



Characterization and Prediction of Anxiety in Adolescents with Autism Spectrum Disorder: A Longitudinal Study

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Abstract

Anxiety is one of the most common comorbidities in youth with autism spectrum disorder (ASD). The current study's aims were: To examine the frequency of elevated anxiety symptoms in adolescents diagnosed with ASD in toddlerhood; To explore the impact of comorbid anxiety in adolescents on clinical presentation; To evaluate variables in toddlerhood that associate with anxiety symptom severity in adolescence. The study included 61 adolescents (mean age = 13:8y) diagnosed with ASD in toddlerhood (T1). Participants underwent a comprehensive assessment of cognitive ability, adaptive skills and autism severity at T1 and again as adolescents (T2), and an evaluation of anxiety symptoms at T2. For the first aim, the most prevalent anxiety subtypes noted in adolescence were separation (39.3%), social (27.9%) and generalized anxiety (18.0%). For the second aim, cognitive ability, autism severity and adaptive skills in adolescents with and without elevated anxiety symptoms scores of any type did not differ significantly. For the third aim, younger age at adolescence was associated with more severe separation and generalized anxiety symptoms. Higher cognitive ability and adaptive skills in toddlerhood were associated with elevated generalized anxiety symptoms in adolescence. Lower adaptive behaviors and repetitive behaviors (RRBs) correlated with elevated social anxiety symptoms. Lower cognitive abilities and more severe RRBs in toddlerhood predicted separation anxiety in adolescence. The study sheds light on early characteristics in ASD that associate with anxiety symptom severity in adolescence. The type of elevated anxiety symptoms presented in adolescence associated with the level of cognitive ability, adaptive skills and RRBs in toddlerhood.

Keywords Autism spectrum disorders · Anxiety · Predictors · Long-term follow up

Introduction

Autism spectrum disorder (ASD) and anxiety disorder are highly prevalent conditions. ASD occurs in 1 in 59 children (Lyll et al. 2017) and is characterized by social-communication impairments and repetitive, restricted interests and behaviors (American Psychiatric Association 2013). Reports of the prevalence of anxiety disorders in the general population range from 3 to 24% in various studies (e.g. Cartwright-Hatton et al. 2006;

Polanczyk et al. 2015). Anxiety disorders are defined by excessive fear and worry that are difficult to control, are associated with physical symptoms, and cause distress and/or functional impairments (APA 2013). These two disorders, while distinct, often interact with one another in phenotypic expression. Anxiety is one of the most common comorbid mental health problems in youth with ASD, with an estimated prevalence ranging from 11 to 84% (Simonoff et al. 2008; White et al. 2014; White et al. 2009). This wide variability in reported prevalence reflects, in part, the complexity inherent in the diagnosis of differential or comorbid anxiety disorders in ASD, as well as the wide range of measures used for the assessment of anxiety symptom severity (Ezell et al. 2019). Kerns and Kendall (2012), in a critical review of the literature on anxiety in ASD, provided some support for the presence of co-occurring anxiety disorders in individuals with ASD and discussed the relationship between these two diagnoses.

Research on predictors of anxiety symptoms in late childhood and adolescence in the typically developing (TD) population has focused mainly on early childhood behavior, temperament and familial environment variables. Several studies

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have reported that increased levels of inhibition in preschool years, a history of maternal anxiety disorders, and parenting profiles with high levels of over-involvement were strong predictors for the subsequent development of anxiety symptoms (Frenkel et al. 2015; Hudson et al. 2018; Ollendick and Grills 2016). Further, inhibited children, particularly boys, with an insecure attachment were at increased risk for an eventual diagnosis of social anxiety (Lewis-Morrarty et al. 2015).

Within the context of ASD, few studies have searched for factors that are associated with later occurrence of elevated anxiety symptoms. Of these studies, most were cross sectional and assessed the contribution of gender, cognitive level, adaptive functioning and autism symptom severity to the severity of anxiety symptoms. Some studies found positive associations between age and anxiety (e.g., Dubin et al. 2015; Mayes et al. 2011; Vasa et al. 2013), while others reported no significant age effects (Strang et al. 2012; Sukhodolsky et al. 2008). Few differences have been noted regarding gender in reported anxiety rates (e.g., Dubin et al. 2015; Magiati et al. 2016), with the exception of a single study, which found social anxiety to be higher in females with ASD compared to males with ASD (May et al. 2014). That lone study (May et al. 2014) indicating differences was methodologically different in two significant ways. First, the sample was approximately 50% female, in comparison with 14.5% (Dubin et al. 2015) and 18.3% (Magiati et al. 2016). Second, only participants without intellectual disability were included in the study, while the two other studies used the entire range of cognitive ability.

Most studies on the prevalence of anxiety in ASD were conducted on individuals with average or above average cognition and reported elevated anxiety symptoms (Kuusikko et al. 2008; Van Steensel et al. 2011). The few studies that have compared individuals with ASD and intellectual disability (ID) to those with isolated ID reported elevated rates of anxiety in those with comorbid ASD and ID (Bakken et al. 2010; Helverschow and Martinsen 2011). It seems, therefore, that there is an elevated risk for anxiety in ASD regardless of intellectual ability (Ezell et al. 2019). Regarding adaptive skills, lower skills were associated with elevated anxiety in children with ASD only in the presence of lower intellectual abilities (Dubin et al. 2015).

No clear picture has emerged from the literature examining the link between autism severity and anxiety levels in adolescence and adulthood. Some work has indicated a positive association (e.g., Kelly et al. 2008; Sukhodolsky et al. 2008; Wood and Gadow 2010), while other studies have reported no such association (Renno and Wood 2013; Strang et al. 2012). Examinations of the link between social communication deficits and anxiety have also generated mixed results. Some have found a positive association (Chang et al. 2012; Eussen et al. 2013), others have reported such an association only in individuals with ASD without comorbid ID (e.g., Bellini

2006; Niditch et al. 2012; Sukhodolsky et al. 2008; Wood and Gadow 2010), and still others have found no association whatsoever (Hollocks et al. 2014; Rieske et al. 2012). In contrast, increased severity of restrictive repetitive behaviors (RRBs) has been consistently associated with increased anxiety in ASD (Rodgers et al. 2012; Sukhodolsky et al. 2008). Magiati et al. (2016) found that RRBs severity predicted specific types of anxiety, including separation, generalized, panic/agoraphobia and obsessive-compulsive anxiety symptoms, while social-communication deficits predicted social anxiety only. Family studies have suggested that anxiety disorders are more common in relatives of individuals with ASD than in relatives of typically developing children or children with other developmental problems (reviewed in Kerns and Kendall 2012). These findings suggest that genetic susceptibility may be a risk factor for later development of anxiety in ASD.

A few studies have examined predictors of anxiety symptoms in short term follow-ups, and/or when the study sample is past early childhood at baseline. Gotham et al. (2015) followed up on 109 individuals with ASD and 56 without ASD at regular intervals between 9 and 24 years of age and found that only being female predicted greater increases in anxiety over time. Teh et al. (2017) examined predictors of later anxiety in children and youth with ASD ranging in age from 5 to 17 years after a short follow-up period of 10–19 months. In that study, anxiety scores at baseline were the strongest predictor for later anxiety, while baseline RRBs severity predicted later anxiety only when baseline anxiety was not controlled. Age, adaptive skills and social-communication impairments did not have significant relationships with later anxiety. In toddlers with ASD, sensory over-responsivity has been found to predict increased anxiety symptoms 1 year later, independent of social-communication deficits and maternal anxiety (Green et al. 2012). Only Baribeau et al. (2019) undertook a large longitudinal study examining early childhood predictors of subsequent anxiety. The researchers found that anxiety symptoms later in life are predicted by RRBs severity as assessed by the ADI-R in toddlerhood.

Understanding early child and family characteristics that may place a child with ASD at risk for later development of anxiety can provide important information regarding early identification, intervention and, potentially, prevention of these symptoms. Of particular interest are factors in the preschool years prior to the onset of anxiety symptoms.

The current study had three aims: 1. To evaluate the type and frequency of elevated anxiety symptoms in adolescents diagnosed at toddlerhood with ASD. 2. To compare cognitive and adaptive behavioral skills and autism severity in adolescents with and without elevated symptoms of anxiety. 3. To evaluate the association between early cognitive and adaptive skills and autism symptom severity in toddlerhood and the severity of anxiety symptoms in adolescence, as well as to examine their predictive power.

This study hypothesizes that there will be a high prevalence of anxiety symptoms among the group of adolescents with ASD. Adolescents with ASD and elevated anxiety symptoms will exhibit more severe ASD symptoms and poorer adaptive skills. Additionally, it is hypothesized that toddlers' autism severity, specifically elevated RRBs symptoms, will correlate with and predict high levels of anxiety symptoms in adolescence. In light of conflicting findings on the association between cognitive ability and anxiety levels among children with ASD, no hypotheses regarding this correlation were made.

Methods

Participants

Participants in this study were children who received an ASD diagnosis prior to age 38 months. The diagnoses were given based on an interdisciplinary assessment at a tertiary medical center between the years 2002–2009.

Of all children diagnosed during these years, only those who received a cognitive evaluation at the time of diagnosis or during the year following the diagnosis were approached for participation in the current study ($n = 142$). Sixty-six of those families (46.5%) agreed to participate in this long-term follow-up study. One participant was excluded due to a recent developmental regression of unknown cause. The final cohort therefore included 65 participants, 60 males and 5 females, but only 61 participants had an anxiety assessment by parent report with age range of 10:5–18:5 years and mean age of 13:8 years. Characterization of the study's sample is detailed in Table 1.

In comparing the characteristics of the families who participated in this research to those who did not respond, no significant differences were found in baseline age, developmental quotient or maternal education. Therefore, selection biases are less likely to be relevant to the final cohort of the study.

Measures

Autism Diagnostic Interview-Revised (ADI-R; Le Couteur et al. 2003; Lord et al. 1994): This is a semi-structured interview administered to parents, designed to diagnose autism according to DSM-IV criteria. For assessment of autism severity, we used the ADI algorithm items with the entire score range (0–3) for the social interaction (SI), communication and restricted and repetitive behaviors (RRB) domains. The range of scoring is for ADI-R is 0–42 for the SI subdomain, 0–39 for the communication subdomain, and 0–18 for the RRB subdomain.

Autism Diagnostic Observation Scales (ADOS; Lord et al. 1999; Lord et al. 2012): This is a semi-structured, interactive

schedule designed to assess social and communicative functioning in individuals who may have ASD. Only one of the modules is administered, depending on the examinee's age and/or expressive language. The ADOS total algorithm score was used to calculate the total severity score using the ADOS calibrated severity scales (CSS) (Gotham et al. 2009). The scores of each of the ADOS subdomains - social affect (SA) and restricted repetitive behavior (RRB) - were used to calculate each subdomain severity score using the SA and RRB calibrated severity scales (CSS) (Hus et al. 2014). Higher scores on the ADOS reflect more severe autism symptoms. These measures have a scale of 1–10. For the ADOS-RRB-CSS the scale starts at 1 and jumps to 5 and then continues linearly to 10. We used the new ADOS algorithm (ADOS-2) for both ADOS at baseline and ADOS-2 editions.

Vineland Adaptive Behavior Scales (VABS; Sparrow et al. 1984; VABS-II; Sparrow et al. 2005): This is a standardized caregiver interview designed to assess adaptive behaviors in children from birth to 18 years of age. The VABS is organized into four subdomains: Communication, Daily Living Skills, Socialization, and Motor Skills, each of which yields a standard score (mean of 100, SD of 15). In addition, the measure yields a total score, the Adaptive Behavior Composite (mean of 100, SD of 15). Higher scores on the VABS reflect better functioning. The VABS first edition was used for adaptive assessment at the time of diagnosis and VABS-II, the second edition, was used at follow-up.

Screen for Child Anxiety Related Emotional Disorders (SCARED; Birmaher et al. 1997) – This anxiety questionnaire compares multiple perspectives on participants' levels of anxiety as reported by the child and/or the parent (child/parent report versions). In the current study, only the parent-report version was used. This version of the questionnaire has 41 items, which are rated on a 0–2 scale (0 = Not True or Hardly Ever True; 2 = Very True or Often True). The parent report version demonstrated excellent internal consistency in the current sample (α parent = 0.95). Item scorings are summed to create a total score and a clinical cut-off of 25 is suggested. In addition, five subdomains including panic / somatic symptoms, generalized, separation, social, and school avoidance scores can be calculated. For each subdomain, a cut-off point is determined based on the test form.

Social Responsiveness Scales-2 (SRS-2): The SRS-2 (Constantino and Gruber 2012) is a 65-item rater report of autistic traits rated on a 4-point Likert Scale (0–3 points). The SRS-2 scoring is aligned with DSM-5 criteria for diagnosis of ASD. The SRS-2 yields a total score and two higher order indices that correspond to the two symptom domains of ASD: Social Communication and Interaction (SCI) and Restricted Interests and Repetitive Behavior (RIRB). In addition, five treatment subscales can be calculated that represent autism-specific behaviors: social awareness, social cognition, social communication, social motivation, and repetitive

Table 1 Characteristics of the study population at T1 and T2

| | T1 | | T2 | |
|---------------------------------|--------|--------------|----------|--------------|
| | Range | M(SD) | Range | M(SD) |
| Age (months) | 15–37 | 25.6(4.5) | 125–221 | 164.8(22.7) |
| Follow-up times (years; months) | – | – | 8;5–16;0 | 11;7(1;10) |
| DQ/IQ | 49–127 | 73.71(18.75) | 40–146 | 70.02(24.98) |
| ADI-R SI | 7–38 | 18.98(6.60) | – | – |
| ADI-R Communication | 1–23 | 11.13(3.46) | – | – |
| ADI-R RRB | 1–10 | 4.72(2.24) | – | – |
| Total SRS | – | – | 43–98 | 70.22(13.53) |
| ADOS-SA-CSS | 2–10 | 6.80(2.35) | 1–10 | 70.22(13.53) |
| ADOS-RRB-CSS | 1–10 | 8.45(1.71) | 1–10 | 7.87(2.03) |
| VABS communication | 54–99 | 69.84(9.22) | 30.108 | 77.48(18.20) |
| VABS DLS | 55–85 | 67.90(6.55) | 25–125 | 77.25(19.35) |
| VABS socialization | 55–87 | 70.02(7.93) | 12–130 | 75.39(22.29) |
| Maternal age(years; months) | 25–46 | 33;10(5;0) | – | – |
| Maternal education | 11–22 | 15(2;6) | – | – |

SRS–Social Responsiveness Scale; ADOS-SA-CSS–ADOS Social Affect Calibrated Severity Scale; ADOS-RRB-CSS–ADOS Restricted Repetitive Behavior Calibrated Severity Scale; VABS–Vineland Adaptive Behavior Scale

interests and restricted behaviors (RIRB). The SRS-2 mean score is 50 with an SD of 10; higher scores indicate more autistic traits. The SRS-2 60 *T*-65 *T*-scores refer to mild severity range, 66–75 *T* is the moderate severity range, and 76 *T*-scores or higher refer to the severe range. *T*-scores ≥ 65 (i.e., 1.5 SDs \geq the population mean of 50) suggest clinically significant autistic traits.

Procedure

Ethical consideration: The research procedure was approved by the Helsinki committee at Shamir (Assaf Harofeh) Medical Center's in Israel. Parents who agreed to participate signed a consent form as required. One of the participants who was older than 18 signed the consent form himself.

At the time of diagnosis (T1), the children underwent a comprehensive assessment that included behavioral, cognitive and adaptive skills assessments. Behavioral assessments were conducted by a skilled interdisciplinary team. Pediatric neurologists obtained medical, developmental and familial histories including on developmental and psychiatric disorders from the parents and conducted a comprehensive neurological examination of all the participants.

The diagnosis of ASD at T1 was based on a comprehensive evaluation including standardized tests, the ADI-R (Le Couteur et al. 2003; Lord et al. 1994) and the ADOS (Lord et al. 1999), and a clinical judgement based on the DSM IV criteria (APA 2000). Sixty-three of the study participants received the ADOS Module 1 and two received the ADOS

Module 2. Developmental levels were assessed using either the Mullen Scales of Early Learning (MSEL; Mullen 1995), the Stanford-Binet (Thorndike et al. 1986) or the Bailey Scales of Infant Development (Bayley 1993). Of the entire group, 57 participants had a cognitive evaluation at the time of their ASD diagnosis and eight participants underwent cognitive tests during the first year after diagnosis. Adaptive skills were assessed using the Vineland Adaptive Behavior Scales-VABS (Sparrow et al. 1984).

At follow-up (T2), extensive evaluations were also performed. Over two visits, each participant met with experienced psychologists who performed a cognitive evaluation using the WISC-IV (Wechsler 2010) or the WAIS-IV (Wechsler 2008), based on the participant's age, and an assessment of autism severity using the ADOS-2 (Lord et al. 2012). At T2, 12 participants received Module 1, nine received Module 2, 39 received Module 3 and four participants received Module 4. One participant did not complete the ADOS-2 assessment at T2. The professionals who performed the ADI-R and ADOS at T1 and the ADOS-2 at T2 established reliability in these standardized tests as required. The parents completed the VABS in a face-to-face interview with a special education expert. At T2, 61 participants had the SCARED evaluation, of them, 60 participants had cognitive assessment, 60 underwent the ADOS assessment, 59 parents completed the VABS interview and 58 parents completed the SRS. It should be noted that the cognitive assessments, ADOS for autism severity and VABS for adaptive skills were administered at both evaluation times (T1, T2) using the age- and

developmentally-appropriate versions. The ADI-R was administered only at baseline and the SCARED and SRS were administered only at follow-up time (T2).

Data Analysis

We first examined the mean scores and standard deviations of the SCARED scores and the frequency of significant clinical scoring in the examined population. We then compared the groups with and without elevated symptoms in at least one SCARED subdomain. For IQ, VABS subdomains, ADOS and SRS-2 subdomain score comparisons, one-way MANOVAs were used. When the MANOVA yielded a significant effect, one-way ANOVAs were applied to each of the examined variables in this analysis. We then examined the correlations of the T1 Developmental Quotient (DQ), VABS scores, and ADOS subdomain scores with T2 parental SCARED scores using Pearson correlation analyses. In addition, correlations between T2 measures of autism severity (ADOS, SRS), IQ, VABS scores, age and SCARED total and subdomain scores were performed. To examine the relative contribution of the toddlers' baseline characteristics and familial variables to the variance in the severity of anxiety scores at adolescence, two hierarchical regression analyses were performed.

Variables at toddlerhood were chosen based on published findings in cross-sectional studies on strong relationships between age (Dubin et al. 2015) cognitive ability (Ezell et al. 2019), adaptive skills (Dubin et al. 2015) and RRB (Rodgers et al. 2012) and the severity of anxiety symptoms. The variable of 'family history of anxiety' was based on published data in the general population on increased prevalence of anxiety in children with a family history of anxiety (Hudson et al. 2018).

The minimal required number of participants for the regression analysis was calculated based on Khamis & Kepler's (2010) equation of $20 + 5K$ (K = number of variables). In the current study, using five variables for K in this equation yielded 45 participants as the minimal adequate cohort needed for the regression analysis.

All continuous variables were normally distributed (skewness and kurtosis ± 1.96) except of the ADOS-RRB-CSS as this measure has a non-linear scale.

Results

For the first aim, frequencies, means and standard deviations (SD) for the SCARED parental report form (total and subdomains) were analyzed. In addition, the percentage of participants with scores above the clinical threshold in each anxiety subdomain was calculated. Overall, 55.7% of the parents of the study population reported at least one type of

anxiety, with 29.5% reporting only one type of anxiety and 26.2% reporting two or more types of anxiety.

As presented in Table 2, the most prevalent subtypes of anxiety were separation anxiety and social anxiety, followed by generalized anxiety. Only a small percentage of the study population showed significant symptoms on the SCARED panic/somatic complaints and school avoidance anxiety subtypes.

For the second aim, we compared autism severity, cognitive ability, and adaptive skills between adolescents with significant symptoms of anxiety in at least one subdomain ($n = 34$) to those who did not have any significant anxiety symptoms ($n = 27$). No significant group effect was found for the examined measures, including ADOS SA, RRB CSS [$F(2,57) = 0.37, p = 0.69$] and SRS subdomains [$F(7,50) = 0.42, p = 0.88$] for autism severity, IQ scores [$F(1,58) = 1.32, p = 0.25$] for cognitive ability and VABS subdomains scores [$F(3,54) = 0.41, p = 0.75$] for adaptive skills.

For the third aim, we examined the correlations of the most prevalent anxiety subdomains - separation, social, and generalized anxiety scores - with the child's characteristics at the time of the ASD diagnosis (Table 3).

As presented in Table 3, SCARED separation anxiety scores correlated significantly and negatively with T1 DQ scores and significantly and positively with T1 ADOS-RRB-CSS scores. SCARED social anxiety scores correlated negatively with T1 VABS scores. SCARED generalized anxiety scores correlated significantly and positively with T1 DQ scores and T1 VABS scores. Age at T2 correlated significantly and negatively with SCARED total generalized and separation anxiety scores. The younger the participants were, the more severe symptoms of anxiety were reported.

Next, the correlations between the participants' characteristics at T2 and the severity of SCARED total and subdomain scores were examined. SCARED generalized scores correlated significantly and negatively with T2 ADOS-SA-CSS and positively with T2 IQ and VABS composite scores. More severe autism symptoms and higher cognitive ability and adaptive skills were associated with more severe generalized anxiety symptoms. Social anxiety correlated significantly and negatively with ADOS-RRB-CSS. More severe social anxiety was associated with less severe RRBs. No significant correlations were found for the other types of anxiety with measures of autism severity (ADOS, SRS), IQ and VABS scores.

We then examined variables in toddlerhood that predict separation anxiety and social anxiety, the two most prevalent anxiety subdomains found in the research cohort, as reported by the parents at T2.

As presented in Table 4, when SCARED separation anxiety scores served as the dependent variable, the model explained 25.0% of the variance. Age at T2 at the first step contributed significantly 9% the explained variance; Younger age was associated with increased separation anxiety

Table 2 Means, standard deviations and percentage above cut-off scores for the SCARED subdomains

| | Cut-off scores | Range | M(SD) | Percentage above cut-off |
|-------------|----------------|-------|------------|--------------------------|
| Panic | 7 | 0–12 | 2.26(2.68) | 6.6% |
| Generalized | 9 | 0–14 | 5.16(3.89) | 18.0% |
| Separation | 5 | 0–12 | 3.67(2.59) | 39.3% |
| Social | 8 | 0–14 | 4.79(3.61) | 27.9% |
| School | 3 | 0–5 | 0.67(1.02) | 3.3% |

scores. Cognitive ability at T1 in the second step contributed 11.0% to the explained variance; the lower the T1 cognitive ability, the greater the T2 separation anxiety scores. Severity of RRBs as measured by ADOS-RRB-CSS at T1 contributed an additional 3.0% to the model (but not significantly); the correlation of the RRB subdomain showed a statistical trend with T2 separation anxiety scores. More severe RRB symptoms at T1 were associated with higher separation anxiety symptoms at T2.

When social anxiety scores served as the dependent variable, the model explained 17.5% of the variance however the model was not statistically significant.

Discussion

This prospective research is one of the few long-term follow-up studies to follow a cohort of children diagnosed with ASD from toddlerhood to adolescence. The focus of this paper was on significant anxiety symptoms at adolescence, frequencies of different anxiety subtypes and factors in toddlerhood that may predict the later appearance of anxiety.

Prevalence of Significant Anxiety Symptoms

In accordance with this study's hypothesis, based on results of the parental report SCARED questionnaire, 55.7% of the adolescents with ASD had sufficient anxiety symptoms to warrant at least one diagnosis of a specific anxiety disorder, significantly more than the prevalence published on TD adolescents (3–24%; Cartwright-Hatton et al. 2006; Polanczyk et al. 2015). Significant symptoms within one anxiety subdomain were documented in 29.5% of the participants, and in two or more anxiety subdomains in 26.2% of the examined adolescents. Separation anxiety was the most prevalent type (39.3%), followed by social anxiety (27.9%), and generalized anxiety (18.0%).

Several previous studies described similar rates of anxiety disorders in ASD (Ezell et al. 2019; White et al. 2014). Ezell et al. (2019) compared rates and predictors of anxiety disorders in adolescents with Fragile X syndrome or ASD (Weller et al. 2000). Similar to the current study's findings, the authors described that 50% of adolescents with ASD met criteria for any anxiety subtype, and 30% met criteria for multiple anxiety subtypes. It is worth noting that social anxiety rates (28%) in the current study were similar to previous studies that used different methods to assess anxiety symptom severity [Ezell

Table 3 Correlations of T1 and T2 measures' scores with SCARED subdomains scores

| | SCARED Generalized | SCARED Separation | SCARED social |
|-----------------|--------------------|-------------------|---------------|
| T1 DQ | 0.29* | -0.27* | 0.03 |
| T1 ADOS-SA-CSS | -0.17 | 0.06 | 0.09 |
| T1 ADOS-RRB-CSS | -0.06 | 0.26* | 0.12 |
| T1 VABS | 0.27* | -0.04 | -0.26* |
| T2 Age | -0.25* | -0.27* | -0.11 |
| T2 IQ | 0.29** | -0.13 | -0.20 |
| T2 ADOS-SA-CSS | -0.29** | -0.10 | 0.18 |
| T2 ADOS-RRB-CSS | -0.13 | -0.06 | -0.28** |
| T2 SRS | -0.04 | 0.13 | 0.16 |
| T2 VABS | 0.26* | -0.11 | -0.02 |

ADOS-SA-CSS Autism Diagnostic Observation Schedule-Social Affect, ADOS-RRB-CSS Autism Diagnostic Observation Schedule -Restricted Repetitive Behavior Calibrated Severity Scale, VABS Vineland Adaptive Behavior Scale

** $p < 0.01$, * $p < 0.05$

Table 4 Hierarchical regression model for T2 SCARED Separation anxiety scores

| Step | Variable | B | SE | β | R ² | ΔR^2 |
|------|-----------------------|-------|------|-------------------|----------------|--------------|
| 1 | Age m. | -0.03 | 0.01 | -0.30* | .09* | .09** |
| 2 | Age m. | -0.04 | 0.01 | -0.31** | 0.20** | 0.11** |
| | DQ | -0.05 | 0.02 | -0.33** | | |
| 3 | Age m. | -0.04 | 0.01 | -0.27* | 0.23** | 0.03 |
| | DQ | -0.04 | 0.02 | -0.29** | | |
| | ADOS-CSS-RRB | 0.26 | 0.19 | 0.17 | | |
| 4 | Age m. | -0.03 | 0.01 | -0.27* | 0.24* | 0.01 |
| | DQ | -0.04 | 0.02 | -0.32** | | |
| | ADOS-CSS-RRB | 0.30 | 0.20 | 0.20 [^] | | |
| | VABS scores | 0.05 | 0.06 | 0.10 | | |
| 5 | Age m. | -0.03 | 0.01 | -0.25* | 0.25* | 0.01 |
| | DQ | -0.04 | 0.02 | -0.32** | | |
| | ADOS-CSS-RRB | 0.29 | 0.20 | 0.19 [^] | | |
| | VABS scores | 0.04 | 0.06 | 0.10 | | |
| | Anxiety in the family | 0.61 | 0.85 | 0.09 | | |

ADOS-RRB-CSS Autism Diagnostic Observation Schedule -Restricted Repetitive Behavior Calibrated Severity Scale, VABS Vineland Adaptive Behavior Scale

** $p < 0.01$, * $p < 0.05$, [^] $p = 0.07$

et al. 2019 (30%); Kerns et al. 2015 (19%); Simonoff et al. 2008 (29%)]. The prevalence of generalized anxiety symptoms in the current study (18%) was similar to the reported prevalence in a previous study (Kerns et al. 2014). However, we found high percentages of separation anxiety symptoms, in contrast to the lower percentages reported in previous studies [Kerns et al. 2014 (10%; mean age = 10.5y); Simonoff et al. 2008 (0.5%; mean age = 11.6y); Sukhodolsky et al. 2008 (10.5%; age range 5-17y)]. In comparison to Kerns et al. (2014), the population of the current study had significantly lower IQ scores (74 vs 102). Since separation anxiety occurs more frequently in younger TD children, it is possible that a population with lower cognitive ability presents more frequently with this type of anxiety. It should be noted that the population in this study was slightly older than the mean age reported in previous studies. Therefore, age differences could not explain the higher percentage of separation anxiety in the current study in comparison to the previous studies.

Clinical Presentation and Severity of Anxiety Symptoms

In contrast to the study's hypothesis, the findings point to a lack of difference in clinical characteristics between children with ASD who do and do not have significant anxiety symptoms. Previous studies reported that anxiety in children with ASD has a negative impact on adaptive functioning, daily

living skills (DLS), and relationships with peers, teachers, and family (Factor et al. 2017; Hallett et al. 2013; Kim et al. 2000). Other studies did not find an association between the severity of anxiety symptoms and the level of functioning in cognitive ability (Ezell et al. 2019; Avni et al. 2018) and autism severity (Avni et al. 2018; Renno and Wood 2013; Simonoff et al. 2008; Strang et al. 2012). The lack of group differences in the current study appears to support the position that anxiety symptoms in children with autism exist independently of other clinical characteristics and are distinct from the autistic symptomatology. However, when looking at the specific anxiety subdomains, more severe generalized anxiety symptoms were associated with elevated autism severity and higher cognitive ability. In the general population, generalized anxiety symptoms are more prevalent with age (Canino et al. 2004). Adolescents with ASD with less severe autism symptoms and higher cognitive ability may follow this trajectory. In addition, elevated social anxiety symptoms were associated with less severe RRBs. It is possible that adolescents who are more aware of their social difficulties became more anxious of the negative social response to their behaviors and therefore attempted to mask their RRBs in order to reduce this negative response (Hull et al. 2017).

Variables at Toddlerhood Associated with Severity of Anxiety Symptoms

The current study is the first to explore the association between early child characteristics at toddlerhood and family history of anxiety and the occurrence of significant anxiety symptoms at adolescence. Cognitive ability at toddlerhood was associated with later development of anxiety but, interestingly, in different directions based on the different types of anxiety. Lower cognitive abilities in toddlerhood were associated with and predictive of future increased symptoms of separation anxiety, while higher early cognitive ability was associated with future increased symptoms of generalized anxiety. It is possible that in children with lower cognition, symptoms of separation anxiety are more apparent and show less decline over time. These findings are in line with previous reports on children with TD and those with ID. In the TD population, separation anxiety is most prevalent in preschool and declines rapidly in prevalence in adolescence (Compton et al. 2000; Hale et al. 2008). However, children with ID show less decline in separation anxiety in early childhood (Green et al. 2015). This may explain the positive association between cognitive level at toddlerhood and later development of generalized anxiety that follows the trajectory seen in TD.

Higher early adaptive skills were similarly associated with increased generalized anxiety symptoms in adolescence. It is possible that symptoms of generalized anxiety are more easily expressed by children with higher cognitive and adaptive abilities. In contrast, lower adaptive skills at toddlerhood were

associated with higher social anxiety symptoms at adolescence, possibly as a cumulative effect of difficulty in communicating with others.

It should be noted that in the current study, the age range of the population at the follow up time was large; therefore, it was possible to look for developmental trajectories of the different anxiety subdomains in adolescence. The severity of anxiety symptoms in general and specifically in separation anxiety and generalized anxiety decreased with age. These findings were partially similar to the reports in the TD population, where separation anxiety was found to rapidly decline in adolescence (Compton et al. 2000; Hale et al. 2008).

Predictors of Severity of Separation Anxiety Symptoms

The primary goal of this study was to search for predictors in toddlerhood of subsequent anxiety in adolescence. The main predictor for separation anxiety was cognitive ability at toddlerhood. Lower cognition predicted higher level of separation anxiety. In accordance with the study's hypothesis, the severity of RRBs at toddlerhood predicted the severity of separation anxiety at adolescence. Several studies in ASD have hypothesized that RRB in ASD are correlated with anxiety levels (Russell et al. 2019; Sullivan et al. 2014). For example, it has been suggested that RRBs serve as a coping strategy for lowering high levels of anxiety in individuals with ASD. Previous studies reported on the association between abnormalities in serotonin (5-HT), a primary neurotransmitter involved in anxiety, and the severity of RRBs in ASD (Lewis and Bodfish 1998). It is postulated that more severe RRBs in early childhood in ASD reflect early signs that precede the later occurrence of separation anxiety symptoms.

Research on predictors for the occurrence of anxiety in late childhood and adolescence in the TD population has focused mainly on early childhood behaviors, temperament and familial environmental variables including genetics (Frenkel et al. 2015; Hudson et al. 2018; Ollendick and Grills 2016). In ASD research, there have been inconsistent results regarding age, gender, cognitive ability, autism severity and adaptive skills as predictors of anxiety. It should be noted that most of these studies were cross-sectional (Bellini 2006; Niditch et al. 2012; Sukhodolsky et al. 2008; Wood and Gadow 2010; Hollocks et al. 2014; Rieske et al. 2012; Rodgers et al. 2012; Magiati et al. 2016). Baribeau et al. (2019) found that RRBs symptom severity in early childhood (median = 37 months) predicted a general measure of anxiety symptoms later in life. Only two longitudinal studies have searched for predictors of later anxiety. Gotham et al. (2015) conducted the initial assessment for children's anxiety at a later age; anxiety at age 9 predicted future anxiety symptoms. In Teh et al. (2017), the study included a large age range in their cohorts (5–17 years) and the follow-up time was short (10–

19 months). To summarize, these findings shed light on early characteristics in ASD that are associated with the expression and severity of anxiety symptoms in adolescence. Yet early cognitive ability may relate in the opposite direction to the different anxiety subtypes. Interestingly, family history of anxiety did not predict the severity of separation anxiety symptoms, as would be expected. It is known that psychiatric disorders in the parents of individuals with autism, including depression and anxiety, are common and can be transmitted to their children (Daniels et al. 2008). It is possible that in other cohorts with a larger population and a wider age range at diagnosis, the association between elevated anxiety symptoms in children with ASD and a family history of anxiety would be stronger.

It should be noted that the relatively low explained variance for the severity of anxiety symptoms in this study points to the difficulty in identifying measures at toddlerhood that are associated with severity of anxiety symptoms at adolescence. This means that the vast majority of variability in severity of anxiety symptoms is not entirely explained by early measures of toddlers' and familial characteristics, but rather is affected by numerous variables and life events that occur during this long follow-up period. One potential explanation that is worthy of investigation is that of bullying and social exclusion, which occur more frequently in children with ASD and comorbidities including anxiety (Anderson 2014). In addition, the relationship between the type of early intervention the children received and the severity of anxiety symptoms at adolescence should be further examined.

The current study has several important clinical implications. First, it is important for clinicians to be aware of the high prevalence of specific types of anxiety disorders in ASD, particularly in thinking about comorbid or differential diagnoses. Second, when clinicians diagnose ASD in toddlers, they should pay special attention to baseline characteristics. For example, severe RRBs in toddlerhood can be a red flag for later elevated separation anxiety symptoms, which should be followed closely. Cognitive functioning and adaptive skills in toddlerhood may be associated with different anxiety subtypes. Close follow-up is crucial for adolescents with ASD who present with elevated anxiety symptoms, as it will be important to implement focused interventions using evidenced-based psychological strategies, parent guidance, and if necessary, pharmacological intervention.

Strengths This is one of very few prospective long-term studies to examine the characteristics of very young toddlers diagnosed with ASD that are associated with a later occurrence of elevated anxiety symptoms. The study has a well-characterized cohort with an adequate size for a long-term follow-up research. In addition, the comprehensive evaluation of the population using standardized measures at baseline has enabled the examination of numerous variables that could be

associated with later elevated anxiety symptoms. This study's findings are novel and address a topic that, until today, has only been examined in the general population.

Limitations The study had a small number of females and therefore the examination of the contribution of gender to outcome in anxiety was limited. This important variable should be addressed in future studies. The assessment of anxiety symptoms was based on standardized questionnaires and not on direct interviewing and assessment of the participants and their parents. However, Stern et al.'s 2014 study supported the use of the SCARED as a valid assessment tool in an ASD population. In addition, Kerns et al. (2014) supported the use of SCARED for its ability to discern the atypical presentations of anxiety in ASD and its validity with other measures of anxiety. Although prior studies focused on the sensitivity of the SCARED total scores, they have not examined the accuracy of the subscale cut-offs.

Building upon this study's findings may assist us in identifying sub-groups at time of diagnosis who are at higher or lower risk for a subsequent diagnosis of an anxiety disorder. It will be important to search for other relevant variables, including those studied in the TD population. Variables such as family characteristics, early childhood difficulties such as emotion dysregulation and behavioral inhibition, along with certain parenting styles may predict or be associated with a later occurrence of elevated anxiety symptoms, as is reported for the general population.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethics Approval The research procedure was approved by the Shamir Medical Center (Assaf Harofeh)'s Helsinki committee. Parents who agreed to participate signed a consent form as required. One of the participants who was older than 18 signed the consent form himself.

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