



Assessing autism in females: The importance of a sex-specific comparison

Sebastian Lundström^{a,b}, Caroline Mårland^{b,c,*}, Ralf Kuja-Halkola^d, Henrik Anckarsäter^b, Paul Lichtenstein^d, Christopher Gillberg^{a,c}, Thomas Nilsson^b

^a Gillberg Neuropsychiatry Centre, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Sweden

^b Centre for Ethics Law and Mental Health (CELAM), Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Sweden

^c Sahlgrenska University Hospital, Gothenburg, Sweden

^d Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

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ABSTRACT

Autism spectrum disorder (ASD) is diagnosed more often in boys than girls. Here, we compared the degree of autism - and related disorders - symptomatology in boys and girls with a registered diagnosis of ASD. We used parent telephone interview A-TAC (Autism-Tics, ADHD and other Comorbidities) ratings of 30,392 twins aged 9 or 12 (including 308 boys and 122 girls with National Patient Register diagnoses of ASD) participating in the Child and Adolescent Twin Study in Sweden. We used z-scores for ASD-symptoms, standardized separately for boys and girls. Boys with a diagnosis of ASD had a higher raw mean score than girls with a diagnosis on the A-TAC ASD domain. However, utilizing the z-scores, girls with a diagnosis of ASD deviated further away from the female population mean than did the boys with ASD from the male population mean. Girls also had higher standardized mean values for symptoms of Attention-Deficit/Hyperactivity Disorder, Learning Disabilities and Oppositional Defiant Disorder. The findings suggest that girls diagnosed with autism may represent an even more extreme end of the female population autistic features distribution, than diagnosed boys from the male population autistic features distribution. Future studies may benefit from examining the use of sex-specific cut-off scores.

1. Introduction

Autism spectrum disorder (ASD) is consistently more commonly diagnosed in boys than in girls, as reflected in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5; American Psychiatric Association, 2013) where a male-female ratio of 4:1 in diagnoses is quoted. A recent meta-analytic approach that took study features (e.g. case-ascertainment, sample-size and age) into account reported a lower, but still elevated, ratio of 3:1 (Loomes et al., 2017). The reason for the male preponderance in autism is unknown, but it is likely multifactorial. Studies indicate that females may be subjected to different clinical thresholds compared to males. For instance, a study including >2400 individuals with an ASD-diagnosis found that females displayed a greater socio-communicative severity, a lower full-scale IQ and adaptive functioning, but less stereotyped and repetitive behaviors (Frazier et al., 2014). The male:female ratio is much lower in cases with moderate-severe learning disability (Gillberg et al., 1991). Also, girls with a diagnosis of autism have been reported to have more etiological risk factors in terms of a higher mutational burden (i.e. an increased number of de novo likely gene-

disrupting mutations and autosomal copy-number variants, Iossifov et al., 2014; Jacquemont et al., 2014) compared to males with a diagnosis. A possible consequence of this is that girls meeting diagnostic criteria for autism show a higher level of intellectual disabilities compared to boys (Volkmar et al., 1993; Yeargin-Allsopp et al., 2003), which may be a more noticeable marker for referral to diagnostic assessment than socio-communicative difficulties. However, it has also been suggested that girls are more likely to be overlooked, as their socio-communicative difficulties may be subtler (Lai et al., 2011), and that girls display fewer stereotyped and repetitive behaviors than boys do (Tillmann et al., 2018). As a consequence, the socio-communicative difficulties in girls with autistic features are under recognized in clinical settings, as is evident since they are more often missed (Kopp and Gillberg, 1992; Giarelli et al., 2010) and diagnosed at a later age (Shattuck et al., 2011; Begeer et al., 2013).

The need to more accurately identify girls with autism has been highlighted, but a notable obstacle is that the diagnostic norms are developed in predominantly male samples (Halladay et al., 2015). The original field trials of the Diagnostic and Statistical Manual of Mental Disorders, Fourth edition (Volkmar et al., 1994) for ASD consisted of

* Corresponding author at: University of Gothenburg, CELAM Rågårdens hus 1, SU-Östra Sjukhuset, 416 85 Gothenburg, Sweden.

E-mail address: caroline.marland@vgregion.se (C. Mårland).

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454 individuals with clinical diagnoses of autism with a male to female ratio of 4.5:1. Similarly, samples reported in validation studies of widely used clinical instruments - such as the Autism Diagnostic Interview, Autism Diagnostic Observation Schedule, and the Diagnostic Interview for Social and Communication Disorders –included substantially more males than females (Rivet et al., 2011; Wing et al., 2002). It is unclear if the instruments, available today, are prone to detect a more “male type” of autism. Epidemiological studies consistently report higher mean values for boys than for girls (Posserud et al., 2006; Anckarsäter et al., 2008). Similarly, the ratio between males and females increases to 8:1 in individuals without intellectual disability (Scott et al., 2002), making it reasonable to assume that it is harder to recognize manifestations of autism in girls compared to boys when IQ is within the normal range.

Taken together, this suggests that girls diagnosed with autism may represent an even more extreme end of the autistic features distribution in the general population of girls, than diagnosed boys as compared with boys in the general population. In the prevailing diagnostic systems (American Psychiatric Association, 2013; World Health Organization, 1992) sex is not considered in the diagnostic algorithm for ASD, neither does any screening instruments exist that suggests different cut-offs for male and females.

The aim of the present study was to compare boys and girls regarding the degree of autism “symptomatology”/autistic features, and “symptoms”/features of other coexisting disorders, using a sex-specific standardized score.

2. Methods

In this study, two sources of data were used: (i) the Child and Adolescent Twin Study in Sweden (CATSS) and (ii) the Swedish National Patient Register (NPR).

2.1. The Child and Adolescent Twin Study in Sweden

CATSS is a prospective study targeting all twins born in Sweden from the first of July 1992 and onwards. CATSS is described in detail elsewhere (Anckarsäter et al., 2011). Briefly, in connection with the twins 9th birthday (during the first three years of the study 12 year olds were also included) their parents are contacted and asked to take part in a telephone interview. The response rate in CATSS is 75%. In this study 30,392 individuals, born between the 1st of July 1992 and the 28th of February 2007 whose parent had responded to the Autism - Tics, ADHD and other Comorbidities inventory (A-TAC) were included (Hansson et al., 2005).

2.2. The Autism-Tics, ADHD and other Comorbidities inventory

The A-TAC is a fully structured telephone interview designed to be used by laymen over the phone. It consists of 96 questions covering virtually all common child and adolescent psychiatric problem constellations. All items are coded ‘no’ (0), ‘yes, to some extent’ (0.5) and ‘yes’ (1) and the average interview time is 27.5 min (Larson et al., 2014). The A-TAC consists of modules corresponding to clinical diagnostic domains, which is summarized in a sum-score. The A-TAC has been extensively validated in four cross-sectional (Hansson et al., 2005; Larson et al., 2010, 2014; Cubo et al., 2011) and two longitudinal validation studies (Larson et al., 2013; Mårland et al., 2018). Of the 96 questions, 17 correspond to the ASD domain, 19 to the Attention-Deficit/Hyperactivity Disorder (ADHD) domain, 3 to the Learning Disabilities (LD) domain and 5 to the Oppositional Defiant Disorder (ODD) domain. The ASD domain versus expert clinical ASD diagnosis has an area under the curve (AUC) of 0.89 (Mårland et al., 2018), and a cut-off of 8.5. This cut-off has a sensitivity of 0.71 and a specificity of 0.95 when cases were compared cross-sectionally with controls, and 0.61 and 0.91, compared to cases, controls and a community sample

(Larson et al., 2010). The ADHD-domain has an AUC of 0.86, the LD-domain of 0.89 and the ODD-domain of 0.85, when compared to clinical diagnosis in a population-based and nation-wide sample (Mårland et al., 2018).

2.3. The National Patient Register

Individuals in Sweden are assigned a personal identification number at birth or when they receive a Swedish citizenship. This identification number is used in all contacts with all governing bodies in Sweden, and thus renders linkage across various registers possible. The CATSS is linked to the NPR, which contains data on all inpatient diagnoses from 1987 through 31st of December 2014, and also includes diagnoses assigned in outpatient clinics from 2001 and onwards. Using the personal identification number, we merged the CATSS sample with the NPR and retrieved relevant diagnostic codes for ASD: ICD-9 299A, ICD-10 F84.0, 84.1, f84.5, f84.8, and f84.9, including date of first diagnosis on the register. The NPR continuously updates its content, and several validation studies of its diagnoses have been conducted. Idring et al. (2012) reported an agreement of 96% between medical records and registered diagnoses of autism when several registers were compared. In addition, other medical conditions has been subjected to validation and been reported to have high validity, e.g. bipolar disorder (Sellgren et al., 2011) and rheumatoid arthritis (Waldenlind et al., 2014).

2.4. Definition of sample

Through the NPR, we identified 308 boys and 122 girls, out of the 30,392 individuals in the CATSS sample, who had been registered with a diagnosis of ASD, resulting in a total CATSS sample registered ASD prevalence of 1.4% and a male-female ratio of 2.5:1.

2.5. Statistical analyses

For descriptive purposes, mean values with 95% Wald confidence intervals were calculated for the sum scores of the ASD, ADHD, ODD and LD modules for all 30,392 individuals. This was done separately for boys and girls.

We then performed linear regression analyses among the 430 individuals with a registered diagnosis of ASD. In a first step, the raw mean score values of the ASD, ADHD, ODD and LD modules were calculated. Four separate linear regressions were conducted with the ASD, ADHD, ODD and LD modules as the dependent and sex as the independent variables. In a second step the procedure was repeated but with a standardized score. The mean and standard deviation from all 30,392 individuals were used to standardize ASD, ADHD, ODD and LD modules of A-TAC into z-scores. This was done separately for boys and girls to account for differences in the distribution between sexes. The z-score has a mean of 0 and a standard deviation of 1 and is obtained by subtracting the population mean from each individual score and dividing the difference with the standard deviation of the population. Thus, positive values are above and negative values below, the sex-specific mean, the value of the z-score represents the difference of the individual value, and the sex-specific mean expressed in sex-specific standard deviations. It should be noted that a standardization does not change the relationship between the variables. As the same scaling applies for boys and girls, a comparison concerning sex-specific standard deviations from the sex-specific mean can be conducted across sexes. This allows us to perform analyses where we assess the regression coefficient as deviations from the sex-specific mean, expressed as sex-specific standard deviations, i.e., account for sex-differences in distributions in the different modules. Analyses were performed in the statistical software SAS version 9.3.

Both the CATSS and the linkage to the NPR have ethical approval from the Regional Ethical Review Board in Stockholm (Dnr 02–289, 2010/597–31/1, 2016/2135–31 and 2010/507–31/1).

Table 1
Population means of the 30,392 individuals.

Raw mean scores (95% confidence intervals) for the entire population		
	♂	♀
ASD	0.99 (0.96–1.02)	0.62 (0.59–0.64)
ADHD	2.49 (2.44–2.55)	1.58 (1.53–1.62)
LD	0.31 (0.30–0.33)	0.25 (0.24–0.27)
ODD	0.51 (0.50–0.53)	0.39 (0.37–0.40)

Table 2
Raw mean and standardized A-TAC module scores for the 308 boys and 122 girls with an ASD diagnosis in NPR plus ASD and linear regression estimates.

Raw and standardized scores (95% confidence intervals) in individuals with an ASD diagnosis and linear regression estimates				
	Raw ♂	Raw ♀	Standardized ♂	Standardized ♀
N	308 boys and 122 girls			
ASD	6.05 (5.55–6.54)	4.86 (4.07–5.59)	2.75 (2.48–3.02)	3.23 (2.65–3.81)
	1.21, $t = 2.59$, $p = 0.0100$		−0.48, $t = 1.68$, $p = 0.0945$	
ADHD	8.16 (7.55–8.75)	6.45 (5.49–7.41)	1.63 (1.46–1.81)	1.85 (1.48–2.21)
	1.70, $t = 2.95$, $p = 0.0033$		−0.21, $t = -1.18$, $p = 0.2403$	
LD	1.20 (1.07–1.32)	1.21 (1.00–1.42)	1.35 (1.16–1.54)	1.61 (1.26–1.96)
	−0.01, $t = -0.12$, $p = 0.9053$		−0.26, $t = -1.37$, $p = 0.1705$	
ODD	1.74 (1.56–1.88)	1.71 (1.43–1.98)	1.32 (1.15–1.49)	1.70 (1.43–2.05)
	0.01, $t = 0.09$, $p = 0.9273$		−0.37, $t = -2.09$, $p = 0.0376$	

3. Results

In Table 1 the mean values of the raw scores of the four A-TAC modules for all 30,392 individuals are shown separately for boys and girls. Boys consistently scored higher on all modules than girls.

In individuals diagnosed with ASD the raw mean scores of the A-TAC modules ASD and ADHD - but not LD or ODD - were significantly higher for boys compared to girls (Table 2). Using the standardized scores the opposite pattern emerged where girls consistently deviated further away from the sex-specific mean than boys). For example, girls diagnosed with ASD scored 3.23 standard deviations above the female mean, while boys scored 2.75 standard deviations above the male mean; thus, girls with ASD-diagnosis deviated an additional 0.48 sex-specific standard deviations further from the girl mean than boys did from the mean for boys.

4. Discussion

The primary aim of this study was to compare boys and girls with a registered diagnosis of ASD with respect to raw and standardized A-TAC domain scores for ASD, ADHD, LD and ODD. Our main finding was that boys with a diagnosis of ASD had higher raw mean A-TAC scores for ASD and ADHD compared to girls. However, by using standardized scores, the result indicates that girls with a diagnosis of ASD are comparable or deviate further away from the sex-specific mean than what boys do on continuous scores of ASD as well as of ADHD, LD and ODD traits.

The degree of dysfunction and suffering is positively correlated with the percentile-based distribution of neurodevelopmental symptoms when collapsing the scores of girls and boys (Garcia et al., 2013). If this hold true for both sexes separately, which seems reasonable, then the present findings suggest that girls with a diagnosis of ASD may actually experience a greater degree of dysfunction and suffering because of their autism, or ‘other’ neurodevelopmental symptomatology than boys; in the face of being rated as having fewer symptoms, which highlights the need to consider the quality, rather than quantity, of the manifest symptoms in clinical assessments.

In the whole CATSS population, girls consistently had lower raw

scores on the A-TAC ASD, ADHD, LD and ODD domains. Several other population-based studies have reported the same pattern by using other screening instruments for ASD such as the Social Responsiveness Scale (SRS, Constantino and Todd, 2003; Kamio et al., 2013), the Autism Spectrum Screening Questionnaire (ASSQ, Posserud et al., 2006, Ryland et al., 2014), the Social Communication Questionnaire (SCQ, Evans et al., 2018) and the Childhood Autism Spectrum Test (CAST, Williams et al., 2008). Sex differences on screening instruments for ASD indicate that it may be appropriate to evaluate the usefulness of sex-specific cut-off values. Furthermore, the result of the present study indicates that some girls with a diagnosis of ASD may not be captured by the use of established cut-off values for the ASD domain in A-TAC or, likely, other screening instruments. Future studies might also benefit from examining if different symptom constellations in girls and boys could predict a diagnosis of ASD. A similar attempt has been made with the Autism Spectrum Screening Questionnaire, Revised Extended Version (Kopp and Gillberg, 2011) where items such as “avoids demands”, “very determined”, “careless with physical appearance and dress” and “interacts mostly with younger children” were significantly more prevalent in girls. Thus, it might be of value to use item-response theory with a view to examining each individual item of the A-TAC ASD domain in order to possibly weight certain items depending on sex.

The main strengths of this study are a) the very large population-based sample combined with b) a high response rate and c) the use of a clinical ASD diagnosis from the NPR. Nonetheless, the result should be considered in the light of some limitations. First, no consideration has been given to the age at diagnosis or whether the diagnosis was registered before or after the A-TAC interview, which may have an effect on the sum scores of the different modules. Still, approximately 50% of the girls and boys had received their diagnosis before the age of 9 or 12. Second, only 122 girls had been assigned a diagnosis of ASD. However, the male-female ratio was in agreement with a recent publication (Loomes et al., 2017). Finally, the result is based on twin data, and it has been suggested that twins have an increased risk for ASD (Greenberg et al., 2001; Betancur et al., 2002). This notion has, however, not been confirmed within the CATSS (Lundström et al., 2015) or in other large-scale epidemiological studies (Croen et al., 2002; Hallmayer et al., 2002; Hultman et al., 2002). Furthermore, it does not seem plausible that female (school age and older) twins with ASD would present with a different symptom constellation, or be assessed differently, than female singletons with ASD.

Declaration of Competing Interest

The authors have declared that they have no competing or potential conflicts of interest.

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Supplementary materials

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