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Examining the Sex Ratio in Autism Spectrum Disorder

Maya N. Matheis
Louisiana State University and Agricultural and Mechanical College, maya.matheis@gmail.com

EXAMINING THE SEX RATIO IN AUTISM SPECTRUM DISORDER

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Maya Matheis
B.A., Bard College at Simon's Rock, 2007
M.S.W., Washington University in St. Louis, 2014
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TABLE OF CONTENTS

ABSTRACT

The higher prevalence of autism spectrum disorder (ASD) among males compared to females is well documented but poorly understood. The ASD sex ratio may provide valuable insight into the underlying neurobiological mechanisms of the disorder. A review of studies examining the prevalence in ASD published in the last 5 years was conducted, revealing a mean male/female (M/F) ratio of 4. Literature examining the ASD sex ratio in relation to risk factors and associated features of ASD was also summarized. The study aimed to examine the ASD sex ratio and its association to various risk factors among an early intervention sample. Participants (n = 12,598) were children aged 17-37 months enrolled in EarlySteps, the State of Louisiana's early intervention program. The Baby and Infant Screen for Children with aUtism Traits- Part 1 (BISCUIT- Part 1) and Battelle Developmental Inventory, Second Edition (BDI-2) were administered to parents/caregivers as part of the EarlySteps assessment protocol. An overall ASD prevalence rate of 12.12% was found using *DSM-5* criteria, along with an overall M/F ratio of 3.15. Significant differences in the M/F ratio were found: between cases with and without cognitive impairment; between cases with and without advanced maternal age; across birth weight categories; and between cases with and without seizure disorder. Advanced maternal age was found to significantly increase the risk of ASD for females but not males. These findings are discussed in relation to previous research as well as theories pertaining to the male predominance in ASD.

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by pervasive impairments in social communication and restricted, repetitive patterns of behavior (American Psychiatric Association, 2013; Volkmar & McPartland, 2014). Recent estimates from the Centers for Disease Control and Prevention (CDC) indicate that 1 in 68 children in the United States have ASD (CDC, 2016). Despite increased research attention in recent years, understanding of the underlying etiology of ASD is limited, with findings highlighting complex and diverse causal pathways (Chen, Peñagarikano, Belgard, Swarup, & Geschwind, 2015; de la Torre-Ubieta, Won, Stein, & Geschwind, 2016; Jeste & Geschwind, 2014; Schaafsma & Pfaff, 2014).

One of the most consistently documented features of ASD is its male predominance, with a male/female ratio of about 4 (male:female, 4:1; Fombonne, 2009; Hill, Zuckerman, & Fombonne, 2016). However, sex ratio estimates have ranged from 1.33 to 16, fluctuating considerably across studies (Elsabbagh et al., 2012; Fombonne, 2009). Although the disparate sex ratio has been well documented, very little is known about contributing factors, with only a handful of studies having directly examined changes in the sex ratio. Factors such as cognitive functioning (CDC, 2016; Honda, Shimizu, Imai, & Nitto, 2005; van Bakel et al., 2015), diagnostic subtype (Bachmann, Gerste, & Hoffmann, 2016; Jensen, Steinhausen, & Lauritsen, 2014), comorbid disorders (Amiet et al., 2008; Ben-Itzchak, Ben-Shachar, & Zachor, 2013), birth weight (Schendel & Bhasin, 2008; Zachor, Ben-Shachar, & Ben-Itzchak, 2013), and parental age at birth (Anello et al., 2009) have been found to affect the sex ratio, suggesting that males and females with ASD may be differentially impacted by associated risk factors and underlying neurobiology. This dissertation aimed to examine theories related to the ASD sex

ratio, recent estimates of the sex ratio, previous research on factors that may affect the sex ratio, and to examine the sex ratio in an early intervention sample. Understanding the male predominance in ASD will provide insight into the neurobiological mechanisms underlying the disorder, increase our understanding of etiology, and help to identify risk factors and biomarkers.

Autism Spectrum Disorder

History of ASD. Autism was first described by Leo Kanner (1943) in a detailed account of 11 children with deficits in socialization, functional communication, and motor stereotypies. These symptoms were hypothesized to be related to a condition that he later labeled as "early infantile autism," which was characterized by impairments in social interaction, cognitive development, language acquisition, and rigid behavior (Kanner, 1944). Hans Asperger (1944) separately described autism among a group of children with similar characteristics, such as deficits in socialization, but who did not have impairments in cognitive development. The conceptualization of autism was further expanded by Michael Rutter (1978) who characterized autism as a stable lifespan disorder present from infancy. Rutter also proposed that the children described by Asperger had a milder form of autism and noted that autism had a higher prevalence in males, unlike disorders such as schizophrenia.

Standardized diagnostic criteria for autism were first introduced in the *Diagnostic Statistical Manual, Third Edition (DSM-III)*, under the new category of Pervasive Developmental Disorders (PDD; APA, 1980). Diagnostic subtypes included infantile autism, child onset pervasive developmental disorder (COPDD), and atypical pervasive developmental disorder (APDD). With the revised edition of the *DSM-III,* infantile autism was renamed autistic disorder and COPDD and APDD were replaced with pervasive developmental disorder- not otherwise specified (PDD-NOS; APA, 1987). In 1994, the *Diagnostic Statistical Manual,*

Fourth Edition (*DSM-IV*; APA, 1994) integrated Asperger's syndrome into the PDD category, following the English translation of Asperger's work in 1991 (Asperger, 1991). Further changes included the introduction of the term ASD, which emphasized that these diagnostic subtypes were conceptualized as a spectrum of disorders ranging in severity, as well as the diagnostic subtypes of childhood disintegrative disorder and Rett's disorder. Each diagnostic subtype had its own set of specific criteria, with the exception of PDD-NOS. The current version of the *International Statistical Classification of Diseases and Related Health Problem- Classification of Mental and Behavioral Disorders (ICD-10)* mirrors *DSM-IV* criteria, with diagnostic subcategories of childhood autism (parallel to autistic disorder), Asperger's syndrome, PDD-NOS, and atypical autism (World Health Organization, 1992).

Diagnostic conceptualization of ASD underwent significant changes with the publication of the *Diagnostic Statistical Manual, Fifth Edition* (*DSM-5*), when the diagnostic subtypes of autistic disorder, Asperger's syndrome and PDD-NOS were replaced with the single diagnostic category of ASD (APA, 2013). Additionally, Rett's disorder and childhood disintegrative disorder were removed. These changes were motivated by concerns related to the ambiguity of the diagnostic subtypes and the lack of consistency in classifying cases (Matson, Kozlowski, Hattier, Horovitz, & Sipes, 2012; Tanguay, 2011), as well as reflecting the conceptualization of autism as a heterogeneous disorder with an array of phenotypes (Lord & Jones, 2012; Volkmar & McPartland, 2014). The *ICD-11*, currently in development, is anticipated to parallel changes made in the *DSM-5* in relation to ASD (Lord & Jones, 2012).

Diagnostic criteria. The current *DSM-5* diagnostic criteria for ASD include: a) persistent deficits in social communication and social interaction across settings; b) restricted, repetitive patterns of behavior, interests or activities (RRBs); c) symptoms present in early

development; d) symptoms result in clinically significant impairment of functioning; and e) symptoms are not better explained by intellectual disability (ID) or global developmental delay, both of which frequently co-occur with ASD (APA, 2013). For the domain of social communication and social interaction, the following impairments must be observed: 1) deficits in social-emotional reciprocity, such as reciprocal conversation and initiation of social interactions; 2) deficits in nonverbal communication, such as abnormal eye contact, use of gestures, or flat affect; and 3) deficits in developing, maintaining, and understanding relationships (APA, 2013). For the domain of RRBs, symptoms must be noted currently or by history in at least two of the following areas: 1) stereotyped or repetitive motor movements, use of objects or speech (e.g., echolalia, motor stereotypies, perseverative language, lining/arranging objects), 2) inflexible adherence to routines, insistence on sameness, or ritualized patterns of behavior (e.g., rigid thinking patterns, difficulties with transitions, routinized behavior); 3) restricted interests that are abnormal in intensity or focus (e.g., perseverative interests, unusual attachment to or preoccupation with unusual objects); and 4) hyper- or hypo-reactivity to sensory input (e.g., aversive reactions to sound or textures, excessive smelling or touching of objects, fascination with lights or movement). Three levels are used to specify the level of support needed based on functional impairments across the domains of social communication and restricted, repetitive behaviors.

Etiology. ASD has a complex etiology with a diversity of genetic mechanisms and environmental risk factors (Hens, Peeters, & Dierickx, 2016; Talkowski, Minikel, & Gusella, 2014). The high heritability of autism is well-established in the literature (Constantino, Zhang, Frazier, Abbacchi, & Law, 2010; Ozonoff et al., 2011), with concordance estimates from twin studies ranging from 70% (Rosenberg et al., 2009) to 90% (Bailey et al., 1995) , which are

higher than for any other known cognitive or behavioral disorder (Rosenberg et al., 2009). Newborns with a sibling with ASD are 20% more likely to develop the disorder than those without affected siblings (Constantino et al., 2010). Copy-number variations (CNVs), structural variants in the number of copies of specific regions of DNA involving deletion or duplication, have been demonstrated to be an important causal factor (Hens et al., 2016; Talkowski et al., 2014; Thapar & Cooper, 2013). *De novo* CNVs, those that present for the first time in a germ cell, have been found to be a particularly strong source of causality for ASD (Ronemus, Iossifov, Levy, & Wigler, 2014; Talkowski et al., 2014). Many mutations linked to ASD affect genes related to protein production and synaptic function (Abrahams & Geschwind, 2008; Talkowski et al., 2014). A number of prenatal and perinatal risk factors have been identified in relation to genetic aberrations and the occurrence of ASD, including maternal infections during pregnancy, gestational diabetes, maternal medication use, parental age, premature birth, birth order, prolonged labor, and multiple gestation (Froehlich-Santino et al., 2014; Gardener, Spiegelman, & Buka, 2011; Mazina et al., 2015; Schieve et al., 2012). The presence of multiple risk factors is associated with higher risk of ASD (Maramara, He, & Ming, 2014).

Sex versus Gender

The terms "sex" and "gender" are often used interchangeably in autism research (Goldman, 2013; M. C. Lai, Lombardo, Auyeung, Chakrabarti, & Baron-Cohen, 2014), with frequent references to both the "sex ratio" (Anello et al., 2009; James, 2005; Lord & Schopler, 1985) and "gender ratio" (CDC, 2016; Hill et al., 2016; Whiteley, Todd, Carr, & Shattock, 2010). However, there has been a push in the social sciences to reconsider the use of these terms, as they refer to different constructs that have distinct implications for research design and interpretation (Johnson & Repta, 2011; Lorber, 1996). Sex is a biological construct that

references the hormonal, genetic, and physiological differences between males and females (Johnson & Repta, 2011), which has important implications for the underlying biological mechanisms of a disorder. Use of the term "sex ratio" therefore underscores the relationship between the differential impact of ASD on males and females and ASD's underlying etiology. Gender refers to the experiences and associated identity an individual develops in response to the roles, responsibilities, and limitations a specific cultural context provides based on their presenting sex/gender (Johnson & Repta, 2011). Gender has important implications for understanding behavioral phenotypes and how symptoms are interpreted and identified.

Gender Differences

The vast majority of research on autism etiology and symptomology has been based on a male phenotype (Horovitz, Matson, Turygin, & Beighley, 2012; Kirkovski, Enticott, & Fitzgerald, 2013; Sipes, Matson, Worley, & Kozlowski, 2011). Many studies do not include female participants, and those that do rarely include enough to accurately perform gender comparisons (Kirkovski et al., 2013; Rivet & Matson, 2011). A meta-analysis of fMRI studies in ASD found a male/female ratio of 15, demonstrating this male bias (Philip et al., 2012). While this gender disparity in research may be due to the skewed sex ratio and the difficulty of recruiting female participants, it remains that the female phenotype of ASD is not well researched or understood. However, studies that have examined the differences between males and females have found differences in symptom presentation.

Socialization and communication. Studies that have investigated gender differences in autism symptomology have reported conflicting results in relation to non-verbal communication, with several studies noting greater impairment in non-verbal communication among boys with ASD (Kirkovski et al., 2013; M. C. Lai et al., 2011; McLennan, Lord, & Schopler, 1993), while

others have found that girls with ASD performed worse in this area (Carter et al., 2007; Hartley & Sikora, 2009; Sipes et al., 2011). Several studies have indicated that girls with ASD demonstrate more appropriate play behaviors in comparison with boys with ASD (Kirkovski et al., 2013; Rivet & Matson, 2011). In particular, research indicates that girls with ASD have superior imaginative play skills (Knickmeyer, Wheelwright, & Baron-Cohen, 2008). Females with ASD have been found to have significantly greater impairments in the formation and maintenance of friendships and appropriate peer relationships than males with ASD (Kirkovski et al., 2013; McLennan et al., 1993; Rivet & Matson, 2011).

RRBs and externalizing/internalizing symptoms. Many studies have found that female toddlers, children, adolescents, and adults with ASD are significantly less impaired than their male counterparts in relation to repetitive and stereotyped behaviors (Hattier, Matson, Tureck, & Horovitz, 2011; M. C. Lai et al., 2011; Mandy et al., 2012; Park et al., 2012; Sipes et al., 2011; Szatmari et al., 2012; Tillmann et al., 2018). In regards to stereotyped language, girls with ASD have been found to be more likely than boys with ASD to have vocal patterns of echolalia (Kirkovski et al., 2013). Males with ASD have been found to demonstrate greater rates of externalizing behavior problems compared to females, such as hyperactivity, inattention, and aggression (Mandy et al., 2012). Females with ASD have been found to have higher rates of anxiety, depression, and other emotional symptoms compared to males with ASD (Mandy et al., 2012; Solomon, Miller, Taylor, Hinshaw, & Carter, 2011).

Theories on Male Predominance

Under-diagnosis of females. Researchers have expressed concerns that females with ASD may be under-recognized and under-diagnosed, skewing the sex ratio (Gould & Ashton-Smith, 2011; Haney, 2016; Wilkinson, 2008). Differential social expectations and environments

may result in ASD symptoms being more noticeable in males compared to females (Haney, 2016; Wilkinson, 2008). Due to gendered socialization, girls may develop better compensatory mechanisms, such as mimicking the social behavior of others, that allow them to better mask their social impairments. Findings from a recent study support these concerns, indicating that girls with ASD demonstrate compensatory behaviors that "camouflage" their social impairments (Dean, Harwood, & Kasari, 2017). Fewer externalizing problems and increased internalizing symptoms may also result in their difficulties going unnoticed by parents and teachers (Gould & Ashton-Smith, 2011; Mandy et al., 2012; Wilkinson, 2008). Given comparable levels of ASD traits, girls have been found to be less likely than boys to receive an ASD diagnosis unless they also experience co-occurring cognitive and behavioral difficulties (Dworzynski, Ronald, Bolton, & Happé, 2012).

The sex ratio is also likely to be affected by the difficulties experienced by females in receiving a diagnosis. Girls with ASD have been found to experience a significant delay in diagnosis compared to their male counterparts (Goin-Kochel, Mackintosh, & Myers, 2006; Manning et al., 2011; Rosenberg, Landa, Law, Stuart, & Law, 2011; Shattuck et al., 2009). This has been found to pertain particularly to females with high-functioning ASD. One study found that girls were diagnosed significantly later for Asperger syndrome (with an average age of 8.9 years compared to 7.0 for boys) and PDD-NOS (5.1 years old versus 3.9), but not for autistic disorder (Goin-Kochel et al., 2006). A national-level study conducted in the Netherlands had similar results, finding that girls with ASD were diagnosed significantly later than boys, and that this disparity was particularly pronounced for girls with Asperger's and PDD-NOS (Begeer et al., 2013). Additional research indicated that parents with a female child with ASD are more likely to experience difficulty in the diagnostic process, and that the time frame from the first

visit to a health care professional to a final diagnosis was significantly longer for females (average of 4 years 2 months) compared to males (average of 2 years 2 months; Siklos & Kerns, 2007). These findings have led to concerns that diagnostic procedures and clinical instruments are biased towards the male phenotype of ASD (Goldman, 2013; Haney, 2016). Other researchers acknowledge that under-diagnosis may contribute towards the male preponderance in ASD while emphasizing that it is very likely that there are underlying biological reasons as well (Baron-Cohen et al., 2011; Constantino & Charman, 2012).

Biological mechanisms. Possible biological mechanisms contributing towards the male predominance are fetal exposures to androgens (e.g., testosterone, estrogen), fewer genetic abnormalities related to ASD on the X chromosome, expression of Y-chromosome linked genes, and reduced penetrance of *de novo* mutations on autosomes in females (Baron-Cohen et al., 2011; Schaafsma & Pfaff, 2014; Skuse, 2000; Werling & Geschwind, 2013). Researchers note that many other neurodevelopmental disorders (e.g., attention-deficit/hyperactivity disorder, dyslexia, Tourette syndrome, etc.) occur more frequently in males compared to females, such that they may have a partially shared etiology (Baron-Cohen et al., 2011; Schaafsma & Pfaff, 2014).

The extreme male brain theory. The extreme male brain (EMB) theory posits that ASD can be conceptualized as an extreme expression of the physiological and psychological attributes of the male brain (e.g., less empathetic, more systematic thinking), such that females require greater physiological abnormalities to exhibit ASD compared to males (Baron-Cohen et al., 2011). First proposed in 1997, the EMB theory has been expanded alongside developing ASD research and linked to findings regarding biological mechanisms such as prenatal exposure to testosterone and X-linked genes (Baron-Cohen et al., 2011; Baron-Cohen & Hammer, 1997).

The EMB theory stems from theories about sexual dimorphism, which posit that males and females experience differences in neurodevelopment, leading the female brain predisposed towards a stronger empathetic drive and the male brain predisposed towards stronger analytical skills (Baron-Cohen et al., 2011). Critics of the EMB theory raise concerns that the assumptions that lie at the base of the theory are sexist, and that the EMB theory applies a masculine perspective to ASD that has contributed towards male bias in the diagnostic process (Krahn & Fenton, 2012).

Threshold model. The threshold model posits that females require a higher level of genetic abnormality in order for ASD symptoms to be expressed (Constantino & Charman, 2012; Kirkovski et al., 2013; M. C. Lai et al., 2014; Werling & Geschwind, 2013). In other words, females have a greater genetic threshold for ASD due to various (currently unknown) protective factors. In this model, the genetic load is carried by relatives of the individuals with ASD, suggesting that family members of females with ASD should have greater likelihood of having ASD and higher levels of related traits. Supporting this theory is the finding that within multiplex families (i.e., those with more than one child with ASD), thought to carry larger genetic loads, females with and without a diagnosis of ASD are significantly more likely to have symptoms related to autism (Constantino & Charman, 2012). However, several other studies have found results that contradict this theory (Banach et al., 2009; Goin-Kochel, Abbacchi, Constantino, & Consortium, 2007).

Multi-factorial model. The multi-factorial model expands on the threshold model by incorporating etiological load beyond genetics (M. C. Lai et al., 2014; Werling & Geschwind, 2013). Female-specific protective factors and male-specific risk factors, whether genetic or environmental, are theorized to shift the threshold required for ASD symptoms to present at

clinically significant levels. This theoretical model links the threshold model with research exploring epigenetic and environmental risk factors for ASD based on the differential distribution of risk between sexes.

Review of the ASD Sex Ratio

Methodological issues in prevalence studies. Epidemiological studies use a variety of approaches to estimate the prevalence of ASD. The vast majority of studies are cross-sectional, estimating the prevalence of the disorder at a certain time point or over a specified period of time (Fombonne, 2005, 2009; Hill et al., 2016). They differ greatly, however, in regards to the methods used to define ASD and identify affected cases, which have important implications for interpreting overall prevalence estimates as well as sex ratio estimates.

Case definition. Changes in diagnostic criteria for autism over the past several decades have presented one of the main challenges in comparing estimates of ASD prevalence and the ASD sex ratio across studies. Early conceptualization of autism was narrowly defined and based on more severe behavioral phenotypes (Volkmar & McPartland, 2014). Changes in case definition impact prevalence rates, with changes in ASD diagnostic criteria thought to be the main factor behind rising prevalence rates over time (Matson & Kozlowski, 2011; Rutter, 2005; Shattuck, 2006). Many diagnostic subtypes of autism have had unclear validity, with several subtypes being removed between editions of the *DSM* and *ICD* (Lord & Jones, 2012; Volkmar & McPartland, 2014).

Despite significant changes in diagnostic criteria over the years, frequently cited statistics regarding mean prevalence and sex ratio of ASD are often derived from epidemiological studies spanning several decades. Three systematic reviews of ASD epidemiological studies reported the same sex ratio range of 1.33 to 16 (Elsabbagh et al., 2012; Fombonne, 2005, 2009). The

studies at the two extremes of this range were published more than two decades before the reviews took place, in 1984 and 1976, respectively (McCarthy, Fitzgerald, & Smith, 1984; Wing, Yeates, Brierley, & Gould, 1976), and used pre-*DSM* case definitions based on Kanner's and Lotter's criteria for autism. Because these previous reviews included all previous epidemiological studies, older studies such as these were included in the sex ratio range and mean, despite significant changes in diagnostic criteria and the publication of more recent population-level epidemiological studies. A recent review of epidemiological surveys of ASD constrained inclusion criteria to studies published since 2000 and found reports of sex ratio ranging from 1.8 – 15.7 (Hill et al., 2016). However, even within this more restricted time frame, the included studies used diagnostic criteria from the *ICD-10, DSM-III, DSM-IV,* and *DSM-IV-TR* to define cases.

The impact of the changes to ASD criteria with the *DSM-5* on prevalence and sex ratio estimates had yet to be fully evaluated. Several studies have retrospectively applied *DSM-5* criteria to previously obtained samples and found reduced prevalence rates compared to criteria from the *DSM-IV-TR* (Huerta, Bishop, Duncan, Hus, & Lord, 2012; Kim et al., 2014; Kočovská et al., 2012; Maenner et al., 2014; Matson et al., 2012). Findings from an early intervention sample indicated that ASD prevalence rates for young girls decreased under *DSM-5* criteria in comparison to *DSM-IV-TR,* while the prevalence rates for young boys increased, suggesting that *DSM-5* changes may impact the sex ratio (Matson et al., 2012). However, another study found that a similar percentage of 8-year-old girls and boys met criteria for ASD under *DSM-5* compared to *DSM-IV* (Maenner et al., 2014). While future research is sure to examine the impact of the *DSM-5* on prevalence estimates, it is important to note that we currently do not have epidemiological estimates of prevalence based on the current conceptualization of ASD.

Case identification. A variety of strategies are used to identify individuals within a target population that meet the specified case definition. Many epidemiological studies rely on identification that is already documented within service provider records (Chien, Lin, Chou, & Chou, 2011; Davidovitch, Hemo, Manning-Courtney, & Fombonne, 2013), national registries (Al-Farsi et al., 2011; D. C. Lai, Tseng, Hou, & Guo, 2012; van Bakel et al., 2015), or special education databases (Baron-Cohen et al., 2009; Maenner & Durkin, 2010). While this data has the benefit of being readily accessible, this methodology limits the sample to individuals who have been in contact with ASD-related services, making it likely that individuals who have not previously been identified or who have not accessed services are not included in prevalence estimates, leading to an underestimation of total prevalence. This limitation is particularly problematic in relation to females, considering concerns that ASD may be under-recognized and under-diagnosed among girls and women (Gould & Ashton-Smith, 2011; Haney, 2016; Wilkinson, 2008). Another limitation of this methodology is that the services underlying the registry or database often target a specific subpopulation of individuals with ASD. For example, two studies that utilized data from different national databases in Taiwan estimated very dissimilar prevalence rates of ASD, with the study examining a health insurance registry (Hsu, Chiang, Lin, & Lin, 2012) finding a much higher prevalence rate (12.3%) compared to the one utilizing a disability registry (.08%; D. C. Lai et al., 2012).

Studies that aim to confirm cases through full diagnostic assessment typically use a two-step process, in which a target population is screened and individuals found to be at-risk are then given a follow-up evaluation. Some studies screen all individuals within the target population, such as all children within a certain age range in a limited geographical area (Kočovská et al., 2012; Nygren et al., 2012), while some systematically or randomly sample the target population

(Eapen, Mabrouk, Zoubeidi, & Yunis, 2007; Raina et al., 2017), and others identify individuals for screening through enrollment in services or by sending screeners to schools or service providers (Isaksen, Diseth, Schjølberg, & Skjeldal, 2012). The major limitation with these approaches is that differential participation in the screening process between children with and without ASD is likely to bias prevalence estimates as it is difficult to measure the number of affected children not identified in the screening stage (Hill et al., 2016).

Prevalence estimates of ASD in the United States are obtained from the Autism and Developmental Disabilities Monitoring (ADDM) Network by the CDC using a two-phase surveillance approach that notably does not involve direct assessment for case identification (CDC, 2016). In the first phase, educational and healthcare records of children of a specific age in a network catchment area are reviewed at a "screening" level to identify potential ASD cases. In the second phase, full records and abstracted evaluations are reviewed by clinicians specialized in the diagnosis of ASD, who determine if the individual meets the specified diagnostic criteria for ASD. This methodology is impacted by the limitations previously discussed as well as the major limitation of lacking confirmation of case identification through direct assessment.

Other considerations. When interpreting the results of ASD epidemiological surveys, it is important to consider the policies and procedures in place in the target region regarding ASD screening and assessment. Access to services and awareness of ASD have considerable implications for screening practices and case identification. Another major factor to consider when interpreting results is the age of the sample as this has important implications for timing of diagnosis, case definition, and changes in service provision over time. All of these factors may contribute towards bias in prevalence estimation rates. In regards to the ASD sex ratio, these

factors may influence male bias, as screening practices may favor the male phenotype of ASD and cultural expectations for gendered behavior may result in under-identification among females.

Search strategies. Epidemiological surveys reporting statistics related to sex distribution published since 2012 were identified (Table 1). These reports were identified from previous reviews of autism spectrum disorder epidemiology (Elsabbagh et al., 2012; Hill et al., 2016), through systematic searches in major scientific databases (i.e., PsycINFO, Medline, PubMed), and by examining the reference lists of relevant studies.

Inclusion and exclusion criteria. Studies were included if they met the following criteria: the full article was published in English; sex distribution was specified; and information was available regarding the number of individuals affected and the diagnostic criteria used to identify cases. For instances in which multiple studies used the same population, the most comprehensive or recent publication was included. When survey results were reported across multiple time points, the most recent time point was selected for inclusion in the review. A total of 17 studies were identified for inclusion, 9 of which were not included in prior reviews (Elsabbagh et al., 2012; Hill et al., 2016).[1] If the sex ratio was not specified within the report, the ratio of males to females (M/F) was calculated using a proportion of the total male cases or the percentage of affected males in the numerator and the total number of female cases or the percentage of affected females in the denominator. Prevalence estimates were adjusted to be estimates per 1,000 for comparison purposes

[1] Studies included in the present review that have not been included in prior reviews: Bachmann, Gerste, & Hoffmann, 2016; Blumberg et al., 2013; CDC, 2016; Hinkka-Yli-Salomäki et al., 2014; Hsu, Chiang, Lin, & Lin, 2012; Jensen, Steinhausen, & Lauritsen, 2014; Lai, Tseng, Hou, & Guo, 2012; Raina et al., 2017; van Bakel et al., 2015.

Table 1. Review of epidemiological studies reporting sex ratio in ASD since 2012

Reference	Country/Region	Time Period	Age (years)	Population	Cases	Diagnostic Criteria	Sex Ratio (M/F)	Prevalence per 1,000	Case identification
Bachmann et al., 2016	Germany	2012	0-24	6.4 million	21,186	ICD-10	2.36	3.8	Review of national insurance registry
Blumberg et al., 2013	USA	2011-2012	6-17	95,677	1,913	DSM-III, DSM-IV	4.6	20	National Survey of Children's Heath; phone survey by parent report
CDC, 2016	USA	2012	8	346,978	5,063	DSM-IV-TR	4.5	14.6	ADDM network; review of medical and educational records
Davidovitch et al., 2013	Israel	2010	1-12	416,700	348	DSM-IV	5.2	4.8	Review of major insurance registry
Hinkka-Yli-Salomäki et al., 2014	Finland	1996-1998 birth cohorts	0-10	>1.2 million	316	ICD-10	3.5	5.37	Review of national hospital registries
Hsu et al., 2012	Taiwan	2007	0-66+	844,771	10,686	ICD-9	2.9	123	Review of national insurance registry
Idring et al., 2012	Stockholm, Sweden	2001-2007	0-17	589,114	5,100	ICD-9, ICD-10, DSM-IV	2.6	11.5	Review of national registries; case validation of random sample with direct assessment
Isaken et al., 2012	Oppland and Hedmark, Norway	1996-2010 birth cohorts	6-12	31,015	158	ICD-10	4.27	5.1	Review of educational records; direct screening and follow-up assessment
Jensen et al., 2014	Denmark	1995-2010	0-65	Population level	14,997	ICD-10	3.85	.38	Review of national health registry
Kočovská et al., 2012	Faroe Islands, Denmark	2009	15-24	7,128	55	ICD-10, DSM-IV	2.72	9.4	Direct screening and follow-up assessment
Lai et al., 2017	Taiwan	2010	3-17	971,456	8,072	DSM-IV-TR	6.6	.79	Review of national disability registry
Nygren et al., 2012	Gothenburg, Sweden	2010	2	5,007	40	DSM-IV-TR	4	8	Direct screening and follow-up assessment
Ouellette-Kuntz et al., 2014	Prince Edward Island, Southeastern Ontario, Canada	2010	2-14	89,786	1082	DSM-IV-TR	4.8	12	Review of educational and medical records
Raina et al., 2017	Himachal Pradesh, India	--	1-10	28,078	42	DSM-IV, ICD-10	1.2	1.5	Direct screening and follow-up assessment
Saemundsen et al., 2013	Iceland	1994-1998 birth cohorts	11-15	22,229	267	ICD-10	2.81	12	Review of national medical registry
Taylor et al., 2013	UK	2004-2010	8	256,278	616	DSM-IV	5.1	2.4	Review of medical records
van Bakel et al., 2015	Haute-Garonne, Isere, Savoy, and Upper-Savoy, France	1997-2003 birth cohorts	7	307,751	1,123	ICD-10	4.1	3.65	Review of disability registry

Prevalence estimates. The results of the 17 surveys that estimated the prevalence of ASD are summarized in Table 1. All selected surveys were published since 2012. The studies were performed in 13 different countries across North America (United States, Canada), Europe (Germany, United Kingdom, Sweden, Norway, Denmark, Finland, Iceland, France), the Middle East (Israel), and Asia (Taiwan, India). Sample sizes ranged from 5,007 to 6.4 million (median: 292,015; mean: 725,748). Included ages ranged from 0 to 66+ years, with 13 of the studies conducted specifically with children younger than 18 years. One study looked specifically at 2-year-olds (Nygren et al., 2012) and another at youths aged 15-24 (Kočovská et al., 2012). The majority of studies utilized case identification methods involving registry and record review. Three studies conducted screening with the target population followed by direct assessment for at-risk cases (Kočovská et al., 2012; Nygren et al., 2012; Raina et al., 2017). A study conducted in Norway used a combination of these methods, reviewing records to identify at-risk cases and then doing targeted screening and assessment (Isaksen et al., 2012). One study in the United States utilized a phone survey method based on parent report (Blumberg et al., 2013). Estimates of ASD prevalence ranged from .38 – 123 per 1,000 with a mean of 14 per 1,000 (1.4%) and median of 5 per 1,000.

Sex ratio estimates. Estimates of the sex ratio (M/F) in ASD ranged from 1.2 – 6.6, with a mean of 4 and a median of 4. The range was reduced compared to the 1.33-16 range reported by a review conducted in 2012 (Elsabbagh et al., 2012) as well as the 1.8-15.7 range reported by a recent review examining studies since 2000 (Hill et al., 2016). This reduced range may be due to the exclusion of older studies using a wider array of diagnostic criteria. The mean sex ratio of 4 is similar to those previously reported by review studies (Elsabbagh et al., 2012; Fombonne,

2005, 2009; Hill et al., 2016) and the 4.5 estimate from the CDC among 8-year-olds in 2012 in the United States (CDC, 2016).

The highest sex ratio (6.6) was found in Taiwan in a study that reviewed a national disability registry, which also reported the second lowest prevalence rate (D. C. Lai et al., 2012). The lowest sex ratio (1.2) was reported by a study conducted in India that directly screened and assessed children across regions representing rural, urban, and tribal populations (Raina et al., 2017). The majority of studies reported sex ratios between 3.5-5.2 (Blumberg et al., 2013; CDC, 2016; Davidovitch et al., 2013; Hinkka-Yli-Salomäki et al., 2014; Isaksen et al., 2012; Jensen et al., 2014; Nygren et al., 2012; Ouellette-Kuntz et al., 2014; Taylor, Jick, & MacLaughlin, 2013; van Bakel et al., 2015).

Review of Factors Examined in Relation to the Sex Ratio

Change over time. Advances in ASD awareness, service provision, and case definition over time have direct implications for prevalence rates of ASD (Matson & Kozlowski, 2011; M. Rutter, 2005; Shattuck, 2006). These factors may also influence the representation of females with ASD. As discussed previously, sex ratio estimates for studies conducted prior to 2000 spanned a wide range (Elsabbagh et al., 2012; Fombonne, 2005, 2009). Since the early 2000's, however, ASD sex ratio estimates appear to have stabilized over time. In 2002 in the United States, the CDC estimated that there was sex ratio of 4.3, similar to the 4.5 estimate reported based on 2012 data (CDC, 2007, 2016). Review of the national insurance registry in Germany revealed similar sex ratio estimates between 2006 (2.13) and 2012 (2.36; Bachmann et al., 2016). Estimates in Taiwan based on review of the national disability registry between 2004-2010 ranged from 6.14-6.6, indicating that the sex ratio has remained relatively stable (D. C. Lai et al., 2012). Similarly, surveillance of medical and educational records in Canada between 2003 and

2010 has revealed a range of 4.5-4.8 (Ouellette-Kuntz et al., 2014), while review of medical records in the United Kingdom between 2004-2010 has revealed a range of 4.3-5.3 (Taylor et al., 2013). The exception to this trend was found in a survey among youth in the Faroe Islands, Denmark that utilized direct screening and assessment for case identification, which found that from 2002 to 2009 the sex ratio decreased from 5 to 2.72 (Kočovská et al., 2012). Because of the older age range examined in the Faroe Islands study (15-24 years), it is likely that changes in ASD related services and policies in the 1980's and 1990's had a greater impact on the prevalence estimates. As a whole, these findings suggest that sex ratio estimates have stabilized since the early 2000's, perhaps due to stabilization in case definition following the *DSM-IV* and *ICD-10* in the 1990s.

Diagnostic subtype. The ASD sex ratio has previously been demonstrated to range considerably between diagnostic subtypes in the *DSM-IV* and *ICD-10,* with lower sex ratios found amongst diagnostic subtypes associated with more severe symptoms (Dworzynski et al., 2012; Kirkovski et al., 2013). However, researchers have expressed concerns that these ratios may be skewed as females with high-functioning ASD may be underdiagnosed (Constantino & Charman, 2012; Kirkovski et al., 2013). More recent research from Europe has demonstrated lower sex ratios amongst individuals diagnosed with Asperger's syndrome and PDD-NOS, suggesting that females are being identified with these subtypes at higher rates than before and that the sex distribution may not be as uneven as previously estimated. For example, a review of a Danish population-level health registry between 1971-2000 noted sex ratios of 3.5 for childhood autism, 4.6 for PDD-NOS, and 15.7 for Asperger's (Lauritsen, Pedersen, & Mortensen, 2004). However, review of the same Danish registry in 1995 and 2010 found that the sex ratio in Asperger's decreased from 8.4 to 3 and that the ratio in PDD-NOS decreased

from 5.7 to 2.77 (Jensen et al., 2014). A population-level study in Finland utilizing direct screening and assessment found a ratio of 1.7 among individuals with Asperger's (Mattila et al., 2011). A survey of a national German insurance registry revealed a sex ratio of 2.24 for Asperger's and 1.33 for childhood autism (Bachmann et al., 2016). Interestingly, it also found a greater proportion of females diagnosed with PDD-NOS, with a male:female ratio of 1:1.6, the only found report of female preponderance in ASD.

Cognitive impairment. Between 50-70% of individuals with ASD are estimated to have comorbid intellectual disability (ID; Matson & Shoemaker, 2009). The sex ratio has been demonstrated to decrease when examining individuals with cognitive impairment, suggesting that a greater proportion of females have below-average cognitive functioning compared to males (Dworzynski et al., 2012; Rivet & Matson, 2011). Findings from the 2002 CDC survey on ASD prevalence found a significant difference in the rate of ID between sexes, with 41.8% of males and 58.2% of females with ASD affected (CDC, 2007). The most recent CDC estimates found a sex ratio of 3.7 among individuals with ASD and comorbid ID and a 5.1 ratio among individuals without comorbid ID, suggesting that this trend has not changed despite increased prevalence estimates over time (CDC, 2016). Similar findings have been demonstrated in other countries. An epidemiological study conducted in Yokohama, Japan between the years 1989-1993 utilizing direct screening and assessment of children aged 0-5 found that the sex ratio among individuals with ASD was 5.3 with IQ $\geq$ 85, 2.3 with IQ $\geq$ 70, and 2.7 with IQ < 70 (Honda et al., 2005). A survey reviewing a disability registry in three regions in France found ASD sex ratios of 5.4 among individuals without ID and 3.2 with ID among children born between 1997-2003 (van Bakel et al., 2015).

Age. Examination of the sex ratio across age bands indicates that the sex ratio decreases with age, indicating that a greater proportion of females are receiving diagnoses at later ages. Review of a national insurance registry in Taiwan from 1997-2005 found that the ASD sex ratio was 4.1 for ages 0-5, 3.1 for ages 6-11, and 2.9 for ages 12-17 (Chien et al., 2011). A study in Scotland that conducted a review of the most recently diagnosed cases from a representative sample of service providers found ASD sex ratios of 5.5 for ages 0-9 and 2.3 for ages 10-18 (Rutherford et al., 2016). These findings are congruent with previous research indicating that females with ASD experience significant delays in diagnosis compared to males with ASD (Goin-Kochel et al., 2006; Manning et al., 2011; Rosenberg et al., 2011; Shattuck et al., 2009).

Simplex vs. multiplex families. The term "simplex" is used to describe families with only one child with an ASD (regardless of the number of unaffected siblings). The term "multiplex" is used to describe families with more than one child with ASD (regardless of the number of unaffected siblings). Multiplex families are considered to have an increased genetic burden for ASD, as they are likely carrying autosomal mutations (Constantino et al., 2010). Given the threshold model, the sex ratio would be expected to be reduced in multiplex families compared to simplex families. Thus far findings do not support this hypothesis. One study found a 3.26 ratio among children with ASD from multiplex families and a 5.82 ratio among those from simplex families (Constantino et al., 2010), while another did not find significant differences in sex ratio between the groups (Zachor et al., 2013).

Race/ethnicity. Children from minority backgrounds have been found to experience greater difficulties accessing ASD related services (Magaña, Parish, Rose, Timberlake, & Swaine, 2012), delayed ASD diagnosis (Mandell et al., 2009; Mandell, Listerud, Levy, & Pinto-Martin, 2002), and increased risk of misdiagnosis (Jarquin, Wiggins, Schieve, & Van Naarden-

Braun, 2011; Mandell, Ittenbach, Levy, & Pinto-Martin, 2007; Morrier & Hess, 2012) compared to white children. Females from racial/ethnic minority groups may experience increased difficulty in these areas compared to their male counterparts. Despite these concerns, very little research has been conducted examining differences in the representation of females among racial and ethnic groups. A survey reviewing medical and educational records in the metropolitan area of Atlanta, Georgia in 1996 found that the ASD sex ratio among white children (3.8) was lower than that among African American children (4.3), suggesting that minority females may be underrepresented (Yeargin-Allsopp et al., 2003).

Parental age. Advanced paternal and maternal age have been found to be significant risk factors for ASD (Croen, Najjar, Fireman, & Grether, 2007; Durkin et al., 2008; Hultman, Sandin, Levine, Lichtenstein, & Reichenberg, 2011; King, Fountain, Dakhlallah, & Bearman, 2009). Advanced paternal age in particular has been examined in the literature due to the association with *de novo* mutations and the role they may place in the etiology of ASD (Kong et al., 2012; Puleo et al., 2012; Sebat et al., 2007). If such mutations affect both sexes equally, as is hypothesized, the male/female ratio would be expected to diminish with advanced paternal age, (Zachor et al., 2013). Findings regarding the ASD sex ratio with advanced parental age are currently mixed. Anello and colleagues (2009) found that the sex ratio significantly decreased with increasing paternal age even when adjusting for maternal age. The sex ratio among children with fathers younger than 30 at time of birth was 6.2, compared to a ratio of 1.2 for children with fathers above 45 at time of birth. A similar trend was found regarding maternal age, though less pronounced (ratios of 5.4 for ages <30 and 2.3 for ages 40+). However, another study did not find significant differences in the sex ratio between older and younger parental groups (Zachor et al., 2013).

Premature birth and birth weight. Premature birth and low birth weight have been indicated as risk factors for ASD (Ben-Itzchak & Zachor, 2014; Gardener et al., 2011; Kuzniewicz et al., 2014). Schendel and Bhasin (2008) found that this risk differentially affects the sexes, as girls with low birth weight are at significantly higher risk for ASD. Sex ratios were also found to be lower with declining gestational age (ratios of 4.1 for ≥ 37 weeks, 2.8 for 33-36 weeks, and 2 for 20-32 weeks) and birth weight (ratios of 5.7 for ≥ 4000 g, 4.3 for 3000-3999 g, 3.1 for 2500-2999 g, and 2.1 for < 2500). Zachor and colleagues (2013) found a similar trend, with ASD sex ratios of 4.4 among individuals with birth weight ≤ 2500 and a ratio of 7.1 among individuals with birth weight > 2500g. These findings suggest that low birth weight and premature birth are more likely to act as causal pathways to ASD for females, perhaps increasing underlying genetic susceptibility as posited in the multifactorial model.

Developmental regression. Developmental regression is estimated to affect a third of individuals with ASD (Parr et al., 2011; Rogers, 2004). Some have suggested that developmental regression may characterize a distinct autism phenotype with a shared etiological factor (Rogers, 2004). Significant differences in the occurrence of regression have been found between the sexes (Ben-Itzchak et al., 2013). Ben-Itzchak and colleagues (2013) found an ASD sex ratio of 4.2 among those who experienced regression and 7.8 among those who did not. However, other research has not found significant differences in the male/female ratio among individuals with ASD who experienced regression and those who did not, indicating that further research is needed (Parr et al., 2011; Shumway et al., 2011).

Head circumference. Higher rates of macrocephaly and microcephaly have been observed in children with ASD compared to children with other neurological disorders (Fidler, Bailey, & Smalley, 2000; Fombonne, Rogé, Claverie, Courty, & Frémolle, 1999; Miles, Hadden,

Takahashi, & Hillman, 2000). Cases of extreme macrocephaly among individuals with ASD have been found to be correlated to specific genetic mutations in the gene phosphatase and tensin homolog (PTEN), with preliminary research indicating that there may be a specific behavioral phenotype associated with such mutations (Klein, Sharifi-Hannauer, & Martinez-Agosto, 2013). Such research is at the forefront of an effort within the field to identify distinct phenotypic subgroups associated with specific biomarkers for ASD. Changes in the male/female sex ratio in correspondence to head circumference would suggest that associated genetic mutations differentially affect males and females. Although one study found significant differences in sex ratio between macrocephalic and normocephalic individuals with ASD (Miles et al., 2000), another found that the prevalence of macrocephaly did not differ significantly between sexes (Ben-Itzchak et al., 2013). Microcephaly has been demonstrated to occur at higher rates among females with ASD compared to their male counterparts, with a sex ratio of 2 among those with microcephaly and a ratio of 7.5 among those without (Ben-Itzchak et al., 2013).

Comorbid disorders. A number of neurological and medical conditions frequently co-occur with ASD. Epilepsy has been found to affect approximately 20-30% of individuals with ASD, exceeding prevalence rates found in the general population (Amiet et al., 2008; Brooks-Kayal, 2010; Frye, 2016). It has been suggested that the high rate of comorbidity may be due to shared underlying mechanisms related to synaptic plasticity and/or genetic mutations (Brooks-Kayal, 2010). Epilepsy has been demonstrated to occur at higher rates among females with ASD versus males with ASD (Amiet et al., 2008; Ben-Itzchak et al., 2013; Bolton et al., 2011; El Achkar & Spence, 2015; van Bakel et al., 2015). A meta-analysis found a sex ratio of 2 among individuals with ASD and comorbid epilepsy and a ratio of 3.5 among individuals with ASD without epilepsy (Amiet et al., 2008). Given the strong association of epilepsy and ID (Amiet et

al., 2008; Bolton et al., 2011; El Achkar & Spence, 2015), these ratios could reflect the higher proportion of females with impaired cognitive functioning. Lower male/female ratios have also been found among individuals with ASD and musculoskeletal deficits (Ben-Itzchak et al., 2013), genetic abnormalities (van Bakel et al., 2015), and those with cerebral palsy or hearing/visual disabilities (van Bakel et al., 2015).

Summary. There is limited amount of previous research examining factors that affect the ASD sex ratio. Table 2 provides a summary of findings of factors studied in relation to the ASD sex ratio, along with an evaluation of the quality of evidence. The extant literature provides substantial support that lower ASD sex ratios are found amongst individuals with

Table 2. Summary of findings of factors related to the ASD sex ratio with quality of evidence rating.

Factor	Summary of Findings Related to ASD Sex Ratio	Quality of Evidence
Change over time	Sex ratio has stabilized over time	Strong
Diagnostic subtype	Lower sex ratios found in subtypes with more severe symptoms	Moderate
Cognitive impairment	Associated with lower sex ratio	Strong
Age	Decrease in sex ratio with increase in age	Weak
Multiplex families	Inconclusive	Inconsistent
Race/ethnicity	Lower sex ratio among white children vs. minorities	Weak
Maternal age	Inconclusive	Inconsistent
Paternal age	Inconclusive	Inconsistent
Premature birth	Associated with lower sex ratio	Weak
Birth weight	Lower birth weight associated with lower sex ratio	Weak
Developmental Regression	Associated with lower sex ratio	Weak
Macrocephaly	Inconclusive	Inconsistent
Microcephaly	Associated with lower sex ratio	Weak
Epilepsy	Associated with lower sex ratio	Strong
Musculoskeletal deficits	Associated with lower sex ratio	Weak
Genetic abnormalities	Associated with lower sex ratio	Weak
Cerebral palsy	Associated with lower sex ratio	Weak
Hearing difficulties	Associated with lower sex ratio	Weak
Vision difficulties	Associated with lower sex ratio	Weak

Note. Levels of support: strong (≥ 5 studies with consistent findings); moderate (3-4 studies with consistent findings); weak (1-2 studies with consistent findings); inconsistent (similar number of studies with conflicting findings).

cognitive impairment and epilepsy, while moderate support is available to suggest that lower sex ratios are associated with diagnostic subtype. A limited amount of support is available regarding other risk factors, with many inconsistent findings, underscoring the need for continued research on variables that influence the ASD sex ratio.

PURPOSE

This study had three main aims. The first aim was to estimate the prevalence of ASD and the ASD sex ratio among children enrolled in EarlySteps, a statewide early intervention program. A previous study on this same topic using EarlySteps data from 2008-2011 found an ASD prevalence of 30.14% and a sex ratio of 2.75 (Worley, Matson, Sipes, & Kozlowski, 2011). As the number of children in EarlySteps being screened for ASD has increased steadily over time (Matheis & Matson, 2015), the current study had a substantially larger sample for analysis. Because EarlySteps is an early intervention program serving children at risk for developmental delays, this sample is considered to have a high-probability for ASD. Based on the nature of the sample and previous findings, it was hypothesized that the prevalence of ASD was significantly higher in the EarlySteps sample compared to estimates found in other United States samples. The sex ratio was hypothesized to remain similar to the previous estimate of 2.75 given trends indicating that estimates of the sex ratio have stabilized since the early 2000s (Bachmann et al., 2016; Ouellette-Kuntz et al., 2014; Taylor et al., 2013). In regards to change over time, it was hypothesized that the ASD sex ratio has remained relatively stable between 2008-2017.

The second aim of this study was to examine changes in the ASD sex ratio across specific phenotypes, risk factors, and associated features. Previous research has demonstrated that the ASD sex ratio fluctuates across such variables albeit with some conflicting results. Based on previous research indicating that a higher proportion of females with ASD are more severely affected (CDC, 2016; Dworzynski et al., 2012; Rivet & Matson, 2011), it was hypothesized that the ASD sex ratio will decrease when examining children with developmental delays, cognitive delays, and more severe ASD symptoms. Further, the sex ratio was expected to decrease among children with premature birth as well as with very low and low birth weight based on previous

findings (Schendel & Bhasin, 2008; Zachor et al., 2013), and similarly expected to decrease among children with comorbid disorders based on previous findings (Amiet et al., 2008; van Bakel et al., 2015). Specific hypotheses were not proposed in regards to parental age or multiplex families due to inconsistencies in the literature. A lower sex ratio among multiplex families would lend support to the threshold model of male predominance while a lower sex ratio with advanced parental age would suggest that males and females are similarly affected by *de novo* mutations.

The third aim of this study was to examine whether males and females with ASD are differentially impacted by factors associated with increased risk for ASD. It was hypothesized that females with ASD would be affected by more risk factors than males with ASD. Confirmation of this hypothesis would lend support to the multi-factorial model of male predominance, which suggests that females require a heavier burden of genetic and environmental risk factors for ASD to be evinced. It was thus also hypothesized that the association between factors such as low birth weight, premature birth, and multiple births with ASD would be moderated by a child's sex.

Working towards a better understanding of the relationship between the ASD sex ratio and ASD risk factors will inform the knowledge base related to the underlying neurobiological and genetic mechanisms of the disorder. Findings of this study contribute to the literature related to the male predominance in ASD as well as that related to pre- and perinatal risk factors for ASD.

METHOD

Procedure

Data for this study was obtained from EarlySteps, the State of Louisiana's early intervention program in compliance with the Individuals with Disabilities Education Act (IDEA), Part C. EarlySteps is a statewide program that provides services to children under the age of 3 years who have developmental delays or a medical condition that places them at risk for developmental delays. Due to the nature of this sample, all participants are suspected of some form of atypical development. Children in EarlySteps undergo assessment upon entry into the program, annually thereafter, and before exiting the program at the age of 36 months. The Battelle Developmental Inventory, Second Edition (BDI-2) is administered at each assessment time-point as part of the standard EarlySteps assessment battery. Additionally, parents and caregivers have the option of completing an ASD screen consisting of the Baby and Infant Screen for Children with aUtIsm Traits, Part 1 (BISCUIT- Part 1) at each assessment time-point. All assessments are done in the child's home or another private setting. Test administrators are EarlySteps providers who are trained and experienced in administering the assessment battery and who hold appropriate degrees and certification/licensure in a number of related fields (e.g., special education, social work, occupational therapy, speech therapy, speech-language pathology, psychology).

Sample

Participants were sampled from a deidentified version of the EarlySteps database provided for research purposes (Figure 1). The original sample included children assessed by EarlySteps between February 2008 and September 2017 (n = 18,996). For instances in which a participant was administered the EarlySteps assessment battery and ASD screen at multiple time-

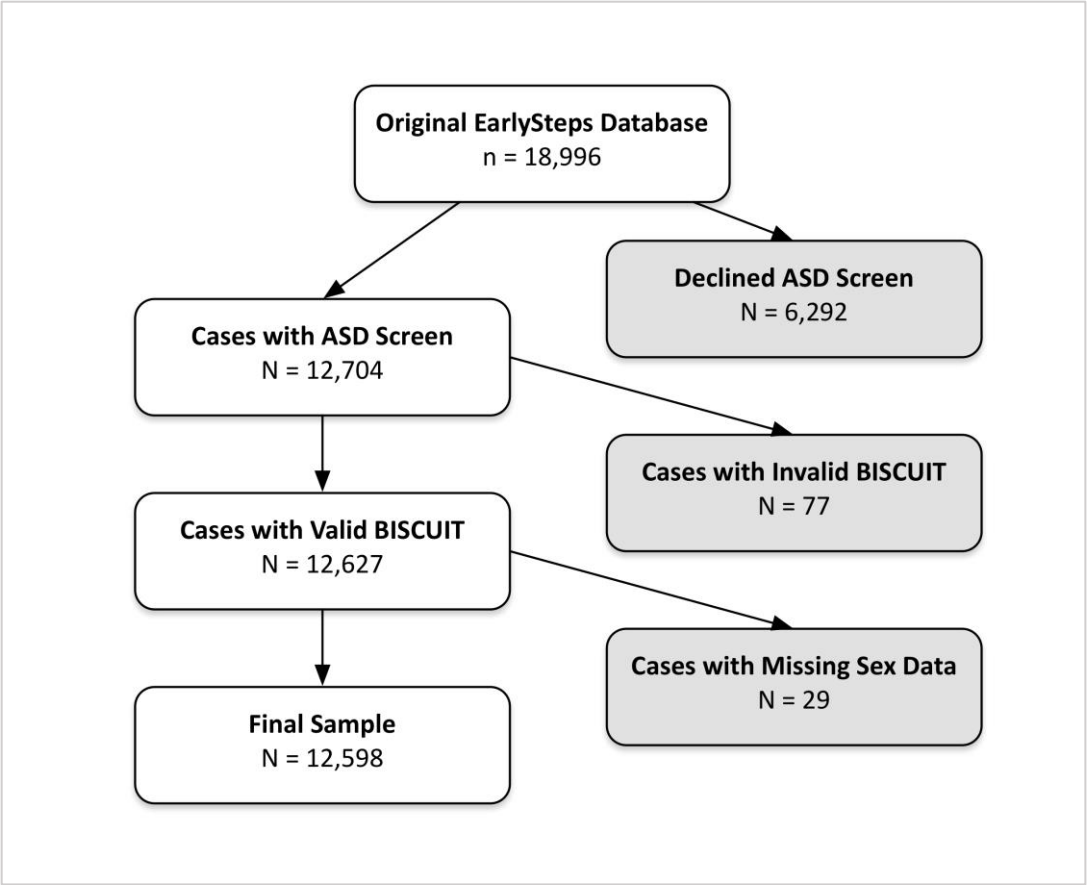

Figure 1. Flow chart of case inclusion/exclusion decision process.

points, the earliest and/or most complete assessment record was be used. Participants for whom a caregiver declined the ASD screen were removed from the sample due to missing data pertaining to ASD symptomatology (*N* = 6,292). Of the remaining cases with ASD screening data, 77 were removed due to invalid BISCUIT- Part 1 data (i.e., participant's age was outside the BISCUIT- Part 1 range of 17-37 months; missing 50% or more of BISCUIT items). From cases with valid BISCUIT- Part 1 data, 29 cases were removed due to missing data pertaining to participant sex. A final sample of 12,598 cases was used for the current study. Demographic information for participants in the final sample are presented in Table 3. The mean age at time

of assessment was 25.43 months (*SD* = 4.68). The majority of the sample was male (68.3%). In regards to race and ethnicity, 50.4% of the sample were identified as white, 37.1% were African America, 4.0% were Hispanic, and 5.8% were of another race/ethnicity.

Table 3: Demographic information and prevalence of risk factors for total sample, cases classified with ASD, and stratified by sex.

	Total (*n*= 12,598)	Total w/ASD (*N*= 1,528; 12.1%)	Males w/ASD (*N*=1,160; 75.9%)	Females w/ASD (*N*= 368; 24.1%)	
	M(SD)	M(SD)	M(SD)	M(SD)	
Age in months	25.43 (4.68)	26.02 (4.64)	26.16 (4.61)	25.61 (4.69)	
	N (%)	N (%)	N (%)	N (%)	M:F
Sex					3.15
Male	8600 (68.3%)	1160 (75.9%)	1160 (100%)	0 (0%)	
Female	3998 (31.7%)	368 (24.1%)	0 (0%)	368 (100%)	
Ethnicity					
White	6347 (50.4%)	698 (45.7%)	544 (48.4%)	154 (42.8%)	3.53
African American	4673 (37.1%)	633 (41.4%)	468 (41.6%)	165 (42.6%)	2.84
Hispanic	506 (4.0%)	57 (3.7%)	42 (3.7%)	15 (4.2%)	2.80
Other	736 (5.8%)	97 (6.5%)	71 (6.3%)	26 (7.2%)	2.73
ASD symptom severity					
No ASD	7854 (62.3%)	26 (1.7%)	19 (1.6%)	7 (1.9%)	2.71
Possible ASD	3012 (23.9%)	379 (24.9%)	288 (24.8%)	91 (24.7%)	3.16
Probable ASD	1732 (13.7%)	1123 (73.5%)	853 (73.5%)	270 (73.4%)	3.16
Developmental delay	2644 (21.0%)	820 (53.7%)	629 (54.9%)	191 (52.8%)	3.29
Cognitive delay	2397 (19.0%)	689 (45.1%)	519 (45.3%)	170 (47.0%)	3.05
Maternal age					
< 35 years	7655 (60.8%)	881 (57.7%)	681 (90.6%)	200 (84.7%)	3.41
≥ 35 years	1091 (8.7%)	107 (7.0%)	71 (9.4%)	36 (15.3%)	1.97
Paternal age					
< 40 years	7492 (59.5%)	848 (55.5%)	651 (90.2%)	197 (87.6%)	3.30
≥ 40 years	896 (7.1%)	99 (6.5%)	71 (9.8%)	28 (12.4%)	2.54
Birth weight					
Very low (<1500 g)	992 (7.9%)	84 (5.5%)	55 (5.5%)	29 (9.4%)	1.90
Low (1500-2499 g)	1620 (12.9%)	201 (13.2%)	135 (13.4%)	66 (23.1%)	2.05
Normal (≥ 2500 g)	8124 (85.2%)	1030 (67.4%)	815 (81.1%)	215 (69.4%)	3.79
Premature birth	1280 (10.2%)	118 (7.7%)	80 (7.0%)	38 (10.5%)	2.11
Multiple births	919 (7.3%)	102 (6.7%)	75 (7.9%)	27 (8.7%)	2.78
Multiplex family	347 (2.8%)	83 (5.4%)	61 (5.6%)	22 (6.3%)	2.77
GDD	215 (1.7%)	45 (2.9%)	33 (2.9%)	12 (3.3%)	2.75
Down syndrome	142 (1.1%)	6 (.4%)	6 (0.5%)	0 (0%)	
Seizure disorder	304 (2.4%)	68 (4.5%)	42 (3.7%)	26 (7.2%)	1.62
Cerebral palsy	150 (1.2%)	26 (1.7%)	19 (1.7%)	7 (1.9%)	2.71

Measures

BISCUIT- Part 1. The BISCUIT is a diagnostic measure based on informant-report designed for children aged 17-37 months (Matson, Boisjoli, & Wilkins, 2007). It consists of three sections, which evaluate for symptoms of ASD, comorbid psychopathology, and commonly associated challenging behaviors. The BISCUIT- Part 1contains 62 items targeting ASD symptomology with a total score that measures ASD symptom severity. Each item is rated on a 3-point Likert scale that compares the child to typically developing peers (0 = not different/ no impairment; 1= somewhat different/ mild impairment; 2 = very different/ severe impairment). Cut-off ranges have been identified, with scores of 0-16 falling in the "No ASD" range, 17-38 in the "Possible ASD" range, and 39-124 in the "Probable ASD" range (Matson et al., 2009). The BISCUIT- Part 1 has been demonstrated to have an overall classification rate of .89 and an estimated internal reliability of .87 (Matson et al., 2009). Convergent validity of .80 has been demonstrated with the Modified Checklist for Autism in Toddlers (M-CHAT; Matson, Wilkins, & Fodstad, 2011). Included in the BISCUIT- Part 1 is a demographics form, which collects information regarding the child's demographics, developmental milestones, medical history, and family information.

BDI-2. The BDI-2 is an comprehensive developmental assessment for children starting at birth and aged up to 7 years 11 months of age (Newborg, 2005). Five domains of functioning (i.e., Personal/Social, Adaptive, Motor, Communication, and Cognitive) are evaluated through a combination of caregiver interview, structured activities, and behavioral observations. Each domain is comprised of two or three subdomains. Items are individually administered based on a child's age, with the full battery typically administered within a span of about 1-1.5 hours. A developmental quotient (DQ) is calculated on a standardized scale for each domain and then

combined to calculate a total DQ. The BDI-2 has been found to have test-retest reliability above .80 for total scores as well as individual subdomains (Alfonso, Rentz, & Chung, 2010). Internal consistency reliability estimates range from .90- .96 for the five domain-level DQs and the total DQ (Newborg, 2005). Content and criterion validity have been demonstrated with multiple populations, including children with developmental delays, ASD, and speech/language delays (Newborg, 2005).

Ethical Considerations

The State of Louisiana's Department of Health and Hospitals International Review Board and the Louisiana State University Institutional Review Board have approved the use of EarlySteps data for research purposes. Personal identifiers of EarlySteps participants (e.g., name, date of birth, zip code), are removed from the database by OCDD before receipt. As the database is archival and deidentified, the Institutional Review Boards determined that the 45 CFR part 46 of the U.S. Department of Health and Human Services regulation does not apply and informed consent was not required.

Variables

Variables of interest were examined for outliers and potential data-entry mistakes. Continuous variables were converted into categorical variables to reflect meaningful qualitative differences using ranges/categories previously specified in the literature to allow for direct comparison of findings.

ASD classification. EarlySteps assessment records were reviewed by a licensed clinical psychologist with over 20 years' experience working with individuals with ASD and developmental disabilities. Diagnostic classifications are made by mapping item results from the BISCUIT- Part 1 and subdomain scores from the BDI-2 onto *DSM-5* ASD diagnostic criteria.

Cases were assigned to groups based on whether they meet criteria for ASD (0 = no ASD; 1 = ASD).

Sex. Data on the sex of participants was obtained from the BISCUIT- Part 1 demographics form. Female sex was used as the reference category (0 = female, 1 = male).

Race/ethnicity. Race/ethnicity was based on parent report and obtained from the BISCUIT- Part 1 demographics form. Data was dummy coded into the following categories: white (0 = non-white, 1 =white), African American (0 = non-African American, 1 = African American), Hispanic (0 = non-Hispanic, 1 = Hispanic), and other (0 = non-other, 1=other).

ASD symptom severity. ASD symptom severity was measured by the total score from the BISCUIT- Part 1. Total BISCUIT- Part 1 score was examined as a categorical variable. Categories were based on cut-off scores previously determined for the BISCUIT-Part 1: 0-16, No ASD; 17-38 Possible ASD/PDD-NOS; 39-124, and Probable ASD/autistic disorder (Matson et al., 2009). Categories were dummy coded for analysis (0 = not within range; 1 = within range).

Developmental delay. Developmental delay classification was based on data from the BDI-2. The total DQ score was recoded dichotomously (0 = no developmental delay [DQ >70], 1 = developmental delay [DQ $\leq$ 70]) using the recommended cutoff score of two standard deviations below the mean (Newborg, 2005).

Cognitive delay. Cognitive delay was based on the Cognitive domain of the BDI-2. The standardized DQ score from the Cognitive domain was recoded dichotomously (0 = no cognitive delay [DQ >70], 1 = cognitive delay [DQ $\leq$ 70]) based on the recommended cutoff score of two standard deviations below the mean (Newborg, 2005).

Premature birth. Caregivers provided information about premature birth as part of the BISCUIT- Part 1 demographics section. Participants for whom premature birth was not reported

were assumed to have been born at full term gestation (≥ 37 weeks). A dichotomous variable was created for premature birth (0 = full term, 1 = premature birth).

Birth weight. Data on birth weight was collected via caregiver report in the BISCUIT-Part 1 demographics section. This variable's measurement was converted from pounds to grams, with responses then dummy coded (0 = not within specified range, 1 = within specified range) into the following categories: very low (< 1500 g), low (1500 – 2499 g), and normal (≥ 2500 g). These categories were based on birth weight ranges and classifications commonly used in the literature (Lampi et al., 2012; Limperopoulos et al., 2008; Linsell, Malouf, Morris, Kurinczuk, & Marlow, 2017; Schendel & Bhasin, 2008).

Parental age. Maternal and paternal age at birth were collected via caregiver report in the BISCUIT- Part 1 demographics section. Maternal age was recoded dichotomously (0 = < 35 years, 1 = ≥ 35 years) along with paternal age (0 = < 40 years, 1 = ≥ 40 years) based on age ranges used in previous research (Durkin et al., 2008; Lampi et al., 2013; Reichenberg et al., 2006).

Multiple births. Information on multiple births (e.g., twins, triplets) was collected via caregiver report in the BISCUIT- Part 1 demographics section. This variable was dummy coded (0 = singleton birth, 1 = multiple births).

Multiplex families. The BISCUIT-Part 1 demographics section collected data on family members with ASD via caregiver report. This information was recoded based on degree of relationship to the participant (i.e., sibling) to indicate whether participants are from simplex or multiplex families (0 = simplex, 1 = multiplex).

Comorbid conditions. Data on previously diagnosed medical conditions and developmental disorders was collected via caregiver report as part of the BISCUIT- Part 1

demographics section. The following diagnoses were recoded dichotomously (0 = no diagnosis; 1 = diagnosis): global developmental delay (GDD), Down syndrome, seizure disorder, and cerebral palsy.

Year of assessment. The date of the EarlySteps assessment was included in the dataset. Date data was recoded to indicate the year of assessment (e.g., 2008, 2009, etc.) to allow for time trend analysis.

Data Analysis

Statistical analysis was conducted using SPSS Statistics Software (Version 25). Descriptive statistics were used to describe the sample in regards to demographics (e.g., age at screening, race/ethnicity). Further descriptive analyses were conducted to estimate ASD prevalence, the ASD sex ratio, and chance in the sex ratio over time in the EarlySteps population. Chi-square tests of independence were used to examine the proportion of males and females with ASD across various risk factors. An independent *t*-test was conducted to examine differences in the mean number of risk factors between males and females classified with ASD. Hierarchical binomial logistic regression models were developed to examine risk factors in relation to ASD classification outcomes, with interaction terms between risk factors and sex allowing for the analysis of differential risk between the sexes.

RESULTS

Descriptive Analysis

Descriptive analyses were conducted to describe the sample in regard to demographics (e.g., age at screening, race/ethnicity; Table 3). Additional frequency analyses were conducted to meet the first aim of the current study, which was to estimate ASD prevalence and ASD sex ratio among the EarlySteps population. Of the total sample (*n* = 12,598), 12.12% of cases (*N* = 1,528) were found to meet DSM-5 criteria for ASD. The ratio of male to females meeting ASD classification was found to be 3.15.

Year of assessment. Changes in the sex ratio over time were examined by calculating the sex ratio for each year available in the dataset (2008-2017). The M/F ratio ranged from 2.81 (2009) to 3.60 (2017) across the ten-year span. The mean sex ratio was 3.20 with a standard deviation of 0.25. The linear trend is displayed in Figure 2.

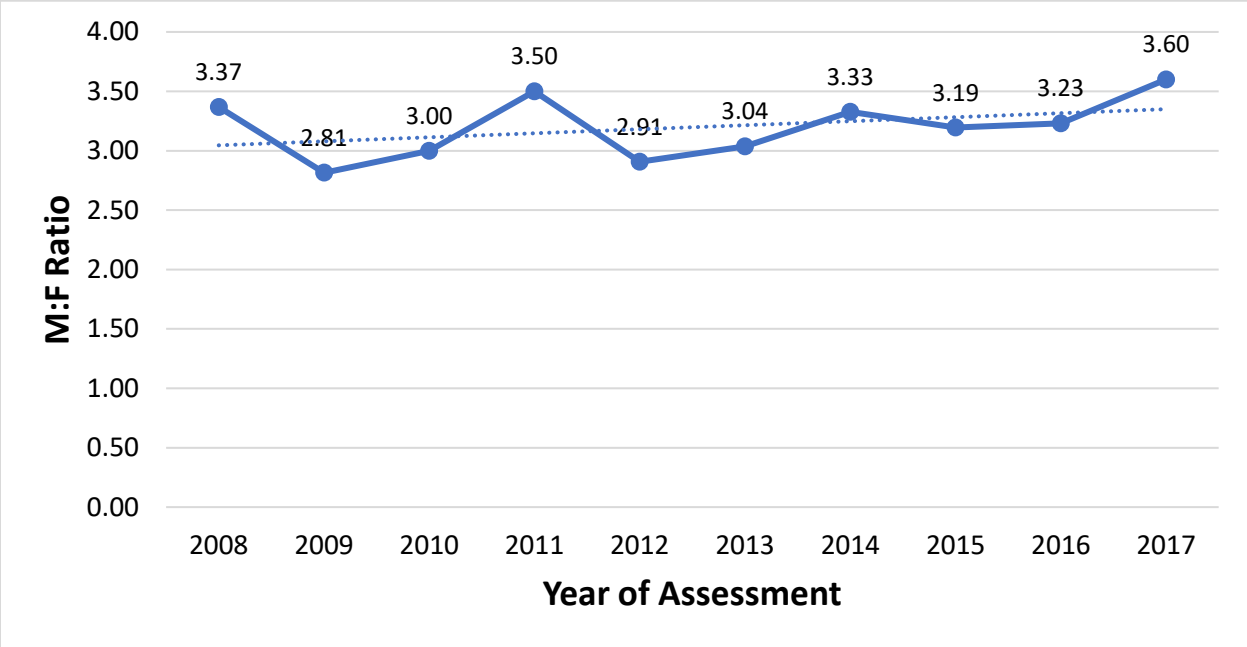

Figure 2. Change in the M:F ratio among children meeting ASD classification criteria between 2008-2017 with linear trend line.

Bivariate Analysis

To meet the second aim of the study, to examine changes in the ASD sex ratio across a range of risk factors and other relevant variables, bivariate analyses were conducted. The ASD sex ratio was compared across the following variables: race/ethnicity, ASD symptom severity, developmental delay, cognitive delay, maternal age, paternal age, birth weight, premature birth, multiple births, multiplex families, GDD, Down syndrome, seizure disorder, and cerebral palsy. Chi-square tests of independence were used to determine if the proportion of males and females with ASD varied significantly across these factors. Previous studies examining the ASD sex ratio have also employed chi-square analyses to examine changes in the sex ratio across various factors (Zachor et al., 2013).

Chi-square test of independence are nonparametric tests used to examine the association between categorical variables (Field, 2013). The assumptions of chi-square tests were considered when computing and interpreting test results. The assumption of independence was confirmed by assuring that only one assessment time-point per participant is included in analysis. The assumption of expected frequencies was confirmed by inspecting contingency tables to make sure that no expected values were below 5 (Field, 2013). When chi-square tests were used between sex and a categorical variable with more than two categories (i.e., with more than one degree of freedom), post-hoc procedures followed significant results to further examine the relationship of sex and categories of the other variable. Standardized residuals were examined to allow for decomposition of the overall association of sex and categories of the other variable (Field, 2013; Sharpe, 2015). Critical values of ± 1.96 ($p < .05$), ± 2.58 ($p < .01$), ± 3.29 ($p < .001$) were used (Field, 2013). The largest contingency table was 2x4 (sex and race/ethnicity) with $df = 3$. A statistical power analysis program, G*POWER, was used to establish necessary

samples size for a chi-square test of independence with a degree of freedom of 3 to demonstrate adequate power. A power of .80 (Field, 2013), alpha of .05, and medium effect size of .25 was used. The result of this analysis indicated that a total sample of 175 would yield the appropriate power and effect size for a chi-square of independence, which was met by the sample size of the EarlySteps dataset for all chi-square analyses.

Race/ethnicity. A chi-square test of independence was conducted between sex and race/ethnicity (Figure 3). Data on race/ethnicity was available for 1,485 cases classified with ASD. All expected frequencies were greater than 5. The M/F ratio among white children (3.15) was found to be higher compared to other racial/ethnic groups (2.84 among African Americans, 2.80 among Hispanics, and 2.73 among those of other race/ethnicity). Differences in the sex ratio across racial/ethnic groups were not statistically significant, $\chi^2(3) = 3.432$, $p = .330$.

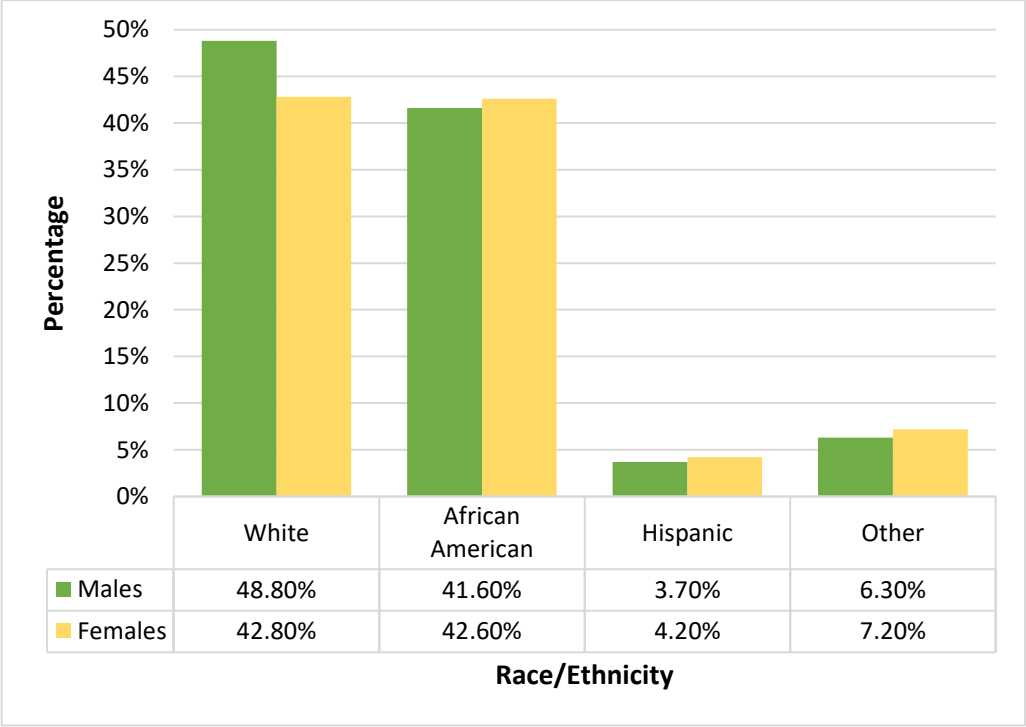

Figure 3. Percentage of race/ethnicity categories among males (N = 1,125) and females (N = 360) with ASD classification.

ASD symptom severity. A chi-square test of independence was conducted between sex and ASD symptom severity, using BISCUIT- Part 1 severity ranges (Figure 4). Data on ASD symptom severity was available for all 1,528 cases in the sample classified with ASD. All expected frequencies were greater than 5. The M/F ratio was 2.71 among cases falling in the No ASD severity range, 3.16 among those in the Possible ASD range, and 3.16 in the Probable ASD range. Differences in the sex ratio did not differ significantly across severity levels, $\chi^2(2) = .117$, $p = .943$.

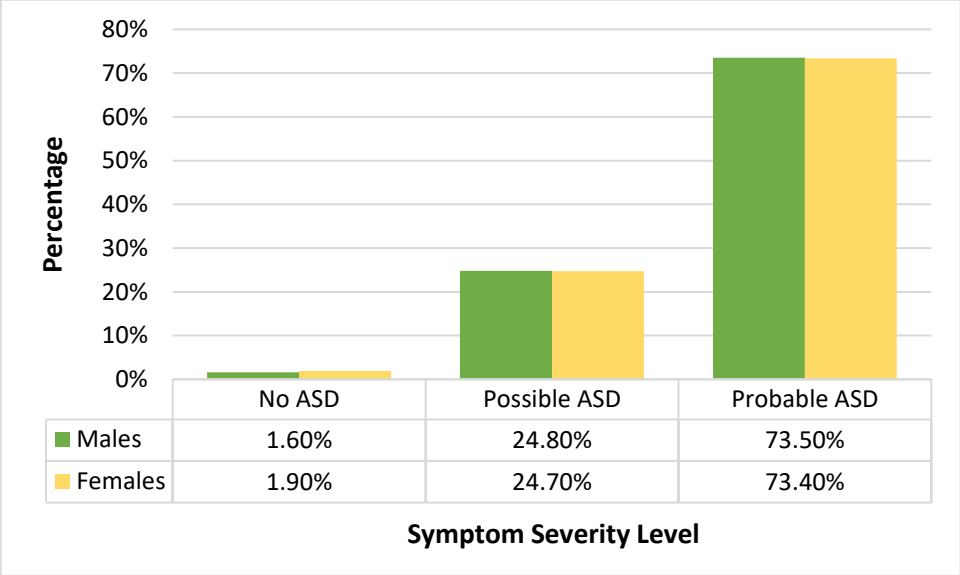

Figure 4. Percentage of BISCUIT symptom severity levels among males (N = 1,160) and females (N = 368) with ASD classification.

Developmental delay. Another chi-square of independence was conducted between sex and developmental delay (Figure 5). Data on developmental delay was available for 1,507 cases classified with ASD. All expected frequencies were greater than 5. The sex ratio among cases with developmental delay was 3.29, with 59.9% of males and 52.8% of females having a Total DQ of 70 or less. Among cases without development delay, the sex ratio was lower at 3.01. The

M/F ratio did not differ significantly between cases with and without developmental delay, $\chi^2(1) = .523$, $p = .470$.

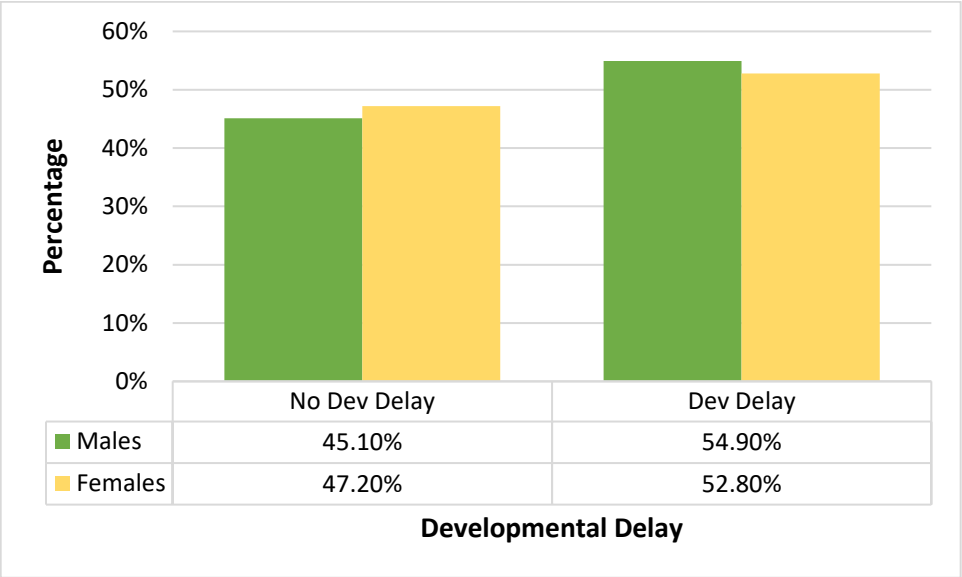

Figure 5. Percentage cases with and without developmental delay among males (N = 1,145) and females (N = 362) with ASD classification.

Cognitive delay. To test for differences in the sex ratio between ASD cases with and without cognitive delay, a chi-square test of independence was conducted (Figure 6). Data on cognitive delay was available for 1,507 cases classified with ASD. All expected frequencies were greater than 5. The M/F ratio among cases with cognitive delay was 3.05, with 45.3% of males and 47.0% of females having a Cognitive DQ of 70 or less. Among cases with Cognitive DQ > 70, the sex ratio was higher at 3.26. The sex ratio was not found to differ significantly between cases with and without cognitive delay, $\chi^2(1) = .296$, $p = .587$.

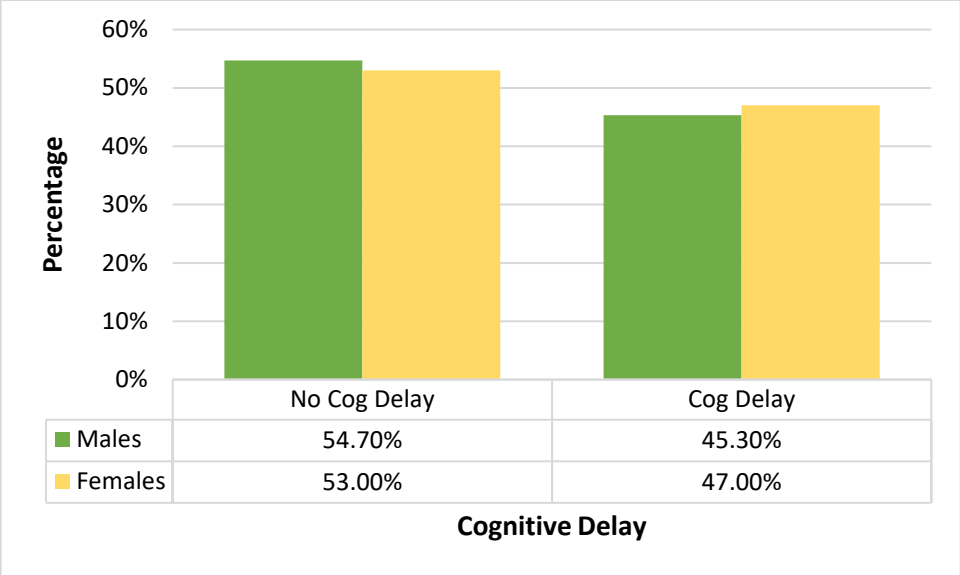

Figure 6. Percentage cases with and without cognitive delay among males (N = 1,145) and females (N = 362) with ASD classification.

Maternal age. A chi-square test of independence was conducted to determine whether the M/F ratio varied in relation to maternal age (Figure 7). Data on maternal age was available for 988 cases classified with ASD. All expected frequencies were greater than 5. Among cases whose mothers were younger than 35 years at their birth, the M/F ratio was 3.41 (90.6% of males and 84.7% of females). Among cases whose mothers were 35 years and older at birth, the M/F ratio was 1.97 (9.4% of males, 15.3% of females). The difference between the sex ratio in these two levels of maternal age at birth was found to be significantly significant, $\chi^2(1) = 6.285$, $p = .012$.

Paternal age. The test for differences in the sex ratio between ASD cases in relation to paternal age, a chi-square test of independence was conducted (Figure 8). Paternal age data was available for 947 cases classified with ASD. All expected frequencies were greater than 5. The M/F ratio among cases whose fathers were younger than 40 years at their birth was 3.30 (90.2% of males, 87.6% of females), while it was 2.54 among those whose fathers were 40 years or older

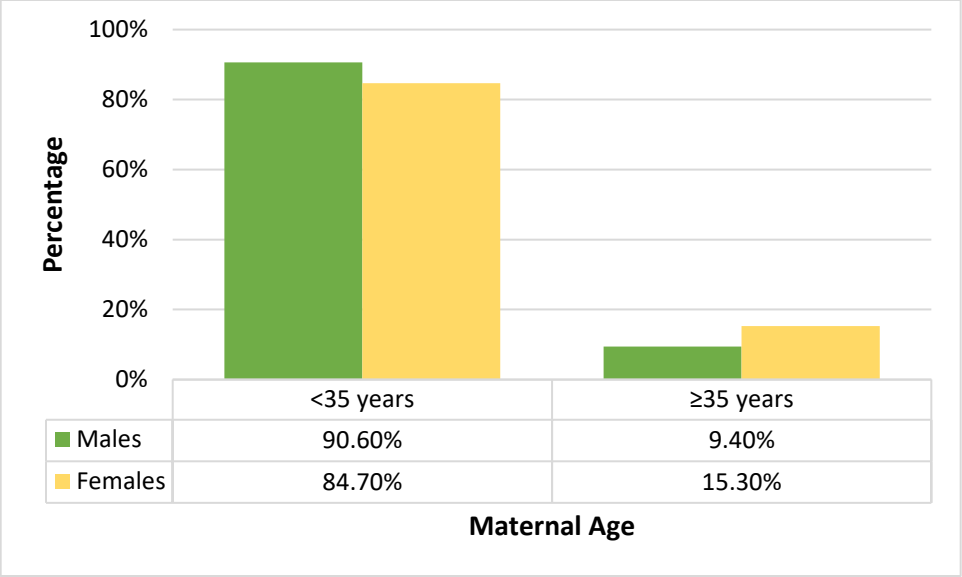

Figure 7. Percentage cases with maternal age <35 years and ≥35 years among males (*N* = 752) and females (*N* = 236) with ASD classification.

at their birth (9.8% of males, 12.4% of females). However, the difference between the sex ratio in these two levels of paternal age at birth was not significantly significant, $\chi^2(1) = 1.249$, $p = .264$.

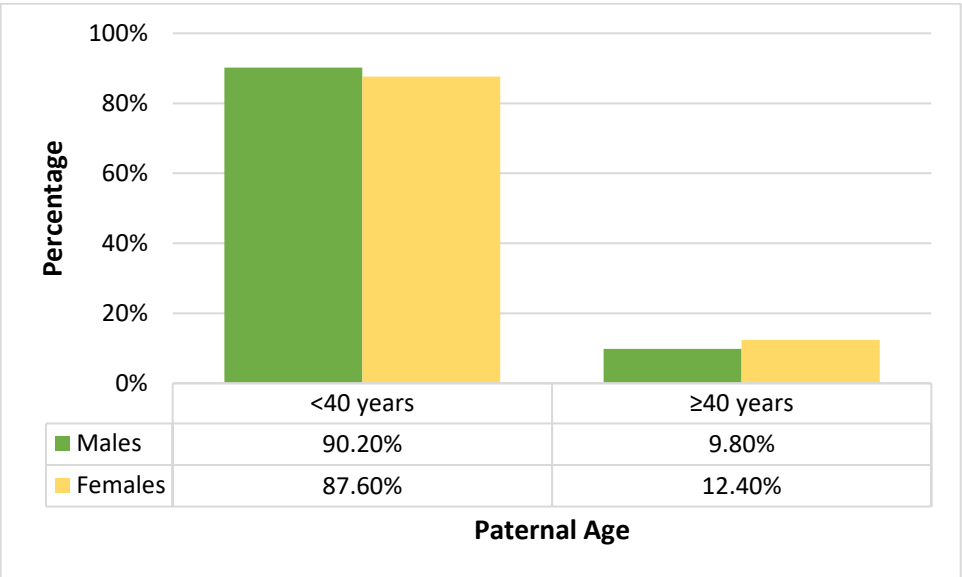

Figure 8. Percentage cases with paternal age <40 years and ≥40 years among males (*N* = 722) and females (*N* = 225) with ASD classification.

Birth weight. A chi-square test of independence was conducted to examine the difference in sex ratio in relation to birth weight (Figure 9). Birth weight data was available for 1,315 cases classified with ASD. All expected frequencies were greater than 5. The sex ratio was 1.90 among cases with very low birth weight (<1500 g), 2.05 among those with low birth weight (1500-2499 g), and 3.79 among those with normal birth weight (≥ 2500 g). The M/F ratio was found to significantly differ in relation to birth weight, $\chi^2(2) = 19.328$, $p < .001$. As this test revealed a significant result with more than one degree of freedom, post-hoc procedures were conducted to examine standardized residuals to further understand the association of sex and birth weight categories (Table 4). Standardized residuals were statistically significant for females with very low birth weight ($z = 2.1$, $p < .01$) and low birth weight ($z = 2.7$, $p < .01$), indicating that more females had very low and low birth weight than expected.

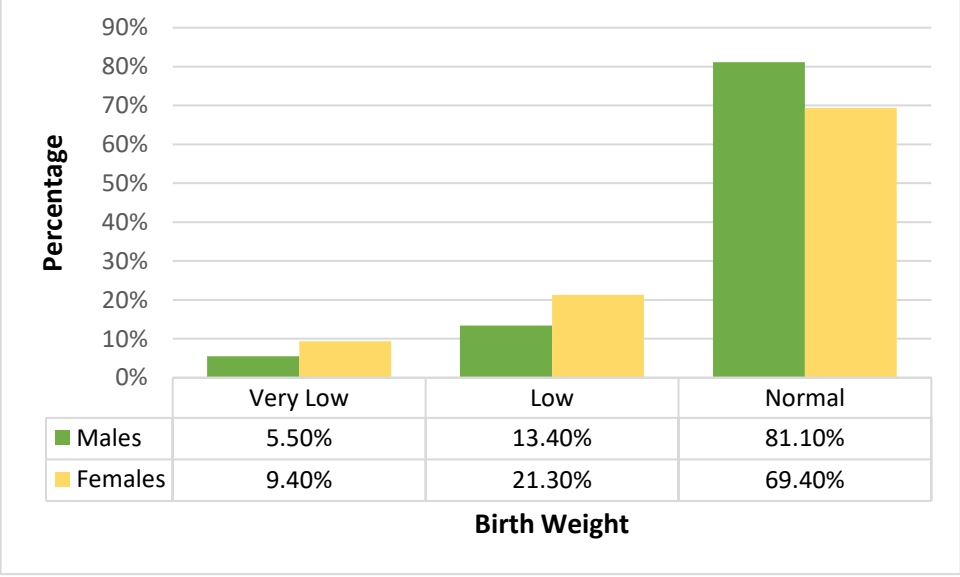

Figure 9. Percentage cases with very low (<1500 g), low(1500-2499 g), and normal birth weight (≥ 2500 g) among males (N = 1,005) and females (N = 310) with ASD classification.

Table 4. Crosstabulation of sex and birth weight categories.

Birth Weight	Sex	
	Male (*N*=1005)	Female (*N*=310)
Very low (<1500 g)	55	29
	(-1.1)	(**2.1)
Low (1500-2499 g)	135	66
	(-1.5)	(**2.7)
Normal (≥ 2500 g)	815	215
	(1.0)	(-1.8)

Note. Standardized residuals appear in parentheses below observed frequencies. Critical values of ±1.96 (*p < .05), ±2.58 (**p < .01), ±3.29 (***p < .001) were used.

Premature birth. To examine differences in the M/F ratio between children with and without premature birth, a chi-square test of independence was conducted (Figure 10). Data on prematurity was available for 1,505 cases classified with ASD. All expected frequencies were greater than 5. The M/F ratio was determined to be 2.11 among cases with premature birth

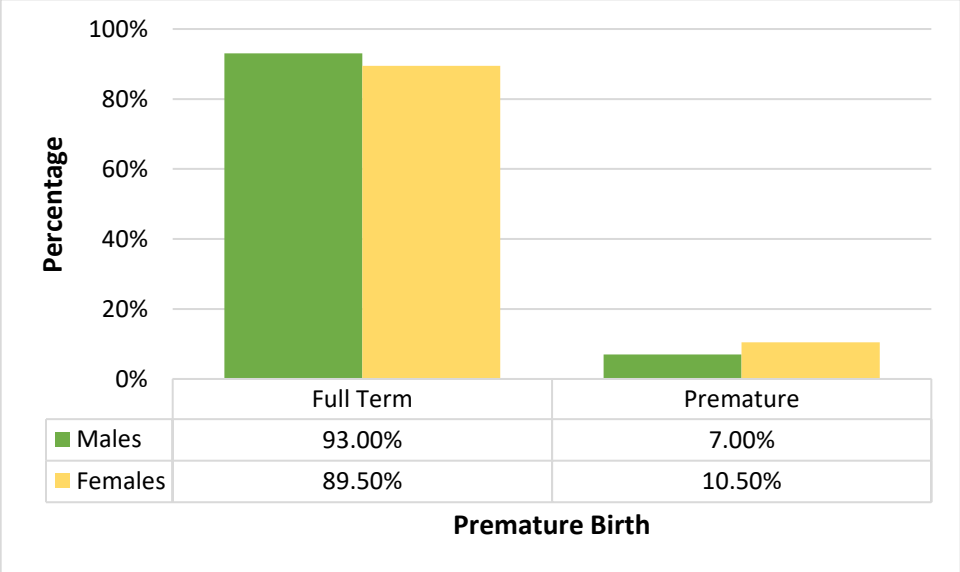

Figure 10. Percentage cases with and without premature birth among males (N = 1,114) and females (N = 361) with ASD classification.

(7.0% of males, 10.5% of females), and 3.29 among those with full term gestation (93.0% of males, 89.5% of females). The difference in sex ratio between cases with and without premature birth was found to be statistically significant, $\chi^2(1) = 4.741$ $p = .029$.

Multiple births. A chi-square test of impendence was conducted between sex and multiple births to examine differences in the sex ratio (Figure 11). Data on multiple births was available for 1,264 cases classified with ASD. All expected frequencies were greater than 5. The sex ratio was found to be 2.78 among cases born as part of a multiple birth (7.9% of males, 8.7% of females), and 3.09 among cases born as part of a singleton birth (92.1% of males, 91.3% of females). The difference in M/F ratio was not found to significantly differ between cases with and without multiple births, $\chi^2(1) = .208$, $p = .648$.

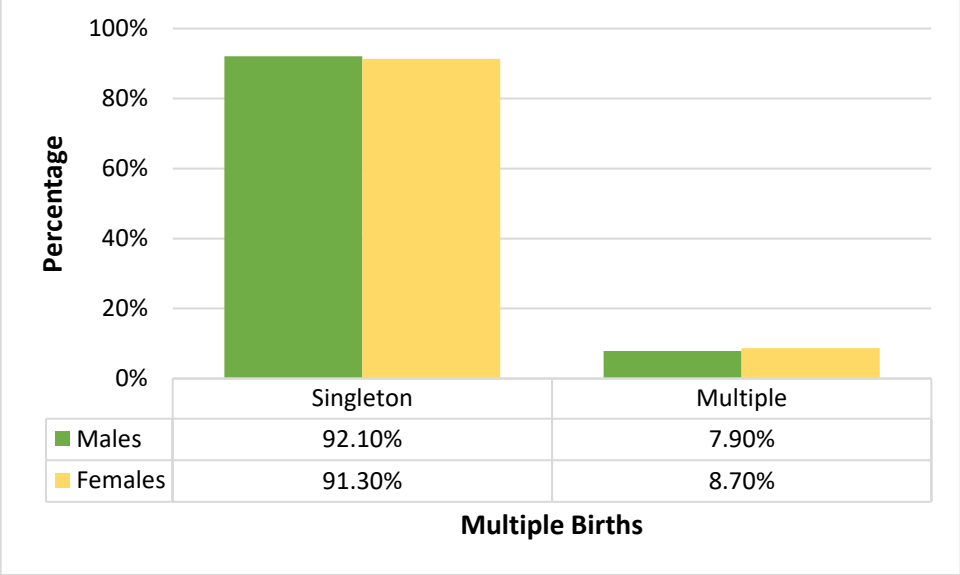

Figure 11. Percentage cases with singleton and multiple births among males ($N = 953$) and females ($N = 311$) with ASD classification.

Multiplex families. Another chi-square test of independence was conducted to examine differences in the sex ratio between cases in multiplex and simplex families (Figure 12). Data on

multiplex families was available for 1,427 cases classified with ASD. All expected frequencies were greater than 5. Among cases from multiplex families, the M/F ratio was 2.77 (5.6% of males, 6.3% of females). Among cases from simplex families, the M/F ratio was 3.13 (94.4% of males, 93.7% of females). The difference in sex ratio was not found to differ significantly between cases from multiplex and simplex families, $\chi^2(1) = .230$, $p = .632$.

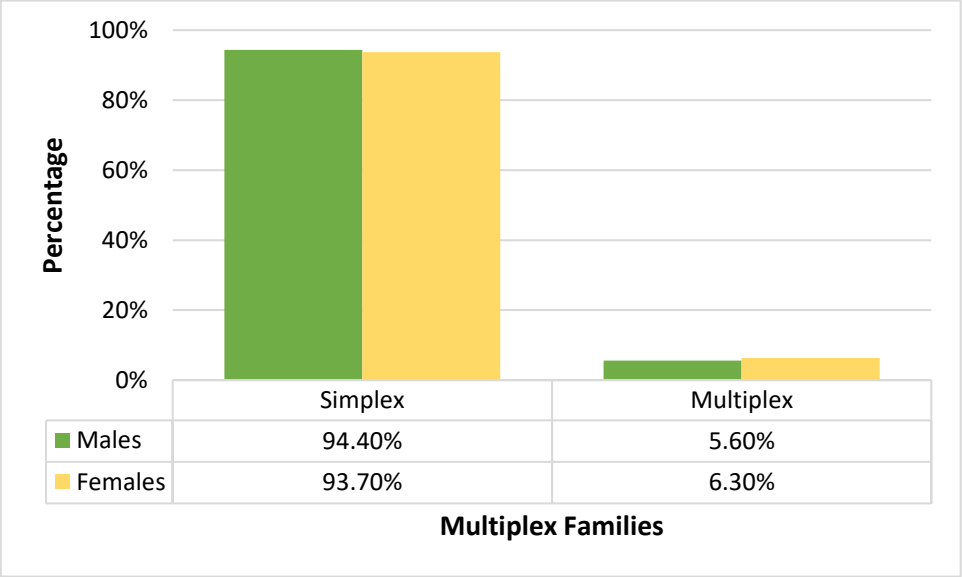

Figure 12. Percentage cases with simplex and multiplex families among males (N = 1,080) and females (N = 347) with ASD classification.

GDD. To examine differences in the M/F ratio between ASD cases with and without comorbid GDD, a chi-square test of independence was conducted (Figure 13). Data on GDD was available for 1,505 cases classified with ASD. All expected frequencies were greater than 5. The sex ratio was 2.75 among cases with GDD (2.9% of males, 3.3% of females) and 3.18 among those without GDD (97.1% of males, 96.7% of females). The difference in the M/F ratio was not found to differ significantly based on the presence of GDD, $\chi^2(1) = .183$, $p = .669$.

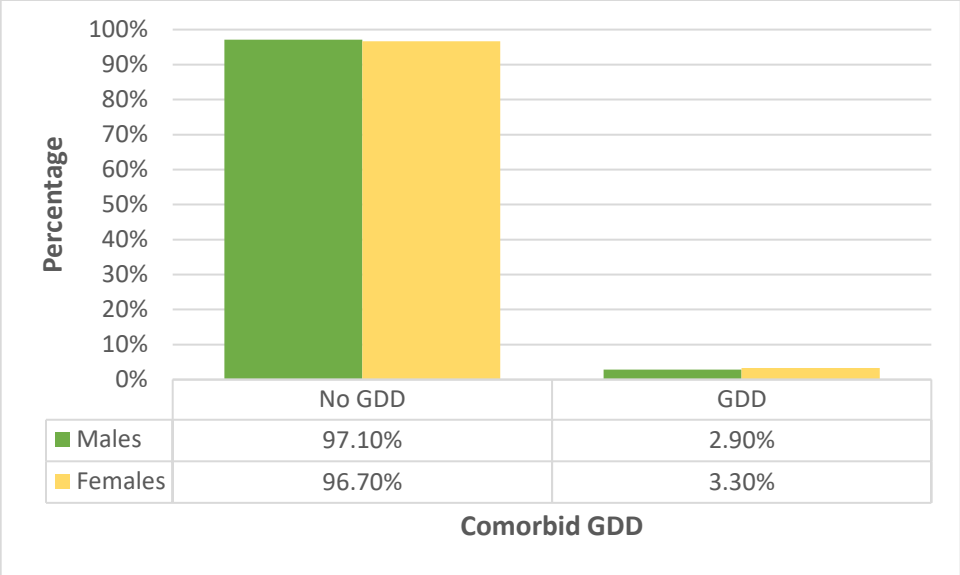

Figure 13. Percentage cases with and without comorbid GDD among males (*N* = 1,144) and females (*N* = 361) with ASD classification.

Down syndrome. A chi-square test of independence was conducted to examine differences in the ASD sex ratio between cases with and without comorbid Down syndrome. Data on Down syndrome was available for 1,505 cases classified with ASD. Two cells (50.0%) of the chi-square had expected counts less than 5, indicating that the assumption of expected frequencies was violated. Therefore, results of the chi-square analysis are not reported. Among males classified with ASD, 6 cases had comorbid Down syndrome; no females classified with ASD were found to have comorbid Down syndrome.

Seizure disorder. A chi-square test of independence was used to examine differences in the ASD sex ratio between cases with and without seizure disorder (Figure 14). Data on seizure disorder was available for 1,505 cases classified with ASD. All expected frequencies were greater than 5. Among cases with comorbid seizure disorder, the sex ratio was 1.62 (3.7% of males, 7.2% of females). Among cases without seizure disorder, the sex ratio was higher at 3.28

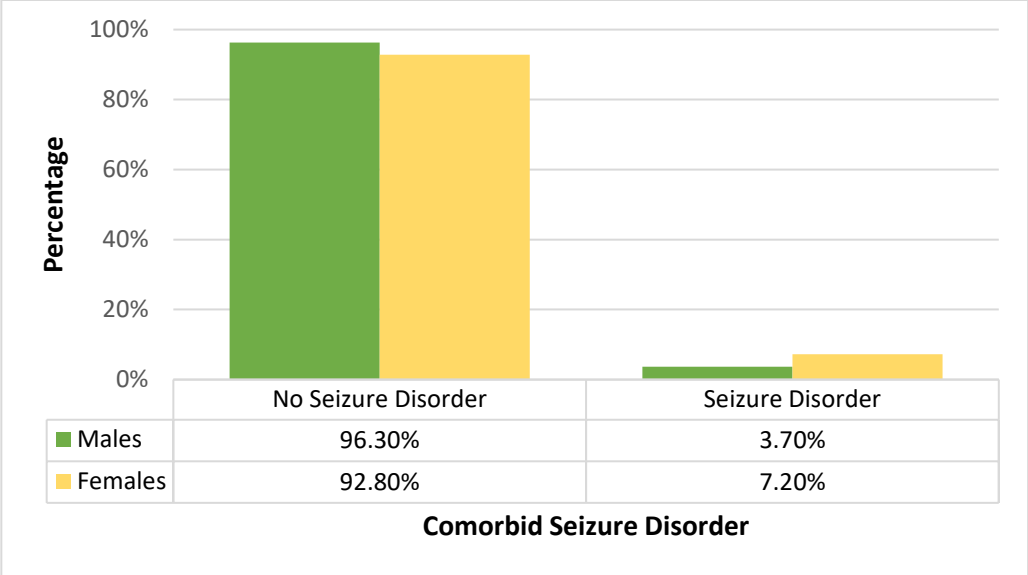

Figure 14. Percentage cases with and without comorbid seizure disorders among males (*N* = 1,144) and females (*N* = 361) with ASD classification.

(96.3% of males, 92.8% of females). The sex ratio differed significantly between ASD cases with and without comorbid seizure disorder, $\chi^2(1) = 7.930$, $p = .005$.

Cerebral palsy. To compare the ASD sex ratio between cases with and without cerebral palsy, a chi-square test of independence was conducted (Figure 15). Data on cerebral palsy was available for 1,505 cases. All expected frequencies were greater than 5. The M/F was found to be 2.71 among cases with comorbid cerebral palsy (1.7% of males, 1.9% of females) and 3.17 among those without comorbid cerebral palsy (98.3% of males, 98.1% of females). The difference in sex ratio was not found to significantly differ between cases with and without comorbid cerebral palsy, $\chi^2(1) = .125$, $p = .724$.

Number of risk factors. Another analysis aimed to determine if females with ASD are affected by a greater number of associated risk factors on average compared to males with ASD. The number of risk factors was calculated by adding the occurrence of the following variables:

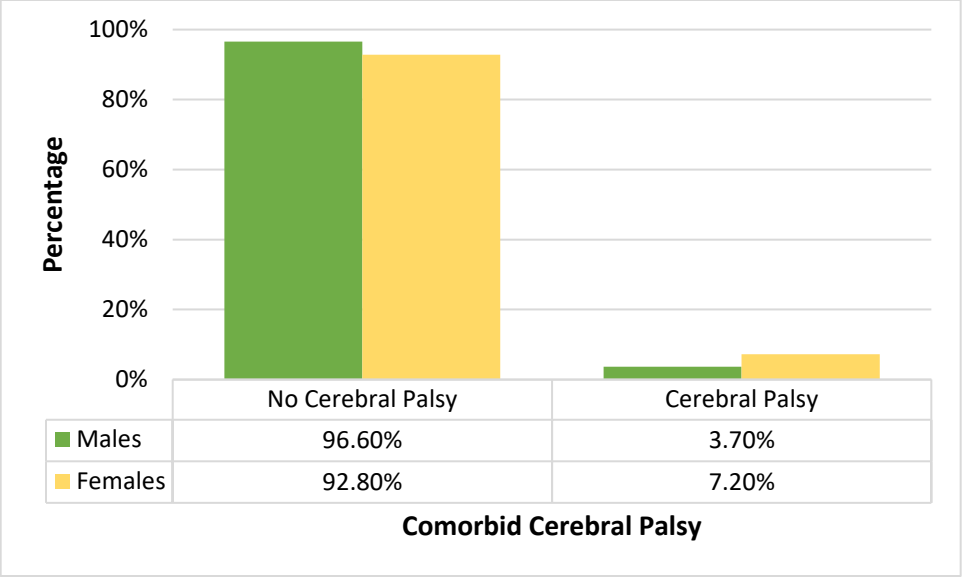

Figure 15. Percentage cases with and without comorbid cerebral palsy among males (*N* = 1,144) and females (*N* = 361) with ASD classification.

maternal age, paternal age, premature birth, very low birth weight, low birth weight, multiple births, and multiplex families. Data on risk factors was available for 1477 cases classified with ASD. An independent samples *t*-test was conducted to compare the average number of risk factors held by males and females with ASD. The dependent variable, risk factors, was continuous and the independent variable, sex was categorical, meeting assumptions for independent samples *t*-tests. The risk factors variable did not have any significant outliers. Although the dependent variable was not normally distributed for each group, the distributions were skewed in a similar manner (Figures 16 & 17). Independent *t*-tests are considered to be robust to violations of normality, especially with large sample sizes (Field, 2013). The assumption of homogeneity of variances was violated, as assessed by Levene's test ($p < .001$). Thus, a separate variances *t*-test was used. Males had a mean of .418 (*SD* = .700) risk factors and females had a mean of .579 (*SD* = .814), with a mean difference of .160 (*SE* = .047). There

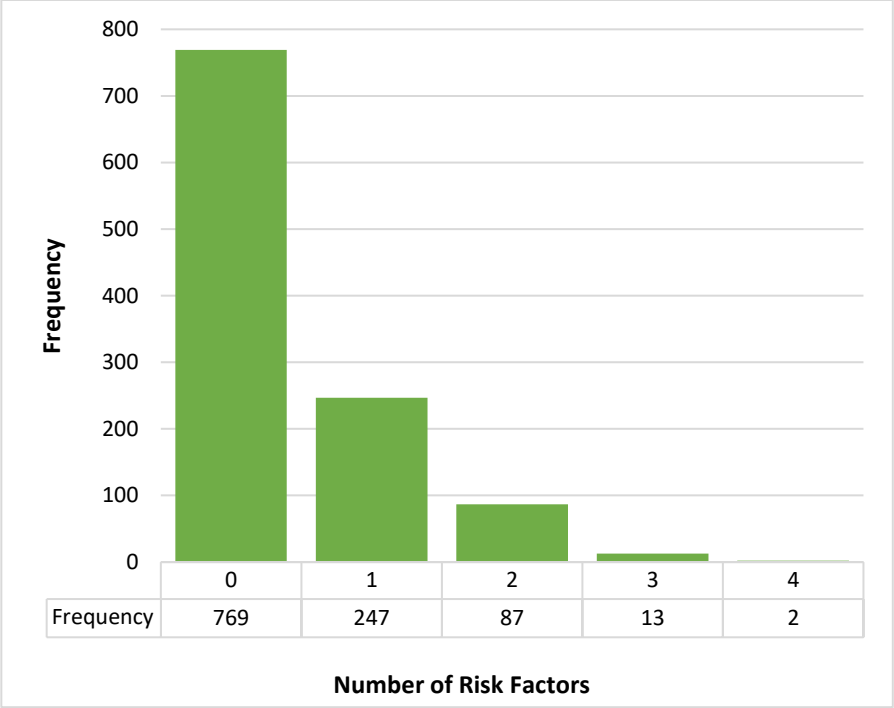

Figure 16. Distribution of the frequency of risk factors among males with ASD classification (*N* = 1,118).

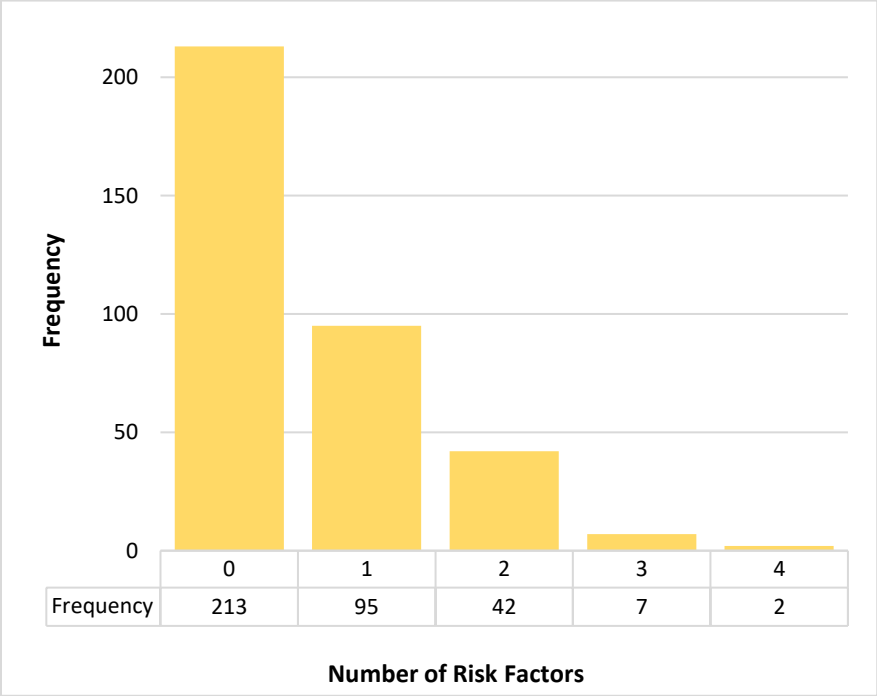

Figure 17. Distribution of the frequency of risk factors among females with ASD classification (*N* = 359).

was a statistically significant difference in mean risk factors between males and females with ASD classification, $t(538.522) = -3.362$, $p = .001$.

Multivariate Analysis

The third aim of the study, to determine if males and females are differentially impacted by risk factors associated with ASD, was addressed through multivariate analysis. The following risk factors were examined: cognitive delay, maternal age, paternal age, premature birth, birth weight, multiple births, and multiplex families. Hierarchical binomial logistic regression models were developed for each of these seven risk factors in relation to the outcome variable of ASD classification (0 = no ASD, 1 = ASD). Models 1-7 had the risk factor and sex entered as predictors in the first block and interaction terms with sex added into the second block (Figure 18). Interaction terms with sex allowed for the examination of differential risk contributing towards the occurrence of ASD (Cohen, Cohen, West, & Aiken, 2002).

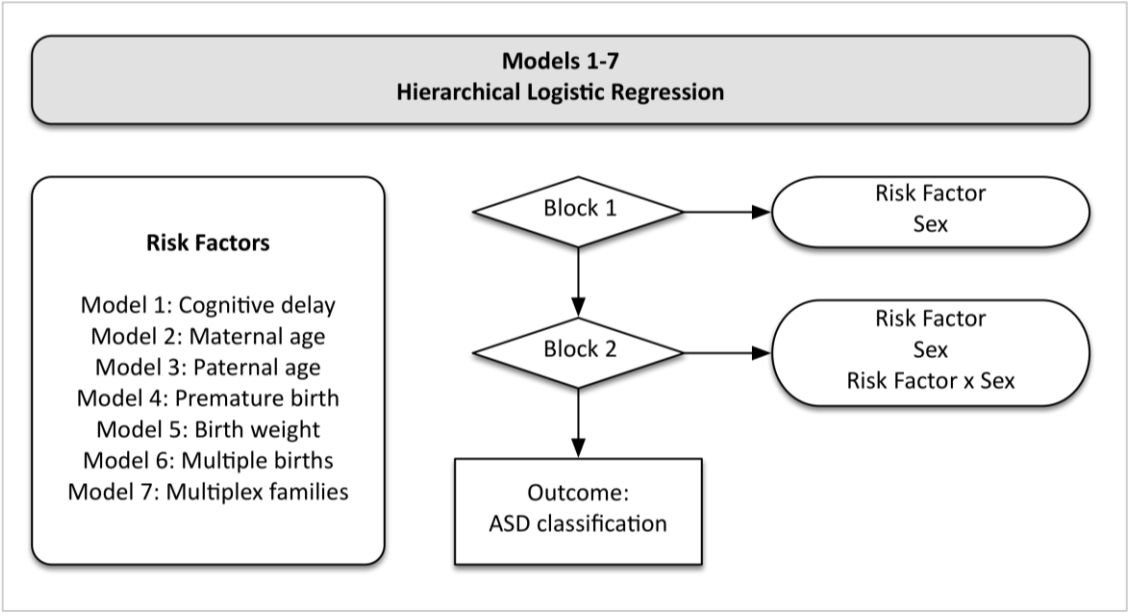

Figure 18. Models 1-7; hierarchical logistic regression models of risk factors associated with ASD classification.

Assumptions of logistic regression were checked for each model. The assumption of independence was confirmed by assuring that only one assessment time-point per participant was included in analysis. The assumption of linearity of independent variables and log odds were met as only categorical variables were included as predictors in the models. Multicollinearity was checked by examining tolerance and VIF values, using the recommended cut-off < 0.1 for tolerance values and > 10 for VIF values (Field, 2013). Data was tested to verify that no significant outliers were present. The following guidelines were followed to ensure adequate sample size for adequate power (Peduzzi, Concato, Kemper, Holford, & Feinstein, 1996): if *p* is the smallest of the proportions of negative/positive cases in the sample and *k* the number of covariates, then the minimum number of cases to include is $N = 10(k/p)$. Therefore, as 12.12% of the sample was classified with ASD and there were 3 covariates in the largest block of Models 1-4 & 6-7, the minimum number of cases required for these models for was $N = 10(3/.1212)$, or $N = 248$. For Model 5, there were 5 covariates in the largest block, requiring $N= 10(5/.1212)$, or $N = 413$. These minimum sample sizes were verified for Models 1-7.

Cognitive delay. Model 1 was a hierarchical binomial logistic regression model developed to determine if males and females were differentially impacted by cognitive delay in relation to the outcome variable of ASD classification (Table 5). The dependent variable was ASD classification. Cognitive delay and sex were entered as predictors in the Block 1, and an interaction term between sex and cognitive delay was added into Block 2. All assumptions of logistic regression were found to be met. Block 1 of Model 1 was statistically significant, $\chi^2(2) = 682.099$, $p = <.001$, and explained 5.3% (Cox & Snell R^2) of the variance in ASD classification. Both sex and cognitive delay were significant predictors of ASD classification. Males had 1.511 times the odds (95% CI [1.329-1.717], $p < .001$) of being classified with ASD compared to

Table 5. Results of Model 1; hierarchical logistic regression analysis for ASD classification with sex and cognitive delay (N = 12,431).

Block	Independent variables	*B*	*SE*	Wald	Odds ratio (95% CI)	R^2	ΔR^2
1	-					.053	-
	Constant	-2.303	.040	3399.520***	.100		
	Sex						
	Male	.413	.065	39.760***	1.511 (1.329-1.717)		
	Female (reference)						
	Cognitive Delay						
	No cognitive delay (reference)						
	Cognitive delay	1.509	.058	672.990***	4.524 (4.037-5.071)		
2	-	-	-	-	-	.054	.001
	Constant	-2.286	.042	2968.956***	.102		
	Sex						
	Male (reference)						
	Female	-.484	.085	32.090***	.616 (.521-.729)		
	Cognitive Delay						
	No cognitive delay (reference)						
	Cognitive delay	1.464	.067	473.004***	4.325 (3.790-4.935)		
	Sex*Cognitive Delay Interaction	.178	.134	1.766	1.194 (.919-1.552)		

Note: Block 1 $X^2(2)=682.099$, $p<.001$, Block 2 $X^2(3)=683.864$, $p<.001$; R^2 (Cox & Snell); *** $p<.001$, ** $p<.01$, * $p<.05$

females. Cognitive delay increased the odds of ASD classification by 4.524 times (95% CI [4.037-5.071], $p < .001$). Block 2 of Model 1 was also statistically significant, $\chi^2(3) = 683.864$, $p = <.001$. However, it only accounted for a .1% increase in the amount of explained variance compared to Block 1. The interaction term between sex and cognitive delay was not significant, indicating that the sexes were not differentially impacted by cognitive delay in regards to ASD classification.

Maternal age. Model 2 was a hierarchical binomial logistic regression model developed to determine if males and females were differentially impacted by maternal age in relation to the outcome variable of ASD classification (Table 6). The dependent variable was ASD classification. Maternal age and sex were entered as predictors in the Block 1, and an interaction term between sex and maternal age was added into Block 2. All assumptions of logistic regression were found to be met. Block 1 of Model 2 was statistically significant, $\chi^2(2) = 39.349$, $p = <.001$, and explained .5% (Cox & Snell R^2) of the variance in ASD classification.

Table 6. Results of Model 2; hierarchical logistic regression analysis for ASD classification with sex and maternal age (N = 8,716).

Block	Independent variables	*B*	*SE*	Wald	Odds ratio (95% CI)	R^2	ΔR^2
1	-					.005	-
	Constant	-1.906	.041	2189.476***	.149		
	Sex						
	Male	.460	.078	34.368***	1.584 (1.358-1.847)		
	Female (reference)						
	Maternal Age						
	<35 years (reference)						
	≥35 years	-.169	.108	2.442	.845 (.683-1.044)		
2	-					.005	0
	Constant	-2.412	.074	1068.160***	.090		
	Sex						
	Male	.521	.084	37.958***	1.683 (1.426-1.986)		
	Female (reference)						
	Maternal Age						
	<35 years (reference)						
	≥35 years	-.176	.190	.854	1.192 (.821-1.731)		
	Sex*Maternal Age Interaction	-.487	.231	4.439*	.614 (.390-.967)		

Note: Block 1 $X^2(2)=39.349$, $p<.001$, Block 2 $X^2(3)=43.633$, $p<.001$; R^2 (Cox & Snell); *** $p<.001$, ** $p<.01$, * $p<.05$

Sex was found to be a significant predictor of ASD classification but maternal age was not. Males had 1.584 times the odds (95% CI [1.358-1.847], $p < .001$) of being classified with ASD compared to females. Block 2 of Model 2 was also statistically significant, $\chi^2(3) = 43.633$, $p = <.001$. However, it did not increase the amount of explained variance compared to Block 1. The interaction term between sex and maternal age in Block 2 was significant, indicating that maternal age differentially impacts males and females in regards to ASD classification. Males with maternal age ≥35 years were found to be less likely to be classified with ASD compared to females with maternal age ≥35 years (OR = .614, 95% CI [.390-.967], p = .035). This indicates that females with maternal age ≥ 35 years were 1.628 (95% CI [1.034- 2.564]) times more likely to be classified with ASD than their male counterparts.

Paternal age. Model 3 was a hierarchical binomial logistic regression model developed to determine if males and females were differentially impacted by paternal age in relation to the

outcome variable of ASD classification (Table 7). The dependent variable was ASD classification. Paternal age and sex were entered as predictors in the Block 1, and an interaction term between sex and paternal age was added into Block 2. All assumptions of logistic regression were found to be met. Block 1 of Model 3 was statistically significant, $\chi^2(2) = 35.142$, $p = <.001$, and explained .4% (Cox & Snell R^2) of the variance in ASD classification. Sex was found to be a significant predictor of ASD classification but paternal age was not. Males had 1.586 times the odds (95% CI [1.355-1.857], $p < .001$) of being classified with ASD compared to females. Block 2 of Model 3 was also statistically significant, $\chi^2(3) = 35.150$, $p = <.001$. However, it did not increase the amount of explained variance compared to Block 1. The interaction term between sex and maternal age in Block 2 was not statistically significant, indicating that paternal age did not differentially impact males and females in regards to ASD classification.

Table 7. Results of Model 3; hierarchical logistic regression analysis for ASD classification with sex and paternal age (N = 8,359).

Block	Independent variables	*B*	*SE*	Wald	Odds ratio (95% CI)	R^2	ΔR^2
1	-					.004	
	Constant	-2.388	.071	1130.412***			
	Sex						
	Male	.461	.080	33.016***	1.586 (1.355-1.857)		
	Female (reference)						
	Paternal Age						
	<40 years (reference)						
	≥40 years	-.004	.113	.001	.996 (.799-1.243)		
2	-					.004	0
	Constant	-2.390	.074	1030.848***			
	Sex						
	Male	.464	.085	29.467***	1.590 (1.345-1.880)		
	Female (reference)						
	Paternal Age						
	<40 years (reference)						
	≥40 years	.012	.211	.003	1.012 (.669-1.530)		
	Sex*Paternal Age Interaction	-.021	.250	.007	.979 (.600-1.597)		

Note: Block 1 $X^2(2)=35.142$, $p<.001$, Block 2 $X^2(3)=35.150$, $p<.001$; R^2 (Cox & Snell); *** $p<.001$, ** $p<.01$, * $p<.05$

Premature birth. Model 4 was a hierarchical binomial logistic regression model developed to determine if males and females were differentially impacted by premature birth in relation to the outcome variable of ASD classification (Table 8). The dependent variable was ASD classification. Premature birth and sex were entered as predictors in Block 1, and an interaction term between sex and premature birth was added into Block 2. All assumptions of logistic regression were met. Block 1 of Model 4 was statistically significant, $\chi^2(2) = 59.431$, $p = <.001$, and explained .5% (Cox & Snell R^2) of the variance in ASD classification. Both sex and premature birth were significant predictors of ASD classification. Males had 1.534 times the odds (95% CI [1.353-1.738], $p < .001$) of being classified with ASD compared to females. Cases with premature birth had .747 the odds (95% CI [.613-.911], $p = .004$) of ASD classification. In other words, cases without premature birth were 1.338 times (95% CI [1.097-1.631], $p = .004$)

Table 8. Results of Model 4; hierarchical logistic regression analysis for ASD classification with sex and premature birth (N = 12,598).

Block	Independent variables	*B*	*SE*	Wald	Odds ratio (95% CI)	R^2	ΔR^2
1	-					.005	-
	Constant	-2.255	.056	1600.627***	.105		
	Sex						
	Male	.428	.064	44.858***	1.534 (1.353-1.738)		
	Female (reference)						
	Premature Birth						
	Full term (reference)						
	Premature birth	-.292	.101	8.311**	.747 (.613-.911)		
2	-					.005	0
	Constant	-2.252	.058	1481.867***	.105		
	Sex						
	Male	.424	.067	39.758***	1.527 (1.339-1.742)		
	Female (reference)						
	Premature Birth						
	Full term (reference)						
	Premature birth	-.321	.178	3.251	.725 (.511-1.028)		
	Sex*Premature Birth Interaction	.044	.216	.041	1.045 (.684-1.597)		

Note: Block 1 $X^2(2)=59.431$, $p<.001$, Block 2 $X^2(3)=59.472$, $p<.001$; R^2 (Cox & Snell); *** $p<.001$, ** $p<.01$, * $p<.05$

more likely to have ASD classification compared to those with premature birth. Block 2 of Model 4 was also statistically significant, $\chi^2(3) = 59.472$, $p = <.001$. However, compared to Block 1, it did not increase the amount of explained variance. The interaction term between sex and premature birth was not significant, indicating that males and females were not differentially impacted by premature birth in regards to ASD classification.

Birth weight. Model 5 was a hierarchical logistic regression designed to determine if the sexes were differentially impacted by birth weight in regards to ASD classification (Table 9). The dependent variable was ASD classification. Sex, low birth weight, and very low birth weight were entered as predictors in Block 1, and two interaction terms between sex and very low/low birth weight were added into Block 2. All assumptions of logistic regression were met.

Table 9. Results of Model 5; hierarchical logistic regression analysis for ASD classification with sex and birth weight (N = 10,693).

Block	Independent variables	*B*	*SE*	Wald	Odds ratio (95% CI)	R^2	ΔR^2
1	-					.006	-
	Constant	-2.255	.063	1277.367***	.105		
	Sex						
	Male	.444	.069	41.381***	1.558 (1.361-1.784)		
	Female (reference)						
	Birth Weight						
	Very low (<1500g)	-.384	.119	10.362**	.681 (.539-.860)		
	Low (1500-2499g)	.013	.083	.025	1.013 (.861-1.192)		
	Normal (≥ 2500g; reference)						
2	-					.006	0
	Constant	-2.288	.072	1021.424***	.102		
	Sex						
	Male	.485	.081	35.905***	1.624 (1.385-1.904)		
	Female (reference)						
	Birth Weight						
	Very low (<1500g)	-.376	.205	3.362	.687 (.460-1.026)		
	Low (1500-2499g)	-.226	.179	1.323	1.186 (.887-1.588)		
	Normal (≥ 2500g; reference)						
	Sex*Very Low Interaction	-.005	.252	.000	.995 (.607-1.632)		
	Sex*Low Interaction	-.226	.179	1.59	.798 (.562-1.133)		

Note: Block 1 $X^2(3)=59.812$, $p<.001$, Block 2 $X^2(5)=61.409$, $p<.001$; R^2 (Cox & Snell); *** $p<.001$, ** $p<.01$, * $p<.05$

Block 1 of Model 5 was statistically significant, $\chi^2(3) = 59.812$, $p = <.001$, and explained .6% (Cox & Snell R^2) of the variance in ASD classification. Both sex and very low birth weight were significant predictors of ASD classification. Males had 1.558 times the odds (95% CI [1.361-1.784], $p < .001$) of being classified with ASD compared to females. Cases with very low birth weight had .681 the odds (95% CI [.539-.860], $p = .001$) of ASD classification. In other words, cases with birth weight ≥ 1500 g were 1.468 times (95% CI [1.162-1.855], $p = .001$) more likely to have ASD classification compared to those with birth weight <1500 g. Block 2 of Model 5 was also statistically significant, $\chi^2(5) = 61.409$, $p = <.001$. There was no change in explained variance between Block 1 and 2. The interaction terms between sex and low/very low birth weight were not significant, indicating that males and females were not differentially impacted by birth weight in regards to ASD classification.

Multiple births. Model 6 was a hierarchical binomial logistic regression model developed to determine if males and females were differentially impacted by multiple births in relation to the outcome variable of ASD classification (Table 10). The dependent variable was ASD classification. Sex and multiple birth were entered as predictors in Block 1, and an interaction term between sex and multiple birth was added into Block 2. All assumptions of logistic regression were met. Block 1 of Model 6 was statistically significant, $\chi^2(2) = 36.923$, $p = <.001$, and explained .3% (Cox & Snell R^2) of the variance in ASD classification. Sex was a significant predictor of ASD classification while multiple births was not. Males had 1.501 times the odds (95% CI [1.311-1.718], $p < .001$) of being classified with ASD compared to females. Block 2 of Model 6 was also statistically significant, $\chi^2(3) = 37.398$, $p = <.001$. However, compared to Block 1, it did not increase the amount of explained variance. The interaction term

Table 10. Results of Model 6; hierarchical logistic regression analysis for ASD classification with sex and multiple births (N = 10,752).

Block	Independent variables	*B*	*SE*	Wald	Odds ratio (95% CI)	R^2	ΔR^2
1	-					.003	-
	Constant	-2.302	.060	1452.245***	.100		
	Sex						
	Male	.406	.069	34.706***	1.501 (1.311-1.718)		
	Female (reference)						
	Multiple Births						
	Singleton birth (reference)						
	Multiple births	-.046	.110	.174	.955 (.770-1.185)		
2	-					.003	0
	Constant	-2.291	.062	1353.081	.101		
	Sex						
	Male	.391	.072	29.488***	1.479 (1.284-1.703)		
	Female (reference)						
	Multiple Births						
	Singleton birth (reference)						
	Multiple births	-.166	.210	.626	.847 (.561-1.278)		
	Sex*Multiple Births Interaction	.169	.246	.494	1.184 (.730-1.918)		

Note: Block 1 $X^2(2)=36.923$, $p<.001$, Block 2 $X^2(3)=37.398$, $p<.001$; R^2 (Cox & Snell); *** $p<.001$, ** $p<.01$, * $p<.05$

between sex and premature birth was not significant, indicating that males and females were not differentially impacted by multiple births in regards to ASD classification.

Multiplex families. Model 7 was a hierarchical binomial logistic regression model developed to determine if the sexes were differentially impacted by multiplex families in relation to the outcome variable of ASD classification (Table 11). The dependent variable was ASD classification. Sex and multiplex families were entered as predictors in Block 1, and an interaction term between sex and multiplex families was added into Block 2. All assumptions of logistic regression were met. Block 1 of Model 7 was statistically significant, $\chi^2(2) = 81.636$, $p =$ <.001, and explained .7% (Cox & Snell R^2) of the variance in ASD classification. Sex and multiplex families were both significant predictors of ASD classification. Males were found to be 1.514 times (95% CI [1.333-1.721], $p < .001$) more likely to be classified with ASD compared to females. Cases from multiplex families had 2.408 times the odds (95% CI [1.868-3.105], $p <$

Table 11. Results of Model 7; hierarchical logistic regression analysis for ASD classification with sex and multiplex families (N = 11,850).

Block	Independent variables	*B*	*SE*	Wald	Odds ratio (95% CI)	R^2	ΔR^2
1	-					.007	-
	Constant	-2.321	.057	1661.792***	.098		
	Sex						
	Male	.415	.065	40.422***	1.514 (1.333-1.721)		
	Female (reference)						
	Multiplex Families						
	Simplex (reference)						
	Multiplex	.879	.130	45.983***	2.408 (1.868-3.105)		
2	-					.007	0
	Constant	-2.321	.058	1594.544***	.098		
	Sex						
	Male	.416	.067	38.384***	1.516 (1.329-1.729)		
	Female (reference)						
	Multiplex Families						
	Simplex (reference)						
	Multiplex	.890	.288	13.280	2.426 (1.509-3.933)		
	Sex*Multiplex Interaction	-2.321	.058	.003	.984 (.559-1.731)		

Note: Block 1 $X^2(2)=81.636$, $p<.001$, Block 2 $X^2(3)=81.639$, $p<.001$; R^2 (Cox & Snell); *** $p<.001$, ** $p<.01$, * $p<.05$

.001) of being classified with ASD compared to those from simplex families. Block 2 of Model 7 was also statistically significant, $\chi^2(3) = 81.639$, $p = <.001$. However, there was not an increase the amount of explained variance between Block 1 and 2. The interaction term between sex and multiplex families was not statistically significant, indicating that males and females were not differentially impacted by multiplex families in regards to ASD classification.

Full multivariate model. Risk factors that were found to be significant predictors of ASD classification or to have a significant interaction term with sex were included in Model 8, a multivariate model that allowed for the control of shared variance across risk factors (Cohen et al., 2002). Risk factors that are not found to be significant predictors of ASD classification or to have significant interactions with sex in Models 1-7 were excluded from Model 8 based on the principle of parsimony and to reduce the number of covariates to maximize power (Cohen et al., 2002; Field, 2013). The risk factors included in the model as covariates were: cognitive delay, maternal age, premature birth, birth weight, and multiplex families. As with Models 1-7, Model

8 had the outcome variable of ASD classification (0=no ASD, 1=ASD) and two blocks of predictor variables: the first included the identified risk factors; and the second included these risk factors as well as interaction terms for each of the risk factors with sex. Block 2 of the model included 13 covariates. Thus, using the guidelines outlined by Peduzzi and colleagues (1996), the minimum recommended number of cases to include in the model was N = 10(13/.1212), or N = 1,073. This minimum number of cases was met, as 7,963 cases were included in the analysis. All assumptions of logistic regression were found to be met. Results of Model 8 are displayed in Table 12.

Block 1 of Model 8 was statistically significant, $\chi^2(7) = 450.370$, $p = <.001$, and explained 5.5% (Cox & Snell R^2) of the variance in ASD classification. Sex, cognitive delay, very low birth weight, and multiplex families were significant predictors of ASD classification in Block 1. When controlling for other covariates, males were found to be 1.526 times (95% CI [1.291-1.804], $p < .001$) more likely to be classified with ASD compared to females. Cases with cognitive delay had 4.470 times (95% CI [3.859-5.179], $p < .001$) the odds of being classified with ASD compared to those without cognitive delay. Cases with very low birth weight had .630 times the odds (95% CI [.444-.892], $p = .009$) of ASD classification, indicating that cases with birth weight ≥ 1500 g were 1.587 times (95% CI [1.121-2.252], $p = .009$) more likely to have ASD classification compared to those with birth weight <1500 g. Cases from multiplex families were 2.281 (95% CI [1.658-3.140], $p < .001$) times more likely to be classified with ASD than those from simplex families.

Block 2 of Model 8 was also statistically significant, $\chi^2(7) = 456.494$, $p = <.001$, and explained 5.6% (Cox & Snell R^2) of the variance in ASD classification. When compared to Block 1, there was a .1% increase in the amount of explained variance. None of the sex

Table 12. Results of Model 8; hierarchical logistic regression analysis for ASD classification with sex and multiple risk factors (N = 7,963).

Block	Independent variables	*B*	*SE*	Wald	Odds ratio (95% CI)	R^2	ΔR^2
1	-					.055	
	Constant	-2.798	.085	1082.265***	.061		
	Sex						
	Male	.423	.085	24.528***	1.526 (1.291-1.804)		
	Female (reference)						
	Cognitive Delay						
	No cognitive delay (reference)						
	Cognitive delay	1.497	.075	397.958***	4.470 (3.859-5.179)		
	Maternal Age						
	<35 years (reference)						
	≥35 years	-.171	.118	2.117	.842 (.669-1.061)		
	Premature Birth						
	Full term (reference)						
	Premature birth	.054	.147	.137	1.056 (.792-1.408)		
	Birth Weight (BW)						
	Very low (<1500g)	-.463	.178	6.756**	.630 (.444-.892)		
	Low (1500-2499g)	-.073	.112	.425	.930 (.747-1.157)		
	Normal (≥ 2500g; reference)						
	Multiplex Families						
	Simplex (reference)						
	Multiplex	.825	.163	25.605***	2.281 (1.658-3.140)		
2	-					.056	.001
	Constant	-2.895	.114	658.910***	.055		
	Sex						
	Male	.550	.129	18.168***	1.733 (1.346-2.231)		
	Female (reference)						
	Cognitive Delay						
	No cognitive delay (reference)						
	Cognitive delay	1.629	.151	116.286***	5.097 (3.791-6.853)		
	Maternal Age						
	<35 years (reference)						
	≥35 years	.043	.216	.040	1.044 (.683-1.596)		
	Premature Birth						
	Full term (reference)						
	Premature birth	.337	.272	1.535	1.401 (.822-2.387)		
	Birth Weight (BW)						
	Very low (<1500g)	-.691	.327	4.446*	.501 (.264-.952)		
	Low (1500-2499g)	-.240	.213	1.263	.787 (.518-1.195)		
	Normal (≥ 2500g; reference)						
	Multiplex Families						
	Simplex (reference)						
	Multiplex	1.205	.293	16.955***	3.338 (1.881-5.924)		
	Sex*Cognitive Delay Interaction	-.171	.174	.962	.843 (.599-1.186)		
	Sex*Maternal Age Interaction	-.296	.258	1.317	.744 (.448-1.233)		
	Sex*Premature Birth Interaction	-.387	.324	1.428	.679 (.360-1.281)		
	Sex*Very Low BW Interaction	.307	.391	.617	1.251 (.765-2.044)		
	Sex*Low BW Interaction	.224	.251	.797	1.251 (.765-2.044)		
	Sex*Multiplex Interaction	-.528	.352	2.256	.589 (.296-1.175)		

Note: Block 1 $X^2(7)=450.370$, $p<.001$, Block 2 $X^2(13)=456.252$, $p<.001$; R^2 (Cox & Snell); *** $p<.001$, ** $p<.01$, * $p<.05$

interaction terms were significant predictors of ASD classification, indicating that males and females were not differentially impacted by these risk factors when shared variance across risk factors is controlled.

DISCUSSION

The higher prevalence of ASD among males compared to females is well documented but poorly understood. A review of recent sex ratio estimates indicated a mean male/female (M/F) ratio of 4, a result similar to those found by previous reviews of ASD epidemiological studies (Elsabbagh et al., 2012; Fombonne, 2009; Hill et al., 2016). The few previous studies that have examined the sex ratio in relation to ASD risk factors have found that the sex ratio is affected by a number of factors, including diagnostic subtype, age, cognitive impairment, parental age, family history of ASD, developmental regression, low birth weight, race/ethnicity, and comorbid disorders. However, there have been some conflicting findings, indicating that more research is needed in this area. In an effort to address this gap in the extant research, this study examined the ASD sex ratio among a statewide early intervention sample.

ASD Prevalence and Sex Ratio

The primary aim of this study was to estimate the ASD prevalence and ASD sex ratio among children enrolled in EarlySteps, Louisiana's early intervention program under Part C of IDEA, which serves children under the age of three at risk for developmental delays. Assessment data from EarlySteps collected between 2008-2017 was analyzed. Of the total sample (n = 12,598), 12.12%, or 121.2 per 1,000, were found to meet *DSM-5* criteria for ASD. This prevalence estimate is lower than the 30.14% previously found in the EarlySteps sample (n = 2,027) using data collected from 2008-2011 and *DSM-IV* criteria (Worley et al., 2011). This decrease in prevalence estimates is likely related to changes in the EarlySteps ASD screening protocol implemented in 2011, which increased provider compliance with screening procedures (Matheis & Matson, 2015), and the subsequent marked increase in the number of children administered ASD screens. Wider administration of ASD screens within the EarlySteps program

is thought to have resulted in screens being administered to children with a more varied range of developmental concerns rather than targeting those suspected of having ASD, thus decreasing bias in the prevalence estimates due to differential participation in the screening process (Hill et al., 2016). Even so, the 121.2 per 1,000 prevalence estimate in the EarlySteps sample is considerably higher than estimates in other samples within the United States, as hypothesized. The most recent estimates from the CDC (2016) indicated an ASD prevalence rate of 14.6 per 1,000, while estimates from the National Survey of Children's Health (NSCH) indicated a prevalence rate of 20 per 1,000 (Blumberg et al., 2013). These differences can be attributed to sample characteristics. Children in the EarlySteps program are at greater risk for ASD than the general population, as they have either demonstrated developmental delays or have risk factors associated with such delays.

An overall M/F ratio of 3.15 was found in the EarlySteps sample. This sex ratio estimate is slightly higher than the 2.75 previously reported using 2008-2011 EarlySteps data and *DSM-IV* criteria (Worley et al., 2011), which may be due to the increase in the number of children screened for ASD. The sex ratio of 3.15 is slightly lower than the average sex ratio of 4 found in the review of prevalence studies published between 2012-2017, and the 4.5 ratio found most recently by the CDC (2016). However, it falls within a similar range to estimates from recent studies, and is closest to the national estimate from Taiwan of 2.9 (Hsu et al., 2012) and the national estimate from Finland of 3.5 (Hinkka-Yli-Salomäki et al., 2014). Previous research has demonstrated that estimates of the ASD sex ratio have stabilized since the early 2000's (Bachmann et al., 2016; CDC, 2007, 2016; M. C. Lai et al., 2012). It was thus hypothesized that the sex ratio within the EarlySteps sample has also remained relatively stable. This hypothesis was confirmed as there was only a ± .79 range found across sex ratio estimates between years

from 2008-2017. Examination of the linear trend shows a very slight increase in the sex ratio over time, which is most likely attributed to the increased sample size as previously discussed (Figure 2).

Risk Factors and the Sex Ratio

The second aim of this study was to examine changes in the ASD sex ratio when considering various risk factors, autistic phenotypes, and features commonly associated with the disorder. The third aim was to determine if risk factors for ASD differentially impact males and females. Significant differences in the M/F ratio amongst cases classified with ASD were found: between cases with and without cognitive impairment; between cases with and without advanced maternal age; across birth weight categories; and between cases with and without seizure disorder. Hypotheses that sex would moderate the relationship between birth weight, premature birth, and multiple births with ASD classification were not supported. Females were found to be differentially impacted by advanced maternal age. Further discussion related to these findings is included below, grouped thematically.

Cognitive impairment and symptom severity. One of the most consistent findings in the extant literature in this area is that the ASD sex ratio decreases when considering individuals with comorbid cognitive impairment, indicating that females with ASD are more likely than their male counterparts to have below-average cognitive functioning (CDC, 2016; Dworzynski et al., 2012; Honda et al., 2005; Rivet & Matson, 2011; van Bakel et al., 2015). This was confirmed in the present study, as a lower sex ratio (3.05) was found amongst cases with cognitive delay compared to cases without cognitive delay (3.26). However, the difference in the percent of cases with cognitive delay between males and females was not statistically significant. Further, while cognitive delay was found to be a significant predictor of meeting ASD diagnostic criteria,

sex was not found to moderate the relationship between cognitive delay and ASD classification. Interestingly, a higher sex ratio was found amongst those with general developmental delays (3.29), compared to those with developmental functioning in normal limits (3.01), although this difference was also not statistically significant. The close sex ratio estimates between cases with and without cognitive delay and general developmental delays may be due to the high occurrence of such delays in the EarlySteps sample by nature of the program.

The sex ratio was also examined in relation to the severity of autistic symptoms, as measured by the severity ranges of the BISCUIT- Part 1. Although there was not a statistically significant difference between the severity ranges, a lower sex ratio (2.71) was found amongst cases in the "No ASD" range, with the least severe symptomatology, compared to cases with more severe symptomatology. Sex ratio estimates of 3.16 were found for cases in both the "Possible ASD" and "Probable ASD" symptom severity ranges. These findings refuted the hypothesis that a lower sex ratio would be associated with more severe ASD symptoms. Children with less severe autistic symptoms may be less likely to be included in the EarlySteps sample, as they have been found to be identified with ASD at older ages (Adelman, 2011; Fountain, King, & Bearman, 2011; Twyman, Maxim, Leet, & Ultmann, 2009). The low sex ratio in the "No ASD" range is most likely due to the low number of cases (N = 26) that scored in this range whilst meeting diagnostic criteria for ASD.

Perinatal factors. Perinatal factors such as premature birth and birth weight have been highlighted in the literature as risk factors for ASD (Ben-Itzchak & Zachor, 2014; Gardener et al., 2011; Kuzniewicz et al., 2014; Lampi et al., 2012). Previous research on the ASD sex ratio has found that lower M/F ratios are associated with low gestational age and low birth weight (Schendel & Bhasin, 2008; Zachor et al., 2013), indicating that these risk factors may

disproportionately affect females. Results from the present study were in line with these previous findings. The M/F ratio was significantly lower amongst cases with premature birth (2.11) compared to cases born full-term (3.29). Significantly lower ratios were also found amongst cases with very low (< 1500 g; 1.90) and low (1500 - 2499 g; 2.05) birth weight compared to those with normal (≥ 2500g; 3.79) birth weight. These findings are of particular interest, as they lend support to the multi-factorial model, which proposes that the sexes are differentially impacted by risk factors, with certain risk factors more likely to increase underlying genetic susceptibility and act as causal pathways to ASD among females vs. males (M. C. Lai et al., 2014; Werling & Geschwind, 2013).

Interestingly, both premature birth and very low birth weight decreased the odds of ASD classification, in contrast to previous findings. Children born full term were 1.338 times more likely to be classified with ASD compared to children born prematurely, and children weighing ≥ 1500 g at birth were 1.468 times more likely to be classified with ASD compared with children weighing < 1500. Sex was not found to moderate the relationship between these factors and ASD classification, suggesting that males and females were not differentially impacted in terms of risk associated with prematurity and very low birth weight. These findings again may be reflective of the nature of the EarlySteps sample, as children born prematurely or with low birth weight may be at greater risk for ASD compared to typically developing children but at lower risk compared to those with other developmental difficulties.

Children born as part of multiple births have been found to have increased risk for ASD compared to those born in a singleton birth (Croen, Grether, & Selvin, 2002; Gardener et al., 2011). However, no previous studies were found that examined this risk factor in relation to the ASD sex ratio. This study found a lower sex ratio (2.78) amongst cases born as part of multiple

births compared to those in a singleton birth (3.09), although this difference was not statistically significant. While this finding provides some suggestion that multiple births may increase the risk of ASD for females, regression analysis revealed that multiple births was not a significant predictor of ASD classification and that sex did not moderate the relationship between multiple births and ASD classification.

Parental age. The possible association between advanced parental age and the occurrence of ASD has been a research focus for some time because such a relationship would have important implications about the etiology of ASD (Durkin et al., 2008; Sandin et al., 2016; Tsai & Stewart, 1983). Advanced maternal and paternal age are associated with d*e novo* mutations, which have been demonstrated to play an important role in the underlying genetics of ASD (Kong et al., 2012; Puleo et al., 2012; Sebat et al., 2007). The current study found a significantly lower sex ratio among cases with advanced maternal age (1.91) compared to those with lower maternal age (3.41). While a lower M/F ratio was also found amongst cases with advanced paternal age (2.54) compared to those with younger parental age (3.30), the difference was not statistically significant. These results are somewhat similar to those found previously by Anello and colleagues (2009), who found significantly lower sex ratios with advanced paternal age and non-significantly lower sex ratios with advanced maternal age, and those found by Zachor and colleagues (2013), who found non-significantly lower sex ratios in relation to both advanced maternal and paternal age. These results collectively indicate that *de novo* mutations are likely to affect males and females similarly, suggesting risk loci on the X chromosome.

Previous findings regarding the association between parental age and ASD are mixed, with some studies finding an association between only advanced maternal age (King et al., 2009), others only with advanced paternal age (Hultman et al., 2011; Reichenberg et al., 2006),

some with both (Croen et al., 2007; Lampi et al., 2013), and some indicating that the relationship between maternal and paternal age is of more importance (Idring et al., 2014; Parner et al., 2012; Sandin et al., 2016). The current study found that neither advanced maternal age nor advanced paternal age were significant predictors of ASD classification. However, sex was found to moderate the relationship between advanced maternal age and ASD classification, with females with mothers aged 35 and older at time of birth having 1.628 times the odds of being classified with ASD compared to their male counterparts. In contrast, the interaction between paternal age and ASD classification was not moderated by sex. While these findings suggest that advanced maternal age may be a risk factor for females but not males, which may have important implications for understanding underlying genetic mechanisms, it should be noted that other studies have not found significant differences in the risk between the sexes for either advanced maternal or paternal age (Croen et al., 2007; Sandin et al., 2016). Additionally, when controlling for significant predictors of ASD (i.e., cognitive delay, premature birth, birth weight, multiplex families), the interaction between maternal age and ASD classification was no longer significant, suggesting that this differential risk may be associated with other risk factors.

Simplex vs. multiplex families. Multiple occurrences of ASD within sibling groups is considered to be an indication of increased genetic burden for ASD (Constantino et al., 2010). The threshold model of ASD male predominance posits that females require a heavier genetic load compared to males in order for ASD to be evinced (Constantino & Charman, 2012; Kirkovski et al., 2013; M. C. Lai et al., 2014; Werling & Geschwind, 2013). If the threshold model holds, a lower sex ratio would be expected in multiplex families compared to simplex families. A sex ratio of 2.77 was found amongst ASD cases from multiplex families, which was lower than that the 3.13 ratio found amongst cases from simplex families. While this difference

was not significant, this finding is notable as previous research examining the ASD sex ratio amongst children from simplex and multiplex families is limited. One known previous study found a significantly higher sex ratio amongst cases from simplex families compared to multiplex families (Constantino et al., 2010). The results of the current study mirror those found by Zachor and colleagues (2013), who also found a lower sex ratio amongst cases from simplex families compared to multiplex, but with a non-statistically significant difference between them. While the trend found across studies lends some support to the threshold model, further research is needed to gain more confidence in this theory.

Comorbid disorders. The ASD sex ratio was examined in relation to a number of co-occurring neurological and medical conditions. A significantly lower M/F ratio was found amongst ASD cases with comorbid seizure disorder (2.75) versus those without (3.18). This is reflective of previous findings indicating that females with ASD have co-occurring epilepsy at higher rates compared to males with ASD (Amiet et al., 2008; Ben-Itzchak et al., 2013; Bolton et al., 2011; El Achkar & Spence, 2015; van Bakel et al., 2015). The underlying neurobiology and/or genetic abnormalities thought to be shared by ASD and epilepsy (Brooks-Kayal, 2010) may differentially impact males and females, lending support to the threshold and multi-factorial models. Lower sex ratios were also found amongst cases with comorbid cerebral palsy (2.71) compared to those without (3.17), as well as amongst cases with comorbid GDD (2.75) versus those without (3.18). However, the differences between sexes for the two disorders were not statistically significant. From the EarlySteps sample, only 6 male cases were found to meet ASD classification with co-occurring cerebral palsy; no female cases were found. This may reflect a significant difference in the sex ratio related to cerebral palsy or may simply be reflective of the small number of affected cases.

Race/ethnicity. Previous findings indicate that children from racial/ethnic minorities experience greater difficulties receiving an ASD diagnosis and accessing ASD related services (Jarquin et al., 2011; Magaña et al., 2012; Mandell et al., 2009; Morrier & Hess, 2012). Given that females are also at risk for delayed and misdiagnosis (Dworzynski et al., 2012; Goin-Kochel et al., 2006; Manning et al., 2011; Rosenberg et al., 2011; Shattuck et al., 2009), females of minority background may be at increased risk. Yeargin-Allsopp and colleagues (2003) found a higher ASD sex ratio (4.3) among African American children compared to white children (3.8), suggesting that African American females may be underdiagnosed. Findings from the current study did not replicate this trend. Lower M/F sex ratios were found amongst African American children (2.84), Hispanic children (2.80), and children from other racial/ethnic backgrounds (2.73) compared to white children (3.15). However, these results should be interpreted with caution, as the ASD classification used for research purposes is not equivalent to a medical diagnosis. Children from minority backgrounds classified with ASD in this study may still encounter delays and barriers to receiving a clinical ASD evaluation and diagnosis.

Number of risk factors. Based on the multi-factorial model of male predominance, it was hypothesized that females with ASD would be affected by a higher number of risk factors compared to males with ASD. This hypothesis was supported, as the mean number of risk factors was found to be significantly higher for females classified with ASD (M = .579) compared to males classified with ASD (M = .418). This finding supports the multi-factorial model, which posits that females require a higher burden of biological and environmental risk factors for ASD to be expressed.

Strengths and Limitations

Limitations of this study should be considered when interpreting results. Most notably, these findings are based on data obtained from a sample of children at greater risk for developmental concerns than the general population, and thus may not be generalizable. Additionally, while similar classification methods have been used in a number of prevalence studies (Fombonne, 2009), the ASD classification used within the study for research purposes is not equivalent to a medical diagnosis of ASD based on comprehensive clinical assessment. However, this study had several important strengths that counterbalance these limitations. The sample of participants with a range of developmental issues and risk factors allowed for the examination of a large number of factors associated with ASD. Additionally, the large sample size provided a large sample of females, allowing for an examination of the sex ratio and the moderating effect of sex in relation to these many risk factors, which has not been possible in previous studies.

Future Directions

Working towards a better understanding of the relationship between the ASD sex ratio and ASD phenotypes and risk factors will inform the knowledge base related to the underlying neurobiological and genetic mechanisms of the disorder. To this end, it is critical that future research focuses on estimating the ASD sex ratio based on representative general population samples to avoid clinical ascertainment bias and potential biases within diagnostic criteria, measurement tools, and assessment procedures. Estimates of the sex ratio based on current *DSM-5* diagnostic criteria will be of particular importance given the numerous changes in diagnostic criteria over the past several decades. Studies examining specific risk factors associated with ASD in relation to the sex ratio are also needed. Advanced parental age and

familial history of ASD are of special interest given the potential to provide insight into genetic mechanisms. A meta-analysis of studies with large ASD samples that examine risk factors would be of interest, as it would allow for the investigation of a larger number of female subjects across studies.

Continued research on gender differences in the presentation of ASD symptoms is needed to further understanding of symptom presentation among females. Research on gender differences in the expression of symptoms in relation to cognitive functioning and comorbid disorders will shed light on possible biological mechanisms. However, as both biological and psychosocial contributors to gender differences should be considered, a biosocial framework would be useful for situating such work. Longitudinal studies examining the presentation of ASD symptoms among males and females would provide valuable insight into gendered socialization. Additionally, further research should be conducted examining whether females are less likely to be diagnosed with ASD, as well as examining characteristics of females above and below the diagnostic threshold of autistic traits. Such research will be critical in regards to understanding and interpreting sex ratio estimates.

Research related to ASD etiology has made many advances in recent years, especially in the fields of genetics and neuroscience, leading to a complex picture of multi-causalities moderated by multiple risk factors. Further research on the male predominance in ASD related to symptom presentation, neurological phenotypes, pre- and perinatal risk factors, and demographic factors will be critical in working towards a cohesive understanding of ASD etiology.

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VITA

Maya Matheis is originally from Pawling, New York. She received her Bachelor of Arts from Bard College at Simon's Rock, where she double-majored in psychology and photography. She received her Masters of Social Work from the George Warren Brown School of Social Work at Washington University in St. Louis, with concentrations in child mental health and research methodology. Her clinical and research interests include the assessment and treatment of autism spectrum disorder and other neurodevelopmental disorders. She is currently completing her predoctoral internship at the University of California Davis MIND Institute. Maya anticipates graduating with her Doctor of Philosophy in August 2019. She will continue her work in the autism field thereafter as a postdoctoral fellow at the University of California Davis MIND Institute.