1 Sex differences in the relationship between social difficulties and executive dysfunction

2 in children and adolescents with autism spectrum disorder

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39 **Abstract**

40 The prevalence of autism spectrum disorder (ASD) in boys is nearly four times higher than in
41 girls, and the causes of this sex difference are not fully known. Difficulties in executive
42 function may be involved in development of autistic symptomatology. Here we investigated
43 sex differences in the relationship between executive function in everyday life and social
44 dysfunction symptoms in a sample of 116 children (25 girls) aged 5-19 years with IQ above
45 70 and with a diagnosis of ASD. They were assessed with the Behavior Rating Inventory of
46 Executive Function (BRIEF) and the Autism Diagnostic Interview Revised (ADI-R). We
47 found no significant differences in BRIEF or ADI-R scores between girls and boys after
48 correcting for multiple testing. Nested linear regression models revealed significant sex
49 differences in the relationship between executive function and both reciprocal social
50 interaction ($p<0.001$) and communication ($p=0.001$) over and above the main effects of age,
51 sex, IQ and comorbid attention deficit/hyperactivity disorder diagnosis. We did not find sex
52 differences in the relationship between executive dysfunction and restricted and repetitive
53 behaviors. Altogether, our results provide a greater understanding of the sex-specific
54 characteristics of ASD and may suggest that boys and girls can benefit from different
55 intervention strategies.

56 Introduction

57 Autism spectrum disorder (ASD) is overrepresented in boys compared to girls. Traditionally,
 58 the male-to-female ratio is thought to be 4:1 ¹. However, a recent meta-analysis of population
 59 based ASD studies concluded that the male-to-female ratio is closer to 3:1, suggesting that
 60 researchers and health professionals may currently overlook ASD in females ². This sex
 61 difference influences the identification of autistic symptoms and obtaining an accurate
 62 diagnosis, as well as intervention options and the provision of suitable resources and services
 63 for people with ASD ³. Furthermore, the underlying causes of the difference in ASD
 64 occurrence between boys and girls are not fully known. Research on females with ASD has
 65 been limited, and most of the literature on ASD is based on boys and young men ⁴. Thus,
 66 there is a growing need for a better understanding of the sex differences in ASD and there is
 67 an increased research focus on girls with ASD ^{1,3,5}.

68
 69 Some studies suggest that the sex difference in ASD prevalence can partially be due to sex-
 70 differential genetic and hormonal factors ⁶. However, the genetic factors underlying the
 71 skewed sex ratio in ASD remains mostly unknown, and cannot be explained by X-linked
 72 variants since most known ASD risk genes are located in autosomal regions ⁶. There is some
 73 evidence for increased mutational burden in females and their families, which indicates an
 74 elevated threshold for developing ASD in girls ⁷. This has been interpreted as a female
 75 protective effect, in other words, a greater resistance to ASD from genetic causes in females ⁸.
 76 Even though there are no complete molecular explanations for this hypothesis ⁹, studies
 77 suggest that the male bias is most likely due to female protective factors rather than male-
 78 specific risk factors. A possible consequence of an increased genetic load in girls, is that those
 79 who reach a clinical diagnosis of ASD often have lower intelligence and more behavioral
 80 problems than boys with ASD ¹⁰.

81

82 An important factor in the prevalence ratio in ASD seems to be related to cognitive level;
 83 lower IQ is associated with a lower male-to-female ratio^{2,5,11}. However, this finding needs to
 84 be treated with caution, since only about half of the studies included in Loomes and
 85 colleague's recent review included sufficient information regarding IQ². It has also been
 86 recognized that the autistic symptoms are less apparent in girls than boys. This phenomenon
 87 might be due better learning of compensatory behaviors and skills to mask their social
 88 challenges^{12,13} and that parents, teachers, and clinicians are less able to recognize autistic
 89 symptoms in girls¹⁴. Girls with ASD tend to have better social skills and less behaviour
 90 problems than boys with ASD, which might make it harder to recognise their autistic
 91 characteristics¹⁰. Furthermore, some have found that girls with ASD have less repetitive
 92 behavior and interests compared to boys with ASD^{1,15}.

93

94 EF deficits constitute one of the main cognitive theories of ASD¹⁶⁻¹⁸, together with Theory of
 95 Mind and Central Coherence¹⁹. Recent meta-analyses confirm that on average, people with
 96 ASD perform worse on executive function (EF) tasks than neurotypical controls^{20,21}. EF
 97 comprises several components including inhibition, working memory, flexibility, emotional
 98 control, initiation, planning, organization, monitoring and self-control^{17,22}. These components
 99 enable the individual to disengage from the present context to effectuate future goals.
 100 Demetriou and colleagues²⁰ found consistent evidence of an overall moderate effect size
 101 (Hedges' $g = 0.48$) of executive dysfunction in ASD, that the deficits are relatively stable
 102 across development, with few differences across subdomains²⁰. In a meta-analysis that also
 103 included children and adolescents with ASD and comorbid attention deficit/hyperactivity
 104 disorder (ADHD), Lai and colleagues²¹ confirmed that children with ASD tend to have
 105 executive dysfunction with small to moderate effect sizes (Hedges' $g = 0.41-0.67$), and that

this was not solely accounted for by the effect of comorbid ADHD or general cognitive abilities. Further, the questionnaire Behavior Rating Inventory of Executive Function (BRIEF) was found to be a better clinical marker of ASD than performance based tests²⁰. This is probably because it can be difficult to generalize from EF assessed in highly structured laboratory settings, and that questionnaires regarding everyday functioning have a higher ecological validity and thus also a better clinical utility than neuropsychological tests^{20,23}. In addition, intelligence and age are factors that might influence EF in children with ASD²⁴.

Sex differences in the relationship between EF and social function might contribute to the skewed sex distribution in ASD. If girls who reach a clinical diagnosis of ASD tend to be more impaired and have a higher genetic burden than boys¹⁰, the relationship between EF deficits and social difficulties may also be different in girls. Studies investigating this relationship have focused on specific subdomains of EF examined mainly by neuropsychological tests^{11,25-27}. Since some EF difficulties may not be observable in a laboratory setting, informant based measures and questionnaires like the BRIEF might add valuable information²³. In addition to EF, there are indications that there also may be sex differences in people with ASD within domains such as mentalizing, emotion perception, perceptual attention to detail, and motor function⁴.

Although studies have identified a relationship between key ASD traits, such as social dysfunction, and EF²⁸, there are few studies focusing on how *sex* might impact the relationship, and the findings have been inconsistent. Some studies have indicated that females with ASD have more impairment in EF compared to males²⁵. In a relatively small group of participants, Lemon and colleagues²⁵ found that only girls showed poorer response inhibition. Others have reported that females with ASD outperform males on executive tasks

related to processing speed and verbal fluency^{11,26}.

With regard to everyday functioning in children with ASD, there is one study, to our knowledge, of sex differences in the relationship between the Autism Diagnostic Interview Revised (ADI-R) and adaptive behavior²⁹, and another study of sex differences in parent-reported EF and adaptive behavior³⁰. Mandic-Maravik and colleagues²⁹ found different associations of autistic symptoms with various aspects of adaptive behavior between the sexes. White and colleagues³⁰ reported a correlation between EF difficulties and decreased adaptive ability in both males and females. However, females had more EF difficulties on the BRIEF and more difficulties on the Daily Living Skills domain on the Vineland Adaptive Behavior Scales. To the best of our knowledge there are no studies of how sex differences influence the relationship between parent-rated EF in everyday life (BRIEF) and autistic symptomatology (ADI-R).

The main aim of the current study was to investigate the relationship between EF in everyday life rated by parents and autistic symptomatology, and to investigate possible sex differences in this relationship. In accordance with the female protective effect hypothesis, that girls would need to be more impaired to have the same amount of ASD symptoms as boys, we hypothesized the relationship between EF deficits and autistic symptomatology to be stronger in girls than boys.

Methods

Participants

The participants were recruited from Norwegian health services specializing in the assessment of ASD and other neurodevelopmental disorders. The study was part of the national BUPgen

network³¹. The current sample consisted of 25 girls and 91 boys with ASD who were recruited between 2013 and May 2018 and assessed at age 5-19 years. Fifteen of the children (2 girls, 13 boys) were diagnosed with childhood autism, 9 (2 girls, 7 boys) with atypical autism, 57 (14 girls, 43 boys) with Asperger syndrome and 35 (7 girls, 28 boys) with unspecified pervasive developmental disorder (PDD-NOS).

The male:female ratio was 3.6:1. In total, 40 children (34.5%) had a comorbid disorder of ADHD. All participants had an intelligence quotient (IQ) within the normal range based on a standardized Wechsler's test (Full-scale IQ ≥ 70) and spoke Norwegian fluently. Exclusion criteria were significant sensory losses (vision and/or hearing).

Clinical assessment

The children were assessed by a team of experienced clinicians (clinical psychologists and/or child psychiatrists and educational therapists). Diagnostic conclusions were best-estimate clinical diagnoses derived from tests, interview results and observations. All diagnoses were based on the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10)³² criteria, and the autistic symptoms were evaluated using the Autism Diagnostic Observation Schedule (ADOS)³³ and/or Autism Diagnostic Interview-Revised (ADI-R)³⁴. In addition, the assessment included a full medical and developmental history, physical examination and IQ assessment. Because ASD and ADHD often co-occur (29), the current study also included children with ASD and comorbid ADHD.

For a subsample of the group $n = 34$ (10 girls), we also had neuropsychological test data from the Delis-Kaplan Executive Function System (D-KEFS)³⁵. We used five of the subtests from D-KEFS. Results are reported as mean scaled scores and standard deviations (10+/-3): 8.48

(3.44) for Trail Making Test Condition 4 Number-Letter Switching ($n = 31$), 8.97 (2.42) for Verbal Fluency Letter Fluency (FAS) ($n = 32$), 8.59 (3.39) for the Color-Word Inhibition Time ($n=34$), 8.44 (3.31) for Color-Word Inhibition/ Switching Time ($n = 32$), 10.39 (3.59) for Twenty Questions Initial Abstract Score ($n = 28$) and 10.19 (2.34) for Tower Test Total Achievement Score ($n = 31$). The subsample with neuropsychological test results was on average older than the total sample (11.8 versus 10.3 year; $p = 0.009$), and fewer had comorbid ADHD than the total sample ($p = 0.043$). However they did not differ from the total sample in sex distribution ($p = 0.185$). Due to a small sample size, the neuropsychological test results are included to describe the group and were not used in further analyses.

Measures

Autistic symptoms: Autism Diagnostic Interview-Revised (ADI-R) diagnostic algorithm was used to assess autistic symptoms. The ADI-R is a clinical diagnostic tool based on a comprehensive interview with parents or primary caregivers of the child/ adolescent³⁶. The interview consists of 93 questions, and a predetermined number of these scores go into a diagnostic algorithm. The interview and scoring follow standardized procedures, and the interviewer records and codes the informant's responses. The algorithm is divided into three functional domains based on the diagnostic criteria (qualitative deviations in): A = Reciprocal Social Interaction, B = Communication, C = Restricted, Repetitive, and Stereotyped Behavior. Higher scores indicate that an individual has a greater number of items representing core ASD deficits and/or more severe symptoms³⁷. All the participants were verbal children, and therefore the algorithm for verbal children was used. We used the Norwegian translation of the ADI-R³⁸.

Executive function (EF): In order to assess EF parents completed the parent version of the BRIEF³⁹. The BRIEF for children and adolescents aged 5 to 18 years includes 86-item parent and teacher forms that allow professionals to assess everyday EF in the home and school environments³⁹. The BRIEF contains eight scales that are grouped in a Behavioral Regulation Index (BRI): Inhibit, Shift and Emotional Control, and a Metacognition Index (MI): Initiate, Working Memory, Plan/Organize, Organization of Materials and Monitor. *T-scores* of ≥ 65 are considered to represent clinically significant areas. The Global Executive Composite (GEC) is a summary score that incorporates all eight clinical scales. The GEC has high reliability in both standardized and clinical samples (Cronbach's alpha = 0.80-0.98). The current study used the Norwegian version of the parent rating form, which has been reported to have high internal consistency (Cronbach's alpha = 0.76-0.92)⁴⁰. Similar levels are described for the English version (Cronbach's alpha = 0.80-0.98)³⁹.

Intelligence Quotient (IQ): IQ was assessed using age-appropriate full-scale Wechsler tests of intelligence⁴¹⁻⁴³. We used the Norwegian versions of the Wechsler tests, which have Norwegian and/or Scandinavian norms⁴⁴⁻⁴⁶.

Statistical analyses

Analyses were conducted using the R statistical environment (version 3.5.0) using the “jmv” (Version 0.7.3.1;⁴⁷) and “cocor” packages⁴⁸. Statistical significance was set at $p < 0.05$ and adjusted according to number of comparisons. When adjusting critical *p*-values for multiple tests it is important to carefully consider the risks of type-I and type-II errors⁴⁹. Thus, we provide justifications below for how we adjusted tests for multiple comparisons to control the Type-I error rate. Conventional values were used for interpreting effect sizes (Effect size values of 0.2, 0.5, and 0.8, were considered small, medium, and large effects, respectively⁵⁰).

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231 Welch's t-tests were conducted to assess sex differences in ADI-R and BRIEF scores. As here
232 we were examining a series of tests and hypothesizing that these groups were not significantly
233 different, we adjusted for 6 tests (critical p-value = 0.008);^{49,51}, with values less than 0.05
234 considered on the border of statistical significance. A chi-squared statistic was calculated to
235 assess the frequency distribution of comorbid ADHD between sexes. For the t-tests, Glass'
236 delta—which is unaffected by unequal variances—was used as a measures of effect size.

237

238 To assess the association between ADI-R sub-scores (i.e., reciprocal social interaction,
239 communication, and restricted, repetitive and stereotyped behavior) and EF (BRIEF GEC),
240 we first calculated a Pearson correlation coefficient. To assess the impact of covariates (i.e.,
241 sex, IQ, age, ADHD, and a sex * EF interaction) on the association between ADI-R sub-
242 scores and BRIEF GEC, we fitted a series of nested multiple regression models and then
243 compared the fit of these models by calculating Akaike information criterion (AIC) values
244 and *F*-ratios for model change. Lower AIC values are indicative of better model fit. As we
245 were interested in three sub-scores from the ADI-R for these multiple regression models, we
246 adjusted the critical value for 3 tests (critical p-value = 0.017), with values less than 0.05
247 considered on the border of statistical significance for the purposes of these analyses.

248 Although this is an arbitrary cutoff for values considered to be on the border of statistical
249 significance, we chose 0.05 as this is the value traditionally used when not corrected for
250 multiple comparisons. To generalise the regression results beyond the given samples, robust
251 regression was performed in the event of non-normally distributed standardized residuals via
252 bootstrapping with 2000 samples. We obtained bootstrapped 95% confidence intervals for the
253 model intercept and slopes and compared these with the confidence intervals from the original
254 model. Similar confidence intervals between original and bootstrapped models would suggest

that there are no considerable problems with non-normal distribution of residuals in the original models. Finally, we assessed the relationship between BRIEF GEC and ADI-R sub-scores in the male and female subgroups and Fisher's z test was used to assess whether these correlations were significantly different. To examine the impact of more closely matched boys and girls on age and IQ, the same model fit and comparison procedure was performed on a subset of the sample, which was generated using the FUZZY extension command in SPSS. These analyses can be found in the supplement section. We allowed cases to be matched on age within 2 years and total IQ within 10 points. Three girls had missing full-scale IQ data, so the 22 girls with no missing values were matched to 44 boys.

Results

Sex differences in age, IQ, ADI-R scores, and BRIEF scores

There were no statistically significant differences between sexes (critical alpha adjusted to $p = .008$) in any of the ADI-R domains, BRIEF GEC, full-scale IQ, or age (Table 1). However, there were tendencies for girls to be slightly older ($p = 0.029$), have some more difficulties on the BRIEF index MI ($p = 0.045$) and to have less difficulties with the ADI-R C domain restricted and repetitive behaviour ($p = 0.038$) than the boys, but these sex differences did not reach the adjusted significance level.

[Table 1 about here]

There was no significant difference in the proportion of males and females with comorbid ADHD ($\chi^2 = 2.96, p = 0.09$).

The association between reciprocal social interaction and executive function

There was a statistically significant correlation (adjusted critical alpha = 0.017) between reciprocal social interaction and EF ($r = 0.31, p < 0.001$), as indexed by scores on the ADI-R-A and BRIEF GEC, respectively. We fitted three nested linear regression models to assess the role of covariates (i.e., sex, IQ, age, and ADHD diagnosis) and the interaction of sex and EF on the relationship between reciprocal social interaction and BRIEF GEC (Table 2A). The first model, which included sex, IQ, age, and ADHD diagnosis, was not statistically significant ($p = 0.49$). The second nested model, which added BRIEF GEC, was on the border of our adjusted statistical significance threshold ($p = 0.04$). The second model (AIC = 630.9) was a significantly better fit of the data than the first model (AIC = 637.4; $F(1, 96) = 8.38, p = 0.005$), indicating that EF is related to reciprocal social interaction, over and above the main effects of sex, IQ, age, and ADHD diagnosis. The third nested model, which added the interaction of BRIEF GEC and sex, significantly predicted social interaction ($p = 0.001$). In this model, BRIEF GEC, sex, and their interaction provided a statistically significant contribution (Table 2A). The third model (AIC = 619.7), which included a sex * BRIEF GEC interaction term, was a significantly better model for the data than the second model, which only included main effects (AIC = 630.9; $F(1, 95) = 13.15, p < 0.001$).

[Table 2A about here]

The standardized residuals from models 1 ($p = 0.02$), 2 ($p = 0.01$), and 3 ($p = 0.003$) were not normally distributed. Confidence intervals for the intercept and slopes of this model were similar to a bootstrapped model (Table S3A), indicating that there were no considerable problems with non-normal distribution of residuals in the model. The relationship between ADI-R A and BRIEF GEC was statistically significant in females ($p < 0.001$), but not males ($p = 0.08$; Figure 1). A formal comparison of these correlations suggested that the relationship

between EF and reciprocal social interaction is stronger in females than males (Fisher's $z = -3.56, p < 0.001$). The same model fit and comparison procedure on subset of participants more closely matched on age and IQ revealed similar results (Supplementary material S2A).

[Figure 1 about here]

Figure 1 Correlations between ADI-R and BRIEF scores for girls and boys

ADI-R: Autism Diagnostic Interview- Revised, diagnostic algorithm. A: Reciprocal Social Interaction domain, B: Communication domain, C: Restricted, repetitive and stereotyped behavior domain.

BRIEF_GEC: Behavior Rating Inventory of Executive Function, Global Executive Composite

Note: BRIEF scores are reported as T scores ($M = 50, SD = 10$) and ADI-R scores are reported as domain scores from the diagnostic algorithm.

The association between communication and executive function

There was a statistically significant correlation (adjusted critical alpha = 0.017) between communication and EF ($r = 0.33, p < 0.001$), as indexed by scores on the ADI-R-B and BRIEF GEC, respectively. We fitted three nested linear regression models to assess the role of covariates and the interaction of sex and EF on the relationship between ADI-R B and BRIEF GEC (Table 2B). The first model, which including sex, IQ, age, and ADHD diagnosis, was not statistically significant ($p = 0.84$). Although the second nested model was also not statistically significant ($p = 0.20$), BRIEF GEC provided a contribution that was on the border of statistical significance ($p = 0.02$). This second model ($AIC = 577.3$) was a better fit of the data than the first model ($AIC = 581.5$; $F(1, 92) = 5.98, p = 0.02$), indicating that EF is related to communication, over and above the main effects of sex, IQ, and ADHD diagnosis. However, this effect was on the border of statistical significance ($p = 0.02$) and needs to be validated in future studies. The third nested model, which added the interaction of BRIEF GEC and sex, significantly predicted communication ($p = 0.004$). In this model, BRIEF GEC, sex, and their interaction provided a statistically significant contribution (Table 2B). The third model ($AIC = 566.9$), which included a sex * BRIEF GEC interaction term, was a significantly better model for the data than the second model, which only included main

effects ($AIC = 577.3$; $F(1, 91) = 12.27$, $p = 0.001$). The standardized residuals from models 1 ($p = 0.004$), 2 ($p = 0.02$), and 3 ($p = 0.01$) were not normally distributed. Confidence intervals for the intercept and slopes of this model were similar to a bootstrapped model (Table S3B), indicating that there were no considerable problems with non-normal distribution of residuals in the model. The relationship between BRIEF GEC and ADI-R B was statistically significant in females ($p < 0.001$), but not males ($p = 0.03$; Figure 1). A formal comparison of these correlations suggested that the relationship between EF and communication is stronger in females than males (Fisher's $z = -2.62$, $p = 0.01$). The same model fit and comparison procedure on subset of participants more closely matched on age and IQ revealed similar results (Supplementary material S2B).

[Table 2B about here]

The association between restricted, repetitive and stereotyped behavior and executive function

The correlation between restricted, repetitive and stereotyped behavior and EF, as indexed by scores on the ADI-R-C and BRIEF GEC respectively, was on the border of the adjusted critical alpha ($r = 0.22$, $p = 0.019$; adjusted critical alpha = 0.017). We fitted three nested linear regression models to assess the role of covariates and the interaction of sex and EF on the relationship between repetitive behavior and EF (Table 2C). The first model, which including sex, IQ, age, and ADHD diagnosis, was not statistically significant ($p = 0.43$). Nor was the second nested model which added BRIEF GEC ($p = 0.12$). This second model ($AIC = 439.9$) was a better fit of the data than the first model ($AIC = 443.1$; $F(1, 93) = 5.08$, $p = 0.03$), but was on the border of statistical significance. The third nested model (adding the interaction of BRIEF GEC and sex) was not statistically significant ($p = 0.06$) (Table 2C).

The third model ($AIC = 438.4$) was a better fit of the data than the second model ($AIC = 439.9$), but this was not statistically significant ($F(1, 92) = 3.3, p = 0.07$). The standardized residuals from models 2 and 3, which included the predictor of EF were normally distributed ($p > 0.05$), however, they were not normally distributed for the first model ($p = 0.01$). Confidence intervals for the intercept and slopes of this model were similar to a bootstrapped model (Table S3C), indicating that there were no considerable problems with non-normal distribution of residuals in the model. The relationship between EF and repetitive behavior was statistically significant in females ($p = 0.007$) but not statistically significance in males ($p = 0.09$; Fig 1). However, formal comparisons of these two correlations showed that they were not significantly different (Fisher's $z = -1.72, p = 0.09$). The same model fit and comparison procedure on subset of participants more closely matched on age and IQ revealed similar results (Supplementary material S2C).

[Table 2C about here]

Discussion

The main finding of the current study is that there are sex differences in the relationship between EF in everyday life and social difficulties related to ASD. We found a strong association between the BRIEF (GEC) scores and the ADI-R domains reciprocal social interaction and communication in girls, while these relationships were small and non-significant in boys. We did not find sex differences in the relationship between executive dysfunction and restricted and repetitive behaviors. These results have implications for understanding the different clinical manifestations of ASD in girls and boys. The findings indicate that girls and boys might have a different relationship between cognitive and behavioural phenotypes, which may provide novel information in search for different etiologies in girls and boys with ASD. Furthermore, it supports the notion that there may be different reasons for the behavioural problems related to ASD in girls and boys, with girls' social and communicative challenges more strongly related to EF deficits. This could also help to develop sex-differentiated interventions.

Of particular note, we found evidence for a relationship between EF deficits and difficulties in the domains social reciprocity and communication, but not for the relationship between EF deficits and restrictive and repetitive behavior (RRB). This differs from previous studies, which found that EF difficulties were mainly related to RRB^{52,53}. However, these studies did not investigate the differences between girls and boys. On the other hand, Kenworthy and colleagues showed that EF deficits, measured with both performance tests and parental questionnaires, were related to all three components of the triad of impairment in ASD²⁸.

We did not find any statistically significant sex differences in the total amount of difficulties with social reciprocity or communication (ADI-R A and ADI-R B). However, we did observe

that girls had slightly less reported problems related to RRB (ADI-R C), which is in line with previous studies⁵⁴. Results from the Simons Simplex Collection showed lower levels of restricted interests in girls⁵⁵, and others have found that girls with ASD have less RBB compared to boys, especially for high functioning girls⁵⁶.

The participants in our study did not significantly differ in the total amount of executive difficulties (GEC), but girls had higher scores (were slightly more impaired) than boys on the metacognitive index from the BRIEF. White and colleagues³⁰ reported that girls showed more EF difficulties in a matched sample of 78 girls and 158 boys with ASD and ADHD symptomatology. The BRIEF (GEC) scores for girls and boys from their study are similar to our results; however, in our study the difference in GEC scores between girls and boys did not reach the corrected level of significance. This might be due to a smaller sample size and a stricter control for multiple testing in our study.

We showed a strong link between EF deficits in everyday life and social dysfunction for girls with ASD. However, EF deficits seem to have a weaker association to social dysfunction for boys, which suggest that their social difficulties may have a different etiology. Despite not collecting any genetic information in our study, the finding is consistent with earlier studies suggesting that girls require a greater genetic load to manifest autistics symptoms, and that their cognitive and behavior characteristics tend to be more severe than boys when they are diagnosed⁵⁷. The main finding in our study is not that girls with ASD have more EF deficits than boys, but that the EF deficits are stronger linked to core ASD symptoms in girls. Our study only investigated the association between EF and social function, and does not give insight into the causal relationship between these two functional areas. Still, it is reasonable to

argue that in girls, EF difficulties might drive social difficulties. This possible causal explanation should be further investigated in follow-up studies.

In typically developed children, girls appear to be more mature than boys, better at adapting to the classroom environment and more sociable⁵⁸. These differences may explain why girls tend to outperform boys in the early school years⁵⁸. Consequently, there tends to be different societal expectations of girls and boys in terms of social functioning. Girls with ASD might have more difficulties socially interacting with other girls, than boys with ASD have socially interacting with other boys^{59,60}. Thus, when EF is impaired in girls with ASD, it may have stronger negative effects on their social functioning because it requires more of their total cognitive resources.

Although the ADI-R together with the ADOS is considered to be the gold standard for assessing ASD^{61,62}, recent studies suggest that these diagnostic instruments may not be equally effective in identifying symptoms in both sexes. Beggiano and colleagues⁵⁴ investigated if the ADI-R items discriminate between males and females, and found that in two large cohorts the ADI-R was better at classifying males than females. They argue that because clinicians use diagnostic tools (like the ADOS and the ADI-R) that are not gender specific, it is likely that girls are underrepresented. Other screening instruments for autism symptoms like the Autism Spectrum Screening Questionnaire (ASSQ) and the Social Responsiveness Scale (SRS) have gender-specific items or different norms for boys and girls, to better to capture the “female phenotype” of autism⁵⁴. Thus, although girls and boys in our study have the same level of difficulties in social reciprocity and communication, they might have different expressions of autism symptoms in everyday life. We did not use the screening tools ASSQ or SRS because ADI-R is considered the gold standard measure of autism

symptomatology. Further, ADI-R involves a clinical rating and not just parent reports, taking into account the clinical judgment.

In our study 34.5% of the children had a comorbid diagnosis of ADHD. Both ASD and ADHD are characterized by executive dysfunction, but the two disorders typically differ in terms of which subdomains of EF that are affected. Where individuals with ADHD usually have problems with inhibition, those with ASD are more likely to have difficulties with flexibility and planning⁶³. Recently, it is suggested that as many as 40-70% of children and adolescents with ASD have a comorbid diagnosis of ADHD^{19,64,65}. This complicates the picture regarding EF deficits, considering that the two disorders typically represent different aspects of EF deficits. In our study we did not have any significant sex differences in the distribution of ADHD. Furthermore, we included ADHD diagnosis as a predictor in our nested regression models (Table 2A-C). ADHD diagnosis did not have a significant contribution to the outcome measures related to social reciprocity, communication or RRB. We argue that it is important to include children and adolescents with comorbid ADHD in research on ASD, because ADHD is a common comorbid disorder in clinical populations. However, it is important to be aware of the possible influence ADHD might have on executive measures. Future research should combine the measurements used in this study with genetic information and/or neuropsychological testing to investigate sex differences in the relationship between EF and social difficulties in more depth.

Potential clinical implications

The finding that executive dysfunction and social difficulties are highly related in girls but not in boys might be important for various aspects of clinical practice. Firstly, when girls present high scores on the ADI-R, it is reasonable to assess for executive difficulties and vice versa.

Furthermore, because girls might have a higher risk for executive dysfunction in combination with their social difficulties, the finding can have implications for the choice of interventions. Following this argument, it is possible that girls (with the same amount of social difficulties as boys) will benefit more from EF interventions. Some existing programs that aim to enhance EF have shown to be effective on both social problems and EF⁶⁶. However, to our knowledge, research is yet to investigate whether this treatment may be more effective for girls than boys. Future studies need to consider that sex differences might influence the effect of interventions.

Strengths and limitations of the study

The study consists of a clinically well-defined sample of children and adolescents with ASD. Even though we have a reasonable number of girls, the total number of girls is still relatively small. The participants were recruited from specialist health care services, which may limit the findings to the more severe conditions. Previous studies have shown that girls referred to specialist clinics have more severe problems than boys⁵⁷. The girls in our study were slightly older than the boys, but age was accounted for in the nested linear models. The BRIEF is based on parent's own observations and evaluations of the child. This parental bias might have influenced the findings, but on the other hand, these instruments have been shown to be ecologically valid measurements of how the child functions in everyday life. We have used the *t*-score from the BRIEF in the analyses, which have age and gender "corrected" norms, since *t*-scores are commonly used in literature, as well as clinical practice, and it is important to understand how different clinical tools influence each other. Both the BRIEF and the ADI-R are based on information from parents and this might bias the findings. However, while the BRIEF is a questionnaire, the ADI-R is a clinical semi-structured interview, which involves a clinical rating. Together, they both give important information about a child's behaviour.

499

500 Another reason for the sex difference in ASD prevalence might be that girls have a different
501 phenotype. Currently, the established diagnostic practices and tools like the ADOS and the
502 ADI-R are not constructed or adapted to measure the subtle difficulties that girls may present
503 with, which differ from the typical presentation of ASD symptoms in boys. Lai and
504 colleagues suggest this might be a circular phenomenon, since an ASD diagnosis is based on
505 behavioral descriptions, and the most common diagnostic tools are largely validated on the
506 classic male phenotype of autism behaviors¹.

507

508 **Conclusion**

509 We report sex differences in the relationship between executive dysfunction and social
510 difficulties in individuals with ASD. Our study found a strong relationship between
511 difficulties with social reciprocity and communication and parent-rated executive dysfunction
512 in girls, while the same relationship was not evident in boys. These results suggest potential
513 underlying factors related to different manifestations of ASD in males and females, which
514 may have clinical implications.

515

516 **Abbreviations**

517 ADHD: Attention Deficit Hyperactivity Disorder; ADI-R: Autistic Diagnostic Interview-Revised; ADOS: Autism
518 Diagnostic Observation Scale; ASD: Autism Spectrum Disorder; BRIEF: Behavior Rating Inventory of Executive
519 Function; BRI: Behavioral Regulation Index; D-KEFS: Delis-Kaplan Executive Function System; EF: Executive
520 Function; GEC: Global Executive Composite; IQ: Intelligence Quotient; MI: Metacognitive Index; PDD-NOS:
521 Pervasive Developmental Disorder – Not Otherwise Specified; RRB: Restrictive and Repetitive Behavior.

522

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526

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531

532 **Availability of data and materials**

533 The datasets used and analyses in the current study are available from the corresponding author on reasonable
534 request.

535

536 **Authors' contributions**

TT, TN, MGØ and OAA planned and designed the study. TT, MGØ, REH, AK, ALH and SH collected the clinical information. TT, TN and DQ analysed the data and interpreted the results. TT wrote the first draft of the manuscript. All the authors contributed to the manuscript and read and approved the final manuscript.

Ethics approval and consent to participate

Written informed consent was obtained from a parent and/or legal guardian for all participants under the age of 18 years who were included in the study. Participants over 18 years gave written consent themselves. The study was approved by the Regional Ethical Committee and the Norwegian Data Inspectorate (REK #2012/1967), and was conducted in accordance with the Helsinki Declaration of the World Medical Association Assembly.

Consent for publication

All the participants consented to publication.

Competing interests

The authors declare that they have no conflict of interest.

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705

Table 1. Age, IQ, BRIEF and ADI-R scores for girls and boys with ASD (N=116)

Scale	Girls Mean (SD)	n	Boys Mean (SD)	n	df	<i>p-value</i>	Glass' delta
Age	12.0 (3.1)	25	10.4 (3.2)	91	39.0	0.029	-0.50
Full-scale IQ	93.5 (9.3)	22	95.6 (13.1)	80	46.5	0.386	0.16
BRIEF	69.4 (10.1)	25	67.2 (10.8)	91	40.3	0.349	-0.20
Global Executive Composite (GEC)							
BRIEF	67.6 (14.6)	25	68.0 (11.8)	86	33.7	0.917	0.03
Behavioral Regulation Index (BRI)							
BRIEF Metacognition Index (MI)	68.6 (8.3)	25	64.5 (11.0)	91	49.9	0.045	-0.37
ADI-R (A)	11.8 (6.1)	25	11.8 (5.1)	91	33.5	0.945	-0.02
Reciprocal Social Interaction domain							
ADI-R (B)	8.8 (5.2)	24	9.2 (4.3)	87	32.4	0.715	0.10
Communication domain							
ADI-R (C)	2.4 (2.1)	24	3.4 (2.2)	88	38.4	0.038	0.47
Restricted, repetitive and stereotyped behavior domain							

$p = 0.008$

Welch's t-tests were conducted for age, IQ, BRIEF and ADI-R comparisons between sexes

IQ = Intelligence Quotient

BRIEF: Behavior Rating Inventory of Executive Functions

ADI-R: Autism Diagnostic Interview-Revised

Note. BRIEF scores are reported as T scores (M = 50, SD = 10) and ADI-R scores are reported as domain scores from the diagnostic algorithm.

Table 2A-C Nested hierarchical models summary

2A Reciprocal Social Interaction domain

ADI-R A	R ²	B	SE B	p
Model 1	0.03			0.486
Constant		19.98	5.20	< .001*
Sex		-0.13	1.32	0.923
IQ		-0.07	0.04	0.104
ADHD diagnosis		-1.26	1.16	0.279
Age		-0.08	0.17	0.618
Model 2	0.11			0.041
Constant		10.68	5.95	0.076
Sex		-0.55	1.28	0.667
IQ		-0.07	0.04	0.106
ADHD diagnosis		-1.88	1.14	0.102
Age		-0.07	0.16	0.650
BRIEF GEC		0.14	0.05	0.005*
Model 3	0.22			<.001*
Constant		44.69	10.93	<.001*
Sex		-29.20	7.99	<.001*
IQ		-0.07	0.04	0.100
ADHD diagnosis		-1.04	1.10	0.345
Age		-0.05	0.15	0.743
BRIEF GEC		-0.37	0.15	0.015*
BRIEF GEC * Sex		0.42	0.11	< .001*

*p = 0.017

ADI-R: Autism Diagnostic Interview- Revised, diagnostic algorithm. A: Reciprocal Social Interaction domain, B: Communication domain, C: Restricted, repetitive and stereotyped behavior domain.

ADHD: Attention deficit/ hyperactivity disorder

IQ: Intelligence Quotient

BRIEF_GEC: Behavior Rating Inventory of Executive Function, Global Executive Composite

B = unstandardized regression coefficients

2B Communication domain

ADI-R B	R ²	B	SE B	p
Model 1	0.01			0.843
Constant		12.86	4.47	0.005*
Sex		-0.42	1.14	0.717
IQ		-0.04	0.04	0.357
ADHD diagnosis		0.44	1.01	0.664
Age		0.01	0.15	0.963
Model 2	0.07			0.200
Constant		6.11	5.16	0.239
Sex		-0.76	1.12	0.500
IQ		-0.03	0.04	0.378
ADHD diagnosis		-0.01	1.00	0.990
Age		0.01	0.14	0.949
BRIEF GEC		0.11	0.04	0.016*
Model 3	0.18			0.004*
Constant		35.20	9.62	< .001*
Sex		-25.36	7.10	< .001*
IQ		-0.03	0.03	0.404
ADHD diagnosis		0.75	0.97	0.439
Age		0.01	0.13	0.916
BRIEF GEC		-0.33	0.13	0.013*
BRIEF GEC* Sex		0.36	0.10	< .001*

*p = 0.017

ADI-R: Autism Diagnostic Interview- Revised, diagnostic algorithm. A: Reciprocal Social Interaction domain, B: Communication domain, C: Restricted, repetitive and stereotyped behavior domain.

ADHD: Attention deficit/ hyperactivity disorder

IQ: Intelligence Quotient

BRIEF_GEC: Behavior Rating Inventory of Executive Function, Global Executive Composite

B = unstandardized regression coefficients

2C Restricted, repetitive and stereotyped behavior domain

ADI-R C	R ²	B	SE B	p
Model 1	0.04			0.435
Constant		5.70	2.16	0.010*
Sex		-1.00	0.55	0.073
IQ		-0.01	0.02	0.478
ADHD diagnosis		-0.39	0.48	0.422
Age		0.01	0.07	0.889
Model 2	0.09			0.118
Constant		2.69	2.50	0.286
Sex		-1.15	0.54	0.037
IQ		-0.01	0.02	0.506
ADHD diagnosis		-0.58	0.48	0.229
Age		0.01	0.07	0.873
BRIEF GEC		0.05	0.02	0.027
Model 3	0.12			0.063
Constant		1.33	4.88	0.037
Sex		-7.62	3.60	0.037
IQ		-0.01	0.02	0.533
ADHD diagnosis		-0.39	0.49	0.428
Age		0.01	0.07	0.857
BRIEF GEC		-0.07	0.07	0.309
BRIEF GEC * Sex		0.09	0.05	0.072

* $p = 0.017$

ADI-R: Autism Diagnostic Interview- Revised, diagnostic algorithm. A: Reciprocal Social Interaction domain, B: Communication domain, C: Restricted, repetitive and stereotyped behavior domain.

ADHD: Attention deficit/ hyperactivity disorder

IQ: Intelligence Quotient

BRIEF_GEC: Behavior Rating Inventory of Executive Function, Global Executive Composite

B = unstandardized regression coefficients