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Diagnostic- and sex-based differences in depression symptoms in autistic and neurotypical early adolescents

Jessica M. Schwartzman[1], **Zachary J. Williams**[2,3,4,5], **Blythe A. Corbett**[1,5,6]

[1]Department of Psychiatry and Behavioral Sciences, Vanderbilt University Medical Center, Nashville, TN

[2]Medical Scientist Training Program, Vanderbilt University School of Medicine, Nashville, TN

[3]Department of Hearing & Speech Sciences, Vanderbilt University Medical Center, Nashville, TN

[4]Vanderbilt Brain Institute, Vanderbilt University School of Medicine, Nashville, TN

[5]Frist Center for Autism and Innovation, Vanderbilt University, Nashville, TN

[6]Vanderbilt Kennedy Center, Vanderbilt University Medical Center, Nashville, TN

Abstract

Prevalence rates of depression are higher in autistic youth than neurotypical peers, yet the effects of ASD diagnosis and sex on depressive symptom severity remain incompletely understood, particularly in specific age groups. Using the Children's Depression Inventory, Second Edition (CDI-2), the present study explored diagnostic- and sex-based differences in depressive symptom severity in a sample of 212 autistic and neurotypical early adolescents (10:0–13:5 years). Significant group differences were found according to ASD diagnosis (d=0.587, 95% CI [0.308,0.867]) and sex (d=0.365 [0.089,0.641]), with more depressive symptoms endorsed in the ASD and female groups. However, the interaction of diagnosis and sex was not significant, suggesting an additive risk of ASD status and female sex. Item-level analyses showed diagnostic differences on nearly half of the CDI-2 items with higher severity in the ASD group (Probability of Superiority range = 0.42–0.65), differences within the sexes, and differences by diagnosis, which persisted when limiting analyses to children with high levels of depressive symptoms. A more nuanced understanding of symptom endorsement and the roles of diagnosis and sex may uncover salient intervention targets for depression in the unique context of ASD.

Keywords

autism; depression; sex; measurement; peers; early adolescent

Correspondence to: Blythe A. Corbett, Ph.D., Vanderbilt University Medical Center, 1500 21st Avenue South, Nashville, TN 37212, blythe.corbett@vumc.org, Tel: (615) 936-0280.

Conflict of Interest

Blythe Corbett is the founder of SENSE Theatre ® but derives no financial compensation from the non-profit 501©(3) entity. Zachary Williams serves on the Family Advisory Committee of the Autism Speaks Autism Treatment Network Vanderbilt site. He also consults for Roche.

Autistic[1] individuals present with co-occurring psychiatric conditions at rates much higher than the general population (Hollocks et al., 2019; Hudson et al., 2019a; Lai et al., 2019; Lugo-Marín et al., 2019; Postorino et al., 2017; van Steensel & Heeman, 2017). Among autistic adolescents, the most common co-occurring psychiatric conditions include anxiety, ADHD, and depression (Joshi et al., 2010). In both autistic and neurotypical (NT) populations, depression often emerges during puberty and may persist into adulthood without intervention (Hudson et al., 2019a; Kaltiala-Heino et al., 2003). In general, earlier intervention for mood disorders has been linked to better outcomes in NT samples (Beardslee et al., 2013; Calear & Christensen, 2010; Gladstone et al., 2011), which may be evident for autistic adolescents. Despite this, an understanding of the roles of sex and ASD diagnosis on the severity of overall and specific depressive symptoms among early adolescents is needed, which are investigated in the present study. Similarly, the roles of sex and diagnosis on the severity of symptoms endorsed by early adolescents with elevated depression scores are explored.

Prevalence of Depression in Autistic Adolescents

Autistic individuals are up to four times more likely to experience depression in their lifetime than the general population, including adolescents (Lugnegård et al., 2011; Mayes et al., 2011a; Mazefsky et al., 2010). Specifically in autistic adolescents, lifetime prevalence rates of depression were estimated at 20.2% (Greenlee et al., 2016), which is greater than the lifetime prevalence rates of 8.4–15.4% in NT youth between 13–17 years old (Merikangas et al., 2010). Despite these advances, a recent systematic review elucidated some challenges to understanding prevalence of depression in ASD across the lifespan including bias in published studies, measurement differences, and few studies on children and adolescents (Wigham et al., 2017). In terms of depressive symptoms, findings from a longitudinal study of 6,091 youth (10–18 years old) revealed higher self-reported depressive symptoms in ASD compared to NT peers across this age range (Rai et al., 2018). Collectively, findings indicate that a diagnosis of ASD places adolescents at an elevated risk for depression and/or higher depressive symptoms.

With regards to youth, two studies reported higher prevalence of depressive symptoms in ASD than NT samples (Bitsika & Sharpley, 2015; Ozsivadjian et al., 2014). In another study, 32 autistic and neurotypical youth reported similar severity of depressive symptoms on the Children's Depression Inventory (CDI; Kovacs, 2012), yet parents of autistic youth reported significantly higher affective scores for their child (Richdale & Baglin, 2015). Despite this, small samples and poor representation of female participants limit the generalization of these results and the investigation of sex differences. Preliminary work from our group extended these findings by analyzing the severity of depressive symptoms per self- and parent-report in 230 autistic and neurotypical early adolescents of both sexes (10:0–13:5 years old; Schwartzman & Corbett, 2020). Self- and parent-rated depressive symptoms were elevated in the ASD group relative to the NT group (5–9 point difference on T-score metrics); however, the interaction of diagnostic group (ASD vs. NT) and rater (self vs.

[1]We used identity-first language (e.g., autistic youth) in this paper to align with preferences of most autistic people (Kenny et al., 2016) and supported by recent research (Bottema-Beutel et al., 2021).

parent) was not significant (Schwartzman & Corbett, 2020). It appears that depressive symptoms are more common in ASD, including early adolescence. Despite this, the effects of sex and diagnosis on the severity of overall and specific depressive symptoms have not been examined in autistic and neurotypical early adolescents. In addition, the association between diagnostic status and severity of depressive symptoms among youth with clinically-elevated symptoms is unclear (Pezzimenti et al., 2019). Therefore, an exploration of symptoms in a clinical subsample (i.e., youth with scores above the clinical threshold) may clarify the relationship of ASD and sex with the severity of depressive symptoms, while better controlling for the increased rates of depression in ASD.

Sex Differences in Depression in Autistic Adolescents

Sex-based differences in depression among NT adolescents are well documented (i.e., higher prevalence among females; Breslau et al., 2017; Kendler & Gardner, 2014). In contrast, an equivalent, vigorous understanding of sex-based differences in depression among autistic adolescents is limited and emerging findings appear mixed. One longitudinal study of anxiety and depression trajectories in autistic individuals from 6-24 years old reported that autistic boys endorsed higher depression than their female peers earlier in development (Gotham et al., 2015). However at older ages, levels of depression became similar across the sexes (Gotham et al., 2015). In contrast, a cross-sectional study of depression and anxiety from distinct developmental periods (e.g., adolescence, middle adulthood, older adulthood) found no age effects (Uljarevic et al., 2020). In these cohorts, female sex and higher autistic traits predicted greater internalizing symptoms (Uljarević et al., 2020).

Findings from a meta-analysis indicated that the prevalence of current depression in autistic individuals across the lifespan was higher in studies with a higher proportion of females (Lai et al., 2019). However, the reviewed studies spanned a wide age range, and the interaction of age and sex was not explored. Furthermore, only a few studies have included autistic youth. Therefore, understanding potential sex-based differences in depressive symptom severity in autistic adolescents would inform risk assessments and tailor treatment plans. Enhanced screening is vital given the association between earlier detection, earlier intervention, and improved long-term outcomes in depression (Calear & Christensen, 2010; Harrington & Clark, 1998). Similarly, adapted interventions informed by empirical study appear more effective than standard delivery for autistic youth (Spain et al., 2015; Walters et al., 2016).

Types of Depressive Symptoms Endorsed by Autistic Adolescents

Recent research has demonstrated that older autistic adolescents and adults exhibit unique cognitive (e.g., black/white thinking; (Pezzimenti et al., 2019), emotional (e.g., difficulty with emotion recognition in self and others; (Conner et al., 2020; Mazefsky et al., 2010), and behavioral (e.g., fluctuations in restricted, repetitive behaviors and interests; (Chandrasekhar & Sikich, 2015; Charlot et al., 2008; Stewart et al., 2006) symptoms of depression. Emerging studies on pre-existing social challenges and depressive symptoms in autistic youth and adults provided preliminary support for a positive relationship such that greater social challenges may be associated with heightened depressive symptoms (Pouw et al., 2013; Sterling et al., 2008). However, findings are limited by a few studies. A recent systematic review reported a link between depression and social functioning that may be

more robust and/or unique in ASD (Smith & White, 2020). Collectively, findings may suggest unique depression symptom profiles in ASD; however, others have not found diagnostic-based differences in depression symptoms (Williams et al., 2020). An exploration into the roles of sex and diagnosis on the severity of specific depressive symptoms among those with elevated depression scores may add insight into screening and treatment efforts.

Item analyses of depression measures (e.g., Children's Depression Inventory, Second Edition; CDI-2; Kovacs, 2010) may demonstrate potential diagnostic- and sex-based differences in types of symptoms endorsed, which would add to the growing literature of depression characterization and measurement in ASD (Pezzimenti et al., 2019). This may identify salient treatment targets, which may improve treatment efficacy and long-term outcomes. These efforts may be particularly important for autistic adolescents, who present with unique cognitive, emotional, and behavioral skills that often require adapted treatment approaches (Walters et al., 2016). Additionally, findings may guide adaptations of evidence-based depression treatments (e.g., Cognitive Behavioral Therapy; CBT; (Beck, 1970) for ASD. Early investigations into autism-specific adaptations to evidence-based treatments (e.g., CBT) for depression have revealed preliminary efficacy (McGillivray & Evert, 2014; Santomauro et al., 2016), yet the identification and targeting of specific depressive symptoms may enhance potency.

Present Study

The goals of the present study were to examine diagnostic- and sex-based differences in the severity of overall and specific depressive symptoms endorsed by autistic and neurotypical early adolescents. The sample includes 212 early adolescents (10:0–13:5 years old) participating in the first year of a longitudinal study on pubertal development (Corbett, 2017). Self-reported depressive symptoms were measured on the CDI-2 (Kovacs, 2010). Similar to older cohorts (Lugnegård et al., 2011; Mayes et al., 2011a; Mazefsky et al., 2010), we expected to find sex- and diagnostic-based differences in the severity of depressive symptoms across the total sample, with those in the ASD group and females reporting more symptoms. We also hypothesized that the severity of certain types of depressive symptoms (e.g., interpersonal problems, negative self-esteem) would be higher in autistic early adolescents. Lastly, an exploratory aim was to examine the effects of diagnosis and sex on the severity of overall and specific depressive symptoms among early adolescents with elevated depression scores (T-score≥60; "clinical subsample").

Methods

Participants

The total sample included 212 early adolescents (144 males, 68 females, 10:0-13:5 years), of which 125 had ASD (93 males, 32 females, mean age = 11.4 years) and 87 did not (51 males, 36 females, mean age = 11.5 years; see Table 1). Due to higher prevalence of ASD in males (Baio, 2012; Loomes et al., 2017), sex distributions differed between diagnostic groups, with more males in the ASD group (ASD: 74.4% males; NT: 58.6% males). Although the sex ratio of participants in the ASD group was not balanced, it resembled the 4:1 sex ratio reported in recent prevalence estimates (Maenner, Shaw, & Baio, 2020;

Shaw, Maenner, & Baio, 2020). The subsample of autistic females in the present study is moderate in size, but expands upon previous studies that only included males (Bitsika & Sharpley, 2015; Ozsivadjian et al., 2014). In terms of ethnic identity, 7.0% participants in the sample identified as Hispanic/Latino, and the following racial identities were endorsed: 82.9% Caucasians, 8.8% African American, 0.4% Asian, and 7.5% Mixed race. Though the sample was not racially diverse, it reflected the demographics of the general region. In the present sample, 65% of the ASD group and 18% of the NT group were reported to take psychotropic medications, with the most common medication classes in both groups being stimulants (ASD: 22.3%, NT: 6.7%) and selective serotonin reuptake inhibitors (ASD: 21.6%, NT: 3.8%).

Participants were part of a longitudinal study of pubertal development in autistic youth (Corbett, 2017). Participants were recruited from a broad catchment area within a 200-mile radius of Vanderbilt University Medical Center through research registries, medical-health related networks, well-check and diagnostic clinics, regional autism/disability organizations, and social media platforms. Inclusion criteria included participants: (a) 10:0–13:5 years old, (b) full-scale IQ (FSIQ) of 70 or above on the four-subtest Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-II; Wechsler, 2011), and (c) able to attend a study visit of approximately 3 hours. To ensure comprehension of task instructions and increase the reliability of self-report measures, individuals with FSIQ<70 were excluded from the study sample. For autistic early adolescents, diagnostic status was later confirmed by the research team (see “Procedures”). When applicable, first-time diagnoses were also provided by a psychologist with expertise in ASD. Additional exclusion criteria of the longitudinal study included: (a) severe aggression based on parent report and clinical observation (i.e., exhibiting harmful behaviors to self or others), (b) a neurological or medical condition known to influence pubertal development (e.g., genetic disorder), and (c) use of medications (e.g., GABA agonists) that are known to alter functions of the hypothalamic-pituitary-adrenal axis due to examination of cortisol in the longitudinal study. For NT participants, additional exclusion criteria included an autistic sibling or a score ≥ 10 on the Social Communication Questionnaire (SCQ; Rutter & Lord, 2003; i.e., suggestive of elevated symptoms characteristic of ASD). Informed consent and assent were collected in writing from parents and participants, respectively, prior to inclusion in the study. All study procedures were approved by the Vanderbilt University Institutional Review Board in accordance with the 1964 Helsinki declaration and its later amendments.

Procedures

To assess study eligibility, participants attended an initial visit (2 hours) at the university-based clinic, during which they completed the WASI-II (Wechsler, 2011) and their parents completed the SCQ (Rutter & Lord, 2003). For autistic participants, diagnosis was confirmed by review of DSM-5 criteria (American Psychiatric Association, 2013) and research-reliable administration of the Autism Diagnostic Observation Schedule–2, Module 3 (ADOS-2; Lord, Rutter, DiLavore, Risi, Gotham, & Bishop, 2012). In a second study visit (3 hours), all early adolescents completed a battery of self-report questionnaires (including the CDI-2; Kovacs, 2010) and behavioral experiments. Participants completed all self-report questionnaires independently of their parents. If a participant appeared confused by items,

study personnel were available to offer assistance by clarifying the wording of items or answering other questions. If needed, study personnel would reiterate the item and its meaning to the participant. These practices enhance the validity of this self-report measure and help to ensure understanding of all items by participants across the range of age and cognitive ability sampled. Although community stakeholders were not involved in the design or execution of the larger pubertal development study, an autistic member of the research team (ZJW) was heavily involved in the analysis, interpretation, and communication of study findings.

Dependent Measure: CDI-2

The Children's Depression Inventory, Second Edition, Self-Report (CDI-2; (M Kovacs, 1995) is a 28-item questionnaire completed by youth 7–17 years old that assesses cognitive, affective, and behavioral depressive symptoms over the previous two weeks. Items are rated on a 3-point scale, with unique responses for each item. All items map onto specific depressive symptoms in the DSM-IV criteria (M Kovacs, 1995). The CDI-2 is comprised of two domains: Emotional Problems (15 items) and Functional Problems (13 items). The domains can further be broken down into two subscales each, with Negative Mood (9 items) and Negative Self-Esteem (6 items) comprising the Emotional problems domain, and Interpersonal Problems (5 items) and Ineffectiveness (8 items) making up the Functional Problems domain. Raw total, domain, and subscale scores are converted to T-scores based on sex- and age-matched samples with the following (T-score) clinical cutoffs: ≤59 (Normal), 60–64 (High Average), 65–69 (Elevated), and ≥70 (Very Elevated). Although the CDI-2 is frequently used to measure severity of depressive symptoms in autistic youth and compared to parent report (Schwartzman & Corbett, 2020), it has not been specifically validated in the ASD population.

Statistical Analysis

The analyses were conducted using SPSS software (version 25; IBM SPSS Statistics, IBM Corporation) and statistical significance was determined at $p<0.05$ using two-tailed tests. Descriptive statistics were calculated using means and standard deviations for continuous variables, while frequencies and proportions were used for categorical variables. Independent sample Student *t*-tests were employed to examine differences between diagnostic- and sex-based groups on demographic variables, and Pearson correlations were examined to determine whether age and IQ were significantly associated with depressive symptom severity across the full sample. Comparisons of CDI-2 scores across sex and diagnostic groups were conducted using analysis of covariance (ANCOVA). In all ANCOVA analyses, we adjusted for WASI-II FSIQ scores due to significant differences across diagnostic groups (NT group mean in above average range, ASD group mean in average range) and the previously described relationship between IQ and depressive symptoms in autistic and neurotypical children (Bain et al., 2003; Mayes et al., 2011a; Zammit et al., 2004). We also adjusted for chronological age due to the well-established positive relationship between age and severity of depressive symptoms (i.e., higher severity among older ages; (Kovacs et al., 2003; Mayes et al., 2011a; Strang et al., 2012).

To test the first hypothesis of diagnostic- and sex-based differences in prevalence and severity of depressive symptoms in the total sample, the two covariates (FSIQ, age) underwent additional screening to determine if they met the ANCOVA assumptions: linearity, homogeneity of regression slopes, and independence of covariates. Following these checks, a two-way ANCOVA was employed to assess diagnostic (ASD vs. NT) and sex-based (male vs. female) differences in CDI-2 Total T-scores while having controlled for the identified covariates. Though CDI-2 Total T-scores were the outcome variable of interest, two-way ANCOVAs were also employed to assess diagnostic- and sex-based differences in T-scores across the four subscales (Negative Mood/Physical Symptoms, Negative Self-Esteem, Ineffectiveness, Interpersonal Problems) while having controlled for the same covariates.

To test the second hypothesis of item-level differences between and within diagnostic and sex groups, several rounds of Mann-Whitney U tests were employed to compare the ordinal response distributions of all CDI-2 items. This method was utilized as the study sample was too small to reliably estimate the parameters of latent variable models in each subgroup (Jiang et al., 2016). The following rounds of Mann-Whitney U tests were employed using all 28 items: (a) between diagnostic groups (ASD vs. NT) in the total sample (N=212), (b) between males and females in the ASD group (n=125), (c) between males and females in the NT group (n=87), (d) between females in the ASD and NT groups (n = 68), and (e) between males in the ASD and NT groups (n=144). In each group comparison, p-values were adjusted based on a 5% false discovery rate (FDR) using the Benjamini-Hochberg procedure (Benjamini & Hochberg, 1995). To represent the magnitude of each comparison, we also provided the non-parametric Probability of Superiority effect size (PS; Ruscio, 2008; Vargha & Delaney, 2000). Values of *PS* range from 0–1 and represent the probability that a randomly-selected individual from one group will have a higher score than a randomly-selected individual from the other group. A *PS* value of 0.5 indicates equality of the group distributions, while values of 0 or 1 indicate complete non-overlap between groups. Under conditions of normality and equal variance, *PS* values of 0.556, 0.638, and 0.714 are equivalent to Cohen's *d* values of 0.2, 0.5, and 0.8 (i.e., standard rules of thumb for "small," "medium," and "large" effects; (Kraemer & Kupfer, 2006). In addition, frequencies were calculated to identify the proportion of early adolescents with scores at or below the CDI-2 clinical threshold by diagnostic group and sex.

To explore the potential effects of diagnosis and sex on depressive symptoms in the clinical subsample of early adolescents with elevated depression scores (CDI Total T-score≥60), the same statistical analyses described above in the total sample were applied to this subsample. First, a two-way ANCOVA with age and FSIQ as covariates was used to examine diagnostic- and sex-based differences in prevalence of depressive symptoms. Second, Mann-Whitney U tests were used to compare the response distributions of all CDI-2 items between diagnostic groups. However, exploration of sex differences in CDI-2 item response distributions of all CDI-2 in the clinical subsample was not feasible due to the small and highly unequal numbers of females across diagnostic groups.

Results

Hypothesis 1: Diagnostic- and Sex-Based Differences on the CDI-2

Based on CDI-2 severity categories, 67% of the total sample reported scores in the Average range, 11% reported scores in the High Average range, 10% reported scores in the Elevated range, and 11% reported scores in the Very Elevated range. In the ASD group, 36.6% of males and 50% of females endorsed symptoms above the clinical threshold, while in the NT group, 13.7% of males and 36.1% of females endorsed symptoms above the threshold (See Table 2). After conducting correlations, FSIQ was significantly related to CDI-2 Total T-scores (r = −0.15, $p = 0.025$) in the total sample, but not age. Within the ASD group, neither FSIQ nor age were significantly related to CDI-2 scores. Within the NT group, FSIQ was significantly related to CDI-2 scores (r = −0.23, $p = 0.030$), but age was not.

A two-way ANCOVA model was fit on the data, regressing CDI-2 Total T-Scores on diagnostic group (ASD vs. NT), sex (male vs. female), the group by sex interaction, FSIQ, and chronological age in the total sample. Table 2 presents the means and standard deviations, as well as adjusted (estimated marginal) means and their standard errors. The two covariates (age and FSIQ) were screened and met the necessary ANCOVA assumptions to carry out analysis with the CDI-2 scores. There was no significant interaction between diagnostic group and sex on CDI-2 Total T-scores whilst controlling for FSIQ and age, $F(2,210)=0.810$, $p=0.369$, $\eta^2_p=0.004$. A significant main effect of diagnostic group on CDI-2 Total T-score was present such that higher scores were endorsed by the ASD group ($M=59.18$; High Average) compared to the NT group ($M=51.79$; Average), $d=0.587$, 95% CI [0.308,0.867], $p<0.001$. Similarly, a significant main effect of sex was also present such that higher scores were endorsed by females ($M=57.36$) compared to males ($M=53.60$), $d=0.365$, 95% CI [0.089,0.641], $p=0.023$. Lastly, the covariates of age and FSIQ were not significant in the two-way ANCOVA; age, $F(1,211)=0.862$, $p=0.354$, $\eta^2_p=0.004$, and FSIQ, $F(1,211)=0.030$, $p=0.862$, $\eta^2_p<0.001$. This same pattern was found for the Ineffectiveness subscale of the CDI-2 (see Supplemental Table S1). For the three remaining subscales (Negative Mood/Physical Symptoms, Negative Self-Esteem, Interpersonal Problems), the main effect of diagnostic group was significant (i.e., higher severity in the ASD group on average), but not sex.

Hypothesis 2: Item-Level Analyses in the Total Sample

In the total sample ($N=212$), analyses revealed significant differences between ASD and NT groups on 12 of 28 items, with participants in the ASD group endorsing numerically higher severity of depressive symptoms for all but two items (*PS* range = 0.42–0.65; see Table 3). Although significant group differences emerged on items from all four subscales of the CDI-2, symptoms from the subscales of Interpersonal Problems (33% of items) and Negative Self-Esteem (33% of items) were reported as significantly more severe in ASD. With regards to the critical Item #8 measuring suicidal ideation, a small but significant group difference emerged ($U=4757.0$, $p=0.036$, $PS=0.56$), with higher severity in the ASD group.

Subsequent item-level analyses within diagnostic groups did not reveal significant sex-based differences in the NT or ASD groups (see Supplemental Tables S2–3). However, analyses

within sex revealed diagnostic-based differences among both males and females with higher severity endorsed by those in the ASD group (see Supplemental Tables S4–5). Among females, autistic females endorsed higher severity on 2 of 28 items as compared to NT females. Among males, autistic males endorsed higher severity on 10 of 28 items as compared to NT males, with the majority of items from the Ineffectiveness and Interpersonal Problems subscales. In order to determine whether diagnostic group differences in individual items were larger in male participants (as opposed to the larger number of group differences being a function of higher statistical power), we conducted a paired *t*-test to compare the differences in *PS* values for each ASD-NT comparison in the male and female subsamples. This exploratory analysis demonstrated that diagnostic group differences were not significantly higher in males than females, $t(27) = -0.615$, $p = 0.544$, mean $\Delta PS_{M\text{-}F} = -0.006$, 95% CI [−0.026, 0.014], thereby suggesting that the small number of "significant" diagnostic group differences in the female sample was the result of lower statistical power rather than systematically smaller effects.

Explorations in a Clinical Subsample

The clinical subsample (i.e., early adolescents with CDI-2 Total T-score≥60) consisted of 50 participants in the ASD group (40% of ASD sample) and 20 participants in the NT group (23% of NT sample). An exploratory, two-way ANCOVA revealed no significant interaction between diagnosis and sex on CDI-2 Total T-scores in the clinical subsample, $F(2,68)=0.001$, $p=0.976$, $\eta^2_p<0.001$. Table 4 presents the means, adjusted means, standard deviations, and standard errors. Diagnostic group ($d=0.568$, 95% CI [0.041,1.095], $p = 0.064$) and sex ($d=0.015$, 95% CI [−0.463,0.493], $p=0.947$) were not associated with statistically significant differences in CDI-2 Total T-scores in this clinical subsample. However, as the effect of diagnosis was moderate in size and similar in magnitude to the same effect in the full sample ($\Delta d=0.019$), the failure to find a statistically significant effect of diagnosis was likely due to reduced statistical power in the smaller clinical subsample. The covariates of age and FSIQ were not significant in the two-way ANCOVA; age, $F(1,69)=0.738$, $p=0.394$, $\eta^2_p=0.011$, and FSIQ, $F(1,69)=0.123$, $p=0.727$, $\eta^2_p=0.002$. Item-level analyses in the clinical subsample revealed significant differences between diagnostic groups on beliefs of worthlessness, with more endorsement in ASD (see Table 5). Notably, while the remainder of items did not show significant diagnostic group differences, autistic youth and elevated depressive symptoms reported numerically higher scores on all 28 of the CDI-2 items with very large effect sizes (*PS* range=0.83–0.93, approximate Cohen's $d=1.35$–2.09).

Discussion

This study was the first to examine diagnostic- and sex-based differences in the severity of overall and specific depressive symptoms endorsed by autistic and neurotypical early adolescents. Our first hypothesis was supported, as findings from the total sample revealed significant main effects of diagnosis (i.e., higher severity in the ASD group) and sex (i.e., higher severity among females) on depressive symptoms. However, no significant sex by diagnosis interaction effects were observed, indicating that the relative increase in depressive symptoms in females is largely equivalent across diagnostic groups. Additionally,

the covariates of FSIQ and age were not significant, which suggests that the significant correlation between FSIQ and CDI-2 scores in our sample was due to confounding of IQ scores by diagnostic status. Our second hypothesis was also supported, as nearly half of the CDI-2 items were endorsed more frequently by autistic early adolescents than their peers. Specifically, the majority of items endorsed in the ASD group were in the interpersonal problems (33%) and negative self-esteem (33%) subscales. Findings from the present study align with some of the existing literature, adding novel information about the specific depressive symptoms reported to be most severe in autistic youth. Future studies are needed to further investigate whether interventions targeting the identified symptoms are superior to standard psychotherapies when treating depression in this population.

The significant main effect of diagnostic group showed that autistic early adolescents endorse more severe depressive symptoms on average (i.e., High Average range) compared to same-aged peers (i.e., Average range), replicating findings from other studies and our previous work (Greenlee et al., 2016; Hudson et al., 2019b). The significant main effect of sex indicates that females report elevated depressive symptoms as compared to males, which appears consistent with sex-based differences in the general population (Avenevoli et al., 2015; Breslau et al., 2017; Essau et al., 2010). Moreover, the effects of female sex and ASD diagnosis on depressive symptoms are additive given the highest symptom severity among autistic females. This may be further evidenced by the finding that 50% of autistic females endorsed scores above the threshold and constituted the most at-risk group for depression in this sample. Across the four CDI-2 subscales, those in the ASD group consistently endorsed more severe depressive symptoms on average compared to same-aged peers; however, sex-based differences only emerged on the Ineffectiveness subscale with females endorsing more severe symptoms. This may tentatively suggest that females, especially autistic females, may experience a greater sense of inability or incompetence to complete desired tasks. These preliminary findings emphasize the need for earlier screening and intervention for depression in ASD, particularly for females.

The current findings of sex-based differences are inconsistent with findings in another study of autistic youth that did not uncover sex-based differences in depression (Mayes et al., 2011b), which may be accounted for by differences in the age of the samples (M=6.6 years in the Mayes study). Sex-based differences may be accounted for by many developmental factors including pubertal timing (Angold et al., 1998; Kaltiala-Heino et al., 2003; Corbett et al., 2020), social expectations for females (Robinson et al., 2013; Rose & Rudolph, 2006), camouflaging and compensatory behaviors (Cage & Troxell-Whitman, 2019; Corbett et al., 2021; Livingston et al., 2019), and other factors yet uncovered (e.g., cultural influences, neurobehavioral pathways). Given that this is the first examination of sex-based differences in depressive symptoms among autistic early adolescents, additional studies with larger samples of autistic females are needed to replicate and extend our preliminary findings.

Item-level analyses revealed higher levels of depressive symptoms specific to interpersonal difficulties in the ASD group, which supports the growing literature on the relationship between depression and social functioning in ASD (Pezzimenti et al., 2019; Pouw et al., 2013; Smith & White, 2020; Sterling et al., 2015; Taylor et al., 2020). Studies in this area suggest pre-existing social difficulties may contribute to the development of depressive

symptoms and/or exacerbate severity. Similarly, associations between negative self-esteem and depression have been identified in the general population (Sowislo & Orth, 2013) and among older autistic youth and adults (Cooper et al., 2017; McCauley et al., 2019). However, this is the first study to uncover an association between diagnostic status and lower self-esteem in relation to depression symptoms in autistic early adolescents. Although additional studies are warranted to expand these initial findings, it appears that negative self-esteem and interpersonal problems may be more salient symptoms of depression among autistic early adolescents. This may establish an initial model for adapting evidence-based treatments (e.g., CBT; Beck, 1960) for depression in the unique context of ASD. For example, CBT adaptations for ASD may include cognitive restructuring techniques to challenge beliefs of low self-esteem.

A closer examination of the four Negative Self-Esteem items endorsed more frequently by autistic youth reveal salient cognitive symptoms of depression (items 2 [hopelessness], 7 [guilt], 8 [suicidality], and 24 [feeling unlovable]). Suicidal ideation and hopelessness have been reported at higher rates among autistic individuals than peers (Hedley et al., 2018; Hu et al., 2019; Segers & Rawana, 2014), but it appears that beliefs of guilt (item 7) and being unlovable (item 24) may also be prominent factors in the development of depression in ASD. Additionally, four Interpersonal Problems items were endorsed more frequently by autistic youth and showed distinct cognitive, emotional, and behavioral symptoms of depression (items 5 [low mood], 19 [loneliness], 21 [peer network], and 25 [peer conflict]). Heightened loneliness, greater peer conflict, and smaller peer networks have been associated with depression in the general population (Crowell et al., 2014; Jaremka et al., 2014; Santini et al., 2015), and may be particularly notable for autistic individuals (Hedley et al., 2018; Mazurek, 2014). On the other hand, it is possible that these four areas of Interpersonal Problems may simply reflect common experiences of autism (i.e., social communication differences, difficulties in social interactions), rather than depression, which warrants continued investigation. Though interpersonal difficulties may occur in individuals with depression, pre-existing challenges common throughout development in autistic individuals may account for elevated scores in this domain. Findings from the present study may guide screening efforts as the administration of measures of suicidal ideation, hopelessness, guilt, feeling unlovable, loneliness, and social conflict may detect autistic early adolescents at risk for elevated depression symptoms. However, as clinical diagnoses of depression were not investigated in the current study, additional investigations employing gold-standard depression diagnoses (e.g., based on multi-informant structured interviews and clinical judgment) are needed to identify the symptoms that best discriminate between depressed and non-depressed autistic youth.

Item analyses within each diagnostic group demonstrated that autistic males and females endorse similar types of depressive symptoms. Females in both diagnostic groups endorsed higher severity of depressive symptoms as compared to their male counterparts, and feelings of loneliness and worthlessness were particularly salient depressive symptoms in both sex groups. In addition, autistic males endorsed certain cognitive, emotional, psychosomatic, and behavioral symptoms of depression (items 5, 12, 15, 19, 21, 24, 25, and 26) significantly more than NT males. However, further analyses demonstrated negligible effect size differences between males and females, suggesting that the smaller number of

depressive symptoms identified as significant in the female subsample resulted from reduced statistical power. Thus, while these findings are preliminary, we found little evidence that the specific depressive symptoms that best discriminate between autistic and neurotypical youth differ according to sex. Additional studies that include larger samples of autistic and neurotypical females are needed to better understand underlying relationships between sex, ASD diagnosis, and specific depressive symptoms.

Exploratory analyses in the clinical subsample showed that nearly half of the autistic early adolescents endorsed symptom severity above the clinical cutoff of the CDI-2, which was almost double the proportion of NT peers with elevated scores. Even in early adolescence, autistic early adolescents appear at elevated risk for clinically significant depression, which mirrors findings in older autistic adolescents and adults (Magnuson & Constantino, 2011; Smith & White, 2020). The factors of diagnosis, sex, and their interaction were nonsignificant in the clinical subsample, yet the diagnostic group difference in depression severity was similar in magnitude to the corresponding difference in the full sample. Nevertheless, sex effects were negligible in size, potentially indicating that the sex differences in depressive symptom severity are attenuated or absent when only examining currently depressed individuals. Notably, these findings are exploratory, and future investigations should examine the roles of diagnosis, sex, and their interaction in predicting depressive symptom severity in larger samples of currently-depressed autistic and neurotypical adolescents. In addition, item analyses in the clinical subsample revealed substantially higher scores on all depressive symptoms on the CDI-2 in the ASD group despite all but one of these differences (worthlessness) being nonsignificant. Beliefs of worthlessness (item 23) appear higher in the ASD group in the clinical subsample, which may be an important risk factor for depression in ASD. Future studies investigating ASD-associated differences in specific depressive symptoms should attempt to match ASD and non-ASD samples on overall depression severity, thereby controlling for group differences that are simply due to the higher prevalence of depression in ASD.

Though this is the first study to examine sex-based differences and item analyses of the CDI-2 among autistic and neurotypical early adolescents, there are several limitations. First, unequal numbers of NT participants and females within each diagnostic group limit findings. Second, the sample sizes of groups in this study did not permit between-group comparisons of latent variable models (cf. Williams et al., 2020), which may be useful in determining whether certain symptoms are uniquely related to depression in ASD while accounting for diagnostic group differences in symptom severity. Third, the current sample included early adolescents of a narrow age range and thus, examinations into middle and late adolescence may reveal different patterns of symptoms in ASD. Fourth, measures of pubertal timing and/or status were not examined in relation to depressive symptoms. Fifth, while the CDI has been used in autistic children and adolescents (Schwartzman & Corbett, 2020), it has not been validated for autistic youth, and thus it remains possible that some differences in observed CDI-2 item/scale scores reflect ASD-associated differences in item response tendencies rather than true differences in depressive symptomatology (Williams et al., 2020). Sixth, though the sample mirrored demographics of the general area from which participants were recruited, the sample was not diverse in terms of ethnic and racial

identities, which limits the generalizability of findings. Lastly, depression ratings were collected at one timepoint and may only provide a snapshot of depressive symptoms.

Future directions of investigation may examine the effects of sex and ASD diagnosis on specific depressive symptoms in larger samples of early adolescents that are matched on key variables such as age, sex, cognitive ability, and overall depression severity. Additionally, larger samples will allow for the use of latent variable models, which can test whether depression symptom structures are equivalent between diagnostic/sex groups and whether practically significant differential item functioning is present in the CDI-2 items. Longitudinal studies are also needed to measure fluctuations in depressive symptoms among diagnostic- and sex-based groups throughout the lifespan. Future investigations may also explore the role of pubertal timing in the onset, prevalence, and type of depressive symptoms in autistic adolescents.

Conclusion

The current findings highlight the roles of diagnosis and sex in depressive symptoms among early adolescents such that the effects of female sex and ASD diagnosis are additive. Autistic early adolescents also report more severe interpersonal problems and negative self-esteem, especially beliefs of worthlessness. Collectively, findings add to the ongoing efforts to characterize and accurately measure depression in ASD revealing a constellation of symptoms associated with heightened interpersonal problems, negative self-esteem, and suicidality. The types of symptoms endorsed in ASD highlight salient treatment targets for this population, which may guide adaptations of evidence-based treatments (e.g., CBT) to potentially enhance efficacy. Additional studies are therefore warranted to determine whether therapies targeting these symptoms are able to provide additional benefit over and above standard psychosocial treatment for depression in autistic youth.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Participant characteristics

	ASD[a] (*n*=125)	NT[b] (*n*=87)		
	***M* (*SD*)**	**M (*SD*)**	**Test Statistic**	***p* value**
Age	11.4 (0.9)	11.5 (1.1)	t=1.032	0.306
Sex	93 males	51 males	χ^2=7.08	0.009
Full Scale IQ	101.2 (20.9)	117.2 (15.1)	t=6.341	<0.001
SCQ[c]	17.2 (8.2)	2.97 (2.9)	t=15.95	<0.001
ADOS-2[d] Total	12.6 (4.6)			
Medication Status	65% taking medications	18% taking medications	χ^2=48.16	<0.001
Stimulants	22.3%	6.7%		
SSRI[e]	21.6%	3.8%		

[a] Autism Spectrum Disorder ;

[b] Neurotypical;

[c] Social Communication Questionnaire ;

[d] Autism Diagnostic Observation Schedule, Second Edition ;

[e] Selective Serotonin Reuptake Inhibitor

Table 2

Means, adjusted means, standard deviations, and standard errors for total depressive symptoms on the CDI-2 for each diagnostic group (ASD vs. NT) and sex (male vs. female) in the total sample

Diagnostic Groups (Total Sample *N*=212)				
	ASD[a]		NT[b]	
	Male	Female	Male	Female
CDI-2[c] Total T-scores				
M	58.07	60.53	49.10	54.24
(SD)	12.58	12.73	7.23	9.51
M_{adj}	58.03	60.33	49.17	54.42
(SE)	1.16	2.01	1.61	1.82
CDI-2[c] Total Severity				
Proportion Below Threshold	63.4%	50.0%	86.3%	63.9%
Proportion Above Threshold	36.6%	50.0%	13.7%	36.1%

[a] Autism Spectrum Disorder;

[b] Neurotypical;

[c] Children's Depression Inventory, Second Edition

Table 3

Item-level analyses of CDI-2 between autistic and neurotypical early adolescents in the total sample

CDI-2 Subscale	CDI-2 Items (item content)	NT[a] (n = 87)	ASD[a] (n = 125)	*U*	*p*	P_{adj}[b]	*PS*[c] *(0-1)*
Significant Differences (12/28 items)							
Negative Mood/Physical Symptoms	Item 15 (sleep quality)	63/17/7	63/41/21	4205.5	0.001	0.006	0.61
	Item 26 (low energy)	83/4/0	93/19/13	4285.0	<0.001	<0.001	0.61
Negative Self-Esteem	Item 2 (hopelessness)	62/25/0	69/51/5	4501.5	0.012	0.034	0.59
	Item 7 (guilt)	70/17/0	84/32/9	4640.0	0.020	0.047	0.57
	Item 8 (suicidality)	80/7/0	99/26/0	4757.0	0.014	0.036	0.56
	Item 24 (being loved)	85/2/0	103/17/5	4600.5	0.001	0.004	0.58
Ineffectiveness	Item 20 (anhedonia)	55/29/3	62/41/21	4455.5	0.012	0.037	0.60
	Item 23 (worthlessness)	65/20/2	64/37/24	3956.0	<0.001	<0.001	0.64
Interpersonal Problems	Item 5 (low mood)	82/5/0	96/27/2	4483.5	0.001	0.004	0.59
	Item 19 (loneliness)	75/12/0	72/40/13	3830.5	<0.001	<0.001	0.65
	Item 21 (peer network)	76/11/0	74/43/7	3862.5	<0.001	<0.001	0.65
	Item 25 (peer conflict)	80/7/0	93/25/7	4474.0	0.002	0.007	0.59
Nonsignificant Differences (16/28 items)							
Negative Mood/Physical Symptoms	Item 1 (low mood)	78/9/0	102/19/4	4981.5	0.095	0.139	0.55
	Item 9 (crying)	74/12/1	105/15/5	5357.5	0.772	0.831	0.51
	Item 10 (irritability)	53/30/4	70/45/10	5110.0	0.393	0.478	0.53
	Item 16 (low energy)	51/32/4	79/30/16	5333.5	0.964	0.999	0.51
	Item 17 (appetite)	74/8/5	91/16/18	4689.0	0.026	0.056	0.57
	Item 18 (somatic)	59/25/3	77/36/12	5003.5	0.242	0.323	0.54
	Item 27 (appetite)	71/10/6	98/13/14	5180.5	0.486	0.544	0.48
Negative Self-Esteem	Item 6 (self-concept)	79/7/1	107/16/2	5155.5	0.259	0.329	0.53
	Item 13 (appearance)	63/23/1	97/26/2	5165.5	0.407	0.056	0.53
Ineffectiveness	Item 3 (daily activity)	75/12/0	95/26/4	4858.5	0.057	0.094	0.55
	Item 4 (anhedonia)	64/23/0	74/50/1	4645.0	0.029	0.0.58	0.57
	Item 12 (concentration)	35/46/6	42/64/19	4762.5	0.108	0.151	0.56
	Item 14 (volition)	50/26/11	60/30/35	4570.5	0.039	0.068	0.58
	Item 22 (school performance)	70/17/0	90/25/10	4840.5	0.091	0.142	0.55
	Item 28 (memory)	44/38/5	49/57/19	4535.5	0.030	0.056	0.42
Interpersonal Problems	Item 11 (peer satisfaction)	68/18/1	98/23/4	5426.0	0.971	0.971	0.50

[a] Number of participants in the group reporting responses of 0/1/2 on each item;

[b] P_{adj}: Benjamini-Hochberg FDR correction;

[c] PS: Probability of superiority

Note: We report frequencies, rather than medians, as we believe this additional information demonstrates the proportion of individuals endorsing symptoms of a certain severity level or higher.

Table 4

Means, adjusted means, standard deviations, and standard errors for total depressive symptoms on the CDI-2 for each diagnostic group (ASD vs. NT) and sex (male vs. female) in the clinical subsample

	Diagnostic Groups (Clinical Subsample *n*=70)			
	ASD[a]		NT[b]	
CDI-2[c] Total T-scores	Male (*n*=16)	Female (*n*=34)	Male (*n*=8)	Female (*n*=12)
M	70.66	70.50	66.25	65.92
(SD)	8.67	9.87	5.19	4.60
M_{adj}	70.74	71.01	65.23	65.33
(SE)	1.36	2.17	4.34	2.52

[a]Autism Spectrum Disorder;

[b]Neurotypical;

[c]Children's Depression Inventory, Second Edition

Table 5

Item-level analyses of CDI-2 between autistic and neurotypical early adolescents in the clinical subsample

CDI-2 Subscale	CDI-2 Items (item content)	NT[a] (n = 20)	ASD[a] (n = 50)	*U*	*p*	P_{adj}[b]	*PS*[c] *(0-1)*
Significant Differences (1/28 items)							
Ineffectiveness	Item 23 (worthlessness)	10/8/2	14/15/21	68.0	0.003	0.012	0.93
Nonsignificant Differences (27/28 items)							
Negative Mood/Physical Symptoms	Item 1 (low mood)	14/6/0	30/16/4	135.0	0.339	0.791	0.86
	Item 9 (crying)	13/4/3	33/12/5	169.0	0.989	1.000	0.83
	Item 10 (irritability)	6/10/4	21/22/7	167.5	0.945	1.000	0.83
	Item 15 (sleep quality)	7/7/6	16/21/13	128.0	0.249	1.000	0.87
	Item 16 (low energy)	3/13/4	21/17/13	144.0	0.561	0.873	0.85
	Item 17 (appetite)	12/6/2	30/8/12	138.0	0.452	0.791	0.86
	Item 18 (somatic)	6/10/4	24/17/9	142.0	0.447	0.834	0.85
	Item 26 (low energy)	15/3/2	31/12/17	154.5	0.766	1.000	0.84
	Item 27 (appetite)	12/5/3	31/7/12	156.5	0.810	1.000	0.84
Negative Self-Esteem	Item 2 (hopelessness)	12/8/0	15/33/2	131.0	0.286	0.889	0.86
	Item 6 (self-concept)	12/4/4	34/14/2	166.0	0.923	1.000	0.83
	Item 7 (guilt)	12/8/0	21/21/8	99.0	0.047	0.439	0.90
	Item 8 (suicidality)	11/7/2	31/19/0	166.0	0.923	1.000	0.83
	Item 13 (appearance)	8/8/4	31/17/2	166.5	0.923	1.000	0.83
	Item 24 (being loved)	20/0/0	32/14/4	90.0	0.024	0.336	0.91
Ineffectiveness	Item 3 (daily activity)	12/8/0	28/18/4	152.0	0.629	0.927	0.84
	Item 4 (anhedonia)	9/11/0	20/30/0	133.0	0.312	0.873	0.86
	Item 12 (concentration)	2/13/5	6/34/10	133.0	0.371	0.742	0.86
	Item 14 (volition)	8/8/4	8/19/23	133.0	0.312	0.794	0.86
	Item 20 (anhedonia)	7/10/3	15/19/16	99.0	0.047	0.329	0.90
	Item 22 (school performance)	14/6/0	25/15/10	130.0	0.273	0.955	0.87
	Item 28 (memory)	6/10/4	11/24/15	163.5	0.858	1.000	0.83
Interpersonal Problems	Item 5 (low mood)	15/5/0	29/19/2	128.0	0.249	0.996	0.87
	Item 11 (peer satisfaction)	8/8/4	29/17/4	167.0	0.945	1.000	0.83
	Item 19 (loneliness)	9/9/2	15/24/11	128.0	0.249	1.000	0.87
	Item 21 (peer network)	12/8/0	22/23/5	137.0	0.368	0.793	0.86
	Item 25 (peer conflict)	12/6/2	27/18/5	147.5	0.534	0.879	0.85

[a] Number of participants in the group reporting responses of 0/1/2 on each item;

[b] P_{adj}: Benjamini-Hochberg FDR correction;

[c] PS: Probability of superiority

Note: We report frequencies, rather than medians, as we believe this additional information demonstrates the proportion of individuals endorsing symptoms of a certain severity level or higher.