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Abstract

There is an ongoing debate as to whether autism spectrum disorder (ASD) is expressed differently in women than men. It is unclear whether differences found are specific to autism or merely reflecting normative development. In this study, we compared sex differences in developmental trajectories of autistic and co-occurring psychopathological symptoms in adolescents with milder forms of autism to those in a normative group matched for intelligence quotient (IQ) and socioeconomic status. Data of five assessment waves from ages 11 to 22 years were analyzed using linear mixed modeling. We found that in adolescence, sex differences in developmental trajectories of psychopathological symptoms specific for autism are confined to the repetitive stereotyped domain (males had higher scores on the sensory/stereotypic and resistance to change domains, the latter difference disappeared during adolescence due to an increase of these problems in females with ASD). Other sex differences, among which an increase over time in affective and anxiety problems in females was the most outstanding, were also observed in typically developing females. These sex-specific differences have relevance in the clinical care of men and women with autism, although they are subtle compared to differences between individuals with and without autism, which are broadly present in internalizing and externalizing problem domains.

Lay abstract

There is an ongoing debate as to whether autism spectrum disorder (ASD) is expressed differently in women than men. Studies on sex differences in autistic symptoms and symptoms of other psychiatric problems present in individuals with autism generally do not include a general population comparison group, making it unclear whether differences are specific to autism or merely reflecting development in the general population. In this study, we compared sex differences in the course of autistic and at the same time present symptoms of other psychiatric problems in adolescents with milder forms of ASD to those in a group of the general population with an equal intelligence quotient (IQ) and socioeconomic status. Data of five assessment moments from ages 11 to 22 years were analyzed using a statistic procedure that allowed us to determine which factors affect the course of symptoms over time. We found that in adolescence, sex differences in the course of psychopathological symptoms specific for autism are confined to the repetitive stereotyped domains. Males had higher scores on the sensory/stereotypic and resistance to change domains, the latter difference disappeared during the course of adolescence due to an increase of these problems in autistic females. Other sex differences, among which an increase over time in mood and anxiety problems in females was the most outstanding, were also observed in females without autism. These sex-specific differences have relevance in the clinical care of autistic men and women, although they are subtle compared to differences between individuals with and without autism.

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Introduction

Like in most neurodevelopmental disorder, there is a male preponderance in autism spectrum disorder (ASD). A recent systematic review and meta-analysis by Loomes and colleagues (2017) summarized the prevalence studies on autism and reported a large variability across studies with an overall male-to-female ratio of 4.2:1 in children aged 0–18 years. Intelligence quotient (IQ) has most consistently been associated with the sex difference in autism (Rivet & Matson, 2011), with the proportion of males increasing among participants with higher IQ (Volkmar & Szatmari, 1993). Another factor is the age of participants, in the meta-analysis of Loomes et al. (2017), the male-to-female ratio was higher in the age group over 6 years than under 6 years. Researchers have also related the disparity to differences in genetic background, hormonal status, and neurocognitive development, but with mixed results (May et al., 2019; Rivet & Matson, 2011). Recently, social and cultural factors that might contribute to underidentification of autism in females have been put forward. More specifically, a steep increase is seen in the number of publications on the hypothesis of a "female autistic phenotype" and "camouflaged" autism symptoms in females diagnosed later in life (adolescence or afterwards) (e.g. Bargiela et al., 2016; Hull et al., 2020). Central to this idea is that that there is a female-specific manifestation of autism symptoms and co-occurring traits. Compared to boys/men, girls/women with autism are believed to show relatively higher social motivation, a greater capacity for traditional friendships, fewer repetitive and stereotyped behaviors, less-externalizing behaviors (hyperactivity/impulsivity and conduct problems), yet more internalizing problems (anxiety, depression, and eating disorders) (Bargiela et al., 2016; Hull et al., 2020). Furthermore, girls/women are believed to be inclined, more than boys/men, to hide their autistic behavior by masking and using compensatory strategies ("camouflaging") to navigate the social world (Lai et al., 2020). As a consequence, girls/females with autism may more often be misdiagnosed (foremost with internalizing and/or personality disorders) or late-diagnosed compared to boys/males with autism. This seems to be especially the case in girls/females at the milder end of the autism spectrum (Lai et al., 2017), in which group, the autistic symptoms are harder to discern from other forms of psychopathology or extremes of normotypic behavior. Despite the apparent clinical validity of this theory, studies on this topic have been mainly conducted with small convenience samples that lack a proper longitudinal case–control design (Fombonne, 2020). One of the alternative explanations for the reported subjective sensations of "pretending" in late-diagnosed females with autism may be social anxiety (Fombonne, 2020).

Consequently, to increase our understanding of sex differences in autism, it is important to have detailed information on these differences in prevalence and course of autistic and comorbid psychopathological symptomatology (i.e. co-occurring internalizing and externalizing symptoms) in autistic persons, while at present, only coarse information is available. Autism has a multifaceted presentation, and it is plausible that sex differences differ along these problem domains within autism; therefore, an analysis of multidomain sex differences is relevant. In addition, a reference sample of same-aged individuals without autism is needed in order to determine if potential sex differences in psychopathology in persons with autism reflect normative (i.e. similar sex differences as in typically developing peers) or autism-specific developmental patterns (i.e. different sex differences compared to typically developing peers). A recent study by Demetriou and colleagues (2021), in which sex differences in cognitive performance shown not to be specific to the autistic group, underlines the importance of the inclusion of a normative group.

In this study, we will focus on sex differences in the development of autism, internalizing (anxiety and depression), attention-deficit/hyperactivity disorder (ADHD) and externalizing (aggression) symptoms in persons with and without a clinical diagnosis of autism from late childhood to early adulthood. In the next paragraph, we will summarize what is already known about sex differences in the developmental course of autism, internalizing, ADHD, and externalizing symptomatology in autistic persons, as well as in the general population.

The course of autistic symptoms during adolescence in males and females

Studies on the developmental course of autistic traits in adolescents in the general population are confined to the social-communicative problem domain of autism. Overall, the literature suggests that boys score higher than girls in early adolescence (Mandy et al., 2018; Robinson et al., 2011); however, the study by Mandy et al. showed an increase in scores in girls from 10 to 16 years that was steeper than in boys. As a result, the sex difference in scores at age 10 disappeared during adolescence. Results on sex differences in autistic symptoms in persons with autism come from cross-sectional studies and are somewhat inconsistent due to a large variability in IQ, age, and autism severity (Fountain et al., 2012; Louwerse et al. 2015; Simonoff et al., 2019; Woodman et al., 2016). In a systematic review and meta-analysis of cross-sectional studies that reported on sex and age differences in

symptom severity in the core triad of autism problem domains as measured by—mainly parent report—standardized instruments (in toddlers and pre-schoolers, children, adolescents and adults), Van Wijngaarden-Cremers et al. (2014) reported no sex differences in social behavior and communication problems, but more repetitive and stereotyped behaviors in boys than girls aged 6–18. Kaat et al. (2021) combined several databases to create a large sample of girls and boys with an autism diagnosis to evaluate sex differences in scores on standardized measures of autism symptoms. When matched for age, IQ, and language level, they found minimal sex differences (effect sizes $<.20$); boys received more severe scores on parent-reported and clinician-administered measures of restricted repetitive behavior. A meta-analysis by Mahendiran et al. (2019) of studies that included a normative comparison group on sex differences in social and communication symptoms in children and adolescents with autism again reported no significant differences between males and females but noted significant heterogeneity in the reviewed studies. Wood-Downie and colleagues (2021) conducted a systematic review and meta-analysis of gender differences on narrow construct domains like social attention and peer relationships and found that autistic females had better social interaction and communication skills than autistic males; for non-autistic individuals, similar gender differences were found. Groups were not matched for IQ. They concluded that standardized measures that are based on broad constructs might not capture these differences which potentially contribute to under recognition of autism in females.

Overall, sex differences in social and communication symptoms as measured by standardized diagnostic instruments in autistic persons seem to be absent. Sex differences found on some subdomains of social interaction, and communication seem to be alike in autistic and non-autistic persons. More repetitive and stereotyped behavior has been reported in males than in females with autism; however, with regard to this symptom domain, we did not find a study which included a normative comparison group.

The course of internalizing, ADHD, and externalizing symptoms during adolescence in males and females

Multiple studies that examined the course of internalizing problems throughout adolescence in the general population have shown that these increase in early adolescence, peak in mid-adolescence and decrease into young adulthood (e.g. Petersen et al., 2018). Females developed higher levels of depressive and anxiety symptoms than males around the onset of puberty (Hankin et al., 1998; Lewinsohn et al., 1998). Distinct gender-specific developmental trajectories of anxiety and depression during adolescence have been identified. With regard to anxiety, females exhibited a slight decrease in symptoms and males exhibited a stable course from mid-to-late adolescence (Legerstee et al., 2013; Ohannessian et al., 2017; Van Oort et al., 2009). A sex difference in the course of depressive symptoms emerged early in adolescence when girls' symptoms accelerated, whereas boys' symptoms accelerated later in adolescence, but did not reach female levels of symptoms indicating a stable higher female-to-male preponderance of depressive symptoms (Hankin et al., 2015; Salk et al., 2016). Thus, sex differences in internalizing problems increase during adolescence and this seems to be driven predominantly by depressive problems.

ADHD symptoms on average decline from approximately age 12, with inattention remaining relatively stable or declining at a modest rate, and hyperactivity/impulsivity waning more strongly and remitting more abruptly (Hartman et al., 2016; Vos et al., 2021). Studies on sex-specific ADHD trajectories through adolescence are scarce and showed contradictory results (e.g. Malone et al., 2010; Murray et al., 2019). The developmental course of ADHD symptoms leads to a decline over time in the sex ratio of ADHD (male-to-female ratio of 3:1 in childhood, closer to 1:1 in adulthood; Huang et al., 2016).

Most studies on the course of externalizing problems (aggression and oppositional behavior) in childhood and adolescence have also demonstrated a decline of symptoms with age (e.g. Bongers et al., 2004; Roskam, 2019). With regard to sex differences in externalizing problems in adolescents, Fernandez et al. (2014) found that boys showed higher levels of externalizing symptoms than girls in a large sample from the general population. These symptoms decreased in both groups from age 11 to 15, indicating stable higher externalizing problems in males than females. Other studies converge on this pattern (Bongers et al., 2004; Karriker-Jaffe et al., 2008) and show that higher aggression in males than females is still present in young adulthood (Boyd et al., 2015).

In children and adolescents with autism, higher levels of depressive and anxiety symptoms than in peers in the general population or peers with other developmental disabilities have been reported (Gotham et al., 2015; Kim et al., 2000; Verheij et al., 2015; Woodman et al., 2016). Sex differences in comorbid psychopathology in autistic adolescents have not been investigated thoroughly, with the findings so far summarized mostly based on cross-sectional data, which were heterogeneous in terms of age, intelligence, and autism severity, and with inconsistent results (Holtmann et al., 2007; Nasca et al., 2019; Oswald et al., 2016; Pisula et al., 2017). In a longitudinal study, Gotham and colleagues (2015) compared trajectories of depressive and anxiety symptoms in participants with autism ($n=56$) and with non-spectrum developmental delay ($n=109$) from school-age (age 6) through young adulthood (age 24) and found that parent-rated symptom levels tended to start and remain higher in the autism group

compared to the comparison group. In both diagnostic groups, anxiety and depressive symptoms were higher in males than in females at study outset and remained relatively stable over time, while symptom level in females increased throughout adolescence causing the sexes to converge on anxiety and depressive symptom in adulthood. These results diverge from the aforedescribed studies in the general population, where boys and girls exhibit around equal internalizing symptoms until adolescence, and subsequently, girls develop higher levels of internalizing symptoms than boys. We did not find studies on the developmental course of ADHD and externalizing symptoms in autistic adolescents.

Aims and hypotheses of this study

This study aimed to determine if sex differences in developmental trajectories of psychopathology in persons with milder forms of autism differ from normative sex-specific developmental trajectories of psychopathology. To this end, we documented sex-specific developmental trajectories of autistic and non-autistic symptoms from childhood through young adulthood in persons with a *Diagnostic and statistical manual of mental disorders: 4th Edition* (*DSM*-IV-TR) ASD classification (American Psychiatric Association [APA], 2000). We compared these with normative levels of these symptoms in typically developing adolescents who were matched for IQ and socioeconomic status (SES). Based on the literature, we expected higher scores for autistic persons with all domains of psychopathology, but specifically in autistic males, higher levels of restricted and repetitive behavior than in females with ASD. This difference would be absent in the normative comparison group due to low levels of these symptoms (Kaat et al., 2021; Van Wijngaarden-Cremers et al., 2014). Furthermore, based on the female phenotype hypothesis, more internalizing and less externalizing symptoms in females compared to autistic males would be expected. Furthermore, based on Gotham et al.'s (2015) longitudinal study, a more refined developmental expectation would be that higher internalizing problems in early adolescence are found in males, while females with and without autism increase in internalizing problems such that the female phenotype hypothesis would hold particularly in late adolescence. Additional and more refined expectations on sex differences throughout adolescence, in particular with regard to ADHD and externalizing symptoms, could not be formulated due to the overall absence of knowledge on developmental differences in autistic males and females.

Methods

Sample

The study is based on data from persons with a clinical *DSM*-IV-TR ASD classification ($n = 152$; 111 males, 41 females) from the clinical cohort of the Tracking Adolescents' Individual Lives Survey (TRAILS; Huisman et al., 2008; Oldehinkel et al., 2015), and a sex, age, and SES-matched comparison group derived from the TRAILS population cohort ($n = 152$). TRAILS is a prospective study aiming to explain the development of mental health from early adolescence (approximately age 11) into adulthood, with bi- or triennial assessments since. In this study, we used five assessment waves (T1–T5) between age 11 and 22. The population cohort started in 2001 and consists of 2230 individuals who were selected from primary schools in five municipalities in the North of the Netherland including both urban and rural areas. The clinical cohort started in 2004 and consists of 543 individuals who had been referred to a child psychiatric outpatient clinic in the Northern Netherlands any time before the age of 11. The TRAILS cohort data were linked to the Psychiatric Case Register Northern Netherlands (PCRNN). The PCRNN registers specialist child, adolescent, and adult mental health care consumption in the three Northern provinces of the Netherlands, which overlaps with the area from which TRAILS participants were recruited. Children and their parents gave consent to link their TRAILS data to health care records in the PCRNN. The PCRNN contained data from 2000 up (4 years preceding the start of TRAILS) on clinical diagnoses, and the potential presence of an autism diagnosis was identified in the PCRNN until age 19. Because only three of the 155 TRAILS CC participants with an ASD classification had an Autistic Disorder classification (*DSM*-IV classification 299.0), we confined our study group to those participants with milder forms of ASD (*DSM*-IV classification 299.80: Asperger's Disorder or Pervasive Developmental Disorder—Not Otherwise Specified).

Matching

We matched an equally sized subsample of the TRAILS general population sample (normative sample) to the sample of autistic persons on characteristics potentially linked to autism which may confound conclusions: that is, sex, IQ, and SES. To this end, we first ensured that we had an equal number of male and female participants in the clinical and normative sample. IQ was a matching variable given its well-known association with severity of autism and comorbid psychiatric problems. Furthermore, we used SES as a matching variable, as family and social characteristics have been implicated in influencing symptom manifestation as well as clinical interpretation of such symptoms in autistic girls (Kreiser et al., 2014), although few studies have specifically investigated SES in this connection, and its association with symptom severity of autism is currently not clear (Mahendiran et al., 2019). Finally, since TRAILS is a homogeneous age cohort, and followed up at same age-intervals over time, age matching was not a priori necessary, although we checked if the two samples

Table 1. Demographic characteristics of persons with and without ASD, comparing males and females at T1[a] (mean (*SD*)).

		Males ($n=222$)	Females ($n=82$)	Total ($n=304$)	Difference f/m
ASD ($n=152$)	Age	11.00 (0.44)	11.02 (0.57)	11.01 (0.48)	n.s.
	IQ	101.67 (15.45)	96.16 (12.27)	100.15 (14.81)	$p<0.05$
	SES	0.97 (0.68)	−0.02 (0.62)	0.64 (0.67)	n.s.
No ASD ($n=152$)	Age	11.23 (0.60)	11.35 (.54)	11.26 (0.48)	n.s.
	IQ	101.77 (14.94)	95.83 (13.71)	100.16 (14.81)	$p<0.05$
	SES	0.91 (0.68)	−0.56 (0.61)	0.52 (0.66)	n.s.
Total ($n=304$)	Age	11.11 (0.45)	11.18 (0.58)	11.13 (0.55)	n.s.
	IQ	101.72 (15.16)	96.00 (12.92)	100.16 (14.79)	$p<0.05$
	SES	0.09 (0.54)	−0.38 (0.61)	0.06 (0.66)	n.s.

ASD: autism spectrum disorder; IQ: intelligence quotient; SES: socioeconomic status; *SD*: standard deviation.
[a]Sample size at different waves: T2: $n=140$ (103 males, 37 females); T3: $n=110$ (80 males, 30 females); T4: $n=117$ (85 males, 32 females); T5: $n=115$ (82 males, 33 females).

were comparable on age, after matching. We first matched the clinical and normative samples on IQ such that the IQ of the matching participant from the normative sample was within 2 IQ points of the IQ of the autistic participant. Next, of those participants who met this criterion, the participant who had the SES closest to the autistic participant was selected. After matching, mean IQ in the clinical sample was 100.15 (*SD* 14.81), in the normative sample mean IQ was 100.16 (*SD* 14.81) (Table 1), which were similar ($p=1.00$); mean SES in the clinical sample was 0.64 (*SD* 0.67) and in the normative sample 0.52 (*SD* 0.66; Table 1), which were similar ($p=0.87$). Table 1 shows further that within the clinical and normative samples, IQ was lower in females than males, but SES was comparable.

Instruments

To assess cognitive ability, the Vocabulary and Block Design subtests of the *Revised Wechsler Intelligence Scales for Children* (Wechsler, 1974) were administered at baseline. IQ was estimated from the scores on these subtests. Family SES was assessed at baseline using five indicators: family income, educational level of the father and the mother, and occupational level of both parents using the standard Classification of Occupations. We created an SES variable by averaging the indicators after standardization.

To capture the heterogeneity of problems of children and adolescents with autism, we used the Children's Social Behavior Questionnaire (CSBQ; Hartman et al., 2006; Luteijn et al., 2000). The parent-reported, 49-item CSBQ is a quantitative measure of autistic traits, with subscales that allow a differentiated description of multitype autistic problems. We report on the four subscales which are the most characteristic of autism as well as two additional subscales: (1) *Reduced contact and social interest (i.e. Social)* and (2) *Difficulties in understanding social information (i.e. Understanding)*, representing the social domain of autism. Furthermore, *subscales* (3) *Fear of and resistance to change (i.e. Change)* and (4) *Sensory stimulation/motor stereotypies (i.e. Sensory)* representing the restricted and repetitive behaviors and interest domains of autism. Finally, subscales (5) *Orientation problems in time*, *place*, *or activity* (*i.e. Orientation*) and (6) *Not optimally tuned to the social situation (i.e. Tuned)* capture aspects of daily-life executive functioning and self-regulation. These scales are less specific of autistic behavior, and results are put in Supplementary Information. The CSBQ was designed to include both subtle forms of autistic behaviors and severe autistic behaviors and has a 3-point Likert-type scale to also allow for quantitative change rather than presence/absence (Hartman et al., 2006). Results are reported at mean item level, ranging from 0 to 2. The validity of the CSBQ has been shown in relation to autistic behavior and brain volumetric correlates of autism (Hartman et al., 2006; O'Dwyer et al., 2014). The CSBQ has been used in various studies with a longitudinal design in which the course of autistic symptoms was examined (e.g. Oerlemans et al., 2018), or as a measure to monitor the outcome of interventions which aim to target autistic behavior (e.g. Pater et al., 2021).

Internalizing (depression and anxiety), ADHD and externalizing (conduct disorder) symptoms were measured with the *DSM*-based scales of the parent-reported Child Behavior Checklist (CBCL; Achenbach, 2001) and the self-report Youth Self Report (YSR; Achenbach, 2001). From age 18, there was a transition from the CBCL to the Adult Behavior Checklist (ABCL; Rescorla & Achenbach, 2004) and from the YSR to the Adult Self Report (ASR; Rescorla & Achenbach, 2004). For externalizing problems, we chose conduct disorder symptoms which have been identified both for the CSBQ, YSR, ASBQ, and the ASR. We used self-report (i.e. YSR/ASR) as the main outcome measure, in particular, given its indispensability for affective problems and anxiety, but put results from parent report in Supplementary Information. Results are reported

at mean item level, ranging from 0 to 2. The Achenbach scales have been used extensively in research on internalizing and externalizing symptoms in adolescents and have demonstrated good validity and reliability (Rescorla & Achenbach, 2004). The evidence for the validity of both the syndrome scales and *DSM*-oriented scales of the CBCL in individuals with ASD is strong (Magyar & Pandolfi, 2017; Pandolfi et al., 2012).

The CSBQ, CBCL, and YSR were administered at T1 (mean age 11.13 years), T2 (mean age 13.12 years), and T3 (mean age 16.02 years). At T4 (mean age 19.05 years), the CSBQ and ASR were administered, and at T5 (mean age 22.06 years) the ABCL.

Data analysis

CSBQ, CBCL, ABCL, YSR, and ASR scores were analyzed using linear mixed modeling (Gardiner et al., 2009). Models contained a random intercept and random slope for age and fixed effects for age at assessment, autism status, sex, and all possible interactions between these variables. The covariance between the random intercept and slope was freely estimated. Age at assessment was continuous and the normative group and males served as reference categories in all models.

In a post hoc analysis, we added IQ as a covariate to adjust for the lower IQ difference that was found to be present between in autistic females compared to autistic males (and through matching also in males and females without ASD). All models were estimated in SPSS, version 26, using maximum likelihood estimation (West, 2009).

To enhance interpretation, we standardized all CSBQ, CBCL, ABCL, YSR, and ASR subdomain scores and mean-centered age.

There was no community involvement in the reported study.

Results

Table 2 provides model estimated means of autistic symptoms, and Figure 1 plots the sex differences in persons with and without ASD. Supplementary Table ST1 provides the regression model estimates and Supplementary Figure SF1 the estimated means separately for males and females with and without ASD. No sex differences for the subscales *Reduced contact and social interest and Difficulties in understanding social information were found* (Table 2, Figure 1(a) and (b), Supplementary ST1, and SF1a/b). In contrast, a three-way interaction effect for the *Fear of and resistance to change* subscale (Table 2, Figure 1(c), ST1, and SF1c) indicated that scores were similar for males and females without autism but higher in autistic males compared to autistic females. These scores decreased in autistic males during adolescence and increased in autistic females relative to the low stable scores in individuals without autism. A three-way interaction effect for *Sensory stimulation/motor stereotypies* indicated that scores were higher in males with autism than females with autism and *decreased for males with age* (Table 2, Figure 1(d), ST1, and SF1d), while there were no sex differences in individuals without autism. The subscales *Orientation problems in time, place or activity*, and *Not optimally tuned to the social situation* showed no sex differences (Table 2, Figure 1(e) and (f), ST1, and SF1e/f).

Internalizing symptoms

Table 3 provides model-estimated means of internalizing, ADHD, and externalizing symptoms, and Figure 2 plots the sex differences in persons with and without ASD. Supplementary Table ST2 provides the regression model estimates, and Supplementary Figure SF2 provides the estimated means separately for males and females with and without ASD. During adolescence, as indicated by two-way sex-by-age interaction effects, self-reported affective and anxiety symptoms increased in females, but decreased in males (Table 3, Figure 2(a) and (b), ST2, and SF2a/b). There were no three-way interaction effects between diagnostic group, sex, and age on either of these two internalizing subscales indicating that these sex differences were not specific for ASD. The parent ratings of affective and anxiety symptoms yielded similar findings (Table 3, Figure 2(e) and (f), ST2, and SF2e/f).

ADHD symptoms

There were no sex differences in self- or parent-reported scores of ADHD symptoms (Table 3, Figure 2(c) and (g), ST2, and SF2c/g).

Externalizing symptoms

No sex differences were found in self-reported conduct problems as shown in Table 3, Figure 2(d), ST2, and SF2d. The parent ratings yielded the same conclusion (Table 3, Figure 2(h), ST2, and SF2h).

Post hoc analyses

Adding IQ as a covariate in post hoc analyses did not alter any of the conclusions drawn from the findings of our main analyses (see the regression model estimates in ST3 and ST4 as compared to the estimates in ST1 and ST2, respectively).

Discussion

The aim of this study was to identify possible sex-specific manifestations of autism during the course of adolescence

Table 2. Model-estimated means of CSBQ domains in standardized scores of males and females with and without ASD between childhood and young adulthood.

			Wave 1 (age ~11 years)	Wave 2 (age ~13 years)	Wave 3 (age ~16 years)	Wave 4 (age ~19 years)
CSBQ	Reduced contact and social interest	Males without ASD	−0.57	−0.53	−0.47	−0.41
		Females without ASD	−0.68	−0.63	−0.56	−0.49
		Males with ASD	0.45	0.46	0.48	0.51
		Females with ASD	0.32	0.35	0.40	0.45
	Difficulties in understanding social situations	Males without ASD	−0.50	−0.53	−0.56	−0.59
		Females without ASD	−0.57	−0.57	−0.57	−0.57
		Males with ASD	0.67	0.55	0.38	0.20
		Females with ASD	0.57	0.52	0.46	0.40
	Fear and resistance to change	Males without ASD	−0.39	−0.40	−0.40	−0.41
		Females without ASD	−0.55	−0.54	−0.52	−0.50
		Males with ASD	0.46	0.39	0.28	0.17
		Females with ASD	0.34	0.42	0.54	0.65
	Sensory stimulation/motor stereotypes	Males without ASD	−0.22	−0.28	−0.36	−0.45
		Females without ASD	−0.37	−0.40	−0.44	−0.49
		Males with ASD	0.71	0.52	0.24	−0.04
		Females with ASD	0.07	0.06	0.04	0.02
	Not optimally tuned into the social situation	Males without ASD	−0.41	−0.46	−0.54	−0.62
		Females without ASD	−0.41	−0.43	−0.47	−0.50
		Males with ASD	0.70	0.54	0.31	0.08
		Females with ASD	0.63	0.52	0.34	0.17
	Orientation problems in time, place, or activity	Males without ASD	−0.42	−0.44	−0.47	−0.50
		Females without ASD	−0.59	−0.62	−0.65	−0.69
		Males with ASD	0.68	0.57	0.40	0.23
		Females with ASD	0.51	0.40	0.23	0.06

CSBQ: Children's Social Behavior Questionnaire; ASD: autism spectrum disorder.

and determine if these differed from normative sex-specific developmental trajectories of psychopathology.

Sex differences specific for autism were only found in the autism domain of restrictive repetitive behavior (*Fear of and resistance to change* and *Sensory stimulation / motor stereotypies*), such that unlike persons without autism, autistic males had higher scores than autistic females. This difference was stable over time for sensory stimulation/motor stereotypies, but disappeared during the course of adolescence for resistance to change, due to an increase of these problems in autistic females. No sex differences were found on the CSBQ social-communicative scale scores. With regard to broader-than-autism psychopathology, sex differences were alike for the autism and the normative groups: a decrease over time in parent- and self-reported affective and anxiety symptoms in males, while in females, these symptoms increased over time. Such similarities in course of symptoms in autism and non-autism participants have also been reported in previous studies that included individuals with non-spectrum developmental delays (Gotham et al., 2015). Thus, our results confirm that found developmental sex differences for anxiety and affective problems, even though they tend to be higher in (both men and) women with than without autism, are not autism specific.

In recent years, the notion of a specific female autistic symptom profile has been developed in the literature (e.g. Hull et al., 2020; Mandy et al., 2012) which has received much attention both in the scientific and in the lay press. Although the first delineations of this female phenotype assumed subtle sex differences in behavior (more restricted repetitive behavior in males, more internalizing problems in females, more externalizing problems in males, superior motor skills in females (Mandy et al., 2012), more recent publications presume a broader set of typical female autistic characteristics, also including social-communicative behavior (Hull et al., 2020). Our results clearly support the former, more limited female autistic symptom profile: sex differences in severity and course of social-communicative behavior were not confirmed in our present analyses. Our results are in line with previous findings that autistic males demonstrate more restricted repetitive behavior than

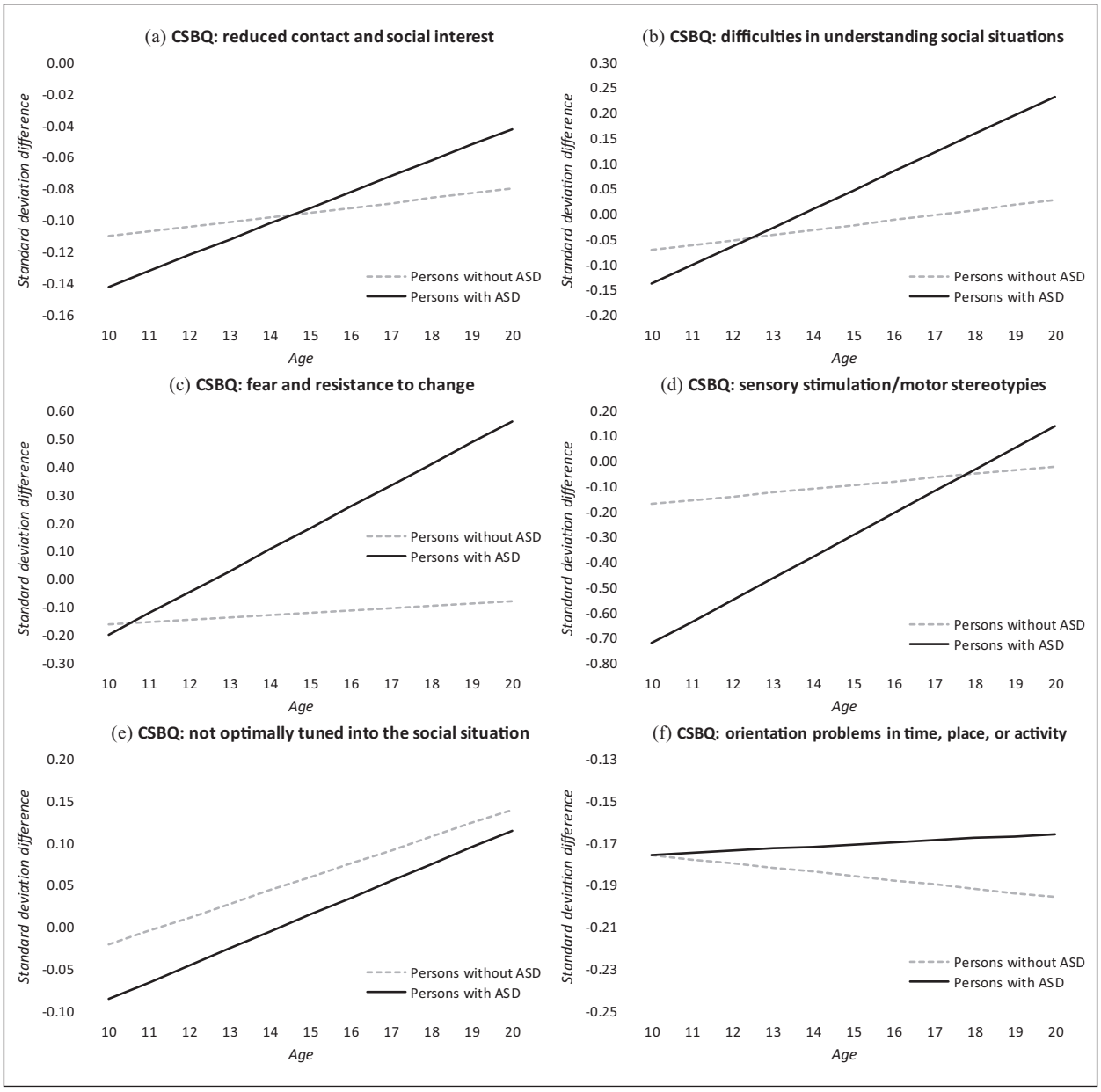

Figure 1. Model-estimated CSBQ female versus male differences in standard deviations using linear mixed modeling between childhood and young adulthood in persons with and without ASD.
CSBQ: Children's Social Behavior Questionnaire; ASD: autism spectrum disorder.

autistic females in adolescence. In addition, we found a sex-specific course through adolescence of the *Fear of and resistance to change* symptoms, which increased in females through adolescence such that the initially higher scores in males disappeared. So far, no research has been conducted on the course of restricted behavior in this age group in autism in a longitudinal design. Thus, we extended previous findings. With respect to the sex differences in internalizing and externalizing symptoms reported by Mandy et al. (2012) and others, we found that a sex-specific course of anxiety and affective symptoms was present both in the autism and the normative samples, while no sex differences in conduct problems and ADHD symptoms were identified. In sum, the sex-specific autistic symptom profile that emerges from our study is confined to higher restricted repetitive behavior in men and higher resistance to change in early adolescent boys—the latter restricted to early adolescence due to subsequent increase of these symptoms in girls. Broader anxiety and affective symptoms showed the well-known developmental increase in girls during adolescence, but this was not confined to individuals with autism (Fernandez Castelao & Kröner-Herwig

Table 3. Model-estimated means of YSR and CBCL domains in standardized scores of males and females with and without ASD between childhood and young adulthood.

			Wave 1 (age ~11 years)	Wave 2 (age ~13 years)	Wave 3 (age ~16 years)	Wave 4/5 (age ~19/22 years)
YSR/ASR	Affective problems	Males without ASD	−0.155	−0.241	−0.37	−0.499
		Females without ASD	−0.273	−0.193	−0.073	0.047
		Males with ASD	0.184	0.104	−0.016	−0.136
		Females with ASD	0.452	0.556	0.712	0.868
	Anxiety problems	Males without ASD	−0.222	−0.264	−0.327	−0.39
		Females without ASD	−0.175	−0.073	0.08	0.233
		Males with ASD	0.064	0.006	−0.081	−0.168
		Females with ASD	0.578	0.656	0.773	0.89
	ADHD problems	Males without ASD	−0.171	−0.203	−0.251	−0.299
		Females without ASD	−0.055	−0.121	−0.22	−0.319
		Males with ASD	0.349	0.259	0.124	−0.011
		Females with ASD	0.376	0.26	0.086	−0.088
	Conduct problems	Males without ASD	0.187	0.083	−0.073	−0.229
		Females without ASD	−0.094	−0.198	−0.354	−0.51
		Males with ASD	0.32	0.218	0.065	−0.088
		Females with ASD	0.033	−0.037	−0.142	−0.247
CBCL/ACBL	Affective problems	Males without ASD	−0.466	−0.468	−0.471	−0.477
		Females without ASD	−0.636	−0.544	−0.406	−0.13
		Males with ASD	0.371	0.357	0.336	0.294
		Females with ASD	0.231	0.355	0.541	0.913
	Anxiety problems	Males without ASD	−0.453	−0.443	−0.428	−0.398
		Females without ASD	−0.544	−0.446	−0.299	−0.005
		Males with ASD	0.386	0.318	0.216	0.012
		Females with ASD	0.481	0.521	0.581	0.701
	ADHD problems	Males without ASD	−0.214	−0.31	−0.454	−0.742
		Females without ASD	−0.471	−0.525	−0.606	−0.768
		Males with ASD	0.794	0.624	0.369	−0.141
		Females with ASD	0.582	0.434	0.212	−0.232
	Conduct problems	Males without ASD	−0.293	−0.285	−0.273	−0.249
		Females without ASD	−0.466	−0.426	−0.366	−0.246
		Males with ASD	0.382	0.372	0.357	0.327
		Females with ASD	0.067	0.069	0.072	0.078

The YSR/ASR were assessed at waves 1–4 and the CBCL/ACBL at waves 1, 2, 3, and 5. YSR: youth self report; ASR: adult self report; CBCL: Child Behavior Checklist; ABCL: Adult Behavior Checklist; ADHD: attention-deficit/hyperactivity disorder.

2014; Hankin et al., 2015; Ohannessian et al., 2017). Sex-specific patterns of externalizing problems were not identified.

Males had a somewhat higher IQ than females in our autism group (and therefore also in our matched normative group) which was not accounted for in our main analysis. The difference in IQ identified in our samples is in line with the literature showing that autistic females are over-represented at the lower end of IQ and underrepresented at the higher end (Kaat et al., 2021). This may have likewise played a role in previous studies on sex differences in autism that have for the most part not studied potential confounding by IQ (Mahendiran et al., 2019). To further explore this, we performed post hoc analysis, and showed that the results regarding sex differences did not differ when adjusted for the IQ differences between males and females (Supplementary Table S3–S4)). Note that in our sample with an average IQ of around 100, the diagnostic barriers for autistic girls such as being more successful at camouflaging their problems as suggested in the literature (Hull et al., 2020) may have led to underdiagnosis of female participants. As a consequence, we cannot fully rule out that when more women with a higher IQ had been present in our autism group, the results regarding sex differences would have been more in line with findings in other studies that suggested a more pronounced female autism phenotype. That said, the composition of our autism group and our findings give a good representation of the sex differences we encounter in clinical practice, including females with lower IQ.

The parallel increase in *Fear and resistance to change* scores and anxiety scores found in autistic girls leads to the

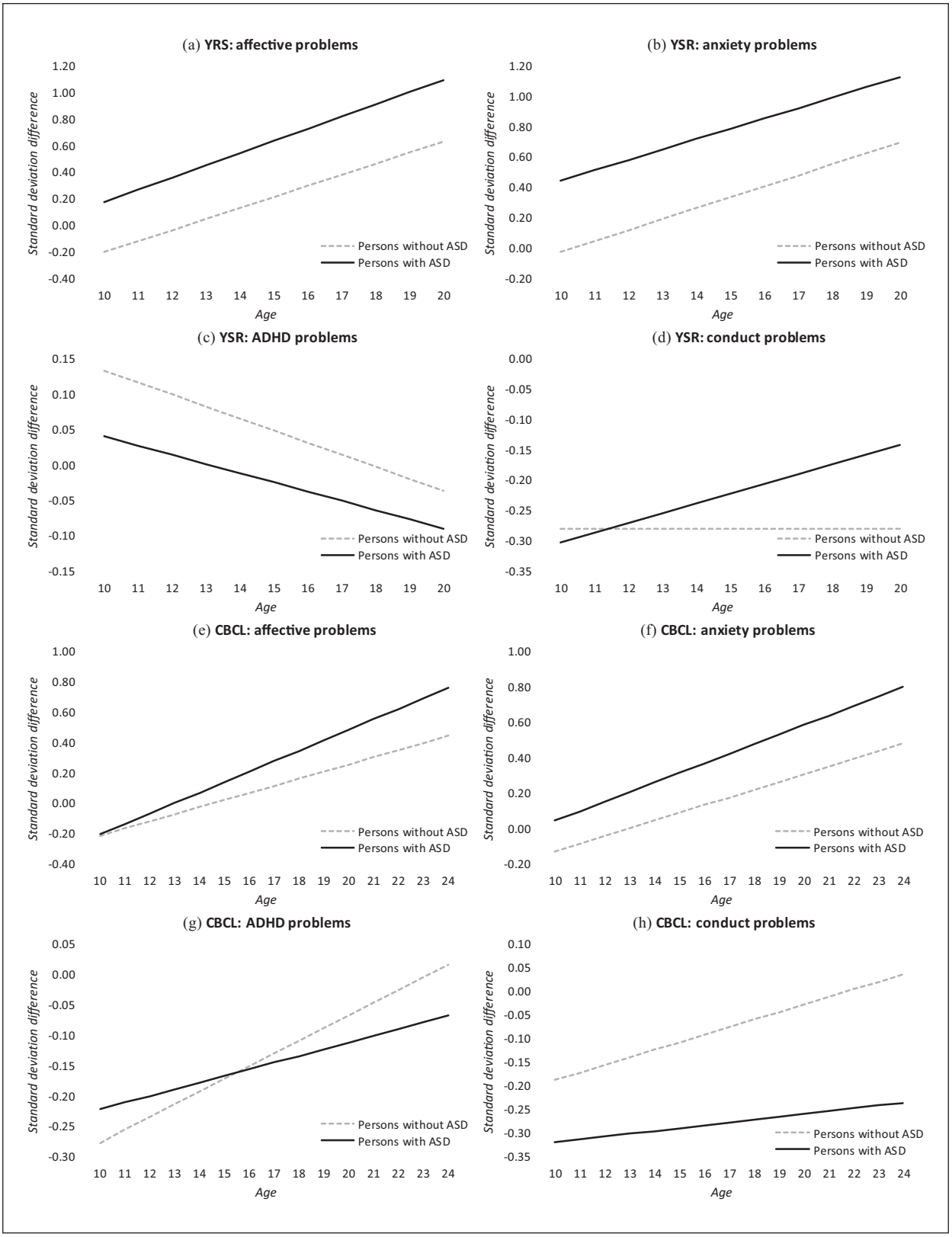

Figure 2. Model-estimated YSR and CBCL female versus male differences in standard deviations using linear mixed modeling between childhood and young adulthood in persons with and without ASD.
The YSR/ASR were assessed at waves 1–4 and the CBCL/ACBL at waves 1, 2, 3, and 5. YSR: youth self report; ASR: adult self report; CBCL: Child Behavior Checklist; ABCL: Adult Behavior Checklist; ADHD: attention-deficit/hyperactivity disorder.

question if, in autism (i.e. unlike anxiety, fear, and resistance to change did not increase in females without autism), these symptom domains are related. Insistence on sameness has been suggested to function as a coping mechanism for anxiety or distress. Lidstone et al. (2014) showed that, in 2- to 17-year olds with autism, insistence on sameness was associated with anxiety, this relation being mediated by sensory sensitivity and sensory avoiding. Baribeau and colleagues (2020) studied longitudinal trajectories of insistence on sameness and anxiety in 421 children with autism at ages 3, 6, and 11 years and found that these trajectories were similar in severity and direction for most of the participants. The group with trajectories with the highest insistence on sameness and anxiety scores had proportionally more girls than the other groups. In line with these findings, our results also suggest a sex-specific association between *Fear and resistance to change* symptoms and anxiety in autism, thus extending the findings of Baribeau and colleagues in childhood to adolescence. Further research on this topic should clarify the strength of the relationship between the restrictive repetitive domain of autism and specific subtypes of anxiety (for instance separation anxiety; see Black et al., 2017). Girls with autism in late adolescence may particularly benefit from interventions focused on anxiety, intolerance of uncertainty and sensory hypersensitivity (Jenkinson et al., 2020; Wigham et al., 2015).

An important limitation of this study is that the initial autism diagnosis was made clinically and assessment was not systematically confirmed by us at inclusion in the study using standardized diagnostic measures. The quality of diagnostic information on autism in TRAILS depends on clinical diagnostic practice, which in the Netherlands accords with the national clinical guideline stating that a best-estimate clinical diagnosis should be based on integrated information from different sources such as anamnesis, hetero-anamnesis, and observation (Kan et al., 2013). The around-to-above threshold-levels of SCQ scores for autism at the time of inclusion in the study at age 11 reported in our previous study appears to confirm the presence of significant autistic behavior in the autism group, although almost all received a clinical diagnosis of PDD-NOS (Horwitz et al., 2020). Nonetheless, in particular in light of the current higher threshold for diagnosing autism in *DSM*-5, it is likely that autism may have been diagnosed more often in our sample than if *DSM*-5 criteria would have been the standard.

Another limitation relates to the possibility of a diagnostic bias against girls, particularly among those without intellectual disability who score high on autistic symptoms but fail to meet the diagnostic criteria for autism (Loomes et al., 2017; Ratto et al., 2018). According to the female autistic phenotype/camouflaging hypothesis, girls with a female-specific autism presentation are likely to be missed out on a timely diagnosis. In our study, we cannot rule out that a female autism group with a more "masculine" autism presentation was included. However, as mentioned, participants with autism were on the milder part of the autism spectrum in our sample, which diminishes chances of having missed substantial numbers of autistic females. In general, it holds that only if diagnostic criteria—that are characteristic for both sexes—are agreed upon and assessment instruments are changed accordingly this situation of potential underdiagnosis in autistic females can be improved.

We conclude that in adolescents with milder forms of autism and an average IQ subtle sex differences are found that are not present in the normative sample: higher scores on the *Sensory stimulation/motor stereotypes* scale in males than in females throughout adolescence, and an increase over time in scores on the *Fear of and resistance to change* scales in females such that the higher scores of males in early adolescence were similarly high in males and females with autism at the start young adulthood. Furthermore, with regard to broader-than-autism psychopathology, a decrease over time in affective and anxiety symptoms in males was found, while in females, these symptoms increased over time. While this sex-specific developmental pattern held for both individuals with and without autism, increasing anxiety and affective problems during adolescence are nonetheless an area of concern in the clinical care of autistic women. Note, however, that sex differences between men and women with autism are more subtle than the differences between individuals with and without autism, which were broadly present for both the internalizing and externalizing problem domains.

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Supplemental material

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