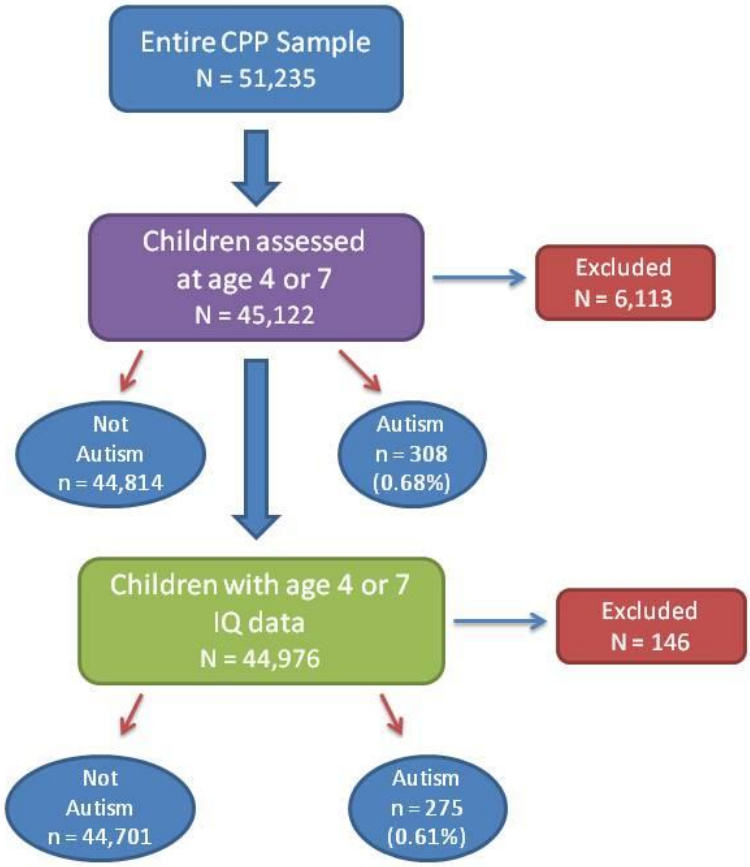
# CHAPTER 3

**Figures**

Figure 1. Selection of Sample



## Tables

Table 1. Demographic Characteristics of the CPP Sample by Autism

| | Not Autism N (%) | Autism N (%) | P-value |
|---|---|---|---|
| **Gender** | | | <.01* |
| Male | 22,494 (99.2) | 180 (0.8) | |
| Female | 22,179 (99.6) | 95 (0.4) | |
| **Race** | | | 0.06 |
| White | 20,012 (99.4) | 113 (0.6) | |
| African-American | 21,916 (99.3) | 154 (0.7) | |
| Asian | 93 (100.0) | 0 (0.0) | |
| Hispanic | 2,287 (99.7) | 7 (0.3) | |
| Other | 218 (100.0) | 0 (0.0) | |
| **Site** | | | <.01* |
| Boston | 9,596 (99.3) | 71 (0.7) | |
| Buffalo | 2,190 (99.9) | 3 (0.1) | |
| New Orleans | 2,220 (98.6) | 31 (1.4) | |
| NY/Columbia | 1,806 (99.5) | 10 (0.6) | |
| Baltimore | 3,519 (99.4) | 23 (0.7) | |
| Virginia | 2,902 (99.0) | 30 (1.0) | |
| Minnesota | 2,547 (99.3) | 19 (0.7) | |
| NY/Medical | 2,692 (99.7) | 7 (0.3) | |
| Oregon | 2,739 (99.5) | 13 (0.5) | |
| Pennsylvania | 8,018 (99.6) | 29 (0.4) | |
| Providence | 3,320 (99.3) | 24 (0.7) | |
| Tennessee | 3,151 (99.5) | 15 (0.5) | |
| **SES Category (quartiles)** | | | 0.01* |
| 1 (lowest) | 11,968 (99.2) | 94 (0.8) | |
| 2 | 10,055 (99.4) | 65 (0.6) | |
| 3 | 10,629 (99.4) | 60 (0.6) | |
| 4 (highest) | 10,859 (99.6) | 47 (0.4) | |

*$p \leq 0.05$

Abbreviations: SES, socioeconomic status.

Comparing 44,701 children without autism to 275 children with autism.

Table 2. Bivariate Analyses Comparing Children with and without Autism on Prenatal Risk Factors

| | Not Autism (n = 44,701) N (%) | Autism (n = 275) N (%) | P-value |
|---|---|---|---|
| **Intellectual Disability** | | | <.01* |
| No | 42,854 (95.9) | 107 (38.9) | |
| Yes | 1,847 (4.1) | 168 (61.1) | |
| **Mother's Age at Birth** | | | <.01* |
| Less than 35 | 41,207 (92.2) | 238 (86.6) | |
| 35 or older | 3,493 (7.8) | 37 (13.5) | |
| **Father's Age at Birth** | | | 0.01* |
| 20 or younger | 2,696 (8.0) | 12 (6.0) | |
| 21 – 29 | 18,699 (55.3) | 95 (47.3) | |
| 30 or older | 12,386 (36.7) | 94 (46.8) | |
| **Bleeding during pregnancy** | | | 0.07 |
| No | 33,166 (74.2) | 191 (69.5) | |
| Yes | 11,535 (25.8) | 84 (30.6) | |
| **Diabetes** | | | 0.05* |
| No | 43,886 (98.8) | 267 (97.5) | |
| Yes | 553 (1.2) | 7 (2.6) | |
| **Birth Order** | | | 0.07 |
| First | 13,009 (29.4) | 66 (24.6) | |
| Second | 9,871 (22.3) | 54 (20.2) | |
| Third or later | 21,336 (48.3) | 148 (55.2) | |
| **Mother born abroad** | | | 0.15 |
| No | 39,943 (90.7) | 250 (93.3) | |
| Yes | 4,088 (9.3) | 18 (6.7) | |
| **Prior fetal loss** | | | 0.75 |
| No | 35,125 (79.8) | 214 (79.0) | |
| Yes | 8,915 (20.2) | 57 (21.0) | |
| **Hypertension** | | | 0.01* |
| 0 or 1 prenatal visits with hypertension | 39,000 (88.8) | 224 (83.9) | |
| 2 or more prenatal visits with hypertension | 4,926 (11.2) | 43 (16.1) | |
| **Proteinuria or albuminuria** | | | 0.06 |
| No | 36,905 (84.4) | 214 (80.2) | |
| Yes | 6,817 (15.6) | 53 (19.9) | |
| **Edema** | | | 0.27 |
| No | 30,719 (69.1) | 180 (65.9) | |
| Yes | 13,772 (31.0) | 93 (34.1) | |
| **Preeclampsia or eclampsia** | | | 0.32 |
| No | 41,957 (94.1) | 253 (92.7) | |
| Yes | 2,629 (5.9) | 20 (7.3) | |

*$p \leq 0.05$

Table 3. Logistic Regression Modeling the Odds of Autism by Prenatal Risk Factors

| | Individually Entered Models, Unadjusted | | Individually Entered Models, Adjusted for Demographics[a] | | Individually Entered Models, Adjusted for Demographics[a] and ID | | Simultaneously Adjusted Model[b] | |
|---|---|---|---|---|---|---|---|---|
| | **OR (95% CI)** | **p-value** | **OR (95% CI)** | **p-value** | **OR (95% CI)** | **p-value** | **OR (95% CI)** | **p-value** |
| **Mother's age at birth** | | | | | | | | |
| Less than 35 | Ref. | | Ref. | | Ref. | | Ref. | |
| 35 or older | 1.88 (1.32 – 2.68) | <.01* | 1.64 (1.13 – 2.38) | <.01* | 1.62 (1.10 – 2.38) | 0.01* | 1.51 (0.97 - 2.37) | 0.07 |
| **Father's age at birth** | | | | | | | | |
| 20 or younger | 0.88 (0.48 – 1.64) | 0.70 | 0.82 (0.44 – 1.51) | 0.52 | 1.02 (0.55 – 1.88) | 0.95 | 0.50 (0.16 - 1.58) | 0.24 |
| 21 – 29 | Ref. | | Ref. | | Ref. | | Ref. | |
| 30 or older | 1.51 (1.13 – 2.02) | <.01* | 1.43 (1.07 – 1.92) | 0.02* | 1.42 (1.05 – 1.91) | 0.02* | 1.27 (0.89 - 1.81) | 0.19 |
| **Bleeding** | 1.33 (1.03 – 1.72) | 0.03* | 1.35 (1.04 – 1.75) | 0.02* | 1.33 (1.01 – 1.75) | 0.04* | 1.32 (0.99 - 1.75) | 0.06 |
| **Diabetes** | 2.06 (0.98 – 4.36) | 0.06 | 2.12 (1.01 – 4.46) | 0.05* | 1.95 (0.90 – 4.22) | 0.09 | 1.96 (0.86 - 4.45) | 0.11 |
| **Birth order** | | | | | | | | |
| First | Ref. | | Ref. | | Ref. | | Ref. | |
| Second | 0.99 (0.69 – 1.42) | 0.96 | 0.93 (0.65 – 1.35) | 0.71 | 0.85 (0.58 – 1.24) | 0.40 | 1.06 (0.71 - 1.58) | 0.78 |
| Third or later | 0.78 (0.58 – 1.03) | 0.08 | 0.78 (0.58 – 1.05) | 0.10 | 0.85 (0.63 – 1.15) | 0.30 | 1.10 (0.76 - 1.59) | 0.61 |
| **Mother born outside of US** | 0.70 (0.43 – 1.13) | 0.15 | 0.72 (0.43 – 1.22) | 0.22 | 0.99 (0.59 – 1.67) | 0.97 | 0.98 (0.57 - 1.67) | 0.93 |
| **Previous fetal loss** | 1.06 (0.78 – 1.42) | 0.73 | 1.01 (0.75 – 1.37) | 0.93 | 0.88 (0.63 – 1.22) | 0.44 | 0.70 (0.49 – 1.02) | 0.06 |
| **Hypertension** | | | | | | | | |
| 0 or 1 prenatal visits with hypertension | Ref. | | Ref. | | Ref. | | Ref. | |
| 2 or more prenatal visits with hypertension | 1.53 (1.10 – 2.15) | 0.01* | 1.49 (1.06 – 2.10) | 0.02* | 1.42 (0.99 – 2.03) | 0.06 | 1.25 (0.87 - 1.82) | 0.23 |
| **Proteinuria or albuminuria** | 1.29 (0.94 – 1.77) | 0.11 | 1.33 (0.96 – 1.83) | 0.08 | 1.32 (0.94 – 1.83) | 0.10 | 1.22 (0.86 - 1.72) | 0.26 |
| **Edema** | 1.13 (0.87 – 1.46) | 0.35 | 1.18 (0.91 – 1.52) | 0.21 | 1.33 (1.02 – 1.74) | 0.04* | 1.35 (1.02 - 1.79) | 0.04* |
| **Preeclampsia or eclampsia** | 1.26 (0.79 – 2.01) | 0.33 | 1.28 (0.80 – 2.05) | 0.30 | 1.03 (0.63 – 1.67) | 0.91 | -- | - |

[a]Demographic characteristics: child's sex, child's race, study site, and family socioeconomic status.

[b]Adjusted for all risk factors, demographic characteristics, and ID. Preeclampsia or eclampsia not included in the fully adjusted model.

Abbreviations: ID, Intellectual Disability.

# APPENDIX

## Supplemental Tables

Table S1. Prenatal Risk Factors for Autism: Comparison of Risk Factors in the Gardener et al. Meta-analysis and Collaborative Perinatal Project (CPP)

| Prenatal Factor | Gardener et al. Meta-Analysis[a] | CPP Study[b] |
|---|---|---|
| Significant Risk Factor in Meta-analysis | | |
| Maternal age at birth | √ | √ |
| Paternal age at birth | √ | √ |
| Bleeding during pregnancy | √ | √ |
| Diabetes | √ | √ |
| Birth order | √ | √ |
| Mother born abroad | √ | √ |
| Maternal medication use during pregnancy | √ | |
| Weak Evidence for an Association in Meta-analysis | | |
| Previous fetal loss | √ | √ |
| Hypertension | √ | √ |
| Proteinuria | √ | √ |
| Preeclampsia | √ | √ |
| Edema | √ | √ |

[a]Gardener H, Spiegelman D, Buka SL (2009) Prenatal risk factors for autism: comprehensive meta-analysis. *The British Journal of Psychiatry*, 195: 7-14.
[b]Risk factors examined in the present study using the CPP data.
A check mark indicates that the variable was examined in the study.

Table S2. Comparison of Autistic Disorder Diagnostic Criteria in the DSM-IV-TR and in the Collaborative Perinatal Project (CPP)

| DSM-IV-TR Autistic Disorder Diagnostic Criteria | | CPP Autistic Disorder Diagnostic Algorithm |
|---|---|---|
| | At least two from (A), one from (B), one from (C), and a total of six (or more) items from (A), (B), and (C). | At least two items from (A), one from (B), one from (C) and abnormal behavior at age 4 or 7 years. |
| **(A) Impairment in social interaction** | | |
| **Symptom** | | **Example of Symptom** |
| | Impairment in the use of nonverbal behaviors | Flat emotional reactivity at 4 or 7 years.<br>Unexpressive facial expression at 4 or 7 years. |
| | Failure to develop peer relationships appropriate to developmental level | *No measures available.* |
| | Lack of spontaneous seeking to share enjoyment, interests, or achievements with other people | *No measures available.* |
| | Lack of social or emotional reciprocity | Failing to respond to name at 8 months.<br>Lack of social smiling at 8 months.<br>Exceptionally shy with examiner at 7 years.<br>Withdrawn at 7 years. |
| **(B) Impairment in communication** | | |
| **Symptom** | | **Example of Symptom** |
| | Delay in, or total lack of, the development of spoken language | Withdrawn at 7 years.<br>Abnormal language expression at 3 years.<br>Abnormal speech at 7 years. |
| | In individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others | Irrelevant and inappropriate communication at 4 years.<br>Lack of spontaneous communication at 7 years. |
| | Stereotyped and repetitive use of language or idiosyncratic language | Echolalia at 3, 4, or 7 years.<br>Perseveration at 3 or 7 years. |
| | Lack of varied spontaneous make-believe play or social imitative play appropriate to developmental level | *No measures available.* |
| **(C)Restricted, repetitive, and stereotyped patterns of behavior, interests, and activities** | | |
| **Symptom** | | **Example of Symptom** |
| | Preoccupation with one or more stereotyped and restricted patterns of interest | *No measures available.* |
| | Inflexible adherence to specific, nonfunctional routines or rituals | Extreme rigidity at 4 or 7 years. |
| | Stereotyped and repetitive motor mannerisms | Purposeless hand motions at 3, 4 or 7 years. |
| | Persistent preoccupation with parts of objects | *No measures available*. |

Abbreviations: DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, text revision. Criteria for Autistic Disorder in the CPP are those developed by the authors for the present study.

Table S3. Diagnostic Criteria for Autistic Disorder, Collaborative Perinatal Project (CPP)

This table includes the age of the child at the time the information was obtained, the CPP measure, how the measure responses were coded, the criteria for diagnosis (the response code(s) that count the child as having that attribute), and the percent of children that had the attribute out of the entire CPP sample (n= 51,235).

| Child's Age at Assessment | Measure | Coding | Criteria for Diagnosis | Prevalence in CPP Cohort |
|---|---|---|---|---|
| **(A) Impairments in Social Interaction (required to have one in each category)** | | | | |
| **A1: Impairment in use of nonverbal behaviors.** | | | | |
| 8 months | Face | 0 - Normal, 1 - Asymmetry, 2 - mask-like, 3 – hyper-mobile, 7 - codes 1-3 & 8, 8 – other | 2, 7 | 0.98 |
| 3 years | unusual posturing | 0 - no, 1 – yes | 1 | 0.5 |
| 7 years | unusual posturing | 0 - no, 1 – yes | 1 | 0.73 |
| 4 years | emotional reactivity | 1 - extremely flat, 2 - somewhat flat, 3 - normal, 4 - mood more variable than average, 5 - extreme instability, 8 - comment only, 9 – unknown | 1, 2, 5 | 14.58 |
| 7 years | emotional reactivity | 1 - extremely flat, 2 - somewhat flat, 3 - normal, 4 - mood more variable than average, 5 - extreme instability, 6 - variable, 8 - comment only, 9 – unknown | 1, 2, 5 | 16.89 |
| 4 years | facial expression | 0 - normal, 1 - Asymmetry, 2 - unexpressive, 3 - combination 1 and 2, 4 - combination 1 and 8, 5 - combination 2 and 8, 8 – other | 2, 3, 5 | 2.97 |
| 7 years | facial expression | 0 - normal, 1 - Asymmetry, 2 - little or no change in expression, 3 - combination 1 and 2, 4 - combination 1 and 8, 5 - combination 2 and 8, 8 - other, 9 – unknown | 2, 3, 5 | 2.53 |
| **A2: failure to develop peer relationships appropriate to developmental level**. | | | | |
| No measures available | | | | |
| **A3: Lack of spontaneous seeking to share enjoyment, interests, or achievements with other people.** | | | | |

| Child's Age at Assessment | Measure | Coding | Criteria for Diagnosis | Prevalence in CPP Cohort |
|---|---|---|---|---|
| No measures available | | | | |
| **A4: Lack of social or emotional reciprocity.** | | | | |
| 8 months | responds to name | 1 - pass, 2 - fail, 3 - marginal, 7 - reported, 8 - not tested, 9 – unknown | 2 | 46.54 |
| 8 months | vocalizes to social stimulus | 1 - pass, 2 – fail | 2 | 0.45 |
| 8 months | reacts to disappearance of face | 1 - pass, 2 – fail | 2 | 0.37 |
| 8 months | social smiles | 1 - pass, 2 – fail | 2 | 0.40 |
| 8 months | intensity of social response | 1 - does not respond to initiation, 2 - responds only direct approach, 3 - as interested in social contact as obj., 4 - behavior strongly affected by person, 5 - over-reacts to person, 6 - varies greatly, 8 - comment only, 9 – unknown | 1 | 0.96 |
| 8 months | nature of social response – examiner | 1 - avoids, 2 - hesitates, 3 - accepts, 4 - friendly, 5 - invites, 6 - varies greatly, 8 - comment only, 9 – unknown | 1 | 1.71 |
| 8 months | nature of social response – mother | 1 - ignores, 2 - hesitates, 3- accepts, 4 - enjoys, 5- demands, 6 - varies greatly, 8 - comment only, 9 – unknown | 1, 2 | 1.28 |
| 8 months | social-emotional development | 1 - advanced, 2 - normal, 3 - suspect, 4 - abnormal, 8 - comment only, 9 – unknown | 4 | 0.79 |
| 1 year | failure to develop social response | 0 - no, 1 – yes | 1 | 0.73 |
| 7 years | rapport with examiner | 1 - exceptionally shy, withdrawn, 2 - shy, 3 - initial shyness, 4 - very friendly, 5 - extreme friendliness, 6 - variable, 8 - comment only, 9 – unknown | 1 | 1.7 |
| 7 years | Withdrawal | 0 - no, 1 - yes, 9 – unknown | 1 | 1.29 |
| 7 years | Cooperation | 1 - extreme negativism, 2 - resistive, 3 - cooperative, 4 - accepts direction more easily, 5 - extremely suggestible, 6 - variable, 8 - comment only, 9 – unknown | 1, 2 | 4.46 |

| Child's Age at Assessment | Measure | Coding | Criteria for Diagnosis | Prevalence in CPP Cohort |
|---|---|---|---|---|
| 7 years | separation from mother | 1 - no concern, 2 - little concern, 3 - reticence, 4 - unusual concern, 5 - very upset, 6 – variable | 1 | 0.9 |
| **(B) Impairments in Communication (required to have one from either category)** | | | | |
| **B1: Delay in, or total lack of, the development of spoken language.** | | | | |
| 3 years | intelligibility of speech | 1 - no difficulty, 2 - some difficulty, 3 - considerable difficulty, 4 - verbalized unintelligible, 5 - no speech, 8 - other, 9 – unknown | 4, 5 | 3.45 |
| 3 years | language expression | 0 - normal, 1 - suspect, 2 - abnormal, 9 – unknown | 2 | 6.25 |
| 3 years | speech mechanism | 0 - normal, 1 - suspect, 2 - abnormal, 9 – unknown | 2 | 2.11 |
| 3 years | speech production | 0 - normal, 1 - suspect, 2 - abnormal, 9 – unknown | 2 | 4.37 |
| 3 years | speech production, struggle behavior | 0 - none, 1 - some, 2 – many | 1, 2 | 0.96 |
| 7 years | Speech | 0 - normal, 8 - other, 9 – unknown | 8 | 7.09 |
| **B2: In individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others.** | | | | |
| 4 years | nature of communication | 1 - nonverbal, 2 - confined to direct questions, 3 - spontaneous conversation, 4 - answers questions, some spontaneous, 5 - irrelevant and inappropriate, 8 - comment only, 9 – unknown | 1, 5 | 2.61 |
| 7 years | nature of communication | 1 - little or none, 2 - confined to direct questions, 3 - readily answers questions, 4 - answers freely, 5 - difficult to follow child's thinking, 6 - variable, 8 - comment only, 9 – unknown | 1, 5 | 1.64 |
| 7 years | lack of spontaneous communication | 0 - no, 1 - yes, 9 – unknown | 1 | 8.07 |
| **B3: Stereotyped and repetitive use of language or idiosyncratic language.** | | | | |
| 3 years | unusual behavior: perseveration (examiner observation) | 0 - absent, 1 – present | 1 | 6.21 |

| Child's Age at Assessment | Measure | Coding | Criteria for Diagnosis | Prevalence in CPP Cohort |
|---|---|---|---|---|
| 3 years | unusual behavior: echolalia (examiner observation) | 0 - absent, 1 – present | 1 | 8.51 |
| 4 years | stereotyped behavior: echolalia (examiner observation) | 0 - absent, 1 - present, 9 – unknown | 1 | 2.82 |
| 7 years | stereotyped behavior: echolalia (examiner observation) | 0 - absent, 1 - present, 9 – unknown | 1 | 0.51 |
| 7 years | perseveration (parent report) | 0 - no, 1 - yes, 9 – unknown | 1 | 0.59 |
| 7 years | echolalia (parent report) | 0 - no, 1 - yes, 9 – unknown | 1 | 0.41 |
| **B4: lack of varied, spontaneous make-believe play or social imitative play.** | | | | |
| No measures available | | | | |
| **(C) Restricted repetitive and stereotyped patterns of behavior, interests, and activities (required to have one from either category)** | | | | |
| **C1: Preoccupation with one or more stereotyped and restricted patterns of interest.** | | | | |
| No measures available | | | | |
| **C2: Inflexible adherence to specific, nonfunctional routines or rituals.** | | | | |
| 4 years | nature of activity | 1 - extreme rigidity, 2 - some rigidity, 3 - flexible, 4 - frequently impulsive, 5 - extremely impulsive, 6 - variable, 8 - comment only, 9 – unknown | 1 | 0.51 |
| 7 years | nature of activity | 1 - extreme rigidity, 2 - some rigidity, 3 - flexible, 4 - frequently impulsive, 5 - extremely impulsive, 6 - variable, 8 - comment only, 9 – unknown | 1 | 0.30 |
| **C3: Stereotyped and repetitive motor mannerisms.** | | | | |
| 8 months | deviant or stereotyped behavior | 0 - absent, 1 - present, 2 - hand motions, 3 - head rolling, 4- rocking, 5 - smiles, 6- excessive crying, 7 - 1-6 & 8, 8 - other | 2, 3, 4, 7 | 8.73 |
| 3 years | unusual behavior, purposeless hand motions | 0 - absent, 1 - present, 9 – unknown | 1 | 0.70 |

| Child's Age at Assessment | Measure | Coding | Criteria for Diagnosis | Prevalence in CPP Cohort |
|---|---|---|---|---|
| 4 years | stereotyped behavior: dropping, throwing, pushing | 0 - absent, 1 - present, 9 – unknown | 1 | 0.81 |
| 4 years | stereotyped behavior: unusual meaningless hand motions | 0 - absent, 1 - present, 9 – unknown | 1 | 0.5 |
| 7 years | stereotyped behavior: unusual meaningless hand motions | 0 - absent, 1 - present, 9 – unknown | 1 | 0.57 |
| 7 years | purposeless hand motions | 0 - no, 1 - yes, 9 – unknown | 1 | 1.46 |
| **C4: Persistent preoccupation with parts of objects.** | | | | |
| No measures available | | | | |

Table S4. Cognitive Ability by Autism

| | Not Autism | | Autism | | |
|---|---|---|---|---|---|
| | **N** | **Mean (SD)** | **N** | **Mean (SD)** | **P-Value** |
| 4 year Full Scale IQ[a] | 38,459 | 97.3 (16.4) | 214 | 60.0 (19.6) | <.001* |
| 7 year Full Scale IQ[b] | 40,292 | 95.8 (14.7) | 248 | 62.1 (21.6) | <.001* |
| Performance IQ[b] | 40,078 | 98.5 (15.2) | 170 | 77.5 917.2) | <.001* |
| Verbal IQ[b] | 40,077 | 94.3 (14.2) | 168 | 73.1 (13.4) | <.001* |

[a]Stanford-Binet Intelligence Scales.
[b]Wechsler Intelligence Scale for Children (WISC).
*$p \leq 0.05$

Table S5: Comparison of Demographic Characteristics among Children Missing and Not Missing the Age 3 Speech, Language, and Hearing Assessment, Analytic Sample

| | Missing age 3 Assessment (n = 20,351) | Not Missing age 3 Assessment (n = 24,625) | |
|---|---|---|---|
| | N (%) | N (%) | P-value |
| **Gender** | | | 0.13 |
| Male | 10,183 (50.1) | 12,491 (50.8) | |
| Female | 10,161 (50.0) | 12,113 (49.2) | |
| **Race** | | | <.01* |
| White | 10,252 (50.5) | 9,873 (40.3) | |
| African-American | 9,449 (46.6) | 12,621 (51.5) | |
| Asian | 63 (0.3) | 30 (0.1) | |
| Hispanic | 470 (2.3) | 1,824 (7.4) | |
| Other | 66 (0.3) | 152 (0.6) | |
| **Site** | | | <.01* |
| Boston | 8,397 (41.3) | 1,270 (5.2) | |
| Buffalo | 134 (0.7) | 2,059 (8.4) | |
| New Orleans | 272 (1.3) | 1,979 (8.0) | |
| NY/Columbia | 391 (1.9) | 1,425 (5.8) | |
| Baltimore | 402 (2.0) | 3,140 (12.8) | |
| Virginia | 713 (3.5) | 2,219 (9.0) | |
| Minnesota | 435 (2.1) | 2,131 (8.7) | |
| NY/Medical | 250 (1.2) | 2,449 (10.0) | |
| Oregon | 434 (2.1) | 2,318 (9.4) | |
| Pennsylvania | 7,501 (36.9) | 546 (2.2) | |
| Providence | 1,027 (5.1) | 2,317 (9.4) | |
| Tennessee | 394 (1.9) | 2,772 (11.3) | |
| **SES Category (quartiles)** | | | <.01* |
| 1 (lowest) | 4,436 (22.5) | 7,626 (31.7) | |
| 2 | 4,297 (21.8) | 5,823 (24.2) | |
| 3 | 5,345 (27.2) | 5,344 (22.2) | |
| 4 (highest) | 5,608 (28.5) | 5,298 (22.0) | |

*$p \leq 0.05$

Abbreviations: SES, socioeconomic status.

Table S6. Logistic Regression Modeling the Odds of Intellectual Disability by Prenatal Risk Factors

| | Unadjusted | | Adjusted for Demographic Characteristics[a] | | Simultaneously Adjusted Model[b] | |
|---|---|---|---|---|---|---|
| | **OR (95% CI)** | **p-value** | **OR (95% CI)** | **p-value** | **OR (95% CI)** | **p-value** |
| **Mother's age at birth** | | | | | | |
| Less than 20 | 1.26 (1.12 – 1.42) | <.01* | 0.96 (0.84 – 1.09) | 0.53 | 1.08 (0.91 – 1.28) | 0.36 |
| 21 – 24 | Ref. | | Ref. | | Ref. | |
| 25 – 29 | 1.10 (0.96 – 1.26) | 0.19 | 1.08 (0.94 – 1.25) | 0.26 | 1.06 (0.89 – 1.26) | 0.50 |
| 30-34 | 1.19 (1.02 – 1.40) | 0.03* | 1.14 (0.97 – 1.34) | 0.12 | 1.11 (0.90 – 1.38) | 0.33 |
| 35 – 39 | 1.05 (0.85 – 1.30) | 0.64 | 0.98 (0.79 – 1.22) | 0.87 | 0.90 (0.68 – 1.20) | 0.49 |
| 40 or older | 1.74 (1.29 – 2.34) | <.01* | 1.54 (1.13 – 2.10) | 0.01* | 1.45 (0.97 – 2.16) | 0.07 |
| **Father's age at birth** | | | | | | |
| Less than 20 | 0.92 (0.73 - 1.15) | 0.46 | 0.76 (0.60 – 0.97) | 0.03* | 0.77 (0.58 – 1.02) | 0.07 |
| 21 – 24 | Ref. | | Ref. | | Ref. | |
| 25 – 29 | 0.95 (0.82 – 1.11) | 0.55 | 1.02 (0.88 – 1.20) | 0.78 | 0.91 (0.76 – 1.10) | 0.33 |
| 30-34 | 1.00 (0.84 – 1.19) | 1.00 | 1.02 (0.84 – 1.19) | 1.00 | 0.89 (0.71 – 1.11) | 0.29 |
| 35 – 39 | 1.02 (0.83 – 1.24) | 0.86 | 0.97 (0.79 – 1.19) | 0.77 | 0.81 (0.62 – 1.06) | 0.12 |
| 40 or older | 1.26 (1.02 – 1.55) | 0.03* | 1.06 (0.86 – 1.32) | 0.59 | 0.83 (0.62 – 1.13) | 0.24 |
| **Bleeding any trimester** | 0.97 (0.87 - 1.09) | 0.63 | 1.02 (0.91 – 1.15) | 0.75 | 1.00 (0.89 – 1.13) | 0.99 |
| **Diabetes Mellitus during pregnancy** | 0.56 (0.32 - 0.99) | 0.05* | 0.74 (0.41 - 1.36) | 0.33 | 0.74 (0.40 - 1.35) | 0.33 |
| **Birth order** | | | | | | |
| First | Ref. | | Ref. | | Ref. | |
| Second | 1.24 (1.07 - 1.43) | <.01* | 1.12 (0.96 – 1.31) | 0.15 | 0.91 (0.77 – 1.08) | 0.27 |
| Third or later | 0.79 (0.71 - 0.89) | <.01* | 0.79 (0.70 – 0.89) | <.01* | 1.27 (1.07 – 1.49) | <.01* |
| **Mother born outside of US** | 0.85 (0.69 - 1.04) | 0.12 | 0.68 (0.54 – 0.85) | <.01* | 0.66 (0.52 – 0.84) | <.01* |
| **Previous fetal loss** | 1.31 (1.16 - 1.47) | <.01* | 1.26 (1.11 – 1.42) | <.01* | 1.14 (0.99 – 1.31) | 0.06 |
| **Hypertension** | | | | | | |
| 0 or 1 prenatal visits with hypertension | Ref. | | Ref. | | Ref. | |
| 2 or more prenatal visits with hypertension | 1.04 (0.89 - 1.21) | 0.64 | 1.16 (0.99 – 1.37) | 0.06 | 1.21 (1.02 – 1.43) | 0.03* |

| | Unadjusted | | Adjusted for Demographic Characteristics[a] | | Simultaneously Adjusted Model[b] | |
|---|---|---|---|---|---|---|
| **Proteinuria or albuminuria** | 1.15 (1.01 – 1.31) | 0.04* | 1.01 (0.88 – 1.16) | 0.85 | 1.05 (0.92 – 1.21) | 0.47 |
| **Edema** | 0.69 (0.62 - 0.77) | <.01* | 0.77 (0.69 – 0.86) | <.01* | 0.78 (0.69 – 0.88) | <.01* |
| **Preeclampsia or eclampsia** | 1.56 (1.33 - 1.84) | <.01* | 1.30 (1.10 – 1.54) | <.01* | -- | - |

*$p \leq 0.05$

[a]Demographic characteristics include child's sex, child's race, study site, and family socioeconomic status.

[b]Adjusted for all risk factors, demographic characteristics, and ID. Preeclampsia or eclampsia not included in the fully adjusted model.

N = 2,015 participants with intellectual disability.

Table S7. Sensitivity Analysis: More Specific Autism Case Definition (N = 75 autism cases), Logistic Regression Modeling the Odds of Autism by Prenatal Risk Factors

| | Individually Entered Models, Unadjusted | | Individually Entered Models, Adjusted for Demographics[a] | | Individually Entered Models, Adjusted for Demographics[a] and ID | | Simultaneously Adjusted Model[b] | |
|---|---|---|---|---|---|---|---|---|
| | OR (95% CI) | p-value | OR (95% CI) | p-value | OR (95% CI) | p-value | OR (95% CI) | p-value |
| **Mother's age at birth** | | | | | | | | |
| Less than 35 | Ref. | | Ref. | | Ref. | | Ref. | |
| 35 or older | 3.24 (1.87 – 5.64) | <.01* | 3.09 (1.73 – 5.52) | <.01* | 3.02 (1.69 – 5.41) | <.001* | 2.68 (1.44 – 5.68) | <.01* |
| **Father's age at birth** | | | | | | | | |
| 20 or younger | 0.55 (0.14 – 2.27) | 0.41 | 0.50 (0.12 – 2.09) | 0.34 | 0.62 (0.15 – 2.63) | 0.52 | 0.51 (0.12 – 2.25) | 0.38 |
| 21 – 29 | Ref. | | Ref. | | Ref. | | Ref. | |
| 30 or older | 1.81 (1.07 – 3.07) | 0.03* | 1.76 (1.03 – 3.03) | 0.04* | 1.78 (1.03 – 3.06) | 0.04* | 1.49 (0.77 – 2.88) | 0.24 |
| **Bleeding** | 1.82 (1.15 – 2.88) | 0.01* | 1.84 (1.15 – 2.94) | 0.01* | 1.85 (1.15 – 2.99) | 0.01* | 1.84 (1.13 – 2.98) | 0.01* |
| **Diabetes** | 1.09 (0.15 – 7.77) | 0.94 | 1.28 (0.18 – 9.31) | 0.81 | 1.09 (0.14 – 8.44) | 0.94 | 1.02 (0.13 – 8.00) | 0.99 |
| **Birth order** | | | | | | | | |
| First | Ref. | | Ref. | | Ref. | | Ref. | |
| Second | 1.60 (0.78 – 3.26) | 0.20 | 0.69 (0.33 – 1.43) | 0.32 | 1.29 (0.62 – 2.68) | 0.50 | 0.67 (0.31 - 1.41) | 0.29 |
| Third or later | 0.95 (0.57 – 1.58) | 0.85 | 1.03 (0.60 – 1.74) | 0.93 | 1.09 (0.64 – 1.85) | 0.75 | 0.55 (0.28 - 1.09) | 0.09 |
| **Mother born outside of US** | 1.20 (0.58 – 2.51) | 0.62 | 1.05 (0.44 – 2.50) | 0.92 | 1.38 (0.51 – 3.73) | 0.52 | 1.08 (0.40 – 2.91) | 0.88 |
| **Previous fetal loss** | 1.45 (0.87 – 2.42) | 0.16 | 1.39 (0.82 – 2.37) | 0.22 | 1.20 (0.70 – 2.05 | 0.51 | 0.97 (0.52 – 1.81) | 0.92 |
| **Hypertension** | | | | | | | | |
| 0 or 1 prenatal visits with hypertension | Ref. | | Ref. | | Ref. | | Ref. | |
| 2 or more prenatal visits with hypertension | 1.26 (0.65 – 2.44) | 0.49 | 1.22 (0.61 – 2.42) | 0.58 | 1.10 (0.55 – 2.21) | 0.78 | 0.85 (0.42 – 1.70) | 0.64 |
| **Proteinuria or albuminuria** | 1.50 (0.87 – 2.58) | 0.14 | 1.45 (0.82 – 2.57) | 0.20 | 1.43 (0.81 – 2.55) | 0.22 | 1.32 (0.73 – 2.37) | 0.36 |
| **Edema** | 1.22 (0.76 – 1.95) | 0.40 | 1.29 (0.81 – 2.08) | 0.29 | 1.57 (0.97 – 2.55) | 0.07 | 1.38 (0.84 – 2.26) | 0.21 |
| **Preeclampsia or eclampsia** | 1.97 (0.95 – 4.09) | 0.07 | 1.93 (0.93 – 4.01) | 0.08 | 1.52 (0.72 – 3.24) | 0.28 | -- | - |

*$p \leq 0.05$
[a]Demographic characteristics include child's sex, child's race, study site, and family socioeconomic status.
[b]Adjusted for all risk factors, demographic characteristics, and ID. Preeclampsia or eclampsia not included in the fully adjusted model.

Table S8. Sensitivity Analysis: More Sensitive Autism Case Definition (N = 418 autism cases), Logistic Regression Modeling the Odds of Autism by Prenatal Risk Factors

| | Individually Entered Models, Unadjusted | | Individually Entered Models, Adjusted for Demographics[a] | | Individually Entered Models, Adjusted for Demographics[a] and ID | | Simultaneously Adjusted Model[b] | |
|---|---|---|---|---|---|---|---|---|
| | **OR (95% CI)** | **p-value** | **OR (95% CI)** | **p-value** | **OR (95% CI)** | **p-value** | **OR (95% CI)** | **p-value** |
| **Mother's age at birth** | | | | | | | | |
| Less than 35 | Ref. | | Ref. | | Ref. | | Ref. | |
| 35 or older | 1.74 (1.29 – 2.33) | <.01* | 1.59 (1.17 – 2.16) | <.01* | 1.59 (1.16 – 2.19) | <.01* | 1.38 (0.95 – 2.01) | 0.09 |
| **Father's age at birth** | | | | | | | | |
| 20 or younger | 0.85 (0.52 – 1.41) | 0.54 | 0.81 (0.49 – 1.34) | 0.42 | 1.00 (0.61 – 1.63) | 0.99 | 0.97 (0.57 – 1.63) | 0.90 |
| 21 – 29 | Ref. | | Ref. | | Ref. | | Ref. | |
| 30 or older | 1.50 (1.19 – 1.90) | <.01* | 1.56 (1.15 – 1.85) | <.01* | 1.47 (1.14 – 1.88) | <.01* | 1.37 (1.02 – 1.85) | 0.04* |
| **Bleeding** | 1.21 (0.98 – 1.49) | 0.08 | 1.24 (1.00 – 1.53) | 0.05* | 1.23 (0.98 – 1.54) | 0.07 | 1.23 (0.98 – 1.55) | 0.08 |
| **Diabetes** | 1.55 (0.77 – 3.13) | 0.22 | 1.59 (0.79 – 3.19) | 0.19 | 1.44 (0.72 – 2.87) | 0.30 | 1.35 (0.64 – 2.87) | 0.43 |
| **Birth order** | | | | | | | | |
| First | Ref. | | Ref. | | Ref. | | Ref. | |
| Second | 0.94 (0.71 – 1.25) | 0.66 | 0.97 (0.73 – 1. 30) | 0.86 | 1.06 (0.79 – 1.44) | 0.69 | 1.00 (0.72 - 1.37) | 0.98 |
| Third or later | 1.18 (0.94 – 1.47) | 0.16 | 1.15 (0.91 – 1.45) | 0.25 | 1.06 (0.83 – 1.36) | 0.62 | 1.02 (0.75 - 1.38) | 0.92 |
| **Mother born outside of US** | 0.82 (0.57 – 1.18) | 0.29 | 0.92 (0.62 – 1.36) | 0.67 | 1.22 (0.83 – 1.81) | 0.32 | 1.25 (0.84 – 1.88) | 0.27 |
| **Previous fetal loss** | 1.08 (0.85 – 1.37) | 0.53 | 1.04 (0.81 – 1.32) | 0.77 | 0.91 (0.70 – 1.18) | 0.49 | 0.77 (0.57 – 1.04) | 0.09 |
| **Hypertension** | | | | | | | | |
| 0 or 1 prenatal visits with hypertension | Ref. | | Ref. | | Ref. | | Ref. | |
| 2 or more prenatal visits with hypertension | 1.64 (1.26 – 2.14) | <.01* | 1.63 (1.24 – 2.13) | <.01* | 1.58 (1.18 – 2.10) | <.01* | 1.44 (1.07 – 1.94) | 0.02* |
| **Proteinuria or albuminuria** | 1.45 (1.14 – 1.85) | <.01* | 1.47 (1.15 – 1.88) | <.01* | 1.47 (1.13 – 1.91) | <.01* | 1.41 (1.07 – 1.84) | 0.01* |
| **Edema** | 1.09 (0.89 – 1.34) | 0.42 | 1.11 (0.90 – 1.37) | 0.32 | 1.24 (0.99 – 1.55) | 0.06 | 1.22 (0.96 – 1.54) | 0.10 |
| **Preeclampsia or eclampsia** | 1.48 (1.04 – 2.10) | 0.03 | 1.51 (1.06 – 2.16) | 0.02* | 1.26 (0.86 – 1.85) | 0.23 | -- | - |

*$p \leq 0.05$

[a]Demographic characteristics include child's sex, child's race, study site, and family socioeconomic status.
[b]Adjusted for all risk factors, demographic characteristics, and ID. Preeclampsia or eclampsia not included in the fully adjusted model.

Table S9. Sensitivity Analysis: Sample Restricted to Children with Record for Age 3 Assessment, Logistic Regression Modeling the Odds of Autism by Prenatal Risk Factors, Collaborative Perinatal Project

| | Individually Entered Models, Unadjusted | | Individually Entered Models, Adjusted for Demographics[a] | | Individually Entered Models, Adjusted for Demographics[a] and ID | | Simultaneously Adjusted Model[b] | |
|---|---|---|---|---|---|---|---|---|
| | OR (95% CI) | p-value | OR (95% CI) | p-value | OR (95% CI) | p-value | OR (95% CI) | p-value |
| **Mother's age at birth** | | | | | | | | |
| Less than 35 | Ref. | | Ref. | | Ref. | | Ref. | |
| 35 or older | 2.24 (1.49 – 3.35) | <.01* | 2.01 (1.32 – 3.06) | <.01* | 2.02 (1.31 – 3.12) | <.01* | 1.81 (1.07 – 3.06) | 0.03* |
| **Father's age at birth** | | | | | | | | |
| 20 or younger | 1.07 (0.55 – 2.10) | 0.84 | 0.98 (0.50 – 1.92) | 0.95 | 1.23 (0.63 – 2.40) | 0.55 | 1.27 (0.62 – 2.57) | 0.51 |
| 21 – 29 | Ref. | | Ref. | | Ref. | | Ref. | |
| 30 or older | 1.57 (1.10 – 2.25) | 0.01* | 1.49 (1.03 – 2.15) | 0.03* | 1.53 (1.04 – 2.24) | 0.03* | 1.33 (0.84 – 2.10) | 0.22 |
| **Bleeding** | 1.40 (1.03 – 1.90) | 0.03* | 1.40 (1.02 – 1.92) | 0.04* | 1.45 (1.05 – 2.01) | 0.03* | 1.37 (0.98 – 1.93) | 0.07 |
| **Diabetes** | 1.83 (0.58 – 5.75) | 0.30 | 1.70 (0.54 – 5.35) | 0.36 | 1.77 (0.54 – 5.77) | 0.34 | 1.49 (0.43 – 5.11) | 0.53 |
| **Birth order** | | | | | | | | |
| First | Ref. | | Ref. | | Ref. | | Ref. | |
| Second | 0.77 (0.50 – 1.20) | 0.25 | 0.83 (0.53 – 1.31) | 0.42 | 0.90 (0.56 – 1.45) | 0.67 | 0.85 (0.52 - 1.39) | 0.51 |
| Third or later | 1.15 (0.83 – 1.60) | 0.40 | 1.13 (0.80 – 1.60) | 0.48 | 1.12 (0.78 – 1.60) | 0.55 | 0.99 (0.63 - 1.54) | 0.96 |
| **Mother born outside of US** | 0.59 (0.33 – 1.06) | 0.08 | 0.75 (0.39 – 1.46) | 0.40 | 1.00 (0.51 – 1.95) | 1.00 | 1.02 (0.52 – 2.00) | 0.96 |
| **Previous fetal loss** | 1.14 (0.81 – 1.61) | 0.44 | 1.08 (0.76 – 1.53) | 0.68 | 1.01 (0.69 – 1.48) | 0.95 | 0.82 (0.53 – 1.27) | 0.37 |
| **Hypertension** | | | | | | | | |
| 0 or 1 prenatal visits with hypertension | Ref. | | Ref. | | Ref. | | Ref. | |
| 2 or more prenatal visits with hypertension | 1.78 (1.18 – 2.68) | 0.01* | 1.76 (1.16 – 2.67) | 0.01* | 1.54 (1.00 – 2.37) | 0.05* | 1.29 (0.82 – 2.02) | 0.27 |
| **Proteinuria or albuminuria** | 1.39 (0.98 – 1.96) | 0.06 | 1.36 (0.95 – 1.95) | 0.09 | 1.44 (0.99 – 2.11) | 0.06 | 1.34 (0.91 - 1.99) | 0.14 |
| **Edema** | 1.24 (0.92 – 1.68) | 0.16 | 1.32 (0.97 – 1.79) | 0.07 | 1.40 (1.01 – 1.94) | 0.04* | 1.38 (0.99 - 1.94) | 0.06 |

| | Individually Entered Models, Unadjusted | | Individually Entered Models, Adjusted for Demographics[a] | | Individually Entered Models, Adjusted for Demographics[a] and ID | | Simultaneously Adjusted Model[b] | |
|---|---|---|---|---|---|---|---|---|
| **Preeclampsia or eclampsia** | 1.51 (0.93 – 2.44) | 0.10 | 1.54 (0.95 – 2.51) | 0.08 | 1.32 (0.79 – 2.22) | 0.29 | -- | - |

*$p \leq 0.05$

[a]Demographic characteristics include child's sex, child's race, study site, and family socioeconomic status.

[b]Adjusted for all risk factors, demographic characteristics, and ID. Preeclampsia or eclampsia not included in the fully adjusted model.

N = 24,625 children total; 189 autism cases.

Table S10. Demographic Characteristics among Children Seen at ages 4 or 7 in the Collaborative Perinatal Project (CPP): Comparison of Children without Autism, Children with Autism, and Children Excluded due to Missing IQ Data

| | Not Autism (n=44,701) | Autism (n = 275) | Missing IQ (n = 146) |
|---|---|---|---|
| | N (%) | N (%) | N (%) |
| **Gender** | | | |
| Male | 22,494 (50.4) | 180 (65.5) | 82 (56.2) |
| Female | 22,179 (49.7) | 95 (34.6) | 64 (43.8) |
| **Race** | | | |
| White | 20,012 (44.9) | 113 (41.2) | 61 (42.7) |
| African-American | 21,916 (49.2) | 154 (56.2) | 56 (39.2) |
| Asian | 93 (0.2) | 0 (0.0) | 1 (0.7) |
| Hispanic | 2,287 (5.1) | 7 (2.6) | 23 (16.1) |
| Other | 218 (0.5) | 0 (0.0) | 2 (1.4) |
| **Site** | | | |
| Boston | 9,596 (21.5) | 71 (25.8) | 35 (24.0) |
| Buffalo | 2,190 (4.9) | 3 (1.1) | 6 (4.1) |
| New Orleans | 2,220 (5.0) | 31 (11.3) | 4 (2.7) |
| NY/Columbia | 1,806 (4.0) | 10 (3.6) | 15 (10.3) |
| Baltimore | 3,519 (7.9) | 23 (8.4) | 8 (5.5) |
| Virginia | 2,902 (6.5) | 30 (10.9) | 3 (2.1) |
| Minnesota | 2,547 (5.7) | 19 (6.9) | 6 (4.1) |
| NY/Medical | 2,692 (6.0) | 7 (2.6) | 15 (10.3) |
| Oregon | 2,739 (6.1) | 13 (4.7) | 11 (7.5) |
| Pennsylvania | 8,018 (17.9) | 29 (10.6) | 21 (14.4) |
| Providence | 3,320 (7.4) | 24 (8.7) | 5 (3.4) |
| Tennessee | 3,151 (7.1) | 15 (5.5) | 17 (11.6) |
| **SES Category (quartiles)** | | | |
| 1 (lowest) | 11,968 (27.5) | 94 (35.3) | 47 (32.9) |
| 2 | 10,055 (23.1) | 65 (24.4) | 33 (23.1) |
| 3 | 10,629 (24.4) | 60 (22.6) | 21 (14.7) |
| 4 (highest) | 10,859 (25.0) | 47 (17.7) | 42 (29.4) |
| **Type of School (7 years)** | | | |
| Public | 35,161 (87.7) | 163 (63.4) | 28 (45.2) |
| Private | 4,655 (11.6) | 13 (5.1) | 5 (8.1) |
| Special | 192 (0.5) | 46 (17.9) | 14 (22.6) |
| No School | 103 (0.3) | 35 (13.6) | 15 (24.2) |

Abbreviations: SES, socioeconomic status.

## Section S1. Description of Prenatal Exposures

The prenatal exposures in the present study include mother's and father's age at birth (categorical variables), bleeding during pregnancy (occurring during any trimester of pregnancy), diabetes (diabetes mellitus occurring during pregnancy), birth order, mother's place of birth (dichotomous variable defined as mother born within the US vs. anywhere outside of the US), previous fetal loss (dichotomous variable defined as no prior losses vs. one or more prior losses), proteinuria (proteinuria or albuminuria occurring at any time during pregnancy), preeclampsia or eclampsia, edema (occurring during any trimester of pregnancy), and gestational hypertension (defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg). Hypertension was measured at each prenatal visit. We compared women with hypertension at two or more prenatal visits to women with hypertension at one or no prenatal visits. Mothers with only one prenatal visit were classified as missing for this variable (n=273 women).

## Section S2. Comparison of Diagnostic Criteria for Autism in Present Study to Prior Study in the Collaborative Perinatal Project

Two previous studies have examined autism in the CPP dataset (Torrey, Dhavale, Lawlor, & Yolken, 2004; Torrey, Hersh, & McCabe, 1975). Both studies were authored by Fuller Torrey. Criteria for Infantile Autism was applied in 1974 and 14 cases of autism were identified for a prevalence of 0.5 per 1,000. In the first study by Torrey et al. (1975), children with autism were matched to two control groups; 14 children with normal IQ and 14 children with low IQ. A number of perinatal risk factors were examined and the authors found that children with autism were more likely to have mothers with bleeding

during pregnancy than mothers of children with normal IQ (64% vs. 29%, $p<0.07$). The high rate of bleeding in the autism group may be clinically important but the findings did not reach statistical significant, nor was the occurrence of bleeding in the case group significantly different from the rate in children with low IQ (36%). In the second study by Torrey et al. (2004), the same 14 children with autism (including one additional case) were compared to all CPP births on head circumference and a nonsignificantly larger head circumference was observed at 4 months in children with autism. These studies demonstrate that children with autism can be identified in the CPP cohort, but the small number of autism cases may explain why some of the findings were not statistically significant.

The 14 autism cases identified by Torrey and colleagues were selected from 30,000 CPP children with computerized records available in 1974. A preliminary search was conducted to indentify children who had significant behavioral disturbances by seven years of age or who were institutionalized or in special schools, which yielded 200 records. The records of the 200 children were then reviewed by a child psychiatrist and pediatrician to select those who met the criteria for autism being used at that time. *Infantile Autism* was defined as having abnormalities in all four of the following by age three: response to external stimuli, affective human contact, language development, and stereotyped or automatic behaviors. Children with major congenital or neurologic abnormalities were excluded. The cases included 11 boys and 4 girls (78% male and 28% female). The IQs of the children for whom data were available were 73, 72, 71, 50, 50, 45, and 37; the others were considered to be untestable. The prevalence of autism was 5

per 10,000, which was consistent with the prevalence being reported at the time (Wing, O'Connor, & Lotter, 1967).

Of the 14 cases identified by Torrey, 10 (71%) were identified by the criteria used in the present study, which shows good agreement between the case definitions. There were four children who did not meet the case criteria of the present study. This was because they did not meet criteria for group A (social impairment) or group C (restricted and repetitive behaviors) symptoms. The algorithm required that children meet both of the two criteria in the social impairment domain (as per the DSM-IV-TR, which requires two of four criteria). In contrast, Torrey and colleagues only required children to exhibit one type of abnormality in "affective human contact." It is therefore likely that some of the children diagnosed with autism by Torrey and colleagues did not meet the minimum criteria of two abnormal social behaviors required in our study. In addition, some of the stereotyped behaviors in the 1974 study are not in the current DSM (e.g. masturbation, nose-picking/lip-chewing). Therefore, children who only exhibited these restricted and repetitive behaviors would not the diagnostic criteria of the present study.

There are a number of reasons why the current study is an improvement on prior work on autism in the CPP. We were able to identify more cases of autism, in particular higher-functioning cases. In the 1974 study, the records of 30,000 CPP offspring were examined to identify cases of autism. The present study used records from all children in the cohort, which increased the number of cases and controls and the power of the study. Torrey and colleagues required the child to be considered behaviorally abnormal at age seven and be institutionalized or in a special school to meet criteria for autism. In contrast, our criteria required the child to be considered behaviorally abnormal at age 4 or

age 7 and there were no requirements with regard to special schooling. The criteria from 1974 are likely to have missed high-functioning cases by restricting the case definition to children in a special school/institutionalized. This is evidenced by IQs of the cases identified by Torrey and colleagues. All of the children with autism had intellectual disability (the highest IQ was 73 and seven children (50%) were considered untestable). In contrast, approximately 40% of children with autism identified in our study did not have intellectual disability.

In summary, the majority of CPP children identified with autism by Torrey and colleagues were also identified by our diagnostic algorithm. However, we identified a much larger number of autism cases, which is likely explained by the broader diagnostic criteria we used as well as differences in our case finding methodology.

## References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## Section S3. Sensitivity Analyses

### *Autism Case Definition*

In a sensitivity analysis we restricted our case definition to require that the child have six total criteria from each of the three diagnostic domains (categories A, B, and C). This resulted in 75 cases with autism from the analytic sample. Given that this is a more narrow case definition (with higher specificity), we would expect that these children have more severe autism and are more likely to be true cases. The findings were similar to our main findings and the effect estimates for maternal and paternal age, bleeding, and edema were stronger (Table S7). This is in line with what we would expect if this group of children is more likely to include true autism cases. It also provides support for the prenatal risk factors that we identified in the study since they are even more strongly associated with autism in this subgroup of more severe cases.

In a second sensitivity analysis we expanded our autism case definition by requiring that the child only had to meet one of the social interaction domain criteria (A1 or A4). This resulted in 418 children with autism from the analytic sample. Given that this is a broader case definition (with higher sensitivity), we would expect that some of these children have less severe autism and maybe not have AD but another milder ASD. The findings were similar to our main findings with somewhat weaker effects seen for maternal age, bleeding, and edema, and stronger effects for paternal age, hypertension, and proteinuria (Table S8). The weaker effects for the risk factors identified in our main analyses are expected if this group is made up of children with less severe autism and/or less likely to be true cases.

### *Missing Data*

A little less than half of the sample was missing data for the age 3 assessment (n = 20,351 from the analytic sample). We used variables measured at age 3 for our diagnostic algorithm, in particular those related to impairment in communication. Children who were missing at age 3 are therefore more likely to be false negatives. Children missing at age 3 were significantly more likely to be White, from study sites in Boston and Pennsylvania, and of higher SES (Table S5). In a sensitivity analysis we restricted the sample to children who were not missing at age 3 and the findings were similar to the main analyses (Table S9). This suggests that including children missing at age 3 in our analysis did not greatly affect the findings. In the event that misclassification occurred, this is unlikely to bias the results because of the small number of children with autism relative to those without autism in our sample.

One hundred and forty-six children were excluded from the analyses because they were missing IQ data (including 33 children with autism). Compared to children with IQ data, these children were more likely to be Hispanic, come from NY/Columbia study site, of lower SES, and to attend special school or no school at age 7 (Table S10). In a sensitivity analysis we classified the children with missing IQ data as having ID because it is likely that many of the children were missing because they were too cognitively impaired to complete the IQ assessment. The results were similar to those from our main analyses (data available upon request), which suggests that excluding these participants did not have a large effect on our results.

## Conclusion

Autism was first described by Leo Kanner in his seminal 1943 paper on 11 children who he described as having "autistic disturbances of affective contact" (Kanner, 1943). The disorder was thought to be rare and later attributed to "refrigerator moms" based on Kanner's observation of the parents of his patients, who he described as cold and intellectual, especially the mothers (Bettelheim, 1967). Since that time our understanding of the features and risk factors for autism has greatly improved, and many more individuals are now being diagnosed with the disorder. But the cause or causes of autism remain unknown. While there is strong evidence for the role of genetic factors, the mode of inheritance is complex and environmental factors likely interact with genetic risk to produce the disease.

The prevalence of autism has steadily increased over the past decades. In the USA, the estimated prevalence of ASD increased by 78% between 2002 and 2008 (Baio, 2012). A study of time trends in ASD diagnoses found that ASD incidence increased from 56 per 10,000 in 2001 to 93 per 10,000 in 2005 (Manning et al., 2011). The most recent data suggest that as many as 1 in 88 children have ASD; with the disorder affecting up to 1 in 54 boys (Baio, 2012).

As the prevalence of ASD continues to rise, more individuals with autism are reaching adulthood and there will be an increasing need to plan for medical and social services. Research into the etiology of autism and comorbid medical conditions is essential to address these needs. Research on autism etiology may lead to preventative interventions based on a better understanding of the biological mechanisms underlying

the development of autism. It can also lead to future research on gene-environment interactions. Research on comorbid conditions, such as epilepsy, can also provide clues to the etiology of autism. For example, the autism-epilepsy subgroup has been helpful to genetic research. Recent sequencing studies in autism have identified genetic variants in a variety of epilepsy-related genes (Neale et al., 2012; O'Roak et al., 2012; Sanders et al., 2012; Veeramah et al., 2012). Information on the co-occurrence of autism and epilepsy is also useful to plan for medical care for persons with ASD.

Contributions of these studies to the literature on comorbidity and etiology of autism:

1) **Population-based estimate of the prevalence of comorbid epilepsy in children with ASD**. Epidemiologic studies on epilepsy in ASD populations are lacking. However, accurate prevalence estimates are needed to determine the frequency with which this comorbidity occurs and to plan for medical services. This information will become increasingly important as children with ASD enter adulthood, specifically given the increased rate of mortality from epilepsy in the autistic population (Pickett, Xiu, Tuchman, Dawson, & Lajonchere, 2011). The first study estimated the prevalence of epilepsy in a large, representative sample of children with ASD. The average prevalence of epilepsy across the sample was approximately 12%, with a cumulative prevalence through 17 years of age of 26%.
2) **Clinical characteristics of children with co-occurring ASD and epilepsy**. The first and second studies identified clinical characteristics of children with co-occurring ASD and epilepsy. The results provide useful information to clinicians and families regarding the risk of epilepsy in ASD and the association between epilepsy

and the autism phenotype. Clinical predictors of epilepsy can help guide prognosis and alert clinicians to patients who are at increased risk. Specifically, our study showed that low IQ is the best predictor of epilepsy in children with ASD. The findings also indicate that onset of epilepsy can occur in late childhood and adolescence in children with ASD and, therefore, clinicians and parents should we aware of the continued risk of epilepsy onset through adolescence. The second study found that children with epilepsy have more autism symptoms and maladaptive behaviors than children with ASD alone, which alerts parents and clinicians to specific symptoms that may occur more frequently in children with epilepsy and ASD.

A biological explanation for the co-occurrence of ASD and epilepsy is not yet known. However, current research suggests that the disorders are caused by common genetic and molecular mechanisms that account for the pathophysiology of both autism and epilepsy (Morrow, 2010; Tuchman & Cuccaro, 2011). The hope is that therapeutic interventions that target common mechanisms will have a broader symptom-modifying effect with benefits to both persons with epilepsy and autism (Tuchman, Moshe, & Rapin, 2009). The two studies on ASD and epilepsy provide information on clinical correlates of these comorbid conditions, which may shed light on the biological association between the disorders.

3) **Children with co-occurring ASD and epilepsy fare worse than individuals with ASD alone, but cognitive ability is a confounder of these associations**. The first two studies show that children with co-occurring ASD and epilepsy fare worse in a number of areas than individuals with ASD alone. Comorbid ASD and epilepsy is

characterized by lower cognitive ability, poorer adaptive and language functioning, a greater likelihood of having a history of developmental regression, and more severe ASD symptoms and maladaptive behaviors, as compared to individuals with ASD alone. These studies sought to not only describe characteristics of individuals with comorbid ASD and epilepsy, but also to better understand why epilepsy is associated with worse functioning. Both studies suggest that lower cognitive ability largely explains poorer functioning in children with epilepsy and ASD. Thus, cognitive ability emerged as a strong confounder of the association between epilepsy and clinical characteristics, autism symptoms, and maladaptive behaviors. Future studies on ASD and epilepsy should consider the role of confounding by IQ.

4) **The prevalence of autism in a cohort from the 1960s is comparable to current estimates**. In the third paper, we applied contemporary diagnostic criteria to the very large Collaborative Perinatal Project study and found an estimated autism prevalence rate of 6.8 per 10,000, which is similar to current estimates for Autism Spectrum Disorder. In contrast, an earlier study from the CPP found an autism prevalence of 0.05 per 10,000 (Torrey, Hersh, & McCabe, 1975). Our results provide evidence that at least part of the increase in autism prevalence can be explained by changes in diagnostic criteria.

5) **Prior associations between prenatal factors and autism confirmed in a large population-based cohort study**. Findings from recent twin studies show a smaller discrepancy between concordance rates in monozygotic and dizygotic twins than previously reported, resulting in lower heritability rates as compared to prior studies (Hallmayer, 2011; Rosenberg et al., 2009). And evidence that concordance rates in

dizygotic twins of 25% to 30% (Hallmayer, 2011; Rosenberg, et al., 2009) are greater than in non-twin siblings of 4 to 18% (Chakrabarti & Fombonne, 2001; Ozonoff et al., 2011; Ritvo et al., 1989; Sumi, Taniai, Miyachi, & Tanemura, 2006) supports the role of environmental risk factors occurring in the *in utero* environment.

Several prenatal characteristics that increase risk of autism were identified in the study including older maternal and paternal age at birth, bleeding during pregnancy, and edema. Our findings are similar to results from several studies and for the most part, replicate findings from a recent meta-analysis of prenatal risk factors for autism (Gardener, 2009). This provides consistency with previous studies, which is beneficial to the autism research field in establishing a clearer link between specific prenatal exposures and autism. In particular, we replicated findings that older maternal is associated with autism, which provides evidence of a potential causal association between the rising trend in older parental age at birth and the increase in autism prevalence.

6) **Intellectual disability is a mild confounder of the association between prenatal risk factors and autism**. A novel aspect of the third study was the consideration of confounding by ID, which was found to be a moderate confounder of the association between prenatal risk factors and autism. In particular, edema became a significant risk factor for autism after adjusting for ID. Edema has been reported in association with autism in only a few studies, and this may be due to previous studies not accounting for ID in their analyses.

## Future Directions

Future directions for research on epilepsy and autism include:

1) **Longitudinal studies of epilepsy in children with ASD**. A longitudinal design can address the methodological limitations of cross-sectional studies by following participants through young adulthood to ensure sufficient time for epilepsy to develop. A longitudinal study in a large, population-based sample is needed to determine the incidence of epilepsy and to examine how seizures impact clinical characteristics, autism symptoms, and maladaptive behaviors over time. In addition, this type of study could examine differences in etiology for early versus late-onset epilepsy in children with ASD.
2) **The association between anti-epileptic drugs and autism symptoms and maladaptive behaviors**. Anti-epileptic drug (AED) use is common in children with ASD and has been shown to affect behaviors associated with autism (Gillberg, 1991). AEDs may modify the association between epilepsy and the autism phenotype. Preliminary findings from our data suggest that AED use is associated with fewer maladaptive behaviors, but further research is needed. A study examining the effect of AEDs on the autism phenotype in a large sample of children with ASD will have potential clinical implications for patients with comorbid ASD and epilepsy.
3) **Epileptiform electroencephalograms (EEGs) abnormalities in children with ASD**. Even less well studied than comorbid epilepsy is the presence of epileptiform electroencephalograms (EEGs) abnormalities. Prior studies indicate that there is a high rate of epileptiform EEGs in children with ASD that occur even in the absence

of epilepsy. Studies show that as many as 30% of children with ASD show signs of epileptiform EEGs (Spence, 2009). These EEG changes are signs of cerebral dysfunction and may play a causal role in autism. The high rate of EEG abnormalities in the absence of epilepsy in persons with ASD is not well understood and risk factors are unknown. At present, no population-based studies of rates of epileptiform discharges among individuals with ASD have been conducted. Large, representative studies of EEG abnormalities would be useful to determine the prevalence of these abnormalities and to identify risk factors.

Future directions for research on autism in the Collaborative Perinatal Project include:

1) **Prenatal risk factors for autism and intellectual disability**. Future studies can examine whether prenatal risk factors for autism differ from risk factors for ID. The findings from the third paper suggest that specific prenatal factors are associated with autism after controlling for ID. However, given the high co-occurrence of ASD and ID, more sophisticated methods are needed to understand whether risk factors specific to autism differ from those specific to ID.
2) **Perinatal and neonatal risk factors for autism**. Future studies can examine perinatal and neonatal risk factors for autism using the CPP dataset. In particular, to attempt to replicate findings from a 2011 meta-analysis by Gardener and colleagues examining risk factors occurring from the onset of labor through delivery and the neonatal period (Gardener, 2011).
3) **Follow-up study of participants with autism in adulthood**. Autism first manifests in young childhood and remains a lifelong disability. Longitudinal studies of adults

with autism are rare, and studies of autism from the pregnancy period through adulthood are even less common. An important area of interest is early life predictors of outcome in persons with autism. A small number of studies have studied early predictors of adult outcomes and these studies have primarily focused on characteristics of the individual (e.g., IQ, language ability) (Seltzer, Shattuck, Abbeduto, & Greenberg, 2004). Very few studies have examined contextual variables (e.g. family socioeconomic status, schooling) or perinatal factors. Addressing the needs of adults with autism is a major public health concern. As the number of adults with ASD increases, there is a growing need for services and treatment for adults, and epidemiologists must employ a life course approach (Bresnahan, Li, & Susser, 2009). The identification of children with autism in the CPP allows for future studies in this cohort. The CPP provides a unique opportunity to study early life risk factors, both with regard to pregnancy and contextual factors, in relation to autism and to follow individuals with autism from the fetal period through adulthood.

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