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Female autism phenotypes investigated at different levels of language and developmental abilities

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Abstract

This study investigated the differences in clinical symptoms between females and males with Autism Spectrum Disorder (ASD) across three verbal ability groups (nonverbal, phrase and fluent speech), based on Autism Diagnostic Observation Schedule module administered to 5,723 individuals in four research datasets. In the Simons Simplex Complex (SSC) and Autism Treatment Network (ATN), females with ASD and phrase or fluent speech had lower cognitive, adaptive, and social abilities than males. In the Autism Genetics Resource Exchange (AGRE) and the Autism Consortium (AC), females with phrase or fluent speech had similar or better adaptive and social abilities than males. Females who were nonverbal had similar cognitive, adaptive, and social abilities as males. Population-based longitudinal studies of verbally fluent females with ASD are needed.

Keywords

Autism Spectrum Disorder; Sex differences; Diagnosis of autism spectrum disorder

INTRODUCTION

The diagnosis of Autism Spectrum Disorder (ASD) is based on clinical behavioral characteristics, including persistent deficits in social communication, as well as restricted and repetitive patterns of behavior and interests (American Psychiatric Association, 2013).

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Males are more likely to be diagnosed with ASD than females, with an approximate male-to-female ratio of 4:1 (ADDM, 2014). More females are diagnosed among children with ASD and profound intellectual disability (male-to-female ratio reaching to 1.3:1), than among children without intellectual disability (male-to-female ratio reaching 8:1) (Fombonne, 2003; Scott, Baron-Cohen, Bolton, & Brayne, 2002; Yeargin-Allsopp et al., 2003). The lower proportion of females among those with ASD without intellectual disability might indicate that females with higher cognitive ability have symptoms that are either different or more subtle than in males, and could therefore lead to under-recognition and delay in diagnosis (Goldman, 2013; Lai et al., 2015). One study of ASD traits among children in a general school population found that at similar levels of ASD-related symptoms, girls were less likely than boys to meet diagnostic criteria for ASD (Dworzynski, Ronald, Bolton, & Happe, 2012), supporting this suggestion.

Early studies into sex differences in ASD examined primarily participants with intellectual disability. These studies found no differences in ASD symptomatology among males and females outside of those related to lower IQ found in females (Konstantareas, Homatidis, & Busch, 1989; C. Lord et al., 1989; C. Lord, Schopler, & Revicki, 1982; Volkmar, Szatmari, & Sparrow, 1993). Subsequent studies focused on individuals with higher IQ, but findings were inconsistent between studies. Some studies have indicated that females have better social communication skills (Lai et al., 2011), while others have indicated no differences between the sexes (Holtmann, Bolte, & Poustka, 2007; Mandy et al., 2012). One study has suggested worse social and behavioral problems for females with ASD (Holtmann et al., 2007). In analyzing restricted, repetitive patterns of behaviors one study found that females with higher IQ scores had less severe symptoms (Mandy et al., 2012). A recent study by Frazier et al. utilized the Simons Simplex Complex (SSC) dataset (Frazier, Georgiades, Bishop, & Hardan, 2014), a large national clinically ascertained dataset which included families with only one child with ASD. In this simplex population, females with ASD had overall more impairments than males with ASD in terms of social-communicative abilities, cognitive and adaptive abilities, and externalizing behaviors. As with prior studies, full-scale IQ appeared to mediate differences in social-communicative and adaptive abilities. The investigators also found lower levels of restricted interests but greater irritability in females, both of which were independent of IQ. Taken together, these studies suggest some differences in ASD symptoms between males and females, particularly among individuals with higher IQ. However, a clear and consistent picture of the female ASD phenotype has not yet emerged in the literature, perhaps due to a large variation in age, intellectual ability, sample size, diagnostic measures, and ascertainment strategies used across studies (Lai et al., 2015).

National datasets provide an opportunity to examine sex differences among individuals with ASD based on large sample sizes and a consistent diagnostic approach, utilizing standardized diagnostic measures. The primary goal of this study was to evaluate sex differences in communication abilities, daily living skills, social skills, adaptive behavior, internalizing and externalizing problems in three subgroups of individuals with ASD based on their verbal ability (minimally verbal, phrase and fluent speech) across four national datasets: the Autism Genetics Resource Exchange (AGRE), Autism Consortium (AC), Autism Treatment Network (ATN), and Simons Simplex Collection (SSC).

METHODS

Participants

Data from four datasets were used in this study: Autism Genetics Resource Exchange (AGRE), Autism Consortium (AC), Autism Treatment Network (ATN), and Simons Simplex Collection (SSC). All datasets included the Autism Diagnostic Observation Schedule (ADOS; C. Lord, DiLavore, & Risi, 2002) as part of the standard battery of instruments, but other measures varied across datasets. In all studies the ADOS was used to verify ASD diagnosis, and the Autism Diagnostic Interview-Revised (ADI-R; Rutter, Le Couteur, & Lord, 2003) was also used when it was available.

Autism Genetics Resource Exchange (AGRE) is a national DNA repository and family registry, housing a database of genotypic and phenotypic information on primarily families with more than one family member affected by ASD (C. M. Lajonchere, 2010). Individuals and families were recruited during community events.

Autism Consortium (AC) is a research and clinical collaboration containing patient information from Boston-area clinically based sites (Shen et al., 2010). Genotypic and phenotypic information was collected on parents and siblings, as well as the affected child. About 10% of ASD participants in this dataset were classified as an affected sibling. About 60% of the subjects were referred from clinic and 40% were recruited through other sources such as community events, website, Interactive Autism Network, and other activities. For this study, AC participants were limited to only those administered ADOS module 3, which is for those with fluent speech, due to limited availability in other groups.

Autism Speaks Autism Treatment Network (ATN) is a patient registry aimed at clinical treatment of ASD that includes information collected from 17 participating clinical sites around the U.S. and Canada (Coury, Jones, Klatka, Winklosky, & Perrin, 2009; C. Lajonchere, Jones, Coury, & Perrin, 2012). About 2% of children enrolled in the ATN also have a sibling with ASD enrolled in the database.

Simons Simplex Collection (SSC) is a dataset including information from 12 clinical sites across the U.S. and Canada. Only families with one child with an ASD diagnosis were recruited to the study (Fischbach & Lord, 2010). The SSC contains genotypic as well as phenotypic information about each affected child, and their unaffected siblings and parents. More than 80% of families have at least one unaffected child.

Measures

Autism Diagnostic Observation Schedule (ADOS) is a semi-structured, standardized assessment of communication, social interaction, play, and restricted and repetitive behaviors. It presents various activities that elicit behaviors directly related to a diagnosis of ASD (Gotham, Risi, Pickles, & Lord, 2007; C. Lord et al., 2000). The ADOS is a widely used tool that has become a “gold-standard” assessment, used in conjunction with caregiver history and clinician judgment, for the diagnosis of ASD in clinical and research settings (de Bildt et al., 2004).

IQ Measures—The cognitive measures varied for each dataset. The cognitive measure used in the AGRE was the Stanford-Binet Intelligence Scales, 5th edition (SB-V; Roid, 2003). In the ATN, an overall IQ score was available, which is based on a SB-V full scale IQ or abbreviated battery. In the AC, an overall IQ score was based on testing using the Differential Abilities Scales (DAS) Early Years and School Years (C. D. Elliott, 1990), the Wechsler Abbreviated Scale of lntelligence (WASI; Wechsler, 1999), the Wechsler Preschool and Primary Scale of lntelligence-Third Edition, 4.0–7.3 (WPPSI-4.0–7.3; Wechsler, 2002), or the Wechsler lntelligence Scale for Children-Fourth Edition (WISC-IV; Wechsler, 2004). In the SSC, the majority of participants completed the DAS and a minority completed other cognitive assessments.

Other Measures—Adaptive functioning was assessed using the Vineland Adaptive Behavioral Scales (VABS; Sparrow, Cicchetti, & Balla, 2005), a widely used standardized assessment of adaptive functioning. Chronological age, gender, geographic region, parent education, race or ethnic group, and community size were considered during the standardization and norm development processes of the VABS, which is based on a national US sample. Severity of ASD traits and symptoms were measured using the Social Responsiveness Scale (SRS), a 65-item parent reported questionnaire (Constantino et al., 2003). The SRS reports scores as T-scores for clinical use, and also reports a raw score for use in research settings. Higher raw scores represent more severe ASD-related symptoms. These scales were created for comparing severity between participants and within the same subject over time, and vary less with IQ and age than do ADOS raw total scores. Emotional functioning was assessed using the Child Behavior Checklist (CBCL) version for school-aged participants (aged 6 to 18 years), a parent-rated questionnaire standardized for evaluating maladaptive behavioral and emotional problems in children (Achenbach & Rescorla, 2001). This tool provides gender- and age-based norms, and generates a T-score, with a mean of 50 and standard deviation of 10 in the aforementioned areas, with higher scores representing more severe difficulties.

Data Analysis

While matching IQ is commonly used approach to create comparisons in individuals with ASD, in many datasets there is limited full scale IQ data for those who have less verbal ability. Instead, verbal and nonverbal IQ proxy measures such as Peabody Picture Vocabulary test and Ravens Colored Progressive Matrices are used. In individuals with ASD, however, these measure are not always a reliable measure of true abilities (Mottron, 2004). In this study we followed the model proposed by Gotham et al. in the revised algorithm for the Autism Diagnostic Observation Schedule (Gotham et al., 2007), dividing participants into groups based on verbal ability, as defined by which ADOS module was administered. ADOS module 1 is for those who are minimally verbal, and is further divided into those who used no words during the ADOS testing (ADOS 1-NW), and those who used some words (ADOS 1-SW). ADOS module 2 is for those with phrase speech. ADOS modules 3 and 4 are for those who are verbally fluent, with ADOS module 3 reserved for children and adolescents, and ADOS module 4 for adolescents and adults. We compared only those patients who met ADOS criteria and ADI-R (where available) for either autism or autism spectrum disorder. Furthermore, we limited our sample to participants who were five years of age or older, in order to ensure stability of diagnosis, and did not include adolescents or adults who were administered module 4 due to limited sample size.

Sex Differences—In this work, we considered each dataset as an independent sample. We conducted within-study sex group comparisons and analyzed each dataset independently. Within each dataset, each measure was used as a dependent variable, comparing male and female sex using two-tailed t-tests. A significance level of $p<0.05$ was used. Age was taken as age at which the ADOS was administered.

To examine whether the four datasets were different with regard to subject distribution across modules, hierarchical loglinear analysis was used. We determined if first level interactions of three variables (the dataset, module, and sex) were significant. Significant interactions were then further examined with the Chi-Square Tukey-type analysis adjusted for multiple testing with $p<0.05$ (A. C. Elliott & Reisch, 2003).

Correcting for Multiple Comparison—In order to correct for multiple testing, we utilized a False Discovery Rate (FDR) approach, based on Benjamini – Hochberg (Benjamini & Yekutieli, 2001) with the expected proportion of errors in the rejected hypotheses (actual findings) set at 0.05. We defined tests within each dataset as a contained family of hypotheses, such that the AGRE dataset contained 28 tests (seven measures across four groups: ADOS Module 1-NW, ADOS Module 1-SW, ADOS Module 2, and ADOS Module 3), the AC dataset contained 10 tests (ADOS Module 3 only), the ATN dataset contained 36 tests, and the SSC dataset contained 40 tests.

Effect sizes were examined by expressing mean differences as standardized mean differences (Cohen's d), and using thresholds for small ($d=0.20$), medium ($d=0.50$), or large ($d=0.80$) effect size as a guide to inference (J. Cohen, 1998; Kraemer et al., 2003)

Data from AGRE and AC was analyzed by author YJH, ATN was analyzed by ATN statisticians, and SSC was analyzed by author EV. JO performed False Discovery Rate analysis, loglinear analysis and Chi-Square Tukey-type analysis.

RESULTS

Participants

Table 1 summarizes the samples included in this study. The total number of participants included was 5,723 (872 females and 4,851 males). The average age of participants in each dataset was similar, ranging from 8.6 years old (ATN) to 9.7 years old (AC).

Using hierarchical loglinear analysis we determined that the interaction terms of the dataset, module and sex were significant (dataset by module $p < 0.001$, dataset by sex $p <0 .001$, and module by sex $p = 0.01$). The follow-up Chi-Square analysis, adjusted for multiple testing, revealed several differences (Table 1). In the total sample, the AGRE dataset had a greater number of females (lower male-to-female ratio) than the ATN and SSC datasets (AGRE: male-to-female ratio = 4.2, ATN: male-to-female ratio = 6.1, SSC: male-to-female ratio = 6.6, $p < 0.05$).

The proportion of participants within each ADOS module subgroup differed across the datasets. In Module 1 NW, the SSC dataset had the lowest percentage of participants (SSC: 5% vs. AGRE: 18%, ATN: 10%, $p < 0.05$); the ATN dataset also had fewer participants in this subgroup than the AGRE dataset ($p < 0.05$). In the Module 1-SW subgroup, the AGRE dataset had the highest percentage of participants (AGRE: 16% vs. ATN: 11%, and SSC: 11%, $p < 0.05$).

In the Module 3 subgroup, the SSC dataset had the highest percentage of participants (SSC: 63% vs. AGRE: 40%, AC: 52%, and ATN: 54%, $p < 0.05$); the AGRE dataset was different from the ATN dataset, having a lower proportion of subjects in this subgroup ($p < 0.05$). The SSC and ATN datasets had a lower proportion of females (higher male-to-female ratio) than the AGRE dataset (SSC: 7.7 and ATN: 6.4 vs AGRE: 4.4, $p < 0.05$).

ADOS Module 1 – Children who were nonverbal

We did not find any differences between sexes among those administered Module 1 of the ADOS (Table 2). Average IQ scores for this subgroup were in the range of intellectual disability, with corresponding Vineland scores. SRS scores were generally high, and CBC data, where available, were higher than average as compared to the general population.

ADOS Module 2 – Children who use phrase speech

Table 3 shows that females had lower Full Scale IQ scores (ATN: $IQ_{Female} = 61$, $IQ_{Male} = 74$, $d = 0.57$, $p < 0.001$; SSC: $IQ_{Female} = 62$, $IQ_{Male}=69$, $d = 0.41$, $p = 0.002$), lower Vineland communication scores (ATN: $Comm_{Female} = 70$, $Comm_{Male}=76$, $d = 0.50$, $p = 0.001$; SSC: $Comm_{Female} = 71$, $Comm_{Male} = 74$, $d = 0.33$, $p = 0.01$), lower daily living skills (ATN: $DLS_{Female} = 71$, $DLS_{Male}=76$, $d = 0.40$, $p = 0.009$), and lower socialization skills in both Vineland (ATN: $Soc_{Female} = 68$, $Soc_{Male} = 72$, $d = 0.33$, $p = 0.013$) and SRS measures (SSC: $Soc_{Female} = 106$, $Soc_{Male} = 99$, $d=0.28$, $p = 0.03$). As Table 3 shows, only Vineland communication and daily living skills in the ATN dataset survived Benjamini-Hochberg correction for false discovery rate in this group.

Females in the SSC dataset had a higher CBCL T-score (more impairment) in externalizing symptoms (SSC: $Ext_{Female} = 59$, $Ext_{Male}=56$, $d = 0.42$, $p = 0.01$) and, as a result, in the number of total problems (SSC: $Tot_{Female} = 64$, $Tot_{Male} = 61$, $d = 0.33$, $p = 0.03$).

ADOS Module 3 – Children and adolescents who are verbally fluent

As shown in Table 4, among children and adolescents who are verbally fluent, IQ scores were similar for females and males across datasets, with the exception of one dataset where females had a lower IQ scores than males (SSC: $IQ_{Female} = 91$, $IQ_{Male} = 95$, $d = 0.20$, $p = 0.02$). Females had lower Vineland daily living skills (SSC: $DLS_{Female} = 79$, $DLS_{Male} = 81$, $d = 0.17$, $p = 0.04$). Females had better social skills in both Vineland (AGRE: $Soc_{Female} = 70$, $Soc_{Male} = 67$, $d = 0.21$, $p = 0.05$; AC: $Soc_{Female} = 84$, $Soc_{Male} = 75$, $d = 0.69$, $p = 0.005$), and SRS measures (AGRE: $Soc_{Female} = 89$, $Soc_{Male} = 97$, $d = 0.25$, $p < 0.05$; AC: $Soc_{Female} = 78$, $Soc_{Male} = 96$, $d = 0.68$, $p < 0.01$). Females in one dataset had fewer internalizing problems (AC: $Int_{Female} = 56$, $Int_{Male} = 62$, $d = 0.59$, $p = 0.042$), and in another dataset females had more externalizing problems (ATN: $Ext_{Female} = 61$, $Ext_{Male}=59$, $d=0.21$, $p =$

0.044). CBC total problem score was therefore conflicting in these two datasets, with less impairment overall for girls in one (Tot_{Female} = 58, Tot_{Male} = 64, d = 0.33, p = 0.028) and greater impairment in the other (ATN: Tot_{Female} = 68, Tot_{Male} = 66, d = 0.22, p = 0.023). As Table 3 shows only the finding of higher Vineland socialization scores for girls in the AC dataset survived Benjamini-Hochberg correction for false discovery rate.

DISCUSSION

In this study we examined sex differences in behavioral characteristics of 6,126 children and adolescents with ASD with a range of developmental functioning using data from four autism research datasets. Differences found between sexes varied based on the subjects' verbal abilities (key findings are summarized in Table 5).

Among nonverbal children (ADOS Module 1), we found no differences between males and females on measures of cognitive, adaptive, and social abilities. This demonstrates on a larger scale what was found in early literature focused on patients with ASD and intellectual disability (Konstantareas et al., 1989; C. Lord et al., 1982; Volkmar et al., 1993). However, among individuals with ASD who used phrase speech (ADOS Module 2) females in both the ATN and SSC datasets were more severely affected, having lower IQ, worse social functioning and more externalizing behavior problems as compared with males. This was not replicated in the AGRE dataset.

In contrast, among individuals with fluent speech (ADOS Module 3), females in both the AGRE and AC datasets had better social skills as compared with males in this subgroup. These findings are consistent with recent research suggesting that females with ASD who have higher cognitive abilities may have better social communication skills and social abilities than males with ASD (Lai et al., 2011; Mandy et al., 2012). This adds further support to the suggestion that verbal abilities may mediate ASD risk more so for females than males, particularly among those with greater verbal abilities (Skuse et al., 2009).

In this study we found differing results with regards to the emotional and behavioral profiles of females as compared with males with ASD and fluent verbal ability. Two datasets demonstrated worse externalizing problems for females (ATN module 3; SSC module 2), and another demonstrating less severe internalizing problems (AC module 3). This differs from previous studies showing that females with ASD and higher intellectual abilities may have more internalizing problems than males (Mandy et al., 2012; Solomon, Miller, Taylor, Hinshaw, & Carter, 2012). However, the average scores on CBCL for both males and females with ASD were elevated as compared with the normative sample (higher T-scores), so it is worth emphasizing that symptoms for females may still be significant, even if rated differently than for males.

A recent study examining sex differences in the SSC dataset found that females with ASD had more impairments in social communication, lower cognitive ability, weaker adaptive skills, and greater externalizing problems as compared to males with ASD (Frazier et al., 2014). Our study had similar findings in the SSC dataset (in ADOS Modules 2 and 3) as the study by Frazer et al., because we analyzed the same data. Furthermore, the analysis of the

ATN dataset in our study also supported findings by Frazier et al, particularly with the ADOS Module 2 subgroup. However, these results were not replicated in all datasets. Among participants with greater verbal abilities (ADOS Module 3), we did not find statistically significant differences between males and females in IQ, communication or daily living skills in the AGRE, AC, or ATN datasets. However, females were rated as having better social skills (in AC and AGRE) and less severe internalizing problems (in AC) as compared with males in this subgroup.

It is possible that our results are affected by ascertainment strategies utilized by the studies, such as recruiting simplex versus multiplex ASD pedigrees. The SSC dataset included only families with one child affected with ASD. The ATN dataset also had very few siblings in their dataset, though not exclusive of siblings. The AGRE primarily recruited families with more than one family member affected by ASD. The AC also included siblings with about 10% of affected individuals classified as siblings. The research datasets also vary in whether participants are recruited from community events or clinical centers.

The proportion of females represented also varies between datasets. The male-to-female ratio was 4.2 in the AGRE and AC datasets, and 6.1 and 6.6 in the ATN and SSC datasets, respectively. The proportion of females was lower among participants with ASD who had fluent speech (ADOS Module 3): 4.4 in the AGRE dataset, 5.9 in the AC dataset, 6.4 in the ATN dataset, and 7.7 in the SSC dataset. The lower proportion of females noted in the SSC as compared with the other datasets suggests that perhaps in families where there is only one child with ASD, females with higher functioning ASD must have more severe symptoms in order to alert caregivers to seek a diagnosis of ASD. This raises the question of whether there might be a "coattail" effect, where females might be more likely to be diagnosed with ASD in families already attuned to ASD symptoms seen in an older sibling.

Inconsistency in findings between multiplex and simplex studies was also demonstrated by Banach et al. (Banach et al., 2009) who, in a study of 194 simplex families and 154 multiplex families, found that in simplex families, females had a lower IQ than boys, but did not find a gender difference in cognition among ASD subjects from multiplex families. In contrast with that study, however, we did not find the very low male-to-female ratio of around 1.1:1 found in their study among subjects from simplex families who had severe intellectual disability (IQ <50). Instead, we found a higher male-to-female ratio in the SSC among nonverbal subjects of 5.2:1. Similar to findings by Banach et al. and our present study, an analysis of ASD infant sibling cohorts, Zwaigenbaum et al. (Zwaigenbaum et al., 2012) also only found subtle cognitive differences between the genders. Other than differences in parental detection of ASD symptomatology among females in simplex and multiplex families, another possibility is that etiologies that result in a simplex pedigree might be more likely to result in more cognitive impairment and ASD phenotype for females. In twin studies, Constantino and Todd found no evidence for the existence of sex-specific genetic influences, and suggested that females may be relatively protected from vulnerability to autistic traits (Constantino & Todd, 2003). The SSC was designed specifically to identify de novo mutations such as copy number or sequence variants that have been shown to contribute to ASD risk (Cook & Scherer, 2008; Fischbach & Lord, 2010), and it may be that in these families, milder autistic symptoms are less likely to be seen as pathologic, or that females are "protected" by biological or environmental factors from ASD symptoms (Robinson, Lichtenstein, Anckarsäter, Happé, & Ronald, 2013).

Another possibility for differences between datasets is that clinically-referred samples may be heterogeneous with regards to the level of symptoms that lead to referral. In the ATN dataset, for example, no differences were noted between males and females in Module 3, except that females had worse externalizing symptoms, suggesting that females may need a greater level of outwardly visible symptoms in order to be referred for evaluation. Population studies have suggested that in children with higher cognitive abilities, greater discrepancies between male and female prevalence could be the result of misdiagnosis, under-reports by caregivers and parents, and thus lower treatment rates in females (Kim et al., 2011; Mattila et al., 2011). Kim et al. conducted a large population-based study consisting of 55,266 children between ages 7–12 years old in general and special education schools in South Korea (Kim et al., 2011). Subjects were screened for ASD symptoms, using the Autism Spectrum Screening Questionnaire (Ehlers, Gillberg, & Wing, 1999), and the authors performed diagnostic evaluation of the children who met scoring cutoffs. They found that 1.89% of those in the general education setting and 0.75% in the special education setting met criteria for ASD. Up to two-thirds of these children had not been previously diagnosed. Of those with new diagnoses, children in the general education setting had a higher proportion of females diagnosed as having ASD as compared with those in the special education setting (male-to-female ratio of 2.5 versus 5.1). Although cultural and societal issues may make this study less generalizable to settings in the U.S., it still raises the possibility that girls with ASD with fewer cognitive concerns may be less likely to be referred for evaluation. In our study, Vineland scores were also in an impaired range for females with ASD who had average IQ, highlighting the need for support services for these individuals and suggesting that there may still be more girls who have impaired daily living skills that may not be evaluated due to adequate perceived social functioning.

A recent large population-based study of 14,997 newly diagnosed cases of ASD in Denmark found that incidence rates for ASD between 1995 and 2010 had increased four times (from 9.0 to 38.6 per 100,000 person years) (Jensen, Steinhausen, & Lauritsen, 2014). Among new diagnoses the number of females has significantly increased, reducing male-to-female ratio from 5.1 to 3.1. Furthermore, new diagnoses in the milder form of autism such as Asperger's syndrome and pervasive developmental disorder-not otherwise specified (PDD-NOS) accounted for the majority of the increase. However, females were at an older age (11 years) as compared with males (9 years). Altogether, this study suggests that prior to 1995 many girls with milder form of autism where not diagnosed and even now girls may be diagnosed at later ages than males, due to a less severe phenotype.

In the United States, the Centers for Disease Control conducts a surveillance program through the Autism and Developmental Disabilities Monitoring (ADDM) Network that includes eleven sites across the US (Centers for Disease Control, 2014), based on school and medical record review of children aged 8 years. Results from the most recent ADDM analysis indicated that the prevalence of ASD in the US has increased from 6.6 per 1,000 in 2002 to 14.7 per 1,000 in 2010. As in Denmark (Jensen et al., 2014), this increase was largely due to the growing number of children who have an average or above average level of intellectual ability. However, the ADDM study found that the male-to-female ratio in the US has not changed, staying relatively constant between 4 and 5 (Centers for Disease Control, 2014). It is possible that girls with higher-functioning ASD may still be missed at age 8 years, as suggested by the older age of diagnosis noted in the study conducted in Denmark.

Limitations

This was not an epidemiological, population-based study, specifically designed to evaluate sex differences in individuals with ASD. This study was limited to a convenience sample of participants who had already received a diagnosis of ASD, and who were ascertained using specific study criteria not directly related to the focus of this study. However, this study highlights a possible bias--even for large-scale national datasets--towards male phenotype for diagnosis and thus study recruitment. This can be seen by the elevated male-to-female ratios in clinically-recruited as compared to community-recruited datasets, with male-to-female ratios in community recruited datasets similar to the latest CDC estimates (Centers for Disease Control, 2014).

Furthermore, as summarized in a recent review article on sex differences in ASD (Lai et al., 2015), comparing males and females with ASD this way may be confounded by normative sex differences; however using measures that have been developed for use in a general population, helps to address this concern.

We grouped participants based on their verbal ability as indicated by the ADOS module they were administered. Although this allowed us to make subgroups for comparison, this approach has not been widely used. Accurately measuring cognitive abilities in individual of ASD has not been established as different measures can provide different findings (Bolte, Dziobek, & Poustka, 2009). The majority of previous studies controlled phenotypic measure for IQ or enrolled participants with a pre-specified IQ range to create more homogeneous subgroups. The suggestion by prior research of a relationship between verbal IQ and risk of ASD supports grouping participants by verbal abilities (Skuse et al., 2009). However, some researchers have questioned utility of ADOS among females with ASD with higher IQ due to the ability of these females to imitate appropriate social skills and mask any weaknesses (Lai et al. 2011). Therefore, in addition to the possible male bias in the research datasets, as mentioned above, we may have excluded females with more subtle ASD symptomatology that is not detected by ADOS.

Despite the limitations described above, this study independently examined four national autism datasets that used state-of-the-art assessment batteries and identified patterns of sex differences that were replicated in more than one dataset.

Conclusion

In summary, sex differences in ASD exist across a range of developmental functioning, and are sensitive to ascertainment methods. Differing results were seen among four large national datasets; two datasets had a significantly greater proportion of females (AGRE and AC) than the other two datasets (ATN and SSC). Two key findings were replicated in at least two datasets, indicating the following pattern. Among individuals with ASD who were minimally verbal, females had similar cognitive, adaptive, and social abilities as males in all datasets. Among individuals with ASD who used phrase-level speech or were verbally fluent, differences in male and female profiles are present. In two datasets (ATN and SSC) females who used at least phrase speech had lower cognitive, adaptive, and social abilities, as well as more externalizing symptoms than males in the same subgroups. However, in the other two datasets (AGRE and AC) females with ASD in the phrase and fluent speech groups had similar or better adaptive and social abilities than males. We hypothesize that the discrepancy in findings between datasets might reflect different ascertainment strategies and recruitment of female subjects. This study contributes to literature suggesting need for wider population-based and longitudinal studies into possible sex-specific symptom profiles in ASD, particularly among verbally fluent females with ASD. This work also contributes to an emerging literature suggesting that girls in higher-functioning categories of ASD may not be diagnosed, despite having significant levels of cognitive, communication, adaptive skill and emotional/behavioral impairments.

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The Autism Consortium is a Boston-based clinical and research collaboration, with 17 institutional members and 125 individual scientist and clinician members, who are collectively dedicated to catalyzing progress in understanding autism and related neurodevelopmental disorders in order to improve diagnosis, clinical care and treatment. With data and samples collected from 525+ families who participated in clinical research, the Consortium's repository is made available for use by the autism research community. The authors are grateful to the Consortium, its members and the families who have made this vital resource possible.

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Table 1

Description of the study population in each of 4 datasets, sub-grouped by which Autism Diagnostic Observation Schedule (ADOS) module was administered

	Autism Genetics Resource Exchange (AGRE)		Autism Consortium (AC)		Autism Treatment Network (ATN)		Simons Simplex Collection (SSC)	
	% in mod (N)	M:F	% in mod (N)	M:F	% in mod (N)	M:F	% in mod (N)	M:F
All Subjects, N [a]	1631	4.2	151	4.2	1680	6.1	2261	6.6
Age in years, Males, Mean (SD)	9.4 (3.5)		10.1 (4.2)		8.6 (3.0)		9.6 (3.3)	
Age in years, Females, Mean (SD)	9.1 (3.3)		9.7 (3.6)		8.8 (2.9)		9.9 (3.5)	
ADOS Module 1 – No words [b]	18% (324)	4.4	--	--	10% (174)	5.7	5% (127)	6.9
ADOS Module 1 – Some words [c]	16% (279)	3.1	--	--	11% (193)	5.7	11% (252)	4.6
ADOS Module 2	18% (326)	4.6	--	--	22% (378)	6.3	18% (420)	5.1
ADOS Module 3 [d,e]	40% (702)	4.4	100% (151)	--	54% (935)	6.4	63% (1462)	7.7

All patients met Autism Diagnostic Interview-Revised and/or Autism Diagnostic Observation (ADOS) criteria for Autism or Autism Spectrum, and were limited to those age 5 years or older. Total number of subjects in the study was 5,723 (872 females and 4,851 males).

[a] The AGRE dataset had a greater proportion of females (lower M:F ratio) than the ATN and SSC datasets ($p < .05$).

[b] The SSC dataset had the lowest proportion of subjects in the Module 1-No words subgroup as compared to AGRE and ATN datasets ($p < .05$).

[c] The AGRE dataset had the highest proportion of subjects in the Module 1-Some words subgroup as compared to the ATN, and SSC datasets ($p < .05$).

[d] The SSC dataset had the highest proportion of subjects in the Module 3 subgroup as compared to the AGRE, and ATN ($p < .05$) datasets. The AGRE dataset also differed from the AC and ATN datasets, having a lower proportion of subjects in the Module 3 subgroup ($p < .05$).

[e] The AGRE dataset had a greater number of females (lower M:F ratio) in the Module 3 subgroup than the SSC and ATN datasets ($p < .05$).

Table 2

Summary of cognitive, adaptive, and behavioral test scores by sex in subjects administered module 1 of the Autism Diagnostic Observation Schedule (ADOS) in 3 research datasets.

	Autism Genetics Resource Exchange (AGRE)				Autism Treatment Network (ATN)				Simons Simplex Collection (SSC)			
	ADOS Module 1 - No Words		ADOS Module 1 - Some Words		ADOS Module 1 - No Words		ADOS Module 1 - Some Words		ADOS Module 1 - No Words		ADOS Module 1 - Some Words	
	M	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Total Subjects	264	60	211	68	148	26	164	29	111	16	207	45
Age in years, Mean (SD)	9.0 (5.3)	9.5 (4.1)	8.9 (4.0)	8.5 (3.7)	7.7 (2.8)	7.5 (2.3)	8.2 (3.1)	7.7 (2.4)	9.2 (3.4)	8.5 (3.4)	8.7 (3.2)	9.4 (3.5)
Full Scale IQ												
Subjects with data, %(N)[a]	9% (25)	13% (8)	21% (45)	16% (11)	34% (50)	27% (7)	55% (91)	55% (16)	99% (110)	100% (16)	99% (205)	100% (45)
FSIQ, Mean (SD)	46 (11)	43 (4)	50 (12)	50 (12)	50 (9)	50 (10)	54 (13)	51 (14)	28 (11)	18 (10)	47 (18)	45 (16)
Vineland Adaptive Behavior Scales Standard Scores												
Subjects with data, %(N)[a]	78% (205)	77% (46)	75% (159)	81% (55)	91% (135)	88% (23)	92% (225)	82% (36)	98% (111)	100% (16)	100% (207)	100% (45)
Adaptive Behavior Composite Standard Score, Mean(SD)	40 (14)	37 (15)	47 (16)	49 (19)	53 (11)	55 (10)	59 (9)	60 (10)	52 (9)	55 (9)	62 (9)	60 (10)
Social Responsiveness Scale Raw Scores												
Subjects with data, %(N)[a]	54% (143)	48% (29)	65% (137)	69% (47)	0% (0)	0% (0)	0% (0)	0% (0)	98% (109)	75% (12)	99% (206)	98% (44)
Raw Total Score, Mean (SD)	125 (24)	127 (26)	122 (24)	120 (27)	-	-	-	-	113 (23)	124 (19)	112 (23)	111 (23)
Child Behavior Checklist (age 6–18 years) T-scores												
Subjects with data, %(N)[a]	0% (0)	0% (0)	0% (0)	0% (0)	52% (77)	58% (15)	55% (91)	62% (18)	76% (84)	56% (9)	56% (167)	76% (34)
Total Problems T-score, Mean(SD)	-	-	-	-	62 (9)	60 (8)	64 (7)	64 (9)	62 (8)	60 (8)	61 (8)	62 (7)

For Social Responsiveness Scale and Child Behavior Checklist, higher scores represent greater impairment.

[a]Percentage of subjects of that sex with available data for each measure.

[b]Males in SSC in ADOS Module 1-no words subgroup had higher IQ scores than females in this sub-group (d (95% CI) = 0.58 (−0.08 to 1.24); p=.04).

Table 3

Summary of cognitive, adaptive, and behavioral test scores by sex in subjects administered module 2 of the Autism Diagnostic Observation Schedule (ADOS) in 3 research datasets.

	Autism Genetics Resource Exchange (AGRE)				Autism Treatment Network (ATN)				Simons Simplex Collection (SSC)			
	M	**F**	**d (95% CI)**	**p**	**M**	**F**	**d (95% CI)**	**p**	**M**	**F**	**d (95% CI)**	**p**
Total Subjects	268	58			326	52			351	69		
Age in years, Mean (SD)	8.1 (2.9)	8.1 (2.5)	0.00 (−0.25–0.25)	.90	7.0 (2.4)	7.7 (2.4)	0.29 (0.00–0.58)	.045	8.3 (3.1)	8.9 (3.1)	0.19 (−0.06–0.45)	.14
Full Scale IQ												
Subjects with data, %(N)[a]	33% (88)	30% (17)			69% (225)	75% (39)			100% (351)	99% (68)		
Mean (SD)	68 (18)	66 (16)	0.10 (−0.35–0.55)	.69	74 (23)	61 (15)	0.57 (0.33–0.82)	<.001	69 (19)	62 (19)	0.41 (0.15–0.68)	.002
Vineland Adaptive Behavior Scales Standard Scores												
Subjects with data, %(N)[a]	84% (225)	76% (44)			91%[b] (296)	94% (49)			100% (351)	100% (69)		
Communication, Mean (SD)	67 (19)	65 (23)	0.11 (−0.27–0.48)	.54	76 (12)	70 (12)	0.50 (0.20–0.79)	.001[c]	74 (11)	71 (11)	0.33 (0.07–0.59)	.01
Daily living skills, Mean (SD)	58 (21)	58 (23)	0.01 (−0.33–0.36)	.94	76 (12)	71 (12)	0.40 (0.11–0.68)	.009[c]	73 (12)	71 (11)	0.23 (−0.01–0.48)	.07
Socialization, Mean (SD)	61 (14)	61 (17)	0.03 (−0.36–0.43)	.84	72 (12)	68 (11)	0.33 (0.05–0.64)	.013	69 (11)	66 (12)	0.26 (0.00–0.53)	.05
Adaptive Behavior Composite, Mean (SD)	59 (17)	59 (20)	0.05 (−0.33–0.42)	.78	72 (11)	68 (10)	0.36 (0.08–0.64)	.014	71 (10)	68 (10)	0.29 (0.03–0.56)	.03
Social Responsiveness Scale Raw Scores												
Subjects with data, %(N)[a]	65% (174)	57% (33)			0% (0)	0% (0)			100% (350)	100% (69)		
Total Score, Mean (SD)	104 (30)	109 (25)	0.17 (−0.16–0.49)	.36	-	-			99 (26)	106 (25)	0.28 (0.03–0.54)	.03
Child Behavior Checklist (age 6–18 years) T-scores												
Subjects with data, %(N)[a]	0% (0)	0% (0)			48% (159)	63% (33)			69% (248)	78% (54)		
Internalizing, Mean (SD)	-	-			60 (10)	59 (10)	0.12 (−0.27–0.50)	.55	57 (9)	57 (9)	0.02 (−0.27–0.31)	.89
Externalizing, Mean (SD)	-	-			58 (9)	60 (10)	0.24 (−0.17–0.65)	.26	56 (9)	59 (8)	0.41 (0.14–0.67)	.01
Total Problems, Mean (SD)	-	-			64 (8)	65 (8)	0.16 (−0.05–0.53)	.37	61 (8)	64 (7)	0.33 (0.08–0.57)	.03

On Social Responsiveness Scale and Child Behavior Checklist higher scores represent more impairment. The Autism Consortium dataset was not analyzed for modules 1 or 2.

[a]Percentage of subjects of that sex with available data for each measure.

[b]N varies: n=297 for Vineland communication and daily living skills scores for males in ATN.

[c]Survived false discovery rate correction.

Table 4

Summary of cognitive, adaptive, and behavioral test scores by sex in subjects administered module 3 of the Autism Diagnostic Observation Schedule (ADOS) in 4 research datasets.

	Autism Genetics Resource Exchange (AGRE)				Autism Consortium (AC)				Autism Treatment Network (ATN)				Simons Simplex Collection (SSC)			
	M	**F**	**d (95 % CI)**	**p**	**M**	**F**	**d**	**p**	**M**	**F**	**d**	**p**	**M**	**F**	**d**	**p**
Total Subjects	571	131			129	22			808	127			1293	169		
Age in years, Mean (SD)	9.9 (3.1)	9.4 (2.7)	0.13 (−0.40 – 0.65)	. 17	9.8 (3.2)	9.6 (3.3)	0.07 (−0.40 – 0.53)	.77	9.2 (2.7)	9.3 (2.8)	0.04 (−0.16–0.23)	.70	9.9 (3.0)	10.2 (3.4)	0.10 (−0.08–0.28)	.27
Full Scale IQ																
Subjects with data, %(N)[a]	41% (233)	38% (50)			94% (121)	100% (22)			73% (592)	64% (81)			100% (1292)	100% (169)		
Mean (SD)	93 (20)	92 (20)	0.01 (−0.13 – 0.15)	. 85	98 (18)	93 (21)	0.29 (−0.22 – 0.81)	.22	92 (20)	92 (20)	0.02 (−0.22–0.26)	.87	95 (19)	91 (21)	0.20 (0.03–0.37)	.02
Vineland Adaptive Behavior Scales Standard Scores																
Subjects with data, %(N)[a]	74% (422)	78% (102)			94%[b] (121)	100% (22)			88%[b] (711)	87 %[b] (111)			100% (1293)	100% (169)		
Communication, Mean(SD)	78 (17)	81 (14)	0.17 (−0.02 – 0.36)	. 11	83 (13)	89 (18)	0.43 (−0.16–1.01)	.08	80 (12)	82 (14)	0.17 (−0.05–0.39)	.12	82 (12)	81 (12)	0.10 (−0.06–0.27)	.21
DLS, Mean (SD)	67 (20)	71 (19)	0.16 (−0.07 – 0.39)	. 16	83 (17)	83 (13)	0.00 (−0.37–0.37)	1. 0	80 (13)	82 (14)	0.13 (−0.09–0.35)	.24	81 (12)	79 (12)	0.17 (0.01–0.33)	.04
Socialization, Mean (SD)	67 (15)	70 (14)	0.21 (0.00–0.42)	. 05	75 (12)	84 (16)	0.69 (0. 12–1.25)	.005[c]	72 (11)	74 (10)	0.15 (−0.03–0.33)	.11	75 (11)	75 (10)	0.00	.93
Composite, Mean (SD)	68 (16)	71 (14)	0.16 (−0.03 – 0.36)	. 14	79 (14)	83 (13)	0.29 (−0.16–0.74)	.21	76 (10)	78 (11)	0.20 (−0.02–0.41)	.07	77 (10)	76 (10)	0.11	.16
Social Responsiveness Scale Raw Scores																
Subjects with data, %(N)[a]	61% (346)	63% (83)			78% (101)	86% (19)			0% (0)	0% (0)		99% (1291)		100% (169)		
Total Score, Mean (SD)	97 (31)	89 (31)	0.25 (0. 01–0.49)	.039	96 (26)	78 (27)	0. 68	.007[c]	-	-			95 (27)	94 (27)	0.02 (−0.14–0.18)	.80
Child Behavior Checklist (age 6–18 years) T-scores																
Subjects with data, %(N)[a]	0% (0)	0% (0)			60% (77)	68% (15)			82% (663)	80% (102)			80% (1187)	92% (156)		
Internalizing, Mean (SD)	-	-			62 (11)	56 (10)	0.58 (0. 05–1.11)	.042	64 (10)	65 (9.0)	0.13 (−0.06–0.33)	.18	61 (10)	61 (10)	0.01 (−0.17–0.19)	.90
Externalizing, Mean (SD)	-	-			57 (11)	54 (11)	0.20 (−0.35–0.76)	.47	59 (11)	61 (11)	0.21 (0.00–0.42)	.044	57 (12)	57 (11)	0.07 (−0.09–0.23)	.39
Total Problems, Mean (SD)	-	-			64 (9)	58 (11)	0.65 (0. 01–1.29)	.028	66 (8)	68 (7)	0.21 (0.04–0.39)	.023	63 (9)	64 (9)	0.09 (−0.07–0.25)	.26

DLS- Daily Living Skills; on Social Responsiveness Scale and Child Behavior Checklist higher scores represent more impairment.

[a]Percentage of subjects of that sex with available data for each measure.

[b]N varies: n=119 for Vineland Composite scores for males in AC; n=719 for males and n=113 for females for Communication and Socialization scores in ATN; n=718 for males and n=114 for females for DLS scores in ATN.

[c]Survived false discovery rate correction.

Table 5

Summary of study findings with regards to sex differences in cognitive, adaptive and behavioral test scores in four research datasets, grouped by which Autism Diagnostic Observation Schedule (ADOS) module had been administered.

Cognitive, adaptive and behavioral test scores	Children who did not use words - ADOS Module 1		Children who used phrase speech - ADOS Module 2		Children and adolescents who were verbally fluent - ADOS Module 3	
	Presentation in females [a]	Supported by dataset [b]	Presentation in females [a]	Supported by dataset [b]	Presentation in females [a]	Supported by dataset
Full scale IQ	Same ability	AGRE, ATN, SSC	Lower ability	ATN, SSC	Lower ability	SSC
Communication ability	Same ability	AGRE, ATN, SSC	Lower ability	ATN*, SSC	Same ability	AGRE, AC, ATN, SSC
Daily living skills	Same ability	AGRE, ATN, SSC	Lower ability	ATN*	Lower ability	SSC
Socialization skills	Same ability	AGRE, ATN, SSC	Lower ability	ATN, SSC	Higher ability	AGRE, AC*
Internalizing problems	Same impairment	AGRE, ATN, SSC	Same impairment	ATN, SSC	Lower impairment	AC
Externalizing problems	Same impairment	AGRE, ATN, SSC	Higher impairment	SSC	Higher impairment	ATN

AGRE – Autism Genetics Resource Exchange; AC – Autism Consortium; ATN – Autism Treatment Network; SSC – Simons Simplex Collection.

[a] Presentation in females as compared to males.

[b] The AC dataset was not analyzed for module 1 or 2.

* Survived false discovery rate adjustment