Does the Severity of Autism Symptoms Change During Childhood? What Characterizes Children Who Increase or Decrease in Symptom Severity?

By

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Abstract

It is unclear how common is change in the severity of autism symptoms during childhood, whether symptoms change consistently across development, and what characterizes children that either increase or decrease in autism symptom severity during childhood. We evaluated these questions across three studies incorporating children from the University of California, Davis MIND Institute's Autism Phenome Project and Girls with Autism imaging of Neurodevelopment cohorts. Autism symptoms and severity level were evaluated using the ADOS Calibrated Severity Score (CSS). Around half (46%-51%) of the children in the cohort changed in symptom severity level over time, with the other half remaining stable. Change in symptom severity was not consistent but rather fluctuated over time; severity decreases were more common during early childhood while severity increases occurred at both early and middle childhood. Most children experienced change during only one period and remained stable during the other. Social-communication challenges and restricted/repetitive behaviors (RRBs) changed differently across childhood. During middle childhood, increase in social-communication symptoms was especially prominent in parallel to RRBs severity decrease. Being female, having higher and increasing IQ, higher adaptive functioning, and having older, more educated parents were associated with decrease in symptom severity. Decreasing RRBs severity during middle childhood was associated with higher anxiety and probability for having an anxiety disorder at 11 years of age. Increasing symptom severity was associated with having lower and stable IQ, lower adaptive functioning and not making peer-equivalent gains over time, lower parental education level and younger parental age at the child's birth. Increasing severity of social-communication challenges during middle childhood was associated with elevated and increasing anxiety, ADHD,

disruptive behavior problems and overall psychopathology. Symptom severity change patterns were not associated with either initial severity level at 3-years-of-age or intervention history. We discuss findings in light of the literature and implications for defining autism severity level and suitable interventions.

Preface

Before starting graduate school, I worked in special education autism preschools in Israel as part of my internship in clinical psychology. This was my first encounter with autism, ten years ago. Each child at the school was unique; they struggled with different challenges, they liked different things and the way to reach out and connect was different with every child. Autism preschools in Israel are funded by the country and so resources and services are embedded in the school setting. Service providers such as psychologists, speech pathologists and occupational therapists practice on a daily basis with different children within the school, as well as special education teachers and aids. Where I worked, it was a ratio of 15 adults per 8 children, a ratio many other places in the world can only wish for. Children entered the school at age 3 and graduated when they were 6-years-of-age. Many of them made exciting gains during their time at the school, developing language, more complex play and social skills that involved other children, gaining cognitive skills and forming meaningful relationships with their therapists and peers. Others, however, did not. Some of the children, it seemed, despite countless hours of intervention and their families' support, were losing skills over time (or not gaining them as expected). Children that started off verbal at age 3 regressed to functional speech, spending most of their time absorbed in their repetitive behaviors and sensory self-stimulation. As time went by, it was harder to reach and to engage them. And yet, for other children, we hardly saw any change in their autism at all. All the children described here received the exact same types and amount of intervention, in the same place and with the same providers, yet went on to have extremely different developmental trajectories during childhood. This fascinated me; it made me want to understand the malleability of the development of autism over time, and why some

children were getting better while others were getting worse. The children at the school led me to the research questions I explored in my dissertation work, and my hope is that one day this work can be translated into real-life benefits for them.

1. Introduction

Autism is a neurodevelopmental condition affecting 1 out of every 44 children in the US today (Maenner et al., 2021). Autism is behaviorally defined by the presence of two core symptom domains: social-communication challenges and restricted/repetitive patterns of behaviors and interests (RRBs) (APA, 2013). In order to receive a diagnosis of autism, an individual must sufficiently exhibit symptoms from both these groups (APA, 2013).

The first domain, social-communication challenges, comprises different aspects of social interaction including socio-emotional reciprocity, use of non-verbal communication methods and forming and maintaining relationships. Impairment must be evident in each of these areas in order to receive a diagnosis of autism. The second domain, RRBs, refers to several types of behaviors including stereotypical movements and object use, insistence on sameness, highly-focused areas of interest and sensory hypo/hyper reactivity.

Autism symptoms present differently within different individuals. Specifically, they range widely in their severity level, i.e., in how impactful they are on the person's everyday behavior. Some individuals experience substantial social-communication difficulties and/or many and severe forms of RRBs. For others, however, these symptoms are less apparent and less restricting in their everyday interactions and life. In order to help clinicians evaluate the presence of core symptoms in an individual's behavior, standardized assessment measures have been developed (Waizbard-Bartov & Miller, 2023). These tools provide a standardized measure for assessing autism symptoms, based on predetermined thresholds for symptom severity levels that likely meet criteria to receive an autism diagnosis (Yu, Ozonoff, & Miller, 2023). One such tool is the

Autism Diagnostic Observation Schedule (Lord et al., 2000; C. Lord et al., 2012), or ADOS, considered the gold standard assessment measure for direct observation of autism symptoms. The ADOS is a semi-structured social interaction that creates opportunities for the assessor to evaluate the presence of core symptoms in the individual's behavior. It includes five modules, each adapted for individuals of a specific age and language ability, from Pre-Verbal/Single words up to Fluent Speech. The ADOS produces both raw scores for symptom levels as well as standardized comparison scores (the Calibrated Severity Scores; CSS) (Gotham, Pickles, & Lord, 2009). The CSS range from 1 (least severe) to 10 (most severe) and are used to quantify the severity level of core symptoms as evident in the assessment. In addition to the total CSS, the ADOS also produces standardized scores to evaluate social-communication challenges (SA CSS) and RRBs (RRB CSS), separately (Hus, Gotham, & Lord, 2014). Because these are standardized scores, they enable comparison of symptom severity levels between different individuals and within specific individuals over time.

Longitudinal studies have used the ADOS CSS repeatedly across measurements to try and understand if autism core symptoms remain stable, or rather change, across the life span. Many studies have indicated that autism symptoms tend to remain stable over time, identifying very large groups of individuals, between 80%-90% across samples, that remain stable in the severity of their core symptoms over time (Gotham, Pickles, & Lord, 2012; Venker, Ray-Subramanian, Bolt, & Ellis Weismer, 2014). Other studies, however, have emphasized change in symptom severity. For instance, Fountain, Winter, and Bearman (2012) found that, in a very large sample (N=6975), most children showed significant change in symptom severity from age 3 to 14. While this study did not utilize standardized assessment tools for autism symptoms (but rather a parent

interview), it has the power of having a very large sample size. Another longitudinal study using the Autism Diagnostic Interview-Revised (ADI-R), (Lord, Rutter, & Le Couteur, 1994), a standardized parent interview for autism symptoms, found that symptoms tended to either change or remain stable in severity across time, to almost equal proportions across individuals in their sample (Shattuck et al., 2007). For participants who did experience change (46%), decreasing severity (26%) was more common than increasing severity (20%), yet both types of change occurred within the sample. Collectively, these studies indicate that some individuals change in the severity of their core symptoms over time, to either increase or decrease, while others remain stable, and it is not clear what proportions of individuals experience change compared to symptom stability.

To further complicate things, studies identifying change in symptom severity have shown that it is not consistent within individuals over time. Severity change can differ in: (a) when it occurs during development (periods of stability compared to periods of change within an individual) (Georgiades et al., 2021); (b) the direction of change (decreasing compared to increasing severity) (Clark, Barbaro, & Dissanayake, 2017); and (c) the rate at which change occurs (e.g., fast/moderate change, consistent pace/slowing with time) (Georgiades, Bishop, & Frazier, 2017; Taylor & Seltzer, 2010). Thus, symptom severity change may manifest differently across various developmental periods.

Change in autism symptoms is also characterized by differences between the two core domains comprising it (Fountain et al., 2012). Evidence suggests that social-communication challenges tend to decrease in severity with age (Bal, Kim, Fok, & Lord, 2019; Fountain et al., 2012; Lord, Bishop, & Anderson, 2015), while RRBs have been found to either decrease (Shattuck

et al., 2007), increase (Lord et al., 2015) or remain stable over time (Gillespie-Lynch et al., 2012). This difference in the tendency for severity change, as well as which type of change occurs, can impact our ability to understand change in the severity of overall autism symptoms (using the ADOS total symptom severity score), as well as separately for each domain.

The three types of differences described above (between-person, within-person-over-time and across-symptom-domains) make change in autism symptom severity extremely variable (Georgiades et al., 2017). Moreover, at the individual level, these differences make it very hard to try and predict if and how a person's core symptom severity will change over time. Yet, there may be additional factors that can assist when attempting to make such a prediction. Autistic individuals often face other, co-occurring challenges in addition to those brought on by core symptoms (Mutluer et al., 2022). These include neurodevelopmental and mental health challenges such as ADHD, anxiety, aggressive behaviors and depression (Lai et al., 2019; Simonoff et al., 2008), intellectual disability (Maenner et al., 2021; Solomon et al., 2018), language disorders (Schaeffer et al., 2023), sleep problems (Chen et al., 2021), gastrointestinal symptoms (Reynolds et al., 2021), epilepsy (Karunakaran et al., 2020) and others. The high prevalence of such comorbidities among autistic individuals suggest that they are a fundamental part of how having autism impacts a person's everyday life (Waizbard-Bartov, Fein, Lord, & Amaral, 2023a). In addition, these co-occurring challenges as well as other developmental and environmental factors also interact with and influence change in core symptom levels throughout the life span.

For instance, being a girl has been associated with a stronger tendency to decrease in the severity of core symptoms during early childhood compared to being a boy (Szatmari et al., 2015). Decreasing in autism symptom severity has also been linked with having average-range IQ; i.e.,

not having intellectual disability (Fein et al., 2013; Georgiades et al., 2021; Gotham et al., 2012; Woodman, Smith, Greenberg, & Mailick, 2015). In contrast, toddlers with developmental delays as well as preschool-aged children who are minimally verbal or have speech delays are less likely to decrease in core symptom severity, especially in the domain of social-communication challenges (Bal et al., 2019; Hinnebusch, Miller, & Fein, 2017). Adaptive functioning has also been associated with change in core symptom severity (Charman et al., 2011; Gotham et al., 2012; Perry, Flanagan, Dunn Geier, & Freeman, 2009), though not consistently (Kim, Macari, Koller, & Chawarska, 2016; Szatmari et al., 2015), making this potential relationship a target for further investigation. Co-occurring mental health challenges may also impact change in core symptom severity. Dealing with comorbidities such as anxiety has been associated with increasing symptom severity (Baribeau et al., 2022), while decreasing levels of mental health problems is associated with marked decreases in core symptom levels (Orinstein et al., 2015). Finally, the literature shows individuals' initial symptom severity levels at the time of diagnosis is not necessarily a good predictor of future change in core symptom levels (Bal et al., 2019; Pellicano, Cribb, & Kenny, 2019; Sutera et al., 2007).

Environmental factors have also been linked with change in core symptom levels during childhood. Sociodemographic factors may impact children's change, and especially the tendency for severity increase. Living in an impoverished neighborhood (Simonoff et al., 2019), having less educated parents, and coming from lower socioeconomic status (Fountain et al., 2012) have all been associated with increasing symptom severity or with having a lower likelihood for decreasing severity (Fountain et al., 2012; Georgiades et al., 2021). It is unclear whether children's intervention history is associated with their symptom severity trajectories. While early

intervention has been established as beneficial for young children on the spectrum (Zwaigenbaum et al., 2015), some studies have found no relationship between intervention history and severity change (Giserman-Kiss & Carter, 2019; Gotham et al., 2012).

Evaluating the literature to date, is not clear how common change in the severity of autism symptoms over time is. Furthermore, there is evidence to suggest that once change does occur, it is not linear in nature but rather can differ across development. We still do not yet understand, however, what characterizes different developmental periods in relation to various types of severity change. The literature consistently shows that the two symptom domains, social-communication challenges and RRBs, have different developmental trajectories over time. But how they change in relation to each other and their differential impact on the total autism symptom trajectory of an individual are not clear. Finally, both developmental and environmental factors impact individuals' core symptom trajectories over time, making it crucial to understand what defines children who either increase, decrease or remain stable in their symptom levels. Understanding the characteristics of the children whose symptoms change over time is important to our understanding both of longitudinal trajectories in autism and how trajectories impact outcomes. This understanding can help us to better provide supports that promote decreases in core symptom levels and prevent potential increases over time, and to identify those who are at risk for other challenges (e.g., mental health) allowing for earlier intervention for these difficulties as well.

In the following set of studies, I evaluated change in the severity of core symptoms for the children of the University of California, Davis MIND Institute's Autism Phenome Project (APP)

and Girls with Autism Imaging of Neurodevelopment (GAIN) studies. I sought to answer the following four questions:

1. Do the core symptoms of autism change in severity over time? And if so, how common is change?
2. Does symptom severity change differ between periods of development? How is change characterized over time?
3. Does change in symptom severity differ between the two core domains? How do these impact change in total autism symptom severity level?
4. What developmental and environmental factors characterize children that either increase or decrease in symptom severity across childhood?

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ORIGINAL PAPER

2. Study 1:

Trajectories of Autism Symptom Severity Change During Early Childhood

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Abstract
Autism symptom severity change was evaluated during early childhood in 125 children diagnosed with autism spectrum disorder (ASD). Children were assessed at approximately 3 and 6 years of age for autism symptom severity, IQ and adaptive functioning. Each child was assigned a change score, representing the difference between ADOS Calibrated Severity Scores (CSS) at the two ages. A Decreased Severity Group (28.8%) decreased by 2 or more points; a Stable Severity Group (54.4%) changed by 1 point or less; and an Increased Severity Group (16.8%) increased by 2 or more points. Girls tended to decrease in severity more than boys and increase in severity less than boys. There was no clear relationship between intervention history and membership in the groups.

Keywords Autism spectrum disorder · Symptom severity · Early childhood · Sex differences

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social communication and social interaction, as well as restricted and repetitive behaviors (American Psychiatric Association 2013) and affects 1 out of every 59 children (Baio et al. 2018) in the United States. While the symptoms of ASD are commonly considered to be stable throughout life (Bieleninik et al. 2017), increasing evidence indicates that at least some individuals demonstrate substantial changes in the core features of ASD and/or comorbid conditions over time (Shattuck et al. 2007; Georgiades et al. 2014; Steinhausen et al. 2016; Hudry et al. 2018; Solomon et al. 2018). One example of substantial change is optimal outcome, defined as a decrease in autism symptoms in individuals previously diagnosed with ASD, so that they no longer meet diagnostic criteria (Fein et al. 2013).

Early indication of the potential for change was documented by Fountain et al. (2012) who described six distinct trajectories of symptom severity change using a very large cohort of participants (N = 6975). They described six developmental trajectories of social, communication and repetitive behavior functioning. While most children showed slow progress or little change, a small group (which they called Bloomers) demonstrated rapid gains between early childhood and adolescence. Although this study had the strength of involving a very large cohort, the conclusions were based on parental or provider reports obtained from the California Department of Developmental Services and not from direct clinical assessments. Change over time in autism symptoms is better assessed through clinical observations that are relatively free of the biases that are often inherent in parental report.

The Autism Diagnostic Observation Schedule (ADOS) has become the standard assessment instrument in the field of autism research (Lord et al. 2000). It is comprised of a series of structured and semi-structured tasks, allowing the trained examiner to evaluate a participant's behavior, communication and social interaction, providing a standardized context for evaluation of autism symptom severity. The ADOS consists of several modules, each used with persons of a specific level of language development, ranging from pre-verbal to fluent speech. Different modules incorporate different tasks and demands and result in different scores, demonstrating the assessment's strength in adapting to

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children's varying language abilities but making it difficult to compare severity levels across individuals or across ages. The ability to reliably assess a child's change in severity over time is a key concern for researchers, clinicians and parents alike (Shattuck et al. 2007; Magiati et al. 2014). To use the ADOS to assess changes in severity over time, Gotham et al. (2009) developed the ADOS Calibrated Severity Scores (CSS). To do so, they first created revised algorithms (Gotham et al. 2007) with the same number of items and similar content across modules that showed minimal association between the ADOS total scores, the child's age and verbal IQ. Second, they used a sample of 1807 assessments from individuals diagnosed with ASD to create 18 age and language-based groups. Within each of the groups, percentiles were calculated for each of the ADOS diagnostic classifications (non-spectrum, ASD and autism). The calculation of percentages in the 18 developmental groups served as a basis for using the raw totals to produce a standardized, 10-point severity metric. This severity metric was found to have more uniform distributions across the developmental groups than raw scores and was less influenced by a participant's characteristics (Gotham et al. 2009). The ADOS CSS has proven to be a better indicator of autism severity because it is relatively independent of verbal ability, age and other childhood characteristics. A number of studies have since employed and validated the CSS for this purpose (de Bildt et al. 2011; Hus Bal and Lord 2015; Messinger et al. 2015) and it has also been used to assess symptom severity change in large scale intervention studies (Estes et al. 2015; Pickles et al. 2016).

Gotham et al. (2012) were the first to use the ADOS CSS to examine autism severity trajectories in a sample of 345 children (63 girls and 282 boys), aged 2–15, each having completed between 2 and 8 assessments. Using generalized linear latent and mixed models statistics, they found that over 80% of participants could be assigned to a stable severity class, with two other small groups showing either an increase or a decrease in severity over time. Venker et al. (2014) explored autism severity trajectories using the ADOS CSS in a group of 129 children (17 girls and 112 boys) over four assessments between the ages of 2.5 and 5.5 years using latent class growth models. Their findings are consistent with Gotham et al. (2012). They identified the same trajectory classes with almost 80% of children showing stable levels of severity over time. In 2015, Szatmari et al. used a semiparametric, group-based approach to study a sample of 421 2–6-year-old children (66 girls and 355 boys) who were assessed at three time points, also using the ADOS CSS. They observed two severity trajectories; a large group (88.6%) characterized with higher initial severity that demonstrated stable severity across time and a small group (11.4%) with initially low severity and decreases over time. Kim et al. (2016) identified subgroups based on autism symptoms and other aspects of clinical profiles and short term outcomes using hierarchical clustering analysis. Their sample included 100 toddlers (16 girls and 84 boys) evaluated in the second and third years of life using the ADOS CSS. Their results indicated that autism symptom severity remained stable over a 1 year period for 84% of their participants while 16% demonstrated an increase in severity.

In 2017, Clark et al. reported on a group of 48 children (12 girls and 36 boys) evaluated for ASD symptoms across three time points using the ADOS CSS, from age 2 to 9 years of age. They divided the sample into groups based on diagnostic stability, producing a non-stable ASD group (13 children) comprised of participants who, as they grew older, no longer met diagnostic criteria and an ASD stable group (35 children), comprised of participants who retained diagnosis over time. Both groups showed significant autism symptom severity change over time. Analysis based on simple main effects demonstrated that the non-stable ASD group consistently decreased in their autism severity over time while the ASD stable group decreased in severity during preschool age but then increased again during school age, to return to their toddlerhood levels. In 2018, Kim et al. identified variability in autism symptom trajectories of 149 toddlers (30 girls and 119 boys), 14–36 months old, referred for autism evaluation. Using latent class growth analysis of the ADOS CSS, they identified four groups: a non-spectrum group (25%); a worsening group (27%) with initially low severity levels that increased over time; a moderately-improving group (25%) that showed a slight decrease in severity and a severely affected group (23%) that maintained high severity levels over time. Recently, Pellicano et al. (2019) evaluated autism symptom severity across a 9 year period, based on two assessments, using the ADOS CSS in a sample of 27 individuals (2 girls and 25 boys). Participants ranged from 8 to 11 years at initial assessment and 16 to 20 years at second assessment. While group mean severity level remained stable over time, there was high variability in individual participant's symptom trajectories. Reliable change in severity levels was identified for more than half the sample: 29% of participants increased in severity over time, 29% decreased in severity and 42% remained stable.

Intervention studies have also demonstrated the ability of treatment to impact and reduce symptom severity levels. The Pre-school Autism Communication Trial (PACT), a parent-mediated social communication intervention targeting autism symptoms, was administered to 152, 2–4-year-old children, autism severity was measured using ADOS CSS and analysis was done using mixed-effect ordinal logistic regression. PACT was shown to successfully reduce autism symptom severity at treatment end point, an effect which remained at follow up assessment almost 6 years later (Pickles et al. 2016). Giserman-Kiss and Carter (2019) evaluated autism symptoms following

intervention for 60 children (8 girls and 52 boys) of diverse backgrounds using two time points; at initial assessment (age 19–34 months) and at follow up assessment (42–70 months) after having received intervention in the community. Paired t-test analysis showed that, on average, children demonstrated significant decreases in symptom severity between initial and follow up assessments. Thus, while earlier studies using the ADOS CSS had emphasized relative stability of autism symptoms for most individuals with small groups either decreasing or increasing with time, more recent studies have highlighted variability in symptom trajectories and a higher proportion of change in severity levels than previously depicted.

In the current study, we used the ADOS CSS to explore changes in autism symptom severity during early childhood i.e. for children between 3 and 6 years of age. Focusing on autism severity changes in early childhood is important for a variety of reasons. First, early childhood is a period of substantial brain growth with the potential for enormous plasticity (Cao et al. 2017; Walhovd et al. 2017; Gilmore et al. 2018; Oldham and Fornito 2018; Lebel et al. 2019). Second, because early childhood is the usual time of initial diagnosis, it has become the primary target age for early intervention (Rogers and Dawson 2010). While previous studies of autism severity have also included early childhood participants, (Venker et al. 2014; Szatmari et al. 2015), the current study has a number of unique strengths. First, this is a single site study; participants were recruited through the Autism Phenome Project (APP), a multidisciplinary longitudinal project in its 14th year at the MIND (Medical Investigation of Neurodevelopmental Disorders) Institute of the University of California, Davis. Participation in the APP includes a comprehensive assessment battery starting when children are 2–3.5 years of age. Thus, the participants' age range at baseline is narrow. Second, and germane to the assessment of symptom severity over time, all clinical evaluations are carried out consistently at the same location (the MIND Institute) by licensed psychologists trained to research standards and under the supervision of the same clinical team. Third, a comprehensive database of information is available for all participants including biological data (such as magnetic resonance imaging), medical records, cognitive and language measures and intervention history. Fourth, increased representation of girls in the cohort enabled evaluation of sex differences in symptom severity change.

The overarching aim in this study was to evaluate trajectories of symptom severity across early childhood and to investigate what associated factors might be influences. We focused on two questions: (1) Does the severity of autism symptoms change in individual children across early childhood and (2) Was the amount or direction of change affected by initial severity levels, intervention intensity, sex, IQ or level of adaptive functioning.

Methods

Participants

Participants were enrolled in the University of California (UC) Davis MIND Institute Autism Phenome Project or Girls with Autism Imaging of Neurodevelopment Study (GAIN). Participants enrolled between 2 and 3.5 years of age. The study protocol includes a comprehensive assessment battery, collecting neuropsychological, medical, behavioral and biological information. The present study reports behavioral data related to autism symptom severity, cognitive function and adaptive behavior collected at Time 1, the baseline assessment, and Time 3, which served as the follow up assessment. Time 2 (1 year following Time 1) is not addressed in the current study since only magnetic resonance imaging data were collected at that time point. Nonetheless, we maintain a consistent timing nomenclature across all publications. The study was approved by the UC Davis Institutional Review Board and informed consent was obtained from the parent or guardian of each participant.

One hundred and twenty-five participants were evaluated, 89 boys and 36 girls. Participant characteristics are provided in Table 1. Inclusion criteria were based on the NIH Collaborative Programs of Excellence in Autism. Participants had received a community diagnosis of ASD that was confirmed by a licensed clinician at the MIND Institute using the ADOS-2 and the Autism Diagnostic Interview-revised (ADI-R) (Lord et al. 1994, 2000). A diagnosis was confirmed if they met the ADOS-2 cut off score for either autism or ASD and exceeded the ADI-R cut off score for autism on either the Social or Communication subscales while being within two points of this criterion on the other subscale. Study participants were required to be English speaking, reside with at least one biological parent, be ambulatory and not diagnosed with any severe motor, vision, hearing or other chronic health issues that might hinder participation.

Measures

We used measures common for assessment of autism symptom severity, cognitive abilities (IQ) and adaptive functioning in children within this age range. These included the Autism Diagnostic Observation Schedule-2: ADOS-2 (Lord et al. 2000), Mullen Scales of Early Learning: MSEL (Mullen 1995), Differential Abilities Scales-II: DAS-II (Elliot 2007), and the Vineland Adaptive Behavioral Scales: VABS II (Sparrow et al. 2005). All assessments were either conducted or supervised by a trained, licensed

Table 1 Demographic information

		Time 1			Time 3		
		All	Boys	Girls	All	Boys	Girls
N (%)		125, 100%	89, 71.2%	36, 28.8%	125, 100%	89, 71.2%	36, 28.8%
Age (months)	$\bar{x}$ (SD)	35.54 (5.58)	34.56 (5.48)	37.97 (5.14)	68.31 (10.90)	67.98 (11.71)	69.14 (8.87)
ADOS CSS	$\bar{x}$ (SD)	7.30 (1.71)	7.37 (1.72)	7.14 (1.69)	7.00 (2.14)	7.27 (2.02)	6.36 (2.32)
Intervention:							
Hours	$\bar{x}$ (SD)	882 (819)	925 (888)	783 (631)	3218 (1848)	3233 (1937)	3180 (1618)
Intensity	$\bar{x}$ (SD)	2353 (712)	2385 (772)	2280 (556)	3790 (1652)	3824 (1715)	3696 (1487)
IQ	$\bar{x}$ (SD)	66.59 (21.18)	65.33 (20.81)	69.79 (22.80)	79.07 (31.45)	77.80 (31.24)	82.22 (32.20)
VABS-II:							
Composite score	$\bar{x}$ (SD)	76.73 (11.21)	78.42 (11.10)	72.59 (10.20)	76.61 (16.35)	76.61 (16.10)	76.61 (17.22)
Motor skills	$\bar{x}$ (SD)	87.38 (13.71)	89.10 (13.39)	83.18 (13.00)	81.54 (14.85)	81.24 (15.66)	82.31 (12.85)
Socialization	$\bar{x}$ (SD)	75.17 (11.80)	76.98 (12.00)	70.71 (10.00)	74.38 (18.65)	74.78 (18.50)	73.42 (19.27)
Communication	$\bar{x}$ (SD)	75.14 (15.32)	76.11 (14.74)	72.74 (16.50)	81.25 (19.67)	80.66 (19.47)	82.67 (20.36)
Daily living skills	$\bar{x}$ (SD)	80.11 (12.44)	81.76 (12.29)	76.03 (12.00)	78.81 (17.80)	79.35 (17.09)	77.51 (19.62)

clinical psychologist who specializes in ASD and who had reached research reliability for these instruments. To increase the likelihood of successful testing and to allow children to demonstrate their full abilities, several accommodations were put in place as part of the assessment procedure. For example, children were given as many breaks as needed to use the bathroom, eat snacks or simply rest. If a child experienced distress at any time, they received a break to rest and gather themselves with the help of their parents. To increase motivation for participation, methods such as sticker charts were used. Testing children as young as these is always challenging. However, the probability of accurate testing was increased since these procedures were carried out by experts in child development. Assessment measures included the following:

Autism Diagnostic Observation Schedule-2: ADOS-2 (Lord et al. 2000)

The ADOS-2 is a semi-structured, standardized assessment instrument considered to be the gold standard for ASD diagnosis. The ADOS-2 includes five modules increasing in difficulty which are assigned based on a participant's language development and age. The Calibrated Severity Score (Gotham et al. 2009) provides a quantitative assessment of increasing severity of autism related symptoms (1–2: "minimal-to-no evidence", 3–4: "low", 5–7: "moderate" and 8–10: "high"), with a score of 4 or above meeting criteria for an ASD diagnosis. All clinical evaluations were carried out consistently at the same location (the UC Davis MIND Institute) by licensed psychologists trained to research standards and under the supervision of the same clinical team. The MIND Institute procedure for ensuring research reliability of clinicians administering the ADOS is adapted from the procedure required by the developers of the ADOS-2. Research reliability is established for all ADOS modules by reaching agreement of 80% or higher (i.e. reliability of 0.80) with a research-reliable clinician on three consecutive ADOS assessments for each module set (Set 1: Modules Toddler, 1 and 2; set 2: Modules 3 and 4). Once reliability is achieved, administrators take part in regular clinical supervision sessions of ADOS administration and coding, facilitated by a certified ADOS trainer. Random double coding was employed using both live assessments and video recordings. A second rater was regularly employed in the case of a child previously meeting criteria for diagnosis but failing to meet at a later assessment or in cases that the first rater felt another professional opinion was warranted.

Mullen Scales of Early Learning: MSEL (Mullen 1995)

The MSEL is a standardized assessment tool which measures cognitive and developmental functioning of children up to 68 months of age. At Time 1, verbal, nonverbal and combined IQ were estimated by calculating ratio developmental quotient scores, dividing average verbal, nonverbal and combined MSEL subscale age equivalents by chronological age. However, due to a substantial proportion of participants achieving the lowest possible standard score, a ratio developmental quotient was calculated (mental age/chronological age * 100) to provide more specific individual estimates of nonverbal, verbal and combined IQ.

Differential Abilities Scales-II (DAS-II) (Elliot 2007)

The DAS-II is a standardized measure that assesses children's cognitive abilities between the ages of 2.5 and 17 years. Participants completed the core battery of either the DAS-II Upper Early Years or the School Age forms. Participants who were not able to achieve basal scores on the DAS-II at Time 3 were administered the MSEL. Developmental quotients (DQ) were used to calculate verbal, nonverbal and combined IQ scores.

Vineland Adaptive Behavior Scales, Second Edition: VABS II, Parent / Caregiver Rating Form (Sparrow et al. 2005)

The VABS II measures adaptive function from birth to adulthood. It yields a standardized composite score, percentile ranks and adaptive levels. The current study analyzed the standardized composite score and four of the domains: Motor Skills, Socialization, Communication and Daily Living Skills, using parents' assessment of their child's behavior.

Services, Treatment and Intervention Data

At each visit, the child's caregiver(s) completed a form inquiring about current and previous intervention received by the child, including information regarding type and duration of treatment. This form was adapted from the Collaborative Programs of Excellence in Autism. An intensity score for intervention was calculated based on the following formula: (weeks of intervention * hours per week * number of adults / number of children present).

Data Analysis

To evaluate the profiles of individual change demonstrated by the participants across time, a severity change score was computed for each participant (Time 3 ADOS CSS–Time 1 ADOS CSS) (Fig. 1). The mean severity change score for the sample was -0.30 (SD: 1.91) and the distribution ranged from − 6 (decrease of 6 points in symptom severity over time) to + 4 (increase of 4 points in symptom severity over time).

We sought to explore the characteristics of children who increased, decreased or remained stable in autism severity. To determine how much change from Time 1 to Time 3 is meaningful, we used the Reliable Change Index statistic (RCI; Jacobson and Truax 1991)

$$RCI_{Z\,SCORE} = \frac{(\text{ADOS CSS Time 3} - \text{ADOS CSS Time 1})}{\sqrt{2\left(SD\sqrt{1 - r_{xy}}\right)^2}}$$

The RCI indicates what amount of change in clinical data can be considered statistically significant (Anderson et al. 2014; de Souza Costa and de Paula 2015; Hudry et al. 2018; Pellicano et al. 2019). The RCI was calculated using the means of CSS at Time 1 (7.30) and Time 3 (7.00), the standard deviation (SD) at Time 1 (1.71) and the reliability of the ADOS CSS, which was assumed to be 0.80 (as this is the minimal value for test–retest reliability). All analyses were performed in R version 3.5.1 (R_Core_Team. 2018).

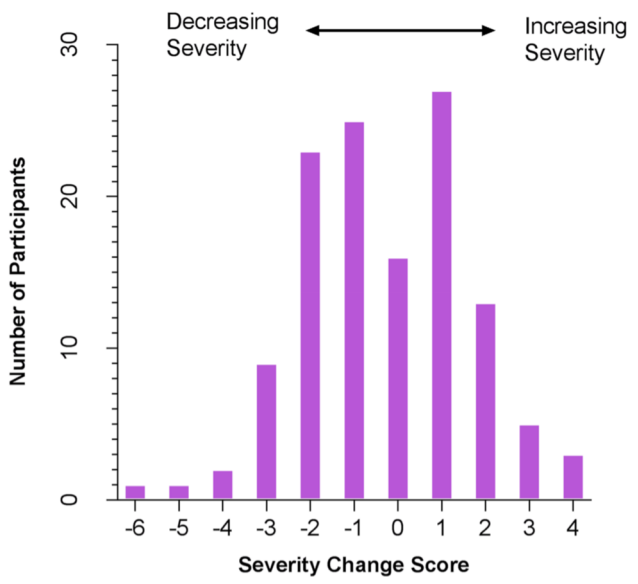

Fig. 1 Distribution of change scores in the sample. Decreases in autism severity from Time 1 to Time 3 are indicated as negative numbers whereas increases in autism severity are indicated as positive numbers

Results

Defining Three Groups based on Change in Severity

The RCI was computed for the entire sample (Brown et al. 2015), yielding a value of 2.12 (or 2.0 rounded to the nearest integer). Thus, by this measure, a change of 2 points or more can be considered to be a significant change over time. Based on these results, we created three groups of severity change: a Decreased Severity Group (DSG) comprised of participants who had a decrease in their ADOS CSS score of 2 or more points from Time 1 to Time 3; a Stable Severity Group (SSG) who had a change of severity score of 1 point or less; and an Increased Severity Group (ISG) comprised of participants with an increase in CSS of 2 or more points (see Table 2).

The largest group of children (54.4% of the sample) showed stable severity over time (stable severity group—SSG). The second largest group of participants (28.8% of the sample) decreased in severity over time (decreased severity group—DSG) and the smallest group (16.8% of the

Table 2 Demographic information and descriptive statistics for the three groups

		DSG	SSG	ISG
N (%)		36 (28.8%)	68 (54.4%)	21 (16.8%)
Sex	Boys (N = 89, 71.2%)	23 (25.8%[a])	48 (53.9%)	18 (20.2%)
	Girls (N = 36, 28.8%)	13 (36.1%)	20 (55.6%)	3 (8.3%)
Age (months)	Time 1: $\bar{x}$ (SD)	34.9 (5.4)	35.8 (5.9)	35.9 (5.0)
	Time 3: $\bar{x}$ (SD)	67.5 (10.1)	69.3 (12.0)	66.3 (8.8)
ADOS CSS	Time 1: $\bar{x}$ (SD):			
	All	7.82 (1.84)	7.35 (1.61)	6.19 (1.17)
	Boys	8.09 (2.00)	7.48 (1.52)	6.17 (1.25)
	Girls	7.38 (1.66)	7.10 (1.83)	6.33 (0.58)
	Time 3: $\bar{x}$ (SD):			
	All	5.27 (2.15)	7.4 (1.71)	8.71 (1.23)
	Boys	5.61 (1.95)	7.52 (1.74)	8.72 (1.27)
	Girls	4.69 (2.43)	7.10 (1.65)	8.67 (1.15)
Change score	$\bar{x}$ (SD)	− 2.55 (0.94)	0.03 (0.88)	2.52 (0.75)
Intervention history	Total hours:			
	Time 1: $\bar{x}$ (SD)	961 (909)	898 (854)	720 (535)
	Time 3: $\bar{x}$ (SD)	2851 (1610)	3415 (1910)	3213 (2026)
	Intensity:			
	Time 1: $\bar{x}$ (SD)	2430 (766)	2340 (748)	2284 (503)
	Time 3: $\bar{x}$ (SD)	3332 (1283)	4028 (1627)	3821 (2170)
IQ	Time 1: $\bar{x}$ (SD)	71.28 (22.95)	66.28 (21.86)	59.53 (12.92)
	Time 3: $\bar{x}$ (SD)	88.50 (30.19)	76.77 (31.76)	70.35 (30.03)
VABS-II	Composite score:			
	Time 1: $\bar{x}$ (SD)	76.97 (10.46)	76.79 (11.55)	76.05 (11.93)
	Time 3: $\bar{x}$ (SD)	81.29 (16.87)	75.36 (16.28)	70.93 (13.01)
	Motor skills:			
	Time 1: $\bar{x}$ (SD)	86.34 (14.21)	88.02 (13.73)	87.16 (13.33)
	Time 3: $\bar{x}$ (SD)	85.52 (13.77)	80.16 (16.20)	78.29 (9.50)
	Socialization:			
	Time 1: $\bar{x}$ (SD)	74.83 (9.86)	75.64 (12.87)	74.21 (11.81)
	Time 3: $\bar{x}$ (SD)	77.26 (20.78)	74.27 (17.95)	68.13 (15.65)
	Communication:			
	Time 1: $\bar{x}$ (SD)	76.80 (13.66)	74.67 (16.50)	73.63 (14.56)
	Time 3: $\bar{x}$ (SD)	86.80 (20.14)	79.76 (19.43)	74.53 (17.36)
	Daily living skills:			
	Time 1: $\bar{x}$ (SD)	81.71 (13.74)	79.08 (11.2)	80.63 (14.15)
	Time 3: $\bar{x}$ (SD)	84.74 (17.77)	76.62 (17.3)	74.2 (17.54)

[a]Percentages out of each sex

sample) increased in severity over time by 2 or more points (increased severity group—ISG) (Table 2). An ANOVA of change scores indicated that all groups were different from each other ($F(2,122) = 232.14$, $p < 0.001$, Eta squared 0.79, Tukey test—all comparisons $p < 0.001$).

To examine possible factors affecting differences between the groups, we considered three variables: participant's age, level of cooperation during the ADOS (based on clinician observations during the administration of the ADOS and measured through the three ADOS items concerning Other Abnormal Behaviors), and type of ADOS module administered. Age did not differ across the three groups (Table 2) at either Time 1 ($F(2,122) = 0.38$, $p = 0.69$) or Time 3 ($F(2,122) = 0.72$, $p = 0.49$). Child's level of cooperation during assessments did not differ across the three groups either: Overactivity/Agitation (Time 1: $F(2,118) = 0.99$, $p = 0.37$, Time 3: $F(2,87) = 0.74$, $p = 0.48$), Tantrums, Aggression, Negative or Disruptive Behavior (Time 1: $F(2,118) = 0.30$, $p = 0.74$, Time 3: $F(2,87) = 0.64$, $p = 0.53$) or Anxiety (Time 1: $F(2,117) = 0.16$, $p = 0.85$, Time 3: ($F(2,87) = 1.74$,

$p = 0.18$). Regarding the ADOS module, at Time 1 most participants were administered module 1 (DSG: N = 28, 77.8%; SSG: N = 55, 80.9%; ISG: N = 19, 90.5%), with fewer participants administered module 2 (DSG: N = 8, 22.2%; SSG: N = 13, 19.1%; ISG: N = 2, 9.5%) and none administered module 3. At Time 1, there were no significant differences in proportions of modules administered across the three severity change groups ($X^2(2) = 1.48$, $p = 0.48$). At Time 3, the DSG had a higher proportion of children tested with module 3 (N = 17, 47.2%) and almost equal proportions of module 1 (N = 10, 27.8%) and module 2 (N = 9, 25%). This indicates that the DSG did not decrease in severity because its participants were being tested with a less demanding module. The SSG had similar proportions of each module (module 1: N = 20, 29.4%; module 2: N = 23, 35.3%; module 3: N = 25, 36.8%) and the ISG showed a higher proportion of module 1 (N = 9, 42.9%), followed by module 2 (N = 7, 33.3%) and module 3 (N = 5, 23.8%). There was no difference between groups ($X^2(4) = 3.7$, $p = 0.45$) in modules administered at Time 3. Thus, neither participant's age, level of cooperation during the ADOS, nor type of ADOS module administered influenced the composition of the severity groups.

Initial Average Severity Levels for the Three Groups

Assignment of participants to groups was based on their change in autism severity over time, regardless of their initial severity scores. To better understand the patterns of severity at the two time points, severity means for the three groups were examined (Fig. 2). An ANOVA of initial severity scores at Time 1 showed significant differences between the groups (F(2,122) = 6.81, $p = 0.001$, Eta squared = 0.10). The ISG had a lower severity score compared to both the SSG ($p < 0.001$, Cohen's d = 0.77) and DSG ($p < 0.001$, Cohen's d = 0.99) who did not differ from each other ($p = 0.21$). The ISG's Time 1 severity level was also significantly lower than the sample's overall mean for initial severity ($p < 0.001$, Cohen's d = 0.68). The DSG and SSG, however, did not differ from the sample's general mean (DSG: $p = 0.14$, SSG: $p = 0.80$) for initial severity level. We also found that severity level at Time 1 was negatively related to the change score (r = -0.31, $p < 0.001$) i.e., a lower Time 1 severity score was associated with a more positive change score (greater increase in severity). Mean group severity levels were also different at Time 3 (F(2,122) = 28.19, $p < 0.001$, Eta squared = 0.40). At time 3, the ISG had the highest severity score compared to both of the other groups (ISG-SSG: $p = 0.01$, Cohen's d = 0.82; ISG-DSG: $p < 0.001$, Cohen's d = 1.84), the DSG had the lowest severity score (DSG-SSG: $p < 0.001$, Cohen's d = 1.13), and the SSG showed an intermediate severity level.

On average, the group of children who increased in severity from Time 1 to Time 3 had the lowest severity level at the first time point. In comparison, the groups of children who experienced either a decrease in severity or had stable severity levels had higher severity levels at Time 1 than the ISG. Both the DSG and SSG demonstrated similarly large ranges of initial severity scores ($p = 0.29$) and their group means were not different from each other ($p = 0.33$) (Fig. 3). While all groups were comprised of some participants with low initial severity levels, 71.4% of children in the ISG had a CSS of 6 or under at Time 1 compared to 27.8% in the DSG and 27.9% in the SSG.

Intervention History for the Three Groups

Intervention history differences (total number of intervention hours received and intensity of intervention based on duration and number of hours per week) were evaluated for the three groups (see Table 2). ANOVA of total number of intervention hours did not show a significant difference between

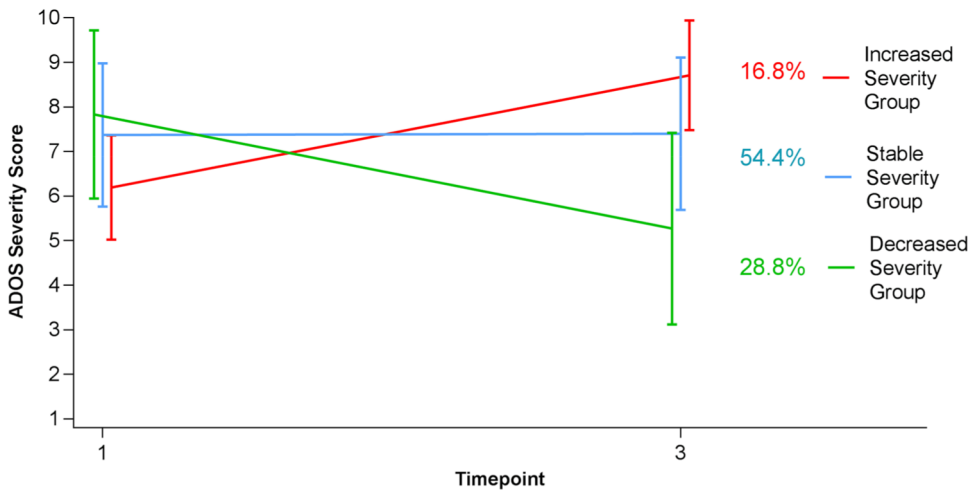

Fig. 2 Group severity trajectories based on group ADOS CSS means at Time 1 and Time 3

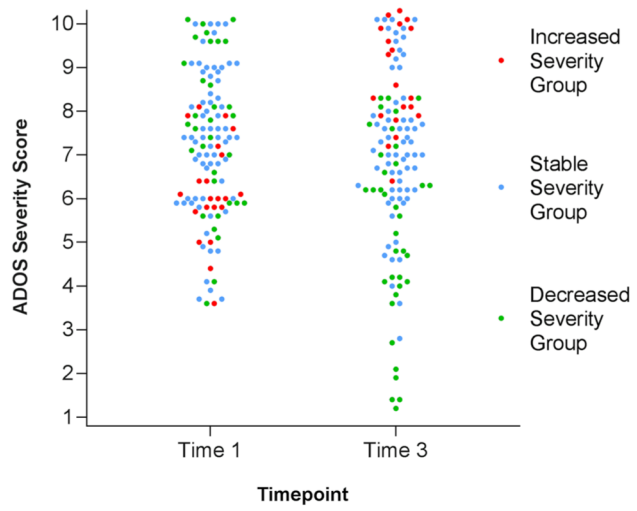

Fig. 3 Scatterplot of individual ADOS CSS of all children in the sample at Time 1 and Time 3, by group membership. The DSG and SSG show a large range of individual severity scores at both Time 1 and Time 3 while The ISG shows a narrower range. Note, scores at Time 1 are plotted with jitter so that all individuals can be seen; participants plotted slightly below 4 actually received an ADOS CSS of 4

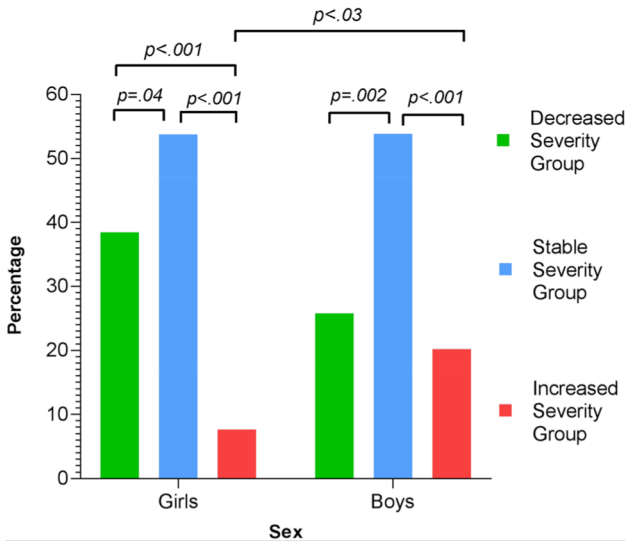

Fig. 4 Percentages of girls and boys in the three groups. There was no significant difference between the proportions of boys in the DSG (25.8%) and the ISG (20.2%). However, there was a significant difference between the proportions of girls in the DSG (36.1%) and the ISG (8.3%)

the groups at either Time 1 (F[2,114] = 1.04, $p = 0.57$) or Time 3 (F[2,114] = 0.56, $p = 0.36$). Similarly, ANOVA of intensity of intervention did not show significant group differences either at Time 1 (F[2,112] = 0.27, $p = 0.76$) or Time 3 (F[2,113] = 2, $p = 0.14$).

Sex Differences in Severity Change over Time

The mean severity level of girls at Time 1 was not significantly different from that of boys (t(65.82) = -0.69, $p = 0.49$). However, at Time 3, girls had, on average, significantly lower severity scores compared to boys (t(57.51) = -2.06, $p = 0.04$, Cohen's d = 0.43). This difference in the way each sex changed in severity from Time 1 to Time 3 was not related to IQ since there were no differences between the sexes in IQ at either Time 1 (t(59.12) = 1.03, $p = 0.31$) or Time 3 (t(63.09) = 0.70, $p = 0.49$).

The proportions of boys and girls across each of the three groups was different (boys -$X^2(2) = 17.42$, $p < 0.001$, and girls -$X^2(2) = 12.17$, $p = 0.002$) (Table 2; Fig. 4). The proportion of boys in the SSG (N = 48, 53.9%) was larger than in the other groups (SSG-DSG: $X^2(1) = 9.91$, $p = 0.002$; SSG-ISG: $X^2(1) = 15.33$, $p < 0.001$). The proportions of boys who either decreased or increased in severity were similar (DSG, N = 23, 25.8%; ISG, N = 18, 20.2%), ($X^2(1) = 0.68$, $p = 0.41$). The proportion of girls who demonstrated stable severity was similar to the boys and different from the other two groups (SSG: N = 20, 55.6%), (SSG-ISG: $X^2(1) = 34.95$, $p < 0.001$; SSG-DSG: $X^2(1) = 4.14$, $p = 0.04$). However, there was a different profile of girls who experienced change in severity compared to the boys. There was a higher proportion of the girls that decreased in severity (DSG) 36.1% (N = 13) than increased 8.3% (N = 3) (DSG-ISG: $X^2(1) = 17.37$, $p < 0.001$). The proportion of girls in the ISG was lower than the proportions of girls in both of the other groups, as well as the proportion of boys in the ISG ($X^2(1) = 4.94$, $p = 0.03$). In other words, the girls were over-represented in the DSG and under-represented in the ISG (Table 2; Fig. 4).

IQ for the Three Groups

Group differences in IQ were examined at Time 1 and Time 3 (Table 2; Fig. 5). The DSG showed significant IQ gains over time (t(65.33) = − 2.72, $p < 0.01$, Cohen's d = 0.64), as did the SSG (t(119) = − 2.24, $p = 0.03$, Cohen's d = 0.38). This was not the case for the ISG (t(27.16) = − 1.52, $p = 0.14$). ANOVA of IQ by group across time showed significant differences in IQ between the groups (F(2,246) = 4.36, $p = 0.01$, Eta squared = 0.04). The DSG demonstrated overall (Time 1 and Time 3 combined) higher IQ than the ISG ($p = 0.01$) and trend level compared to the SSG ($p = 0.09$); the ISG and SSG did not differ ($p = 0.35$). Analysis of time points separately showed that the DSG had a higher mean IQ than the ISG at both Time 1 (t(54.97) = − 2.47, $p = 0.02$, Cohen's d = 0.59) and Time 3 (t(42.16) = − 2.2, $p = 0.03$, Cohen's d = 0.60).

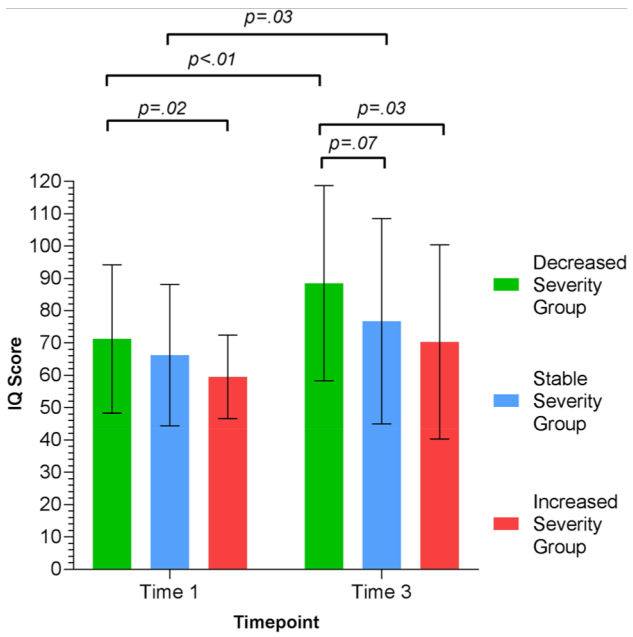

Fig. 5 Mean IQ scores at Time 1 and Time 3 for the three groups. The DSG and SSG made substantial IQ gains over time. The DSGs' mean IQ was higher than the ISG at both Time 1 and Time 3. The ISG remained stable in IQ over time

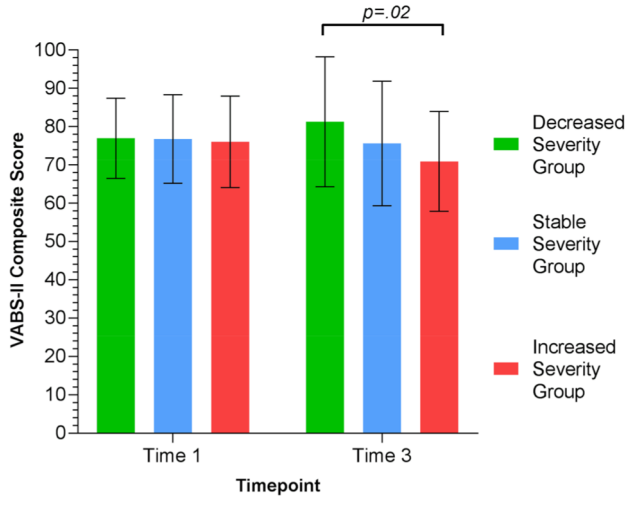

Fig. 6 Mean adaptive function (VABS-II composite score) at Time 1 and Time 3 for the three groups. There were no differences between the groups at Time 1. At Time 3, the DSG had a higher adaptive function score compared with the ISG

Adaptive Functioning for the Three Groups

Adaptive functioning differences were examined mainly using the VABS-II composite score as well as the domains scores (Table 2; Fig. 6). At Time 1, all groups had similar levels of adaptive functioning ($F[2,114] = 0.04$, $p = 0.96$). At time 3, the DSG had higher adaptive functioning than the ISG ($t(34.35) = -2.34$, $p = 0.02$, Cohen's $d = 0.65$). The SSG did not differ from the DSG ($t(67.9) = 1.68$, $p = 0.1$) or the ISG ($t(25.58) = -1.13$, $p = 0.27$). The DSG was the only group to make gains in Communication ($t(59.82) = -2.43$, $p = 0.02$, Cohen's $d = 0.58$); its mean score at Time 3 was higher than the ISG ($t(30.6) = 2.18$, $p = 0.04$, Cohen's $d = 0.63$). This group also showed higher Daily Living Skills at Time 3 compared to the SSG ($t(68.77) = 2.19$, $p = 0.03$, Cohen's $d = 0.47$) and trend level improvements compared to the ISG ($p = 0.06$, Cohen's $d = 0.60$). This was also the only group that did not experience a decrease in Motor Skills over time ($t(63.46) = 0.24$, $p = 0.81$).

Optimal Outcome

A total of seven participants, 5.6% of the sample, had an ADOS CSS below the ASD cutoff at Time 3, thus potentially demonstrating optimal outcome. Six of these children were in the DSG (four girls and two boys) and one boy was in the SSG. These children had a mean severity level of 5 at Time 1 (range 4–7) and 1.8 at Time 3 (range 1–3). Their mean severity change was − 3.1 (range − 1 to − 6). All showed an increase in IQ over time, with IQ rising from a mean of 85.8 (range 75–95.8) to a mean of 105.3 (range 91–115). Adaptive functioning change (using the VABS-II composite score) was less consistent, as two children showed decreases and four showed increases over time (one child did not have a score at Time 1). Mean Time 1 adaptive function was 79.3 (range 71–92) and mean Time 3 was 89.6 (range 71–122).

Discussion

The goal of the current study was to examine trajectories of autism symptom severity change in a rigorously diagnosed and recently ascertained cohort of autistic children between 3 and 6 years of age. Change scores were analyzed based on the Reliable Change Index and yielded three groups of different trajectories of autism symptom severity. A Decreased Severity Group (DSG) included children who decreased by 2 or more ADOS CSS points and comprised 28.8% of the total sample. This group was characterized by a large range of individual severity scores at Time 1, was over-represented with girls, had higher mean IQ at both time points and higher adaptive functioning at Time 3. The Stable Severity Group (SSG) included children with a change score of 1 point or less and comprised 54.4% of study participants. This group had an equal proportion of boys and girls, made IQ gains over time but remained stable in adaptive functioning. The Increased Severity Group (ISG) was comprised of participants who increased in severity by at least 2 points and accounted for 16.8% of the participants. Surprisingly, this group had the lowest mean severity score at Time 1 but the

highest at Time 3. Girls were under-represented in this group and it showed lower and stable IQ and adaptive function scores over time. There were no significant differences in intervention intensity between the three groups.

Comparison of Findings with Previous Studies

The amount and direction of change in autism severity described in previous studies has not been consistent. The current study demonstrates both similarities and differences with previous publications. In the earliest study using the ADOS CSS, Gotham et al. (2012) found that over 80% of participants demonstrated stable severity, with small groups decreasing or increasing over time. Their findings were largely corroborated by Venker et al. (2014). Szatmari et al. (2015) also reported mostly stable severity (89%) with a small group of participants which decreased in severity. Kim et al. (2016) reported 84% stability and a small group that increased in severity. These ealier studies were the basis for the general conclusion that the severity of a individual's autism does not change much following diagnosis. However, more recent studies have challenged this prevailing view. Kim et al. (2018) reported that only 23% of their participants remained stable over time and 52% either increased or decreased in severity. Pellicano et al. (2019), reported that 42% of their sample remained stable while 58% experienced a reliable increase or decrease in severity over time. Clark et al. (2017) also reported that, on average, children in their sample experienced significant change in symptom severity over time. Our own findings are consistent with a greater amount of change. While about half (54.4%) of the children in the Autism Phenome Project showed stability over time, 45.6% showed significant change. The potential for greater change of autism severity actually has a fairly long history from studies using a variety of measurement tools for symptoms (McGovern and Sigman 2005; Shattuck et al. 2007; Fountain et al. 2012; Gillespie-Lynch et al. 2012; Gulsrud et al. 2014; Barbaro and Dissanayake 2017; Hudry et al. 2018; Bal et al. 2019).

The direction of autism severity change has not been consistent in previous studies. Most previous studies reported some decrease in severity but the percentage of participants varied from 7–14% (Gotham et al. 2012; Venker et al. 2014; Szatmari et al. 2015) in earlier studies to 25–29% in more recent studies (Kim et al. 2018; Pellicano et al. 2019). Clark et al. (2017) indicate that, on average, children experienced a decrease in severity levels across early childhood. Consistent with these more recent studies, 28.8% of the participants in the current study decreased in severity. Significant decreases in autism symptom severity in young children has been demonstrated in several intervention studies either using a symptom-focused intervention (Pickles et al. 2016) or community-based interventions (Giserman-Kiss and Carter 2019).

Previous studies of severity have also identified individuals who increased in severity over time. Most previous studies indicate that 8–16% of their participants demonstrate a worsening trajectory (Gotham et al. 2012; Venker et al. 2014; Kim et al. 2016), while more recent studies report rates as high as 27–29% (Kim et al. 2018; Pellicano et al. 2019). The proportion of participants who increased in severity in the current study (16.8%) lies well within the range of those depicted in the past literature using the ADOS CSS.

Sex Differences in Symptom Severity Change

We found that autistic girls decrease in severity more than boys and increase in severity less than boys during early childhood. These findings are somewhat at odds with the common notion that girls with autism are generally more impaired than boys (Lord et al. 1982; Carter et al. 2007). Yet, our results are consistent with many recent studies that suggest that girls might actually demonstrate better developmental outcomes than boys in the areas of cognition (Lai et al. 2012) sociability (Head et al. 2014), and pragmatic communication skills (Conlon et al. 2019). Mahendiran et al. (2019) showed that young girls diagnosed with ASD tend to show better social adaptive function compared to boys and Mandy et al. (2018) demonstrated that during early childhood girls show lower autistic social traits compared to boys. Infant sibling studies (6–12 months) have demonstrated that at-risk females show enhanced attention to social stimuli compared to both high-risk males and low risk males and females (Chawarska et al. 2016). Consistent with our findings, Szatmari et al. (2015) also found that girls were more likely to have less severe and decreasing symptoms, while boys were more likely to have more severe and stable symptoms. In fact, in a recent review of sex differences in the behavioral presentation of autism, Lai and Szatmari (2019) concluded that young autistic girls were more likely to have better cognitive development, less intense autistic symptoms and reduction of symptoms over time.

What could be leading to this sex difference? One possibility, as suggested by Lai et al. (2018), is that the social and cultural environments children grow up in impact girls and boys differently and may, in turn, influence brain function over the life span. For example, there is an expectation that girls participate in more social interactions compared to boys (Kreiser and White 2014; Bargiela et al. 2016). Parents have been shown to use more emotional references (such as emotion words) when talking with very young girls compared to boys (Aznar and Tenenbaum 2015). These sex differences emphasize girls' socioemotional development from a young age (Chaplin and Aldao 2013) which might serve as

"naturalistic interventions", potentially supporting and leading to symptom severity decrease over time (Lai et al. 2018).

Another possibility relates to the increasingly accepted notion that girls and boys with autism might be characterized with different clinical presentations of symptoms (Frazier et al. 2014) which also develop differently across life (Mandy et al. 2018; Mahendiran et al. 2019). This presents a real challenge for current measurement instruments, as these sex-based behavioral differences might not be sufficiently captured by standard measures (Lai and Szatmari 2019). In a recent review, Lai and Szatmari (2019) characterized female autism to include female-gender-typical narrow interests, higher social attention, linguistic abilities, motivation for friendship and more camouflaging behaviors than autistic males. Camouflaging of autistic characteristics is a social compensatory behavior, or coping strategy, aimed at masking one's symptoms in social situations (Hull et al. 2017). In an observational setting such as the ADOS, engaging in camouflage could lead to less severe scores as atypical social-communication features are masked from the assessor (Livingston and Happe 2017; Lai et al. 2018; Ratto et al. 2018). Camouflage has been shown to be more prevalent in females diagnosed with ASD compared to males across different age ranges, including adult women (Lai et al. 2017; Schuck et al. 2019), 10-year-old (Ratto et al. 2018) and 7–8-year-old (Dean et al. 2017) girls. Thus, the fact that more of the girls in this study appear to have decreased in autism severity based on the ADOS may actually be due to an increasing number of girls compared to boys who, with age, have learned how to mask their symptoms. We will explore this possibility in future studies.

Is Initial Autism Severity a Predictor of Severity Change?

For most children who were participants in this study, their autism symptom severity level at age 3 was not a good predictor of the severity change they underwent during early childhood. We found that a large range of initial severity scores could lead to relative stability, decreasing severity or increasing severity. This is consistent with Pellicano et al. (2019) who found no association between initial severity level and the change an individual underwent across a 9 year period. Other studies have also failed to identify a relationship between early severity levels and future symptom change (Sutera et al. 2007; Bal et al. 2019). The children in the current study who remained stable or decreased in severity over time were characterized by large individual variation in severity levels at 3 years of age. Interestingly, the group of children who increased in severity showed significantly lower severity levels at age 3 and their severity scores were less variable than the other groups. Lower initial severity levels for groups that increase in severity over time were also observed in previous studies (Gotham et al. 2012; Venker et al. 2014; Kim et al. 2016, 2018).

Is Intervention History Associated with Differences in Severity Change?

The large majority of children in the Autism Phenome Project and GAIN study have received substantial amounts of intervention across childhood. Analysis of intervention history (total number of hours of intervention received and intensity of intervention) did not show significant differences between the groups. These results are consistent with Gotham et al (2012) and Giserman-Kiss and Carter (2019), who found no association between intervention characteristics and severity change. Thus, it is unlikely that differences in symptom severity change are determined by differences in intervention history. That is not to say that there might be subtle differences between the groups in intervention experiences. For example, the children in the ISG had both the lowest symptom severity level at Time 1 and the lowest number of intervention hours received by Time 1 compared to the other groups. By Time 3, as they increased in symptom severity, their mean number of intervention hours had increased and was no longer the lowest of the groups. At Time 3, it was the DSG that had the lowest mean number of intervention hours up to that point and their intervention intensity had decreased compared to Time 1 as well. Thus, for the DSG, as their symptom severity decreased so did the amount of intervention they received. A number of studies have shown that children with lower symptom severity levels receive less or less intensive intervention (White et al. 2007; Anderson et al. 2009; Wei et al. 2014; Kim et al. 2018). Our observations are consistent with this.

Is IQ Associated with Differences in Severity Change?

IQ demonstrated a significant, negative relationship with symptom severity change; as IQ scores increased from age 3 to age 6, symptom severity levels decreased. While both the DSG and SSG made IQ gains over time, the ISG did not. The DSG also had higher IQ compared to the ISG at both time points and compared to the SSG at Time 3. Findings that those with higher IQs were more likely to show a reduction in ASD symptoms is consistent with previous results in the APP cohort (Solomon et al. 2018). Gotham et al. (2012) also reported verbal IQ (VIQ) was a significant predictor of severity group membership. Children who decreased in symptoms were initially higher in VIQ, made the greatest gains and had the highest VIQ scores at age 6. IQ is considered to be the strongest predictor of outcomes for individuals with ASD (Volkmar 2002; Howlin et al. 2004). The current study's results support this, showing that children

who decreased in severity had higher IQs and made greater gains over time.

How is Adaptive Function Associated with Autism Severity Change?

Adaptive Functioning also demonstrated a significant, negative relationship with severity change. As symptom severity decreased from age 3 to age 6, adaptive functioning increased. While there were no differences between the groups in level of adaptive functioning at age 3, by age 6 the DSG had higher adaptive function scores compared to the ISG. The interdependence of autism symptom severity and adaptive functioning has been previously documented (Perry et al. 2009; Charman et al. 2011; Gotham et al. 2012), yet other studies (Szatmari et al. 2015; Kim et al. 2016; Pellicano et al. 2019) showed little overlap between symptom severity and adaptive functioning trajectories.

While previous studies have shown mixed results concerning the relationship between symptom severity change and adaptive functioning, we found that it was the DSG specifically who, in addition to declining in symptoms, demonstrated better adaptive skills in multiple domains compared to the other groups. This group increased in both the Communication and Daily Living Skills domains and was the only group not to have experienced a decline in Motor Skills domain. Both language development (Bavin et al. 2014) and non-verbal communication skills (Kjellmer et al. 2012; Lobban-Shymko et al. 2017), two areas within the communication domain, have previously been shown to associate with or predict autism symptom severity levels. Motor ability has also been demonstrated to be relevant to symptom severity; typical motor development at a young age is a predictor for optimal outcome (Helt et al. 2008), while delays in motor skills have been shown to be prevalent in the ASD population (Lloyd et al. 2013).

Optimal Outcome and Severity Change over Time

This study was initially motivated by the phenomenon of optimal outcome. Optimal outcome is traditionally defined as a decrease in autism symptoms in individuals previously diagnosed with ASD, so that they no longer meet diagnostic criteria (Fein et al. 2013). A total of seven participants, 5.6% of our sample, received an ADOS CSS below the ASD cut-off (1–3) at Time 3. Six of these children were in the DSG (four girls and two boys) and one boy was in the SSG. Since Optimal outcome is defined based on different aspects of function as well as autism symptom level (Fein et al. 2013), additional evaluations would have to be carried out concerning both the home and educational environments to confirm that these children have actually achieved optimal outcome.

Optimal outcome might also be interpreted more generally as indicating significant intra-individual change rather than the attainment of a specific cut-off score. This definition takes a wider approach to understanding the complex and variable ways in which children with autism grow and develop (Georgiades and Kasari 2018). If we apply this perspective to the current study's results, the notion of optimal outcome would be relevant to many more children in the DSG who, while not decreasing below the ASD cut-off score, experienced substantial personal decrease in autism severity over time.

Limitations

This study had some limiting factors. First, the sample size of 125 participants is modest compared to the size of the samples used in some of the previous reports. However, this sample incorporates participants with a wide range of severity, cognitive and function levels. Moreover, the clinical assessment and cognitive testing is rigorously carried out at one site and administered by experts in child development. Second, the current study is based on two early childhood time points. We hope to gather further longitudinal information in the future and to extend these findings in time. Third, the change in autism severity is based only on the calibrated severity score of the ADOS. It would be valuable to employ other objective measures of autism severity to confirm our findings and to explore potentially "artifactual" decreases in autism severity that may result from sex differences in symptom manifestation across time. Fourth, the current study raises several important issues which require further investigation, such as the relationships between IQ, initial severity level, and type and intensity of intervention received, in relation to symptom change over time.

Implications

Studies of autism severity change are of particular interest to parents and clinicians alike. There is good news in the current study that nearly 30% of young children have less severe autism symptoms at 6 than they did at 3; some even lose their diagnosis entirely. We do not currently know how to predict with certainty which children will follow this positive trajectory. Somewhat more disheartening is the finding that a sizable group of children will experience a worsening of autism symptoms following diagnosis. Again, it is not possible to predict who these children are so that they might receive added intervention. An emerging literature indicates that there are a variety of risk factors related to outcomes, and also points out the need to gain a better understanding of protective factors (Elsabbagh 2020).

Prospective studies focusing on at-risk populations for ASD (infant sibling studies) have shown that a regressive onset of symptoms might be the rule rather than the exception (Ozonoff and Iosif 2019). Most toddlers diagnosed with ASD seem to lose social-communication abilities that had already been acquired in infancy, prior to the development of autism symptoms. Thus, it is possible that the increased severity group is showing an extension of this regressive course into early childhood. Longitudinal studies of larger groups of participants that combine both intensive behavioral as well as biological assessments may ultimately define biomarkers that are better able to assign a child to one of the severity trajectory groups. This would be an important first step to promoting decreases and reducing increases in autism severity over time. Several intervention methods have demonstrated the ability to impact symptom severity levels, each utilizing a different therapeutic approach. These include the Early Start Denver Model (Dawson et al. 2012; Estes et al. 2015), Neurofeedback and Biofeedback (Goodman et al. 2018), parent-mediated social communication therapy (PACT) (Pickles et al. 2016; Torjesen 2016) and the Early Social Interaction (ESI) model (Wetherby et al. 2018). There is a growing emphasis on identifying specific predictors of symptom change in order to "match" interventions with child characteristics (Hudry et al. 2018). In this regard, it would be helpful to identify which type of approach would be most beneficial for the developmental profiles of children who either increase, decrease or remain stable in severity across early childhood.

Conclusions

This study is consistent with a growing literature that indicates that there is the potential for substantial change in autism symptom severity over time. Because the current study had a higher proportion of girls than previous studies, it became evident that girls tend to decrease more and increase less in autism severity than boys over time. The reason(s) for this sex difference need further exploration. The current study focused on overall autism severity and did not attempt to break down severity into its social communication and repetitive behavior components. We plan to explore this issue as well and to extend in time the trajectory of autism severity as the participants of the Autism Phenome Project enter middle childhood and adolescence. We appreciate that this work will be relevant for families, professionals and researchers as it establishes expectations for long term outcome once a diagnosis is obtained. "Tailoring" intervention according to a child's prognosis and needs could support future severity decreases and attempt to prevent severity increases, in order to maximize the potential of each child.

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Author Contributions EW-B involved in design, analysis, drafting manuscript, and figure preparation. EF and GSY involved in statistical consultation. BH contributed to data collection and database management. SR, CWN, and MS involved in study design and manuscript editing. DGA contributed to design, drafting manuscript, and manuscript editing.

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Compliance with Ethical Standards

Conflict of interest Dr. Amaral is on the Scientific Advisory Boards of Stemina Biomarkers Discovery, Inc. and Axial Therapeutics. Other authors declare they have no conflicts of interest.

Research Involving Human Participants and/or Animals The study was approved by the UC Davis Institutional Review Board and informed consent was obtained from the parent or guardian of each participant. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and / or national research committee (UC Davis Institutional Review Board number 220915) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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RESEARCH ARTICLE

3. Study 2:

Identifying autism symptom severity trajectories across childhood

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Abstract
An individual
prevalence and direction of change, however, are still not well understood. Nor are the characteristics of children that experience change. Symptom severity trajectories were evaluated from early to middle childhood (approximately ages 3 11) for 182 autistic children. Symptom severity change was evaluated using individual change scores and the Reliable Change Index. Fifty-one percent of participants experienced symptom severity change: 27% of children decreased in severity, 24% increased and 49% were stable. Symptom severity decreases were more common during early childhood. Severity increases occurred at both early and middle childhood but increase in social affect severity was especially prominent during middle childhood. Most children experienced significant change during only one period and remained stable during the other. Girls decreased more and increased less in symptom severity than boys. Children that increased in severity decreased in adaptive functioning across childhood. Exploratory analyses indicated that a decrease in severity was associated with higher parental education level and older parental age at the time of the child
autism severity was associated with lower parental education level and younger parental age at the child
symptom severity change is more likely than previously appreciated. An understanding of the role of both biological and sociodemographic factors in determining a child
and type of interventions distributed to young autistic children.

Lay Summary: We studied whether a child
diagnosis until middle childhood (ages 3
decreased in severity, 24% increased and the rest stayed the same. Symptom severity decreases were more common during early childhood while severity increases were more prominent during middle childhood. We also found that girls were more likely to decrease than boys. Whether a child decreased or increased is related, in part, to parental characteristics.

KEYWORDS
ADOS, autism spectrum disorder, calibrated severity scores, longitudinal, severity change, sex differences

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental condition currently affecting 1 out of every 44 children in the United States (Maenner et al., 2021). A diagnosis of ASD i dependen on altered socia affective (SA) behaviors and the occurrence of restricted and repetitive behaviors (RRB) (APA, 2013). ASD exhibits a range of severity that can be quantified using the Calibrated Severity Score (CSS) of the Autism Diagnostic Observation Schedule-2 (ADOS-2) (Gotham et al., 2009; Lord et al., 2000). Some studies suggest that symptom severity

generally remains stable over time (Gotham et al., 2012; Szatmari et al., 2015; Venker et al., 2014). Other studies, however, have found much greater potential for change across childhood (Clark et al. 2017 Georgiades et al., 2021) and into adolescence (Zachor & Ben-Itzchak, 2020). Some individuals experience such substantial decreases in their symptoms that they no longer meet the diagnostic criteria for autism (Fein et al., 2013). We previously evaluated symptom severity trajectories for a group of 125 autistic children between 3 and 6 years of age. Nearly half of the children showed significant decreases or increases in symptom severity (Waizbard-Bartov et al., 2021). The current study extended these observations into what we refer to as middle childhood (ages 6 until 11) to determine longer term prevalence and direction of severity change.

Several factors have been associated with an individuals

eth-

nicity, minority status and educational level, have also been linked to differences in symptom trajectories (Fountain et al., 2012). Finally, intervention history either has (Pickles et al., 2016) or has not been (Gotham et al., 2012; Venker et al., 2014; Waizbard-Bartov et al., 2021) associated with symptom severity changes.

In the current study, we evaluated autism symptom severity trajectories for the children of the MIND Institute

middle childhood, approximately age 6

following questions: (1) How common is symptom severity change across childhood? We predicted that groups of children would continue to demonstrate differences in severity change trajectory. (2) Does symptom severity change differ across periods of childhood? We suspected that there may be fewer decreases in severity in middle childhood due to increased social challenges. (3) What factors characterize children that decrease or increase in symptom severity? We examined factors such as IQ, adaptive functioning and sociodemographic variables such as parental age and education.

Previous studies have used several analytic approaches to evaluate change in symptom severity across time. These include: evaluating differences between mean severity levels across time points (Giserman-Kiss & Carter, 2020); identifying homogenous subgroups of individuals with different severity change trajectories using mixture methods (Gotham et al., 2012); or assessing, for each individual separately, change in severity in relation to their previous measurements (Pellicano et al., 2020; Shattuck et al., 2007). It is possible that these different analytic approaches may have contributed to the inconsistent conclusions found in the literature. We compared two analytic approaches for evaluating symptom severity change: the first examined the symptom severity trajectory for all children combined and the presence of subgroups using Latent Change Score (LCS) and mixture models; the second evaluated change in symptom severity within individuals across measurements using individual change scores and the Reliable Change Index.

METHODS

Participants

This study included 182 participants, 128 boys (70.3%) and 54 girls (29.7%), who were evaluated at up to three time points across childhood (Table 1). Participants enrolled in the University of California (UC) Davis MIND Institute Autism Phenome Project (APP) or Girls with Autism Imaging of Neurodevelopment Study (GAIN) between 2 and 3.5 years of age (Nordahl et al., 2021). The study protocols are identical and include a comprehensive assessment battery collecting medical, biological, neuropsychological and behavioral information. The present study includes behavioral data concerning autism symptom severity collected at Time 1 (T1-beginning of early childhood), Time 3 (T3-end of early childhood), and Time 4 (T4-middle childhood). Time 2 is not included since only magnetic resonance imaging data were collected. The study was approved by the UC Davis Institutional Review Board and informed consent was obtained from the parent or guardian of each child.

Inclusion criteria were based on the NIH Collaborative Programs of Excellence in Autism. Participants had received a community diagnosis of ASD that was confirmed by a licensed, research-reliable clinician at the MIND Institute using the Autism Diagnostic Observation Schedule-2 (ADOS-2) and the Autism Diagnostic Interview-Revised (ADI-R) (Lord et al., 1994, 2000). A diagnosis was confirmed if the participant met the ADOS-2 cut off score for either autism or ASD and exceeded the ADI-R cut off score for autism on either the Social or Communication subscales while being within two points of this criterion on the other subscale. Participants resided with at least one biological parent, were English speaking, and not diagnosed with severe motor, vision, hearing or chronic health issues that could impair participation.

One-hundred and eighty-two participants entered the study at T1. Due to attrition, T3 included 147 participants (46 girls) and T4 included 110 participants (23 girls) (Table 1). All children in the current study contributed data to at least two of the three time points. Comparison

TABLE 1 Sample characteristics

			Time		Time	Time 4
N		Al	18		14	110
		Girl	54, 29.7		46, 31.3%	23, 20.9%
		Boy	128, 70.3		101, 68.7%	87, 79.1%
Age (months		Al	37(6		68(10	138(11)
		Girl	38(6		67(9	137(10)
		Boy	37(6		68(11	138(12)
Time interval (months), including rang		Al		31(8), 24	68(15), 33	
		Girl		30(6), 25	67(18), 33	
		Boy		32(8), 24	68(14), 39	
Symptom severit	ADOS CS	Al	7.4(1.7		7.1(2.1	7.6(1.9)
		Girl	7.3(1.8		6.6(2.2	7.0(1.8)
		Boy	7.5(1.7		7.3(2.0	7.7(1.9)
	SA CS	Al	6.9(1.6		6.5(2.0	7.3(1.8)
		Girl	6.9(1.7		6.1(2.1	6.9(1.8)
		Boy	7.0(1.6		6.7(2.0	7.4(1.8)
	RRB CS	Al	8.3(1.6		8.3(1.7	8.2(1.8)
		Girl	8.1(1.6		8.0(1.9	8.0(1.2)
		Boy	8.3(1.6		8.4(1.6	8.2(1.9)
ADOS CSS chang	Early childhood T1-T	All				
		Girls				
		Boy		0.0(2.0)		
	Middle childhood T3-T	Al			0.23(2.0)	
		Girls				
		Boy			0.42(2.1)	
	Across childhood T1-T	All				
		Girls				
		Boy		0.0(2.5)		
ADOS-2 Module,	Mod	Al	15		4	30
		Girl	4		1	7
		Boy	11		3	23
	Mod	Al	2		4	11
		Girl	1		1	1
		Boy	1		3	10
	Mod	Al			5	69
		Girl			1	15
		Boy			3	54
I		Al	64(21		79(31	78(31)
		Girl	65(22		80(33	76(33)
		Boy	63(21		79(31	79(31)
Adaptive functionin	Adaptive composit	Al	75(11		77(16	70(18)
		Girl	71(10		76(17	66(18)
		Boy	76(11		77(16	71(18)
	Communicatio	Al	74(16		80(20	72(18)
		Girl	71(16		80(21	68(20)
		Boy	75(16		81(19	74(17)
	Daily living skill	Al	78(12		78(18	74(19)
		Girl	74(11		76(19	72(19)
		Boy	79(12		79(17	75(19)

(Continues)

TABLE 1 (Continued)

			Time	Time	Time 4
	Socializatio	Al	73(11	76(18	67(20)
		Girl	69(10	74(18	61(17)
		Boy	75(11	76(18	69(20)
	Moto	Al	87(13	82(14)	
		Girl	83(14	82(13)	
		Boy	88(13	82(14)	

Note: Mean (SD); ADOS, SA, and RRB severity are based on the entire sample at each time point. ADOS severity change scores for each period (T1 T4) are based on the children that had data available at both time points for that period.

of children who participated in all three time points with those with partial data indicated that there was a higher proportion of girls with partial data (35.8%) than with complete data (20.5%) ($p < 0.01$). This difference resulted from the fact that many of the girl participants had not yet reached T4 age when the current study was conducted. The only other difference in the children who did not participate in all three time points was that they had a lower mean adaptive functioning standard score at T1 (73) compared to children with complete data (77) ($p < 0.01$).

Measures

Common measures were collected for assessing children autism symptom severity, cognitive ability and adaptive functioning The Autism Diagnostic Observation Schedule-2 (ADOS-2) was used to evaluate autism symptoms over time (Lord et al., 2000). ADOS-2 is a standardized assessment tool for ASD diagnosis and is considered to be the gold standard for autism assessment. It evaluates the presence of autism symptoms across the two symptom domains: Social Affect (SA) symptoms and Restricted Repetitive Behaviors (RRB) The CSS (Gotham et al., 2009) is a standardized 10-point severity metric that provides a quantitative assessment of symptom severity (1 3 5 and 8 above meeting criteria for an ASD diagnosis. This standardized metric allows comparison of severity levels across individuals and within an individual across age and developing abilities. SA CSS and RRB CSS were evaluated separately (Hus et al., 2014). The ADOS-2 includes five modules, each adapted to individuals of a specific language development level, ranging from no speech to fluent speech. Participants in the current study had undergone ADOS-2 assessments using either Module 1 (Pre-Verbal/Single words), Module 2 (Phrase Speech), or Module 3 (Fluent Speech). As the choice of module depends on the child child is assessed with can change across time based on gains in verbal ability. Table 1 details module composition for the sample at each time point. Assessments were carried out at the UC Davis MIND institute and conducted by trained, licensed clinical psychologists, specialized in ASD and research reliable for this instrument. The MIND institute procedure of establishing research reliability on the ADOS-2 was based on the requirements of the developers of the ADOS-2 Reliability is established separately for Modules 1 with inter-rater reliability of at least 0.8 to be considered research-reliable. Once reliability has been achieved, administrators take part in regular clinical supervision sessions by a certified ADOS trainer. Random, double coding was employed using live assessments and video recordings, with a minimum of 0.8 inter-coder agreement for consensus. The specific ADOS-2 administrator at T1, T3, and T4 as well as the child were not related to symptom severity change ($p > 0.5$).

The term relates to the severity level determined by the ADOS CSS. The authors recognize that traditional medical model terms related to autistic traits, such as and have the potential of contributing to stigmatization and marginalization of autistic people. In this article, we looked at a particular set of traits as evaluated on the ADOS-2, and since our analyses are centered on the Severity Score generated from that measure, the use of these historical terms is unavoidable to maintain consistency with earlier articles evaluating change in autistic characteristics over time using the ADOS CSS.

Cognitive ability (IQ) was evaluated using either the Mullen Scales of Early Learning (MSEL) (Mullen, 1995) o the Differentia Abilitie Scales-I (DAS-II) (Elliot, 2007) based on the child Adaptive functioning was assessed using standard scores from the Vineland Adaptive Behavioral Scales (VABS II) (Sparrow et al., 2005). Demographic information and intervention history were collected from parents or caregivers. At the time of study entry, the child caregivers provided a summary of the child history including type and duration of treatments, whether intervention was individual or group based and

the ratio of class size to therapist. A questionnaire was adapted from the Collaborative Programs of Excellence in Autism. For a full description of these measures see Waizbard-Bartov et al. (2021).

Data analysis

Symptom severity change was analyzed using two analytic approaches. First, the ADOS severity trajectory was modeled for all children across early and middle childhood, using LCS models (McArdle, 2001) with Mplus software (Muthén & Muthén, 1998). Models were specified to allow the parameters that define the symptom trajectory to vary between childhood periods. Mixture models were used to identify latent classes or subgroups of the symptom severity trajectories (Muthén & Muthén, 2000). Various fit indices were compared across models to determine the most plausible solutions. Second, severity change was also evaluated for each individual child using change scores across early childhood (T1
duration of childhood (T1
available only at T1 and T4. The Reliable Change Index statistic (RCI) (Jacobson & Truax, 1991) was used for each period separately to determine a reliable change in symptom severity during *that* period. This was calculated using the following formula (example shows early childhood calculation):

$$RCI\ T1\ to\ T3_{Z\ SCORE}\ EARLY\ CHILDHOOD = \frac{\text{ADOS CSS Time 3}}{SD_{xy}^{2}}$$

Sex, IQ, and adaptive functioning were evaluated as potential covariates. Exploratory multivariate analyses evaluated possible associations between sociodemographic variables and children
tom severity change, while controlling for their joint effect. Sociodemographic variables included: parental age at child

sional degree; (6) graduate degrees: master
The child
able with six categories (Asian, African American/Black, American Indian/Alaska Native, Caucasian, Mixed, and Other) and as a binary variable (Caucasian vs. non-Caucasian). Intervention history was also evaluated and included the number of intervention hours received at the time of study entry and an intensity of intervention score which was calculated based on the following formula: (weeks of intervention hours per week number of adults/number of children present). Intervention history was collected for 163 participants; 19 participants were excluded due to missing data.

RESULTS

LCS ADOS CSS trajectory for all children combined and latent subgroups

The ADOS CSS trajectory for the entire sample was modeled using LCS. This analysis indicated an overall small decrease in severity during early childhood (T1
($p < 0.001$), followed by an overall small increase in severity during middle childhood (T3 $p < 0.001$) (Figure 1; Table S1). Model parameters indicated, however, that there was substantial variability in symptom severity change across individuals, i.e. large individual differences in change among children. For example, whereas the mean expected change in ADOS CSS during early childhood was
from
average LCS trajectory did not fully capture the heterogeneity of severity changes experienced by children in the sample.

Mixture models (Muthén & Muthén, 2000) were conducted to explore the variability in severity change and potentially identify subgroups of children with different severity trajectories. The model of best fit identified 2 subgroups; one small group of children (5%) that consistently decreased in symptom severity, and a second larger group (95%) that showed a very small, significant decrease in ADOS severity from T1 to T3 followed by a small significant increase in severity from T3 to T4 (Table S2 and Figure S1). These results suggested that the mixture models were not sensitive enough to parse

FIGURE 1 ADOS CSS latent change score trajectory for all children combined. A very small, significant decrease in symptom severity was evident during early childhood and a very small significant increase during middle childhood

out the very substantial variability evident in severity and detect meaningful subgroups of children with different symptom trajectories. This motivated us to analyze severity change using the RCI method as we had done in our previous publication (Waizbard-Bartov et al., 2021).

Reliable change analysis for individual children symptom severity change

Computation of reliable change in symptom severity

We evaluated individual subject change scores and reliability was determined using the RCI. Each child
vidual change scores were calculated across the periods for which data were available (Table S3). A child
ADOS CSS was subtracted from their T3 ADOS CSS, creating a change score for early childhood. Similarly, a child

only at T1 and T4, the child
T4 ADOS CSS, representing the child
childhood. Change scores were calculated for 145 children for the early childhood period (T1
the middle childhood period (T3
across the duration of childhood (T1
control for length of time between the two time points because the child
potential confounder for symptom severity change. To determine what constituted significant change in severity during each of the periods evaluated, the RCI was calculated for each period separately (Table S3). The RCI indicated that an increase or decrease of 2 or more points in ADOS CSS during each of the periods evaluated constituted significant change in symptom severity.

Assignment of children into the three longitudinal change groups

We used the RCI to parse children into three subgroups, based on their individual change tendencies. A Longitudinal Decreased Severity Group (L-DSG) was defined as experiencing a decrease in symptom severity at either early childhood (T1
across childhood (T1
severity during any of these periods. A Longitudinal Increased Severity Group (L-ISG) was defined as experiencing an increase in severity at either early childhood (T1
hood (T1
The Longitudina Stable Severity Group (L-SSG) included children who did not experience either an increase or decrease in severity across childhood. This could be achieved by either (1) having stable severity changes (ADOS CSS change score 1 / 0 /
childhood or (2) by experiencing contrasting change patterns during the two childhood periods (decrease and then increase or vice versa). The defining characteristics of the three change groups are illustrated in Figure 2.

Autism symptom trajectories for the three longitudinal change groups

The L-DSG (N 49) included 26.9% of children in the sample. They had, on average, the highest ADOS severity score compared to other groups at T1 (Table 2, Figure 3). On average, children in this group decreased in severity across early childhood ($t(38)$ $p < 0.001$, Cohen $t(15)$ $p < 0.01$, Cohen d: 0.9), and across the duration of childhood ($t(8)$ $p < 0.001$, Cohen
have the lowest group ADOS severity score at both T3 and T4 (Table S4). The L-SSG (N 89) included 48.9% of the participants who were characterized as having stable ADOS mean severity levels across childhood (T1 p 0.4, T1 p
L-ISG (N 44) included 24.2% of the participants. They had the lowest group ADOS mean severity score at T1. Children in this group increased in severity during early childhood ($t(33)$ $p < 0.001$, Cohen d: 0.9), middle childhood ($t(20)$ 4.5, $p < 0.001$, Cohen d: 1), and across childhood ($t(8)$ 10.6, $p < 0.001$, Cohen d: 3.5) to have the highest group ADOS mean severity at T4 (Figure 3).

Symptom domain trajectories for the three longitudinal change groups

The two symptom domains, SA CSS and RRB CSS, were evaluated independently within the three longitudinal change groups across time (Table 2, Figure 4). At T1, the L-DSG had the highest mean scores for both SA and RRB severity compared to the other groups (Table S4). This group decreased in both domains across early childhood (SA: ($t(38)$ $p < 0.001$, Cohen d: 1; RRB: ($t(39)$ $p < 0.001$, Cohen
mean SA and RRB severity compared to the L-ISG at T3. By T4, the L-DSG
were lower compared to its T1 levels (SA: ($t(44)$ 4.3, $p < 0.001$, Cohen d: 1.1; RRB: ($t(47)$ 2.9, $p < 0.01$, Cohen

$t(34)$ 4.2, $p < 0.001$, Cohen
and in SA severity during both early ($t(33)$ 2.6, p 0.01, Cohen t
(20) 7, $p < 0.001$, Cohen d: 1.5). The increase in SA severity experienced by the L-ISG was larger in middle childhood compared to in early childhood ($t(49)$
$p < 0.01$, Cohen d: 0.9). At T4, this group had higher

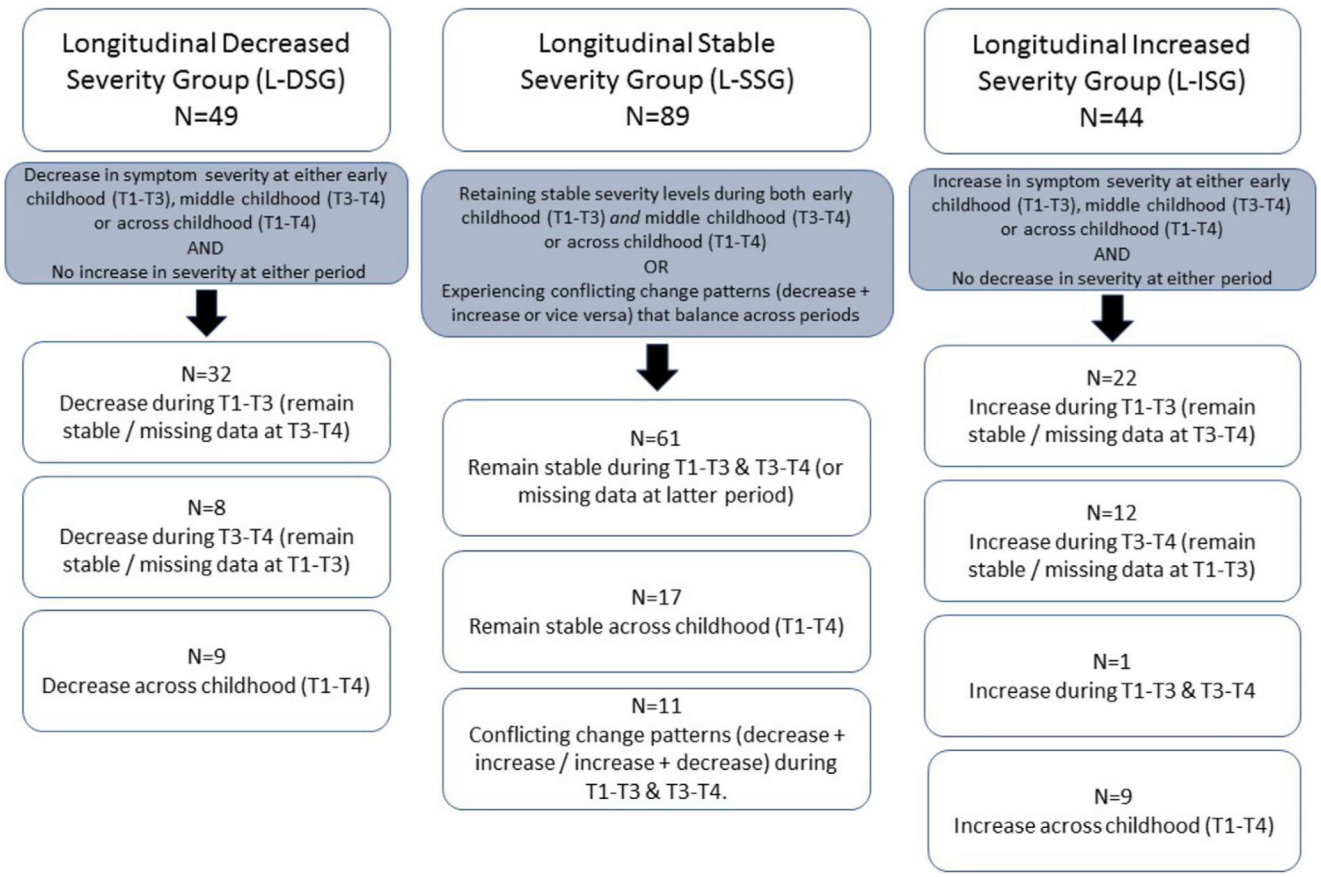

FIGURE 2 Group inclusion criteria (shaded boxes) for assignment of participants into three longitudinal change groups

mean RRB and SA severity than its T1 levels (RRB: (t (53) 2.2, p 0.04, Cohen d: 0.5; SA: (t(69) $p < 0.001$, Cohen
of all groups. Subtle differences were evident in domain severity change for the L-SSG during middle childhood (T3-T4). Children in this group decreased in RRB severity (t(37) < 0.01, Cohen d: 0.5) but the group mean SA severity trended towards increased severity (t (125) p 0.06, Cohen d: 0.3). While RRB severity did not differ between the groups at T4, SA severity significantly differed between all three groups (Figure 4).

Does symptom severity change differ across periods of childhood?

We next evaluated whether symptom severity change differed across early and middle childhood. As a whole, the L-DSG showed a larger decrease in ADOS severity during early compared to middle childhood (t (35) p 0.01, Cohen d: 0.7). The L-ISG showed similar increases in ADOS severity during both early and middle childhood (p 0.8). For children who had data available at all three time points and thus had two distinct change scores, change scores for early (T1 T3) and middle (T3
There were 73 participants with data at all three time points. Most (N 61) children experienced significant change in ADOS severity during one period and remained stable during the other (or remained stable during both periods (Figure 5). Twelve children experienced significant change in severity during both periods. Of these, one child increased in severity during both periods and belonged to the L-ISG. Eleven children experienced opposite changes in symptom severity during early and middle childhood; their changes
out across time leading to their inclusion in the L-SSG (Figure 5).

Sex differences in symptom severity change

Participants sex was associated with longitudinal change group membership (X^2(2) 7.3, p 0.03) (Figure S2). Girls that showed symptom severity change were more likely to decrease than to increase in severity (X^2(1) $p < 0.001$), while boys were equally likely to decrease or increase (p 0.5). Boys did not significantly differ in their tendency to increase or have stable severity levels (p 0.06), and they were more likely than girls to increase in severity across childhood (X^2(1) < 0.01).

TABLE 2 Characteristics of longitudinal severity change groups

			L-DS	L-SS	L-ISG
N,	182		49, 26.9	89, 48.9	44, 24.2%
Se	Girls (*N*, % of all girls		18, 33.3	30, 55.6	6, 11.1%
	Boys (*N*, % of all boys		31, 24.2	59, 46.1	38, 29.7%
Symptom severit	ADOS CS	T	8.5(1.6	7.3(1.7	6.4(1.3)
		T	6.2(2.4	7.2(1.9	7.8(1.5)
		T	6.1(1.8	7.5(1.8	9.1(1.2)
	SA CS	T	7.7(1.5	6.8(1.6	6.3(1.3)
		T	5.9(2.2	6.6(2.0	7.1(1.7)
		T	6.0(1.7	7.3(1.6	8.6(1.1)
	RRB CS	T	8.8(1.2	8.3(1.7	7.7(1.6)
		T	7.7(2.2	8.4(1.5	8.8(1.0)
		T	7.9(1.3	8.0(1.8	8.6(2.0)
Symptom severity chang	ADOS CS	T1		0.0(1.3	1.5(1.7)
		T3			1.7(1.7)
		T1		0.0(0.8	2.6(0.7)
	SA CS	T1		0.0(1.7	0.9(1.9)
		T3		0.4(2.0	2.4(1.6)
		T1		0.1(1.3	1.9(0.9)
	RRB CS	T1		0.3(1.9	1.3(1.8)
		T3			
		T1			1.0(1.3)
ADOS-2 Modul	T	Mod	3	7	38
		Mod	1	1	6
		Mod			0
	T	Mod	1	2	12
		Mod 2	12	21	10
		Mod 3	14	28	13
	T	Mod	1	1	7
		Mod			5
		Mod 3	13	38	18
I		T	65(25	63(21	62(19)
		T	79(33	80(32	77(29)
		T	76(32	82(32	74(30)
Adaptive functionin	Adaptive composit	T	75(11	74(11	76(11)
		T	80(17	76(15	76(16)
		T	72(20	71(19	66(16)
	Communicatio	T	75(17	73(14	75(16)
		T	83(22	79(19	80(18)
		T	74(21	74(18	69(16)
	Daily living skill	T	80(14	75(11	80(11)
		T	82(19	75(17	78(17)
		T	76(19	75(20	71(18)
	Socializatio	T	73(9	73(12	74(11)
		T	78(17	74(18	77(18)
		T	68(21	69(20	62(18)
	Motor developmen	T	86(13	87(14	86(12)
		T	83(14	83(13	79(16)

Note: Mean (SD); Group ADOS, SA, and RRB severity are based on the entire group at each time point. ADOS, SA and RRB severity change scores for each period (T1

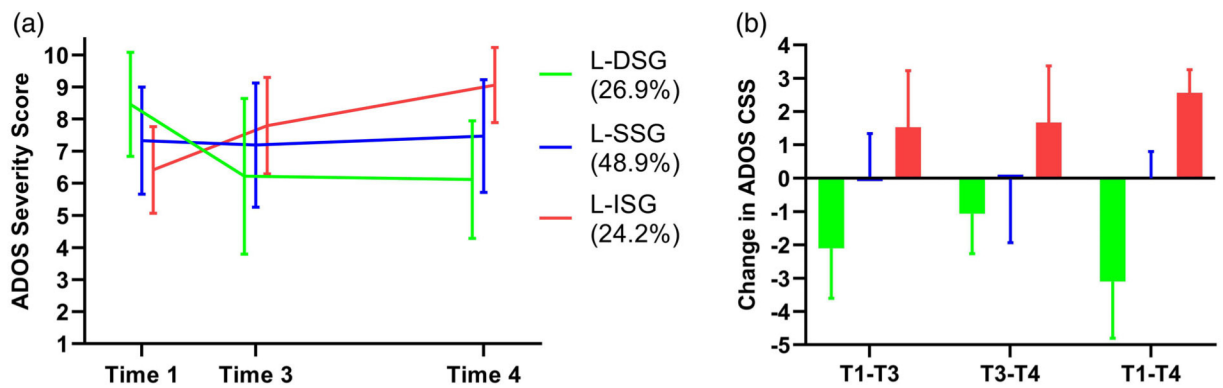

FIGURE 3 (a) Mean ADOS CSS trajectories (with SD) for the three longitudinal change groups across childhood. The L-DSG had the highest mean ADOS severity at T1 but decreased across childhood to have the lowest severity at T3 and T4. The L-SSG retained stable severity levels across childhood. The L-ISG had the lowest mean severity at T1 but increased in severity across childhood to have the highest mean severity level by T4. (b) Longitudinal change groups
and less during middle childhood. The L-SSG did not change in severity and the L-ISG increased in severity during early and middle childhood

FIGURE 4 The three longitudinal change groups
RRB and SA mean severity levels at T1 but decreased in both domains across childhood. At T4 this group had lower severity levels compared to its T1 levels in both domains and the lowest SA severity of all three groups. The L-ISG increased in RRB severity during early childhood and in SA severity during early and middle childhood, to have the highest group mean SA severity at T4. The L-SSG showed a tendency to decrease in RRB severity and increase in SA severity during middle childhood. Group differences in RRB severity grew smaller across childhood while differences in SA severity grew larger

The relation of IQ to symptom severity change

The three longitudinal change groups did not differ in IQ at any time point ($p > 0.05$). All three groups made IQ gains across early childhood (L-DSG: t(66) p 0.03; L-SSG: t(107) $p < 0.001$; L-ISG: t (54) $p < 0.001$) and remained stable across middle childhood (L-DSG: p 0.7, L-SSG: p 0.7, L-ISG: p

Children that increase in symptom severity decrease in adaptive functioning

While the L-DSG and the L-SSG experienced minimal changes in standard scores of adaptive functioning (L-DSG: T1 p 0.1, T3 p 0.1 T1 p 0.5; L-SSG: T1 p 0.4, T3 p 0.2, T1 T4: p 0.3), the L-ISG decreased in adaptive function over the period under study. It is important to note that standard score decreases over time do not represent a loss of specific skills, but rather a slowing of the trajectory of gains compared to a normative group. During early childhood, the L-ISG trended to decrease in motor ability standard scores (t(36) 1.7, p 0.09, Cohen d: 0.5) whereas during middle childhood the L-ISG decreased in socialization standard scores (t (50) 3, $p < 0.01$, Cohen d: 0.8), communication standard scores (t(50) 2.4, p 0.02, Cohen d: 0.7) and in the composite standard score (t(49) 2.2, p 0.03, Cohen d: 0.6). Across childhood, these children decreased in daily living skills (t(41) 2.5, p 0.02, Cohen d: 0.7), socialization (t(41) 3.2, $p < 0.01$, Cohen d: 0.9) and in the composite standard score (t(49) 2.8, $p < 0.01$ Cohen d 0.7) (Figure S4).

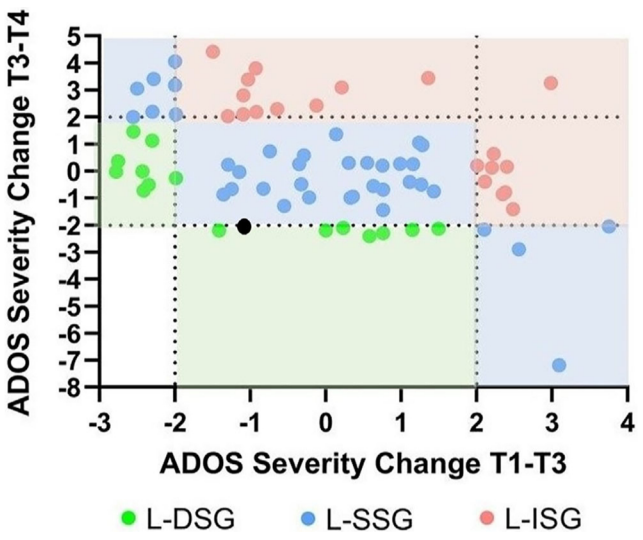

FIGURE 5 Scatterplot of individual ADOS severity change scores during early (T1
membership, for individual children with data available at all 3 time points (*N*

stable severity presentation across childhood (upper-left and lower-right, blue-shaded areas). Note: Dotted lines represent threshold for significant change. To increase visibility individual subjects appear with jitter

Sociodemographic characteristics, intervention history and symptom severity change: an exploratory analysis

In order to examine the joint effect of sociodemographic and intervention variables relating to symptom severity change we conducted an exploratory multivariate analysis of several predictors (i.e. paternal education, maternal education, paternal age at the child
maternal age at the child
intervention received by T1, intensity of intervention received by T1). A MANOVA suggested a potential relationship between parental characteristics and membership in one of the three longitudinal change groups (Table 3). Paternal educational level ($F(2)$ p 0.02) and paternal age at child $F(2)$ 3.3, p 0.04) were both significantly associated with longitudinal change group membership; maternal educational level approached significance ($F(2)$ 2.7, p 0.07). Follow-up analysis confirmed that the three longitudinal change groups differed in paternal educational level ($F(2)$ 3.4, p 0.03), paternal age at child $F(2)$ 4.1, p 0.02) and maternal educational level ($F(2)$ 3.4, p 0.04). Mothers and fathers of children in the L-ISG had lower mean educational levels compared to the mothers and fathers of children in the L-DSG. Mothers from the L-ISG also had a lower mean educational level compared to mothers from the L-SSG (Table S4, Figures S5 and S6). For the L-ISG, mean paternal and maternal ages were lower at the birth of their child (i.e., parents were younger) compared to parents of children in the L-SSG, and close to significantly lower than parents of children in the L-DSG (Table S4). As expected, parental education levels and parental age at the child
associated with younger parental age at the child
(r
The child $F(2)$ 1.7, p 0.2), number of intervention hours received ($F(2)$ 0.7, p 0.5) and the intensity of intervention received by study entry (F (2) 0.62, p 0.5) were not associated with group membership once parental age and educational level were controlled.

A group of children who ultimately did not meet criteria for an autism diagnosis

Ten children (5.5% of the participants at Time 1), 5 girls and 5 boys, decreased in ADOS severity to such an extent that by their final individual measurements at either T3 or T4, they had an ADOS CSS < 4 and thus did not meet the ADOS-2 criteria for an ASD diagnosis. Seven of these children belonged to the L-DSG and three to the L-SSG. Six children decreased in severity during early childhood (T1
during middle childhood (T3 and one child decreased in severity across childhood (T1
children decreased in total ADOS CSS severity across childhood (T1: 5.7, T3: 3.3, T4: 2.4; $t(12)$ 4.3, $p < 0.01$, Cohen d: 2), as well as in SA CSS severity (T1: 5.8, T3: 3.7, T4: 2.8; $t(12)$ $p < 0.01$, Cohen d: 1.7) and RRB CSS severity (T1: 7.3, T3: 5.3, T4: 5.8; $t(9)$ 2.5, p 0.04 Cohen d 1.3) The

TABLE 3 Parental characteristics

		Al	L-DS	L-SS	L-ISG
Parental education[a]: mean (SD	Maternal education (1	4.1(1.4	4.3(1.4	4.2(1.4	3.6(1.5)
	Paternal education (1	3.8(1.6	4.3(1.5	3.8(1.6	3.4(1.5)
Parental age at child	Maternal ag	32.0(5.3	32.6(5.5	32.3(5.3	30.5(4.6)
	Paternal ag	34.9(6.3	34.8(6.1	36(6.4	32.5(5.6)

[a]Education levels: 1: did not complete high school; 2: high school graduate/GED/with less than 1 year college credit; 3: technical college/vocational school; 4: associate degree; 5: bachelor/professional degree; 6: graduate degree.

proportion of girls within this group was higher than the proportion of girls in the rest of the sample (X^2(1) 5.2, p 0.02). Fathers of children in this group had a higher mean educational level compared to fathers of the rest of the children (t(12) 2.5, p 0.03, Cohen d: 0.6) and mothers trended to be older at the time of the child t(10) 2.1, p 0.06, Cohen d: 0.6) and more educated (t(10) 2.1, p 0.06, Cohen d: 0.6).

DISCUSSION

Summary of findings

The overarching goal of this study was to extend our observations of trajectories of autism severity change from early childhood (Waizbard-Bartov et al., 2021) into middle childhood based on analyses of children in the MIND Institute Autism Phenome Project We established the presence of groups of children that were characterized by long term changes in the severity of their autism based on ADOS scores. Twenty-seven percent decreased in severity between approximately 3 and 11 years, 24% increased and 49% had stable severity across childhood. Change in autism symptom severity was not linear and often differed between early versus later childhood. Symptom severity decrease was more commonly observed during early childhood. Severity increases occurred during both early and middle childhood, but SA severity specifically tended to increase during middle childhood. Most children experienced significant change in severity (either increase or decrease) during one period and remained stable during the other. Girls demonstrated a stronger tendency to decrease and a weaker tendency to increase in autism symptom severity compared to boys. While adaptive functioning standard scores were not different in the groups with decreased or stable severity, children that increased in autism severity decreased in adaptive functioning across childhood. On average, children in the study made IQ gains during early childhood and then plateaued during middle childhood. Exploratory analyses showed that children that increased in severity had parents that were younger and less educated compared to children that decreased or remained stable in severity.

Comparison of current and previous findings

Previously (Waizbard-Bartov et al., 2021) we evaluated changes in autism symptom severity between 3 and 6 years of age using ADOS CSS. In both the current and the previous study, we identified three distinct groups of children with different severity change patterns during childhood; decreased, increased and stable severity. Sex differences were also evident across studies, with girls consistently decreasing in severity across childhood and to a larger extent than boys. In both studies, decreased adaptive functioning was associated with increase in autism symptom severity. Finally, in neither study did we find that intervention history was a significant predictor of severity change in the context of other predictors. The relation between IQ and symptom severity change, however, differed between the studies. We previously found that children that decreased in severity during early childhood had higher mean IQ at ages 3 and 6 than those that increased in severity. In the current analysis, there was no clear relationship between IQ and symptom severity change across childhood. All three longitudinal groups made significant IQ gains between 3 and 6 years of age. Thereafter, IQ remained relatively stable into middle childhood for all groups. It is possible that the association between IQ and symptom severity change is stronger during early childhood compared to middle childhood. If so, it could explain why IQ predicted symptom severity change in groups based solely on severity change during early childhood but not in groups based on change across childhood.

Comparison of current findings with previous studies

Just over half of the children in the current study experienced significant symptom severity change across early to middle childhood. But, severity change for individual children was highly variable. Our findings are consistent with previous work showing variable severity change patterns across the toddler years (Kim et al., 2018), childhood (Fecteau et al. 2003) adolescence (Shattuck et al., 2007) and even adulthood (Pellicano et al., 2020). However, symptom severity change was more common in the current sample (51% of children) compared to

several previous publications using the ADOS CSS. Evaluation of younger children (2 to 3 years-of-age) over a shorter duration resulted in rates of severity change of 16% (Kim et al., 2016). For children 2
Szatmar et al (2015) observed 11% and Venker et al. (2014) observed 22% change and change from early childhood into adolescence was reported to be 16% by Gotham et al. (2012). We found that change from early to middle childhood was not necessarily linear. Some children demonstrated significant change in either early or middle childhood but not both. This is consistent with publications that studied severity change between early and middle childhood (Clark et al., 2017; Georgiades et al., 2021) and between adolescence and adulthood (Taylor & Seltzer, 2010).

The current study employed two analytic approaches for evaluating change: LCS and mixture models as well as the RCI. It appeared that mixture models were not effective in identifying meaningful subgroups of children with different symptom change trajectories. It is possible that our sample did not have sufficient sampling density for such groups to be identified. This prompted us to use the RCI method, similar to the strategy employed in our previous publication (Waizbard-Bartov et al., 2021). This analytic strategy proved to be more sensitive in identifying meaningful severity change subgroups. The fact that the RCI method identified a higher proportion of individuals that experienced change compared to the mixture models is consistent with much of the literature in the area. While studies using mixture models have typically identified smaller groups of individuals showing change in symptom severity (Gotham et al., 2012; Szatmari et al., 2015; Venker et al., 2014; Visser et al., 2017), studies analyzing individual change across time have identified larger subgroups that experience change (Pellicano et al., 2020; Shattuck et al., 2007).

In the current study, children that decreased in symptom severity did so from a wide range of initial severity levels at around age 3. The ability to decrease in the severity of symptoms from both high and moderate levels has been previously demonstrated (Visser et al., 2017) and is also consistent with studies showing no association between severity level at age 2 and future change in severity (Bal et al., 2019; Sutera et al., 2007). Collectively, these findings suggest that a child
level is not a particularly valuable predictor of future autism severity.

Children that decreased in severity below the ADOS-2 cut-off score for autism

Ten children decreased from a moderate severity level on average to a low/minimal level on the ADOS-2, and were no longer in the CSS range for a diagnosis of autism. This is similar to what is described by Fein et al. (2013) as optimal outcome and by Anderson et al. (2014) as very positive outcome. This group included a higher proportion of girls than in the entire sample and their parents tended to be more highly educated than other children in the sample.

Why does autism symptom severity decrease in early childhood and increase in middle childhood?

We found that decreases in autism symptom severity occurred mostly during early childhood and resulted from a decrease in both SA and RRB severity. Increases in symptom severity, in contrast, occurred during both early and middle childhood. Previous studies have shown that if a child is going to decrease in symptom severity, it is likely going to happen in early childhood (Clark e al. 2017 Fountain et al. 2012 Georgiades et al., 2021). Later in childhood and during the early school years, the tendency for improvement is either reduced (Fountain et al., 2012), plateaus (Georgiades et al., 2021) or shifts to an increase in severity (Clark et al., 2017). The transition to school, which takes place at around age 6, presents children with new and complex challenges such as increasing social demands, needing to communicate and establish beneficial relationships with teachers and peers, and adjusting to an unknown environment and schedule (Bolourian et al., 2019; Nuske et al., 2019). Georgiades et al. (2021) suggested that this major transition creates a at around age 6 for many autistic children that can exacerbate their symptoms or halt improvement. Our results support this perspective, emphasizing the importance of identifying potential developmental for symptom severity increases.

Sex difference in symptom severity trajectories across childhood

We previously found that girls decrease in symptom severity more and increase less than boys during early childhood (Waizbard-Bartov et al., 2021). The current study extends these results, showing that girls tendency to decrease in symptom severity continues across childhood. These findings are consistent with the idea that a reduction in symptoms over time is a characteristic of the female autism phenotype (Lai & Szatmari, 2020). Why do girls seemingly improve in symptom severity across childhood more than boys? Our data do not directly address this issue. However, it may be that autistic girls are better able to take advantage of interventions designed to increase social skills. They may also have more positive socioemotional interactions with parents than autistic boys, similar to neurotypical girls (Aznar & Tenenbaum, 2015). Conversely, it is possible that rather than truly decreasing in symptom severity, girls are better

than boys at masking (or camouflaging) their symptoms with age (Dean et al., 2017; Ratto et al., 2018). Camouflaging is a coping strategy meant to mask one autism symptoms in social situations (Hull et al., 2017) and is more prevalent among autistic females than males (Lai & Szatmari, 2020). This is a topic we hope to explore in future research.

Sociodemographic features potentially influence symptom severity change

An exploratory evaluation of sociodemographic features suggested that children who increased in severity were more likely to have younger, less educated parents than other children in the study. These results are consistent with Fountain et al. (2012) who found that children with less-educated mothers were less likely to experience rapid improvements in symptoms, while children with well-educated mothers were more likely to be high-functioning Differences in sociodemographic factors can potentially affect availability of resources and support afforded to the children and their families, quality and intensity of intervention and the efficacy with which parents advocate for their children (Fountain et al., 2012). These can, in turn, affect other developmental outcomes such as symptom severity in a cascading way. These suggestions require validation in larger longitudinal studies where intervention quality and intensity are reliably evaluated.

Limitations

The current study has several limitations. First, the sample of 182 children was not sufficiently large to carry out a more fine-grained investigation of the variability in change across time. Both the L-DSG and L-ISG included children that changed in symptom severity during either early or middle childhood, as there were not enough individuals in each group to compare those who changed in severity during early versus middle childhood. The mixture models may not have detected meaningful subgroups in the sample because our data did not have sufficient sampling density. The L-SSG was heterogenous; all children showed stable symptom severity levels across the duration of childhood, but while most children did not change during either early or middle childhood, two small groups did change in each period, in opposite directions. There are likely to be substantial differences in the profile of these children compared to the rest of the group, but the numbers of children in these subgroups were too low to rigorously evaluate them separately. Second, the sample used in the current study is a convenience sample collected at a center associated with a large university campus and thus somewhat biased towards a more educated population. A more diverse sample would be needed to comprehensively investigate the preliminary results we obtained for the relationships between sociodemographic features and severity change patterns. Third, assessment of IQ was conducted using the MSEL at T1 and the DAS-II at T3 and T4 (for the majority of children). These measures were chosen based on their suitability to assess cognitive ability in children with ASD of a certain age. However, it is also possible that the usage of two different measures in the collection of IQ scores across childhood might have contributed to scores being artifactually higher or lower at different time periods. As the current study did not report a relationship between IQ and symptom severity change, this is not a critical limitation. Last, due to attrition associated with longitudinal studies such as the Autism Phenome Project, the number of participants decreased across time points. While girls made up almost 30% of the sample at T1, they comprised 21% of participants at T4. Since girls tend to decrease in symptom severity more than boys, and they made up a smaller proportion of the sample at older time points, it may be that the lower decreases of severity in middle childhood may be partially accounted for due to this difference. Thus, our findings on sex difference will need to be replicated with longitudinal studies that have closer parity of the sexes.

Conclusions

More than half of the children in the current study experienced significant change in autism symptom severity across childhood. Severity change, however, was different across early and middle phases of childhood. A substantial group of children increased in symptom severity, many of them due to a worsening in their social-communication symptoms during middle childhood. While several factors including sex, adaptive functioning, and parental characteristics were associated with children

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CONFLICT OF INTEREST

Dr. Amaral is on the Scientific Advisory Boards of Stemina Biomarkers Discovery, Inc. and Axial Therapeutics. Other authors declare no potential conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher

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4. Study 3:

Original Article

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Changes in the severity of autism symptom domains are related to mental health challenges during middle childhood

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Abstract

Many autistic children experience changes in core symptom severity across middle childhood, when co-occurring mental health conditions emerge. We evaluated this relationship in 75 autistic children from 6 to 11 years old. Autism symptom severity change was evaluated for total autism symptoms using the autism diagnostic observation schedule calibrated severity score, as well as social-communication symptoms calibrated severity score, and restricted/repetitive behaviors calibrated severity score. Children were grouped based on their symptom severity change patterns. Mental health symptoms (attention-deficit hyperactivity disorder, anxiety, disruptive behavior problems) were assessed via parental interview and questionnaire and compared across the groups. Co-occurring mental health symptoms were more strongly associated with change in social-communication symptom or restricted/repetitive behavior severity than with total autism symptom severity. Two relevant groups were identified. The social-communication symptom-increasing-severity-group (21.3%) had elevated and increasing levels of anxiety, attention-deficit hyperactivity disorder, and disruptive behavior problems compared with children with stable social-communication symptom severity. The restricted/repetitive behavior-decreasing-severity-group (22.7%) had elevated and increasing levels of anxiety; 94% of these children met criteria for an anxiety disorder. Autism symptom severity change during middle childhood is associated with co-occurring mental health symptoms. Children that increase in social-communication symptom severity are also likely to demonstrate greater psychopathology, while decreases in restricted/repetitive behavior severity are associated with higher levels of anxiety.

Lay abstract

For many autistic children, the severity of their autism symptoms changes during middle childhood. We studied whether these changes are associated with the emergence of other mental health challenges such as anxiety and attention-deficit hyperactivity disorder. Children who had increased social-communication challenges had more anxiety and attention-deficit hyperactivity disorder symptoms and disruptive behavior problems than other children. Children who decreased their restricted and repetitive behaviors, on the contrary, had more anxiety. We discuss why these changes in autism symptoms may lead to increases in other mental health concerns.

Keywords

anxiety, attention-deficit hyperactivity disorder, autism spectrum disorders, behavioral measurement, development, psychiatric comorbidity, repetitive behaviors and interests, school-age children, social cognition and social behavior

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by the presence of two core symptom domains: social-communication symptoms (SA) and restricted/repetitive behaviors (RRB) (American Psychiatric Association, 2013). Autism may also be associated with

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several additional mental health conditions; 70% of autistic individuals have at least one co-occurring condition and 41% have two or more (Simonoff et al., 2008), making mental health challenges a common part of autistic life (Waizbard-Bartov et al., 2023). The most common co-occurring mental health conditions experienced by autistic individuals are attention-deficit hyperactivity disorder (ADHD), anxiety disorders and disruptive, impulse-control, and conduct disorders (Lai et al., 2019; Mutluer et al., 2022).

Many mental health challenges develop during middle childhood, starting around age 6–7 years (Kessler et al., 2007). For neurotypical children, ADHD tends to emerge between ages 6 and 8 years and anxiety disorders between ages 8 and 13 years (Solmi et al., 2022; Visser et al., 2014). For autistic children, anxiety has been identified starting from the preschool years and across the duration of childhood (Vasa et al., 2020) while emotional difficulties (e.g. often feeling unhappy and downhearted) and hyperactivity are reported to emerge at around age 7 years (Colvert et al., 2021).

Higher autism symptom severity has been associated with higher levels of emotional and behavioral problems (Colvert et al., 2021; Jang & Matson, 2015; Lindor et al., 2019; Simonoff et al., 2019), as well as clinically significant ADHD symptoms (Avni et al., 2018; Colvert et al., 2021; Hollingdale et al., 2019; Zachor & Ben-Itzchak, 2019) and higher levels of social anxiety (Stark et al., 2022). Evaluating core symptom domains independently, similar associations emerge. More severe SA (Duvekot et al., 2018) as well as RRB (Baribeau et al., 2020; Gotham et al., 2013) have been linked to higher anxiety levels. The nature of this relation, however, is not clear. It could be that having heightened levels of core symptoms contributes to children's mental health symptoms. Alternatively, dealing with mental health challenges could impact children's core symptom presentation. Moreover, while these studies depict a positive association between co-occurring psychopathology and autism severity *levels*, less is known about the relationship between psychopathology and autism severity *change*. One recent study found that as anxiety levels decreased during Cognitive-Behavioral Therapy, both SA and RRB were also reduced (Fuselier et al., 2023).

Finally, individual characteristics, such as the birth-assigned sex of the individual, also influence total autism severity. For example, girls tend to decrease in autism symptom severity more than boys during childhood (Szatmari et al., 2015; Waizbard-Bartov et al., 2022; Waizbard-Bartov et al., 2020). Furthermore, decreases in autism severity are associated with having higher intelligence quotient (IQ; Hus et al., 2014; Solomon et al., 2018). However, it is not clear how characteristics such as IQ and birth-assigned sex are related to changes in the severity of the two core autism symptom domains. Cognitive ability, for one, has been found to moderate the relationship between change in SA and mental health. Sukhodolsky et al. (2008) showed that for children with typical-range IQ, greater impairment in social reciprocity was associated with more severe anxiety. The high rates of ASD and mental health co-occurrence make understanding the heterogeneity of symptom severity change in relation to mental health an important area for research (Pender et al., 2020).

This study is the third in a series evaluating change in the severity of autism symptoms in the children of the University of California (UC) Davis MIND Institute Autism Phenome Project (APP). We previously showed that about half of children experienced change in the severity of their autism symptoms during childhood: 46% during early childhood, from age 3 to 6 years (Waizbard-Bartov et al., 2020) and 51% across the duration of childhood, from age 3 to 11 years (Waizbard-Bartov et al., 2022). Of these, 28% showed change from age 6 to 11 years, that is, during middle childhood: 12% decreased in symptom severity while 16% increased. The goal of this study was to focus on children's autism symptom severity change during middle childhood and determine whether it was associated with the emergence of co-occurring mental health symptoms.

We evaluated the most common co-occurring mental health conditions in autistic individuals: ADHD, anxiety, and disruptive behavior problems, as well as their additive impact using a general psychopathology measure. As the severity of SA and RRB may change differently across childhood (Kim et al., 2018; Waizbard-Bartov et al., 2022), change was analyzed for both the total autism symptoms score (autism diagnostic observation schedule calibrated severity score (ADOS CSS)) as well as the two domain scores, separately (social-communication symptoms calibrated severity score (SA CSS) and restricted/repetitive behaviors calibrated severity score (RRB CSS)). We hypothesized that (1) increases in autism symptom severity (for ADOS CSS, SA CSS, and RRB CSS) would be associated with increased mental health symptoms. Conversely, (2) decreases in autism symptom severity would be associated with fewer mental health challenges. (3) Change in the severity of the core symptom domains will show similar associations with mental health symptoms and (4) the relationship between change in the severity of core symptoms and mental health challenges would be moderated by individual characteristics including sex and cognitive ability.

Methods

Participants

Participants enrolled in the longitudinal UC Davis MIND Institute APP when they were between 2 and 3.5 years of age (Time 1; T1) (for a full description of the APP cohort,

Table 1. Sample characteristics.

		T3	T4
N	75		
Female	15 (20%)		
Age		68.9 (12)	136.3 (10)
Autism symptom severity	SA CSS	6.6 (2.0)	7.3 (1.8)
	RRB CSS	8.5 (1.5)	7.9 (1.9)
Autism severity change	SA CSS	0.72 (2.1)	
	RRB CSS	−0.57 (1.7)	
IQ		78 (32)	81 (31)
Psychopathology: CBCL	Internalizing behaviors	58 (9)	61 (10)
	DSM anxiety	55 (7)	58 (9)
	Anxious/depressed	54 (6)	60 (9)
	DSM ADHD	58 (8)	61 (8)
	Attention problems	62 (8)	66 (10)
	Externalizing behaviors	56 (9)	56 (9)
	Total behavior problems	59 (9)	63 (9)
Psychopathology: ADIS/ASA	CSR	–	4.3 (2.2)
	Proportion with anxiety disorder	–	0.73 (0.45)

Note: means (SD).
SA CSS: social-communication symptoms calibrated severity score; RRB CSS: restricted/repetitive behaviors calibrated severity score; ADHD: attention-deficit hyperactivity disorder; DSM: Diagnostic and Statistical Manual of Mental Disorders; CSR: Clinical Severity Rating; ADIS: Anxiety Disorders Interview Schedule; ASA: Autism Spectrum Addendum.

see Nordahl et al. (2021)). In the present report, we focus on change in autism symptom severity during middle childhood based on information collected at the beginning (Time 3; T3, approximately age 6 years) and end (Time 4; T4, approximately age 11 years) of middle childhood.

This study includes 75 children (15 girls) enrolled in the APP. These children are a subset of samples in previous publications (Waizbard-Bartov et al. (2020), $N=125$; Waizbard-Bartov et al. (2022), $N=182$) who completed behavioral evaluations of autism symptoms at T3 and T4 as well as for co-occurring mental health symptoms and IQ (Table 1; sample characteristics at T1 appear in Supplementary Table S1). There were no differences between the current subsample ($N=75$) and the larger sample in any of the variables evaluated in this study ($p>0.05$). The study was approved by the UC Davis Review Board, and informed consent was obtained from the parent or guardian of each participant.

Inclusion criteria for the study were based on the National Institutes of Health (NIH) Collaborative Programs of Excellence in Autism. Participants had received a diagnosis of ASD in the community that was confirmed by a licensed clinician at the MIND Institute using the Autism Diagnostic Interview–Revised (ADI-R) and the Autism Diagnostic Observation Schedule-2 (ADOS-2) (Lord et al., 2000, 2012, 1994). An ASD diagnosis was confirmed if they met the ADOS-2 cut-off score for either autism or ASD and exceeded the ADI-R cut-off score for autism on either the social or communication subscales while being within two points of this criterion on the other subscale. Participants also needed to be English speaking, reside with at least one biological parent, be ambulatory and not be diagnosed with a severe motor, vision, hearing, or chronic health issue that could hinder participation in the study. There was no community involvement in the design or interpretation of this study.

Measures

Standardized assessment measures in children are included in the following sections.

Assessment of autism symptoms

ADOS-2 (Lord et al., 2000, 2012): the ADOS-2 (Lord et al., 2000, 2012) and calibrated severity scores (CSSs; Gotham et al., 2009) were used to evaluate autism symptoms across childhood. Autism symptom severity was also evaluated separately for SA (SA CSS) and RRB (RRB CSS) (Hus et al., 2014). A detailed account of this measure and its use in this study appears in Waizbard-Bartov et al. (2022).

Assessment of co-occurring mental health symptoms

Anxiety Disorders Interview Schedule-IV–Parent Interview: ADIS-P (Albano & Silverman, 1996) and the Autism Spectrum Addendum (ASA) (Kerns et al., 2017): the ADIS-P is a semi-structured parent interview aimed at assessing the presence of anxiety disorders in children. Assessments included four modules, each focused on a different childhood anxiety disorder:

separation anxiety, social anxiety disorder, specific phobia, and generalized anxiety disorder (these disorders were not substantially changed in the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; DSM-5) thus can be assessed using the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; DSM-IV)-based measure). The ASA is a series of specific guidelines and prompts included in the ADIS-P to adapt it for use with autistic children. It includes five modules to assess distinct expressions of anxiety that often arise in ASD. These include other social fear (i.e. social anxiety without a fear of negative evaluation), uncommon phobias, fear related to special interest areas, fear of change, and negative reaction to change. The ADIS/ASA produces a Clinical Severity Rating (CSR) for each module, ranging from 0 to 8 and representing the child's overall anxiety level and interference in life. A score of 4 on this scale is the cut-off for anxiety that is considered "clinically significant" with scores of 4 or higher signifying a potential anxiety diagnosis. Anxiety was measured using the ADIS/ASA in two ways: (1) the child's highest CSR of all modules (for either DSM anxiety disorders or distinct anxiety characteristics of ASD) was used as an indicator of the child's highest anxiety level and (2) whether the child meets criteria for having an anxiety disorder based on the CSR (a binary "yes/no" score). All interviewers were trained to criterion, had achieved reliability on this instrument, and attended weekly supervision meetings. The ADIS/ASA was administered at T4 and taken as an indication of the level of anxiety symptoms at the end of middle childhood.

Child Behavior Checklist/6–18 years (CBCL): the CBCL is a standardized, parent-report questionnaire assessing emotional and behavioral problems in children and adolescents (Achenbach & Ruffle, 2000). It has been validated for use with children diagnosed with ASD (Pandolfi et al., 2012). The CBCL includes "DSM-oriented" subscales aimed at capturing DSM-defined symptoms as well as norm-referenced *T*-scores for specific syndrome subscales and broadband scales. Anxiety was measured using three CBCL scales: (1) internalizing behaviors broadband scale, (2) DSM anxiety scale, and (3) anxious/depressed syndrome subscale. ADHD was measured using two scales: (1) DSM ADHD scale and (2) attention problems syndrome subscale. Disruptive behavior problems were measured using the externalizing behaviors broadband scale. The total behavior problems broadband scale was analyzed as an indicator of overall psychopathology. Clinically significant elevation in symptoms is indicated by *T*-scores of 64 and higher on broadband scales and 70 and higher on syndrome subscales.

Assessments of cognitive ability

Differential Abilities Scales-II (DAS-II): the DAS-II assesses children's cognitive abilities between 2.5 and 17 years of age in a standardized manner (Elliot, 2007). Participants completed either the DAS-II Upper Early Years or the School Age forms. Sixteen children were not able to achieve basal scores, that is, achieve a full-scale IQ $>$ 25 on the DAS-II at T3 and so were instead administered the Mullen Scales of Early Learning. Developmental quotient (DQ) scores were used to calculate IQ scores. Seven children were not able to achieve basal scores on the DAS-II at T4. For statistical analyses, IQ scores $<$ 25 were converted to a score of 24. Two children did not complete IQ testing at T4 due to non-cooperation.

Mullen Scales of Early Learning (MSEL): the MSEL measures cognitive and developmental functioning from infancy and up to 68 months of age in a standardized manner (Mullen, 1995). Verbal, non-verbal, and combined IQ were estimated by calculating ratio DQ scores, dividing average verbal, non-verbal, and combined MSEL subscale age equivalents by chronological age. As a minority of participants achieved the lowest standard score, a ratio DQ was calculated (mental age / chronological age $\times$ 100) to provide more specific individual estimates of cognitive ability (non-verbal, verbal, and combined IQ).

Data analysis

The first part of the analysis employed methods used in previous publications (see Waizbard-Bartov et al. (2020) and Waizbard-Bartov et al. (2022) for a detailed description). In brief, autism symptom severity change across middle childhood (T3–T4) was evaluated for each child using three change scores: one for change in overall autism symptom severity (ADOS CSS), a second for change in SA (SA CSS), and a third for change in RRB (RRB CSS). The distribution of severity change scores appears in Supplementary Figure S1. The Reliable Change Index Statistic (RCI) (Jacobson & Truax, 1991) was used to determine statistically significant changes in severity across childhood (Supplementary Table S2). The RCI indicated that changes of two ADOS CSS points, of three SA CSS points, and of two RRB CSS points in either direction, constituted significant changes in CSS. Children were grouped based on their individual severity change patterns (decrease, increase, or stable) for ADOS total, SA, and RRB severity. Symptom severity levels, cognitive ability, and sex composition were compared across groups.

The second part of the analysis evaluated co-occurring mental health symptoms for the established change groups. ADHD symptoms, anxiety symptoms, disruptive behavior problems, and total psychopathology were

compared across the groups at T3 and at T4 and within groups from T3 to T4. For some mental health conditions, different measures capture distinct aspects of the condition. We thus used various measures and scales in order to have as much convergent information as possible to evaluate that condition. For example, anxiety was evaluated using two measures: the CBCL and the ADIS/ASA. ADHD, disruptive behavior problems, and overall psychopathology were measured using the CBCL. For variables for which we had several measures and subscales (e.g. anxiety, ADHD), we used a multivariate analysis of variance (MANOVA) to evaluate group differences. This approach finds a linear combination of the various measures that maximizes differences between groups and allows examination of the unique contribution of each measure to the differences. Clinical thresholds were also used to evaluate significant elevation in symptom levels for the CBCL and the ADIS/ASA.

Results

Children in the study were divided into three groups based on their severity change pattern during middle childhood. We first evaluated groups of children with common change patterns in overall autism symptom severity (decreasing, increasing, and stable severity levels). We found that the associations between change in total ADOS CSS and mental health symptoms were weak across these groups. There were minimal group differences in levels of anxiety, ADHD symptoms, disruptive behavior problems and overall psychopathology at T3 and T4, and either no or small within-group differences in mental health levels over time (see Supplementary Information). Next, we evaluated groups of children based on their severity change patterns from T3 to T4 in either of the two domain scores, SA CSS and RRB CSS. These analyses yielded stronger associations between symptom change and the emergence of psychopathology, described in greater detail below. Information about the ADOS, SA, and RRB change groups at T1 and from T1 to T3 appears in the Supplementary Information and in Supplementary Tables S3 and S4. The overlap between children in the different change groups is described in Supplementary Table S5 and Figure S2. All differences reported, both between-groups and within-groups, are statistically significant.

SA CSS change: comparing children that increased with children that remained stable

An analysis of children's SA severity change resulted in the following two groups. The SA-increasing-severity-group ($N = 16$, 21.3%) included children that increased significantly in SA severity (by three or more SA CSS points). The SA-stable-severity-group ($N = 57$, 76%) comprised children that varied by two or less SA CSS points. As only two children significantly decreased in SA severity, they were not included in these analyses.

Characterizing the SA CSS change groups

Concerning autism symptoms, the SA-increasing-severity-group had a lower SA CSS compared to the SA-stable-severity-group at T3 (Supplementary Table S7; Table 2 and Figure 1). But, from T3 to T4, the SA-increasing-severity-group greatly increased in SA CSS to have higher SA CSS at T4 compared to the SA-stable-severity-group. Concerning cognitive ability, at T3, the SA-increasing-severity-group had higher mean IQ than the SA-stable-severity-group (Supplementary Table S7). Both groups maintained stable IQ levels from T3 to T4. Last, the SA change groups differed in birth-assigned sex composition: the SA-increasing-severity-group was comprised only of boys (16 boys) while the SA-stable-severity-group included all girls in the sample (42 boys and 15 girls) (Supplementary Table S7 and Table 2).

Summary. At T3, the SA-increasing-severity-group had lower SA CSS and higher IQ compared to the SA-stable-severity-group. This group increased in SA severity from T3 to T4 to have higher SA CSS and borderline-higher IQ compared to the SA-stable-severity-group at T4. No autistic girls ($n = 15$) were included within the SA-increasing-severity-group.

Co-occurring mental health conditions in the SA CSS change groups

Anxiety. At T3, the MANOVA-based F-test indicated that the SA-increasing-severity-group and the SA-stable-severity-group differed in CBCL DSM anxiety (yet a follow-up t-test did not indicate significant group differences; see Supplementary Tables S6 and S7 for statistical results). Other CBCL anxiety scales did not differ (Table 2 and Figure 2). From T3 to T4, both groups increased in anxiety symptoms: the SA-increasing-severity-group increased in anxious/depressed symptoms and the SA-stable-severity-group increased in both anxious/depressed and DSM anxiety (Supplementary Table S7). At T4, the SA-increasing-severity-group had clinically elevated levels for the CBCL internalizing behaviors and the ADIS/ASA CSR and the SA-stable-severity-group had borderline-elevated ADIS/ASA CSR. The SA-increasing-severity-group's mean CBCL internalizing behaviors and anxious/depressed symptoms were also higher than the SA-stable-severity-groups; but DSM anxiety levels were similar.

ADHD. There were no group differences at T3 in ADHD symptoms between the SA-increasing-severity and

Table 2. SA CSS and RRB CSS change groups.

			SA-I	SA-S	RRB-I	RRB-S	RRB-D
N, %	75 = 100%		16, 21.3%	59, 78.7%	7, 9.3%	51, 68%	17, 22.7%
Females	*N*, %**		0, 0%	15, 100%*	0, 0%	13, 86.7%	2, 13.3%
ADOS Symptom Severity	SA CSS	T3	4.7 (1.5)	7.1 (1.8)*	5.9 (2.5)	6.9 (1.8)	6.2 (2.2)
		T4	8.4 (1.4)↑	7.1 (1.7)*	6.3 (2.3)	7.5 (1.7)↑	7.1 (2.0)
	RRB CSS	T3	8.3 (1.1)	8.5 (1.6)	6.0 (2.5)+^	8.8 (1.1)	8.5 (1.2)
		T4	7.3 (3.0)	8.1 (1.4)	8.4 (1.9)	8.6 (1.2)	5.8 (2.1)↓*+
ADOS Severity Change	SA CSS	T3–T4	3.8 (0.7)	0.1 (1.2)	0.4 (1.6)	0.7 (1.9)	0.9 (2.8)
	RRB CSS	T3–T4	−1.1 (2.3)	−0.4 (1.4)	2.4 (0.8)	−0.3 (0.7)	−2.8 (1.3)
IQ		T3	92 (28)	74 (32)*	82 (34)	77 (32)	81 (31)
		T4	92 (27)	77 (32)	79 (35)	81 (31)	82 (33)
Psychopathology: CBCL	Internalizing behaviors	T3	61 (10)	58 (8)	56 (12)	59 (8)	59 (9)
		T4	66 (7)	60 (10)*	58 (15)	60 (10)	64 (8)
	DSM anxiety	T3	59 (9)	54 (6)	54 (6)	55 (6)	56 (10)
		T4	63 (11)	58 (8)↑	55 (9)	58 (8)↑	60 (10)
	Anxious/ depressed	T3	56 (7)	54 (6)	55 (9)	54 (5)	54 (7)
		T4	65 (9)↑	59 (9)*↑	54 (5)+^	60 (9)↑	62 (10)↑
	DSM ADHD	T3	57 (6)	59 (8)	55 (8)	59 (8)	57 (7)
		T4	65 (9)↑	61 (8)	61 (10)	61 (8)	62 (8)
	Attention problems	T3	61 (8)	63 (8)	55 (8)	63 (7)^	61 (7)
		T4	70 (12)↑	66 (10)	63 (10)	67 (11)	66 (8)↑
	Externalizing behaviors	T3	56 (8)	56 (9)	51 (9)	57 (9)	56 (9)
		T4	60 (6)	55 (10)*	56 (8)	56 (9)	56 (10)
	Total behavior problems	T3	60 (10)	58 (9)	55 (12)	59 (8)	58 (10)
		T4	69 (5)↑	61 (9)*	59 (11)	62 (9)	65 (7)↑
Psychopathology: ADIS/ ASA	CSR	T4	5.0 (1.9)	4.2 (2.2)	3.1 (2.5)	4.2 (2.4)	5.0 (1.3)
	Proportion with anxiety disorder	T4	0.86 (0.36)	0.70 (0.46)	0.43 (0.53)	0.70 (0.47)	0.94 (0.24)*+

Note: means (SD).
SA CSS: social-communication symptoms calibrated severity score; RRB CSS: restricted/repetitive behaviors calibrated severity score; ADHD: attention-deficit hyperactivity disorder; DSM: Diagnostic and Statistical Manual of Mental Disorders; CSR: Clinical Severity Rating; ADIS: Anxiety Disorders Interview Schedule; ASA: Autism Spectrum Addendum; CBC: Child Behavior Checklist.
*: difference between SA-I and SA-S is $p < 0.05$; *: difference between RRB-D and RRB-S is $p < 0.05$; +: difference between RRB-D and RRB-I is $p < 0.05$; ^: difference between RRB-S and RRB-I is $p < 0.05$; ↑: increase from T3 to T4 is $p < 0.05$; ↓: decrease T3–T4 is $p < 0.05$; **: percentage of all girls; group names: SA-I: SA-increasing-severity-group, SA-S: SA-stable-severity-group, RRB-I: RRB-increasing-severity-group, RRB-S: RRB-stable-severity-group, RRB-D: RRB-decreasing-severity-group.

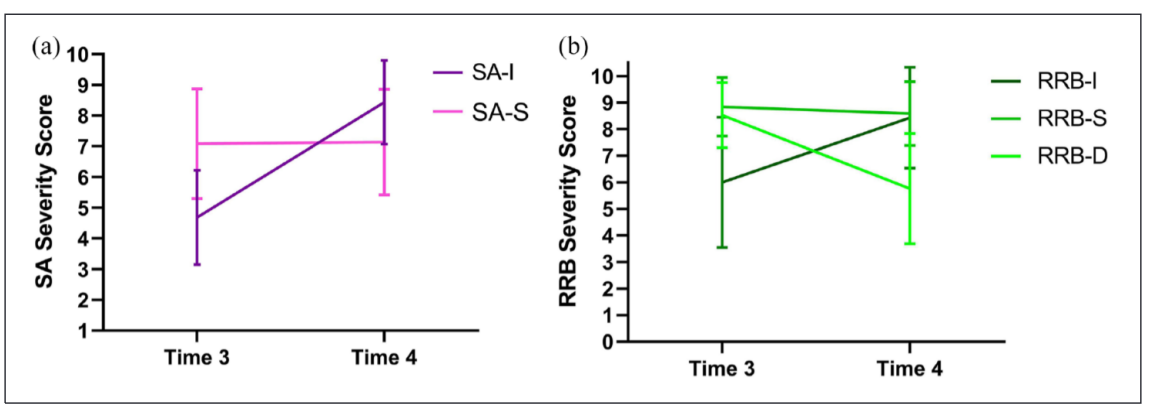

Figure 1. Autism symptom trajectories across childhood. (a) The SA-increasing-severity-group (SA-I) had lower SA severity compared to the SA-stable-severity-group (SA-S) at T3. From T3 to T4, however, the SA-increasing-severity-group increased in SA severity to have a higher severity level compared to the SA-stable-severity-group at T4. (b) The RRB-increasing-severity-group (RRB-I) had the lowest RRB severity level at T3. From T3 to T4, the RRB-decreasing-severity-group (RRB-D) decreased in RRB severity to have a lower severity level compared to the other two groups at T4, while the RRB-increasing-severity-group (RRB-I) increased in severity.

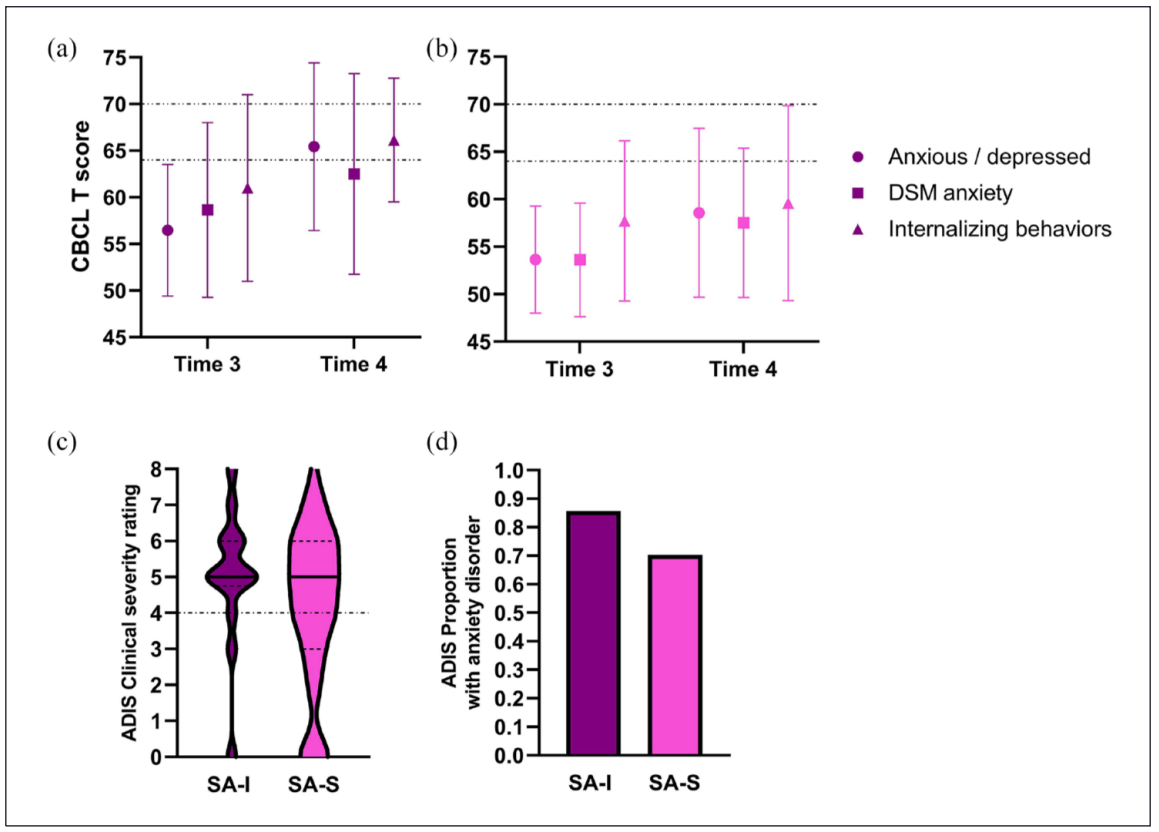

Figure 2. Trajectories of CBCL anxious/depressed symptoms, DSM anxiety and internalizing behaviors for the (a) SA-increasing-severity-group (SA-I) and (b) SA-stable-severity-group (SA-S). The lower line (64) represents the clinical significance threshold for internalizing behaviors, the upper line (70) for anxious/depressed symptoms. (c) ADIS CSR medians for the SA change groups at T4. The dotted line (4) represents the clinical significance threshold. (d) Proportion of children in the SA change groups with anxiety disorder. Both the SA-increasing-severity-group and SA-stable-severity-group increased in anxious/depressed symptoms from T3 to T4, and the SA-stable-severity-group also increased in DSM anxiety. At T4, the SA-increasing-severity-group had clinically elevated CBCL internalizing behaviors, its internalizing behaviors and anxious/depressed symptoms were higher than the SA-stable-severity-groups, and it had clinically elevated ADIS/ASA anxiety symptoms.

SA-stable-severity-groups (Supplementary Tables S6 and S7). From T3 to T4, the SA-increasing-severity-group increased in CBCL DSM ADHD and attention problems while the SA-stable-severity-group remained stable in both (Table 2 and Figure 3). At T4, there were no group differences in attention problems, but the SA-increasing-severity-groups' mean level was clinically elevated.

Disruptive behavior problems. At T3, there were no group differences in disruptive behavior problems (Supplementary Table S7). But, by T4, the SA-increasing-severity-group had higher disruptive behavior problems compared to the SA-stable-severity-group (Table 2 and Figure 4).

Overall psychopathology. At T3, there were no group differences in overall psychopathology (Supplementary Table S7). From T3 to T4, the SA-increasing-severity-group increased in overall psychopathology to have a clinically elevated level at T4, that was also higher than the SA-stable-severity-groups' level (Table 2 and Figure 5).

Summary. The SA-increasing-severity-group demonstrated greater symptoms of anxiety, ADHD, and overall psychopathology from T3 to T4. The SA-stable-severity-group increased in anxiety symptoms and had stable ADHD symptoms and overall psychopathology levels. At T4, the SA-increasing-severity-group had clinically elevated levels of anxiety, attention problems, and overall psychopathology, while the SA-stable-severity-group had borderline levels for anxiety and non-elevated ADHD symptoms and overall psychopathology level. Finally, at T4, the SA-increasing-severity-group had higher anxiety symptoms, disruptive behavior problems, and overall psychopathology than the SA-stable-severity-group.

RRB CSS change: comparing children that increased, remained stable, and decreased in severity

Evaluating children's RRB severity change, three groups were defined: an RRB-decreasing-severity-group ($N = 17$,

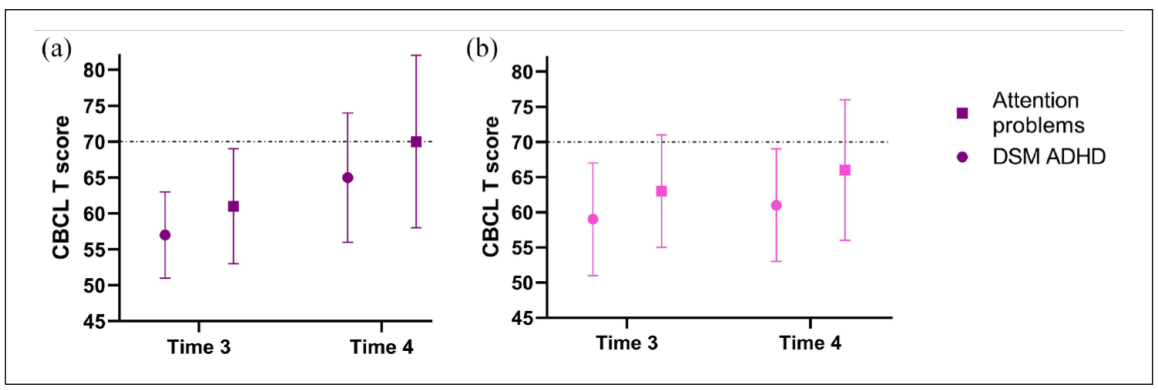

Figure 3. Trajectories of CBCL DSM ADHD symptoms and attention problems for the (a) SA-increasing-severity-group (SA-I) and (b) SA-stable-severity-group (SA-S). The dotted line (70) represents the clinical significance threshold for attention problems. The SA-increasing-severity-group increased from T3 to T4 in CBCL DSM ADHD and attention problems, while the SA-stable-severity-group remained stable. At T4, the SA-increasing-severity-group had clinically elevated CBCL attention problems.

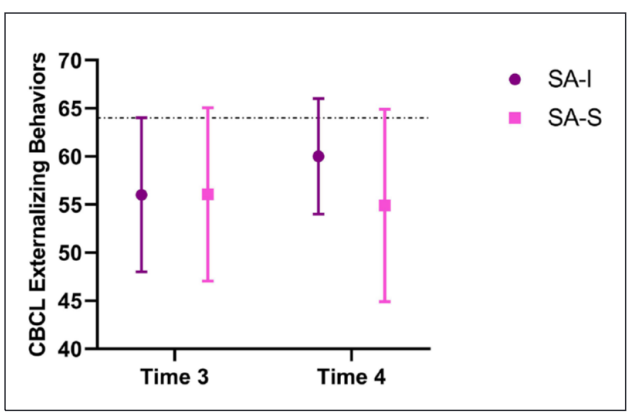

Figure 4. Trajectories of disruptive behavior problems (measured via CBCL externalizing behaviors) for the SA-increasing-severity-group (SA-I) and SA-stable-severity-group (SA-S). The dotted line (64) represents the clinical significance threshold. At T4, the SA-increasing-severity-group had higher disruptive behavior problems compared to the SA-stable-severity-group.

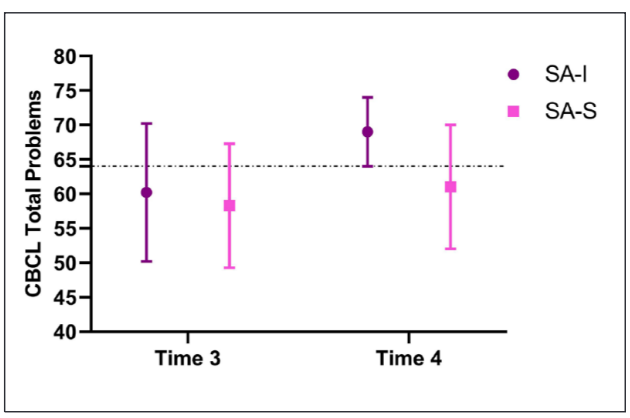

Figure 5. Trajectories of overall psychopathology (measured via CBCL total behavior problems) for the SA-increasing-severity-group (SA-I) and SA-stable-severity-group (SA-S). The dotted line (64) represents the clinical significance threshold. The SA-increasing-severity-group increased from T3 to T4 to have a clinically elevated overall psychopathology score at T4 that was higher than the SA-stable-severity-groups.

22.7%) comprised children that significantly decreased in RRB severity (by two or more RRB CSS). An RRB-stable-severity-group ($N = 51$, 68%) included children that changed by one point or less, and an RRB-increasing-severity-group ($N = 7$, 9.3%) comprised children that significantly increased in RRB severity by two or more RRB CSS.

Characterizing the RRB CSS change groups

At T3, the RRB-increasing-severity-group had the lowest RRB severity, while the other two groups did not differ (Supplementary Table S8; Table 2 and Figure 1). From T3 to T4, the RRB-decreasing-severity-group decreased in RRB severity, while the RRB-stable-severity-group remained stable and the RRB-increasing-severity group trended toward increasing severity (the increase in this group likely did not reach statistical significance due to the small number of children in the group and thus low power to detect differences over time using *t*-tests). At T4, the RRB-decreasing-severity-group had a lower RRB severity level compared to both other groups, which did not differ. There were no group differences in IQ at either T3 or T4 and groups did not change in IQ from T3 to T4 (Supplementary Table S8 and Table 2). Last, there were no differences in birth-assigned sex between the RRB change groups (Supplementary Table S8 and Table 2).

Summary. At T3, the RRB-increasing-severity-group had the lowest RRB severity level. The RRB-decreasing-severity-group decreased in RRB severity from T3 to T4 to have the lowest level at T4.

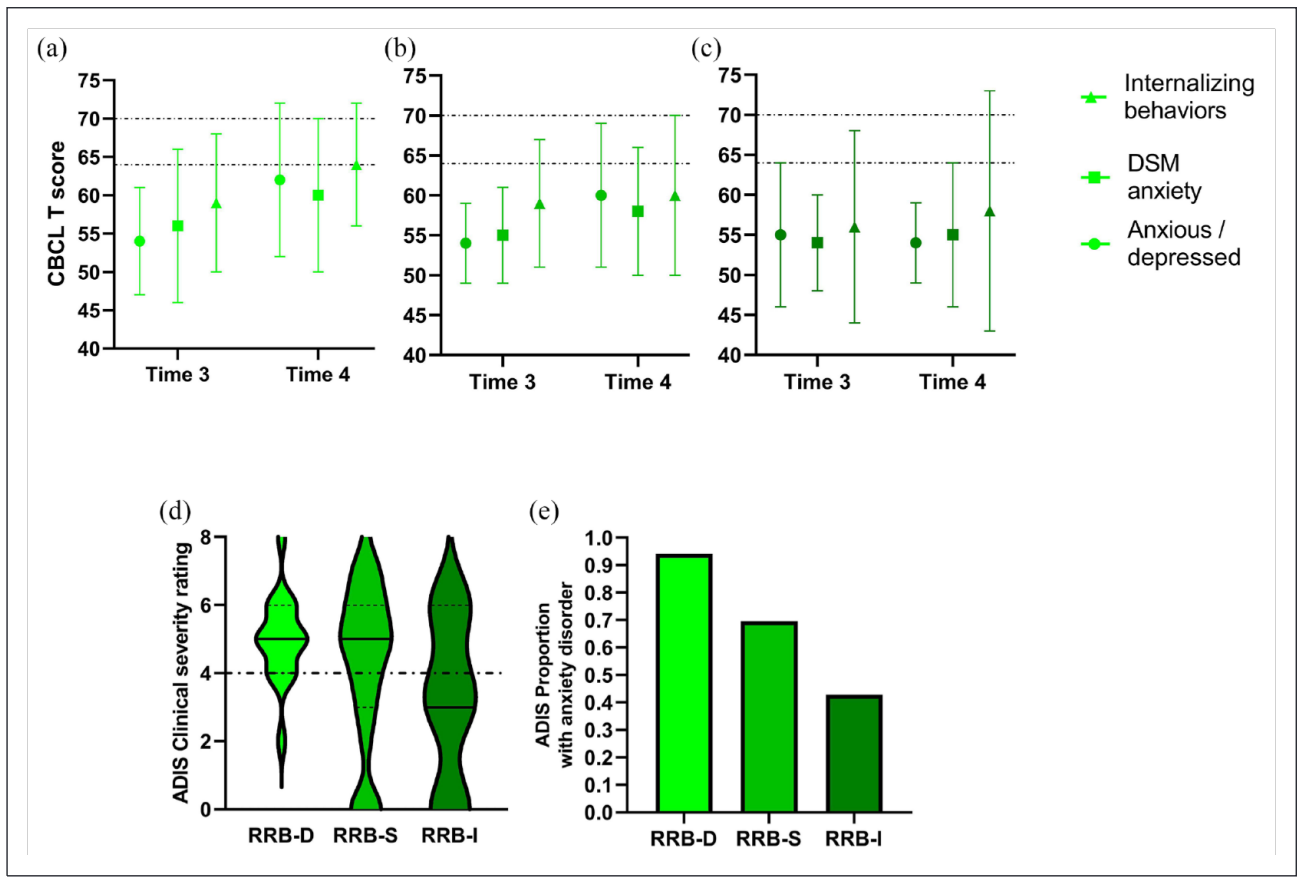

Figure 6. Trajectories of CBCL anxious/depressed symptoms, DSM anxiety, and internalizing behaviors for the (a) RRB-decreasing-severity-group (RRB-D), (b) RRB-stable-severity-group (RRB-S), and (c) RRB-increasing-severity-group (RRB-I). The lower line (64) represents the clinical significance threshold for internalizing behaviors and the upper line (70) for anxious/depressed symptoms. (d) Median ADIS CSR for the RRB change groups at T4. The dotted line (4) represents the clinical significance threshold. (e) Proportion of children in the RRB change groups with anxiety disorders. From T3 to T4, the RRB-decreasing-severity-group and RRB-stable-severity-group increased in CBCL anxious/depressed symptoms, and the RRB-stable-severity-group also increased in DSM anxiety. At T4, the RRB-decreasing-severity-group had clinically elevated CBCL internalizing behaviors and ADIS/ASA CSR and included a higher proportion of children (94%) with anxiety disorders than both other groups. The RRB-increasing-severity-group had the lowest CBCL anxious/depressed symptoms.

Co-occurring mental health conditions in the RRB CSS change groups

Anxiety. There were no group differences in anxiety levels at T3 (Supplementary Tables S6 and S8). From T3 to T4, the RRB-decreasing-severity-group increased in CBCL anxious/depressed symptoms, and the RRB-stable-severity-group increased in both CBCL anxious/depressed and DSM anxiety symptoms (Table 2 and Figure 6). The RRB-increasing-severity-group had stable anxiety levels. At T4, the RRB-decreasing-severity-group had clinically elevated CBCL internalizing behaviors. The RRB-increasing-severity-group, in comparison, had the lowest CBCL anxious/depressed symptoms. The three RRB change groups also differed at T4 in the ADIS CSR and proportion of children that met criteria for an anxiety disorder. The RRB-decreasing-severity-group had a higher proportion of children (94%) that met criteria for an anxiety disorder than both other groups, which did not differ. The RRB-decreasing-severity-group also had a clinically elevated ADIS/ASA CSR.

ADHD. At T3, the RRB change groups differed in CBCL attention problems (Supplementary Tables S6 and S8 and Figure S3; Table 2). Follow-up comparisons showed that the RRB-increasing-severity-group had lower attention problems than the RRB-stable-severity-group. There were no differences between RRB change groups in DSM ADHD at T3. From T3 to T4, the RRB decreasing-severity-group increased in attention problems while the other two groups remained stable. There were no group differences in ADHD symptoms at T4.

Disruptive behavior problems. There were no group differences in disruptive behavior problems or changes over time for the RRB change groups (Supplementary Table S8 and Figure S4; Table 2).

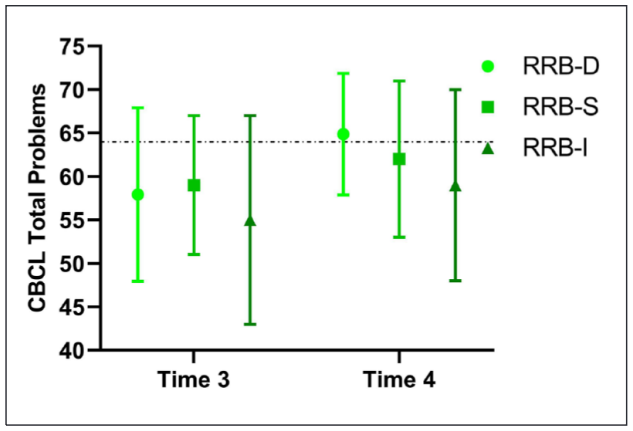

Figure 7. Trajectories of overall psychopathology (measured via CBCL total behavior problems) for the RBB change groups. The dotted line (64) represents the clinical significance threshold. The RRB-decreasing-severity-group increased in overall psychopathology from T3 to T4 to have a clinically elevated level at T4.
RRB-I: RRB-increasing-severity-group; RRB-S: RRB-stable-severity-group; RRB-D: RRB-decreasing-severity-group.

Overall psychopathology. There were no group differences in overall psychopathology at T3 (Supplementary Table S8 and Figure 7; Table 2). From T3 to T4, the RRB-decreasing-severity-group increased in overall psychopathology to have a clinically elevated level at T4, while the other groups remained stable. There were no significant differences at T4.

Summary. From T3 to T4, the RRB-decreasing-severity-group increased in anxiety symptoms, attention problems, and overall psychopathology. The RRB-stable-severity-group increased only in anxiety symptoms. The RRB-increasing-severity-group did not show increases in anxiety, ADHD, or overall psychopathology levels. At T4, the RRB-decreasing-severity-group had clinically elevated levels for anxiety (on both CBCL and ADIS/ASA) and for overall psychopathology, and it included the highest proportion of children (94%) meeting criteria for an anxiety disorder. The RRB-increasing-severity-group had, by contrast, the lowest anxiety levels based on the CBCL and non-elevated levels based on the ADIS/ASA. The RRB-stable-severity-group had non-elevated anxiety based on the CBCL and borderline levels based on the ADIS/ASA.

Discussion

Summary of findings

This study evaluated the relationship between change in autism symptom severity during middle childhood (from ages 6–11 years) and the occurrence of mental health symptoms. Change in overall autism symptom severity (ADOS CSS) was weakly related to increasing psychopathology during middle childhood. Because change in SA and RRB severity was often orthogonal, it proved more informative to evaluate them separately in relation to mental health challenges. Increases in the severity of social-communication symptoms were associated with increases in, and higher levels of, psychopathology during middle childhood. Decreases in RRB severity were associated with having higher and clinically significant anxiety levels later in childhood. The fact that change in the severity of the two core domains showed opposite associations with mental health symptoms was unexpected. Importantly, both domains were independently associated with the occurrence of mental health symptoms as there was only a 30% overlap between children that increased in SA severity and decreased in RRB severity (Supplementary Table S5 and Figure S2).

Why are increases in SA severity associated with more severe and increasing mental health symptoms?

During middle childhood, challenges including severe social-communication symptoms (Duvekot et al., 2018), reduced social competence, or greater peer rejection (Hunsche et al., 2022) have all been associated with higher anxiety levels. Autistic youths with co-occurring ADHD and anxiety have greater social challenges than youths without such co-occurring conditions (McVey et al., 2018). These previous studies depict positive associations between co-occurring psychopathology and *levels of* social-communication symptoms and challenges, but not with *change* in autism symptoms. This study thus extends previous results and is the first, to our knowledge, to demonstrate an association between co-occurring mental health symptoms and *increases* in the severity of social-communication difficulties for autistic children. These findings are in line with our hypothesis that increases in autism symptom severity would be associated with increased mental health symptoms.

While findings of associations between co-occurring mental health symptoms and changes in severity of social-communication symptoms in autistic children are in line with past work, the nature or directionality of this relationship is unclear; why are increases in social-communication symptoms and mental health challenges linked over time? One possibility is that children's early elevated psychopathology prevents them from properly mastering social skills across childhood, leading to worsening social development with time. We gained a sense of this by analyzing CBCL scores at T1, when children were 3 years old (analysis and data presented in Supplementary Information), where we found that the SA-increasing-severity-group had clinically elevated levels for both externalizing and internalizing behaviors at T1. This is consistent with the literature. Neuropsychiatric comorbidities such as ADHD have

been suggested to influence the development of autism impairments (Hawks & Constantino, 2020), and higher anxiety levels precede more severe social challenges later in childhood (Duvekot et al., 2018). Conversely, it is also possible that children's increasing autism-related social-communication difficulties during middle childhood contribute to the emergence of their mental health challenges. Elevated autism symptoms, and specifically difficulties in the area of social skills, have been associated with (Spain et al., 2018) and suggested to lead to (Bellini, 2006; Stark et al., 2022) elevated levels of social anxiety. Moreover, this link may be moderated by reduced social competence (Stark et al., 2022) as well as children's cognitive ability (Sukhodolsky et al., 2008). For children with typical-range IQ, having anxiety is associated with greater impairment in social reciprocity. The fact that children in the SA-increasing-severity-group had typical-range IQ suggests that they are aware of their reduced social competence and added challenges (e.g. feel confused and embarrassed in social situations). This, in turn, could lead to feelings of anxiety and distress in social situations. These findings are in line with our prediction that the relationship between change in children's core symptoms and mental health challenges would be moderated by individual characteristics such as cognitive ability.

Why does decreasing RRB severity lead to high and increasing anxiety levels?

The literature consistently shows a relation between having more frequent and more severe RRB and elevated anxiety levels (Baribeau et al., 2020; Cashin & Yorke, 2018; Kim et al., 2020; Rodgers et al., 2012; Sukhodolsky et al., 2008). Whether having RRB contributes to having higher anxiety levels, or, whether individuals perform more RRB *because* they feel anxious (Jiujias et al., 2017) have never been clear. Anxiety has been identified as an intrinsic motivation for autistic individuals to perform RRB (Joosten et al., 2009) and performing RRB is linked with experiencing positive emotion (Mercier et al., 2000). Autistic adults report that performing certain types of RRB acts as a self-regulation mechanism (Kapp et al., 2019), an idea also suggested by special education teachers of autistic children (Jaffey & Ashwin, 2022). These findings support the hypothesis that some forms of RRB can reduce anxiety and the increased arousal brought on by it (Spiker et al., 2012; Stratis & Lecavalier, 2013; Wood & Gadow, 2010). Despite this, autistic individuals might try to avoid performing RRB if they feel it conflicts with social expectations or can lead to negative reactions from others (Kapp et al., 2019; Wood & Gadow, 2010), such as stigmatization and bullying (Forrest et al., 2020).

We found that a decrease in RRB severity during middle childhood was related to higher levels of anxiety in late childhood. This is contrary to our prediction that decreases in autism symptom severity would be associated with having less mental health symptoms. However, if RRB function is viewed as a strategy for anxiety reduction, then elimination of this form of expression could indeed lead to increased anxiety. This position has previously been suggested (Jiujias et al., 2017) that if individuals are unable to or choose not to perform RRB, their absence can lead to heightened anxiety levels. Interestingly, we found that children that *increased* in RRB severity had fewer mental health challenges.

Our findings suggest that interventions focused on reducing RRB severity should be implemented cautiously, while monitoring children's anxiety levels and providing them with alternative self-regulation strategies to prevent increases in anxiety. This is especially relevant as a child's autism symptoms are predictive of receiving supportive services at school while their internalizing symptoms, such as anxiety, are not (Rosen et al., 2019). In addition, rather than target individuals, interventions focused on RRB can involve modifications to the environment, as to not provoke RRB and to encourage destigmatization of RRB (Kapp et al., 2019).

Using different measures to evaluate anxiety in children with autism

The CBCL has been validated for use with 6- to 18-year-old children with autism (Pandolfi et al., 2012). Its utility, however, differs based on children's cognitive ability and has been found to be better at identifying behavioral and emotional problems of autistic children without concurrent intellectual disability compared to those with intellectual disability (Dovgan et al., 2019). The ADIS/ASA, in comparison, has been successfully implemented with children of varied intellectual functioning (Kerns et al., 2020). We found that the CBCL identified emotional and behavioral problems, especially anxiety, in the SA-increasing-severity-group which was characterized by cognitive ability in the average-range (IQ means: T3 and T4 = 92), while the ADIS/ASA indicated a borderline-clinical anxiety level for this group. Conversely, the ADIS/ASA identified clinically significant anxiety symptoms in the RRB-decreasing-severity-group which is also characterized by lower-than-average cognitive ability (IQ means: T3 = 81, T4 = 82), while the CBCL identified borderline-elevated levels of anxiety in this group. Thus, these measures' differential functioning in detecting anxiety in our sample might be related to the children's varied cognitive abilities. Alternatively, it could also be that this difference results from the types of anxiety evaluated by each measure. The CBCL targets only traditional forms of anxiety (e.g. separation anxiety) while the ADIS/ASA assesses a broader construct of anxiety including both traditional and distinct anxieties characteristic of youths with ASD (Kerns et al., 2014).

Limitations

In considering the conclusions of this study, it is important to point out certain limitations. First, the need for longitudinal behavioral data reduced our sample to 75 participants. This sample size limited our ability to evaluate subgroups and so our findings will need to be replicated and extended with larger samples. Second, while most measures in the study were used longitudinally, the ADIS/ASA was administered only at T4, restricting the longitudinal evaluation of anxiety. Also, we analyzed the ADIS in terms of each child's highest CSR (the anxiety type with the highest severity level), which does not account for type of anxiety or children who meet criteria for several anxiety disorders. Our sample size was not sufficient to evaluate specific types of anxieties within the groups. Third, both the CBCL and ADIS/ASA are based on parental report. Parental report can be unreliable and may be impacted by rater bias (Ozonoff et al., 2018). Specifically, parents might have generalized their child's behavior from one aspect to the other, a bias known as the "halo effect" (Thorndike, 1920), reporting behaviors resulting from increases in autism severity as relating to increased psychopathology and vice versa. Fourth, several of the children did not achieve basal scores in cognitive assessments. Since, to our knowledge, there is currently no formal way to evaluate IQ scores < 25, these participant's scores were converted to a score of 24. Fifth, in the statistical models, we did not correct for multiple comparisons as any correction with this sample size would compromise the significance level of any individual analysis. This does, however, increase the risk of chance findings. Furthermore, it is important to make clear that this work describes patterns of associations which will need to be empirically tested in order to determine causality, as well as the possibility that a third factor might be impacting both change in autism symptoms and psychopathology levels. Last, our findings suggest that increasing SA severity during middle childhood is more characteristic of boys than girls. Our sample, however, included only 15 girls and only addressed birth-assigned sex (not gender identity). Future studies with larger numbers of girls are needed to comprehensively investigate this sex difference.

Conclusion

Our findings indicate a relationship between change in children's autism symptom severity and increases in mental health challenges during middle childhood. Surprisingly, both increases and decreases in autism severity were associated with mental health symptoms, and these patterns differed between the two symptom domains. Children who increased in social-communication symptoms had higher and increasing psychopathology levels during middle childhood, while children who increased in RRB severity actually had more modest levels of mental health challenges. It was the children who decreased in RRB severity that had higher anxiety levels at age 11 years. Furthermore, change in the severity of core domains was more strongly associated with mental health symptoms than change in total autism severity. Our findings suggest that children's mental health challenges should be evaluated in relation to other developmental processes such as change in core symptoms over time. This is especially important for adapting intervention and support to optimize outcomes across development.

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Supplemental material

Supplemental material for this article is available online.

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5. Discussion:

Summary of results

Autism symptom severity change was evaluated for the children of the University of California, Davis MIND Institute's Autism Phenome Project (APP) and Girls with Autism Imaging of Neurodevelopment (GAIN) study. We evaluated symptom severity change across three studies. In study 1 core symptom trajectories were examined for 125 autistic children during early childhood, from 3 to 6 years of age. In study 2 symptom trajectories were evaluated across the duration of childhood from age 3 to 11 (spanning both early and middle childhood), for 182 autistic children. In study 3 symptoms trajectories were evaluated for 75 autistic children across middle childhood, from age 6 to 11. In addition, sex, IQ, adaptive functioning, initial symptom severity level at study entry, co-occurring mental health challenges, parental characteristics and intervention history were evaluated as potential correlates of symptom severity change. Autism symptoms were evaluated using the Autism Diagnostic Observation Schedule (Lord et al., 2000; C. Lord et al., 2012) and the Calibrated Severity Score (CSS) (Gotham et al., 2009) and analyzed for both total autism symptoms (ADOS CSS), as well as for social-communication symptoms (SA CSS) and restricted/repetitive behaviors (RRB CSS), separately (Hus et al., 2014). Symptom severity change was evaluated using individual change scores across measurements and the Reliable Change Index (Jacobson & Truax, 1991). Children were grouped based on their symptom severity change patterns during childhood. First, we evaluated how common is change in autism symptom severity. During early childhood (study 1), 28.8% of children decreased in symptom severity by 2 or more CSS points, 54.4% changed by 1 point or less and 16.8% of the sample increased by 2 or more points. Evaluating change across the duration of childhood (study 2), 51%

of participants experienced symptom severity change: 27% of children decreased in severity, 24% increased and 49% were stable. Finally, during middle childhood (study 3), 21.3% of children increased in the severity of their social-communication symptoms while 22.7% decreased in the severity of their RRBs and 9.3% increased in the severity of their RRBs (and the remainder of children were stable).

Second, we evaluated what characterizes symptom severity change across time and development. Severity decreases were more common during early childhood while severity increases occurred during both early and middle childhood. Furthermore, most children experienced significant change during only one period and remained stable during the other. Third, we evaluated trajectories of social-communication challenges and RRBs, separately. The two symptom domains showed differential trajectories across childhood. Increase in social-communication symptom severity was especially prominent during middle childhood, more so than in early childhood, while decrease in RRBs severity was also evident during middle childhood.

Last, we evaluated what factors correlate with change in autism symptom severity. Concerning individual characteristics, girls tended to decrease in severity more and increase less than boys at both early and middle childhood. During early childhood, children that decreased in symptom severity had higher IQs compared to other children and made gains over time, while children that increased in severity had lower IQs that remained stable. IQ was not associated with change in total symptom severity during middle childhood. IQ was, however, associated with change in social-communication symptoms; children that increased in the severity of social-communication symptoms from age 6 to 11 had higher IQs at age 3 compared to other children.

Increasing in total symptom severity was associated with having lower adaptive functioning during early childhood and also with decreasing adaptive functioning compared to other children across childhood (that is, these children did not lose abilities but decreased in the level of their abilities compared to their peers over time). During middle childhood, children that increased in the severity of their social-communication symptoms also had elevated and increasing levels of anxiety, ADHD, disruptive behavior problems and overall psychopathology compared to other children. Children that, on the other hand, decreased in the severity of their RRBs had elevated and increasing anxiety levels at age 11, with most (94%) meeting criteria for an anxiety disorder. Evaluating environmental characteristics, decrease in total symptom severity was associated with higher parental education level and older parental age at the time of the child's birth. Conversely, increase in autism severity was associated with lower parental education level and younger parental age at the child's birth. There was no clear relationship between intervention history and whether a child experienced change in symptoms severity across childhood. There was also no relationship between a child's initial severity level at the time of study entry (age 2 – 3.5) and if or what type of severity change they will undergo over time.

Question 1- How common is change in the severity of autism symptoms during childhood?

Our first question addressed how common autism symptom severity change is during childhood. Evaluating the three studies combined, around half of the children in the sample changed in the severity of their symptoms over time, with the other half remaining stable. Both study 1 and study 2 evaluated change in total autism symptoms showing that 47% of children changed in severity from age 3 to 6 and 51% changed from age 3 to 11. Evaluating change in symptom domains separately (study 3) we found that 21.3% of children changed in the severity

of their social-communication symptoms and 32% changed in the severity of their RRBs during middle childhood (and 42.7% changed in the severity of their total symptoms during this period).

Our findings are compatible with those of other large, longitudinal studies, finding that the severity level of autism symptoms is not static, but rather often changes over time (Elias & Lord, 2022). Between 11%-58% of autistic individuals have been shown to change in the severity of their core symptoms across life (Waizbard-Bartov & Miller, 2023). Furthermore, and congruent with our findings, change does not happen in a uniform way and tends to differ between individuals. Studies utilizing the ADOS have indicated that 7%-29% of autistic individuals improve (decrease) in core symptom severity over time (Georgiades et al., 2021; Pellicano et al., 2019; Szatmari et al., 2015; Venker et al., 2014; Waizbard-Bartov et al., 2022; Waizbard-Bartov et al., 2020). Moreover, some individuals decrease in symptom severity to such a degree that they no longer meet the diagnostic criteria for autism. This phenomenon is called Loss of Autism Diagnosis (Eigsti, Fein, & Larson, 2022) (previously known as optimal outcome (Fein et al., 2013). In comparison, between 8%-29% of individuals with autism worsen (increase) in the severity of symptoms (Gotham et al., 2012; Kim et al., 2016; Pellicano et al., 2019; Waizbard-Bartov et al., 2022; Waizbard-Bartov et al., 2020). Thus, our findings are compatible with those of other large studies indicating change in autism symptom severity is a common finding in autistic individuals.

Question 2- What characterizes symptom severity change and is it consistent over time?

Our second question investigated what characterizes change in autism symptoms over time and whether it is consistent across development. We found that change was not consistent but rather fluctuated over time. In study 2 we evaluated autism symptoms across childhood, from age 3 to 11, and compared change during early and middle childhood periods. Across all children

combined, symptom severity decreases were more common during early compared to middle childhood, while severity increases occurred at both periods (but increase in social-communication challenges specifically was especially prominent during middle childhood). At the individual level, most children experienced significant change during only one period and remained stable during the other.

Our results are compatible with other studies, showing severity change is not linear in nature and often happens differently within an individual across time. Symptom severity change can differ in either direction (e.g., decrease/increase or increase/ decrease) as well as the rate at which it occurs within an individual across development (Georgiades et al., 2017; Georgiades et al., 2021; Taylor & Seltzer, 2010; Waizbard-Bartov et al., 2022). Such differences in severity change patterns are evident in our findings with children experiencing competing change patterns over time (increase followed by decrease or vice versa). Decreasing severity has been shown to be more common during early childhood (Bal et al., 2019; Fountain et al., 2012; Lord, Luyster, Guthrie, & Pickles, 2012), while during middle childhood symptoms can either continue to decrease (Waizbard-Bartov et al., 2022), plateau (Georgiades et al., 2021) or even shift to increasing severity (Clark et al., 2017). Moreover, change, especially decreasing severity, occurs at a faster rate during earlier compared to later ages and slows down with time (Fountain et al., 2012; Taylor & Seltzer, 2010; Waizbard-Bartov et al., 2022). Our findings are in line with this literature, with children in the cohort having a stronger tendency for severity decrease during early childhood while in middle childhood increasing severity became more common than before.

The fact that severity decrease is more common during early childhood might be attributed to the fact that language tends to develop during this time (Miller, 2012). For autistic children, developing language before age 5 is a predictor of good outcome (Tager-Flusberg & Kasari, 2013) and is linked to improving social-communication symptom trajectories (Bal et al., 2019). In contrast, as individuals grow (i.e., moving from early to middle childhood) services and supports often lessen and are also less accessible compared to early childhood (Lord et al., 2022; Towle, Vacanti-Shova, Higgins-D'Alessandro, Ausikaitis, & Reynolds, 2018), a fact that could hinder gains during this period.

Question 3- Does change in symptom severity differ between the two core domains?

Our third question evaluated symptom trajectories for social-communication challenges and RRBs separately. We found that the two symptom domains showed differential severity change patterns across childhood. Increase in social-communication severity was especially prominent during middle childhood (it also occurred during early childhood but to a lesser extent), while decrease in RRBs severity was prominent during middle childhood as well (studies 2 and 3). Furthermore, analyzing domain trajectories for children considered stable in total symptom severity across childhood (study 2), we found they had slightly competing trajectories for social-communication challenges and RRBs (increasing vs decreasing).

Our results are in line with the literature indicating change in autism symptoms is characterized by differences between the two core domains (Fountain et al., 2012; Hus et al., 2014; Lord et al., 2015; Waizbard-Bartov, Ferrer, et al., 2023; Waizbard-Bartov et al., 2022). But, in our cohort many of the children experienced increasing social-communication symptom

severity during middle childhood, which is contradictory to the literature showing social-communication challenges tend to decrease in severity over time (Bal et al., 2019; Fountain et al., 2012; Lord et al., 2015). Our results indicating RRBs either decreased or remained stable in severity across childhood are in line with previous publications evaluating trajectories of RRBs (Gillespie-Lynch et al., 2012; Shattuck et al., 2007).

During middle childhood children transition into the school system. Many challenges characterize this period including heightened anxiety and social pressure, the need to communicate and form relationships with teachers and peers, adjust to a schedule, engage in the classroom, and multiple attention and sensory challenges (Bolourian, Stavropoulos, & Blacher, 2019; Nuske et al., 2019; Sanz-Cervera, Pastor-Cerezuela, Gonzalez-Sala, Tarraga-Minguez, & Fernandez-Andres, 2017; Sparapani, Morgan, Reinhardt, Schatschneider, & Wetherby, 2016). It might very well be that such challenges, especially if there are additional co-occurring conditions faced by the child, could contribute to increasing severity of social-communication symptoms.

Question 4- What factors characterize children that decrease or increase in symptom severity over time?

Our last question investigated what factors correlate with change in autism symptom severity during childhood. Being female, having higher IQ that increases over time, having higher adaptive functioning and consistently gaining more skills, and being born to older, more educated parents are all associated with decrease in total symptom severity during childhood. Decreasing RRBs severity during middle childhood was associated with higher anxiety levels and high

probability of having an anxiety disorder at age 11. Increasing severity of autism symptoms, on the other hand, was associated with having lower and stable IQ during early childhood, having lower adaptive functioning and not making peer-equivalent gains over time, as well as lower parental education level and younger parental age at the child's birth. Increasing severity of social-communication challenges, specifically during middle childhood, was associated with having elevated and increasing levels of anxiety, ADHD, disruptive behavior problems and overall psychopathology, as well as with having typical-range IQ at age 3. Finally, children experienced different symptom severity change patterns regardless of either their initial severity level at time of study entry, or the interventions they received during toddlerhood and childhood.

Many of our findings are compatible with previous literature in the field. For instance, young girls have been previously shown to decrease in autism symptom severity more than young boys (Harstad et al., 2023; Szatmari et al., 2015). Decreasing in symptom severity has also been repeatedly associated with having relatively higher cognitive ability (and no intellectual disability) (Fein et al., 2013; Fountain, Winter, Cheslack-Postava, & Bearman, 2023; Georgiades et al., 2021; Gotham et al., 2012; Hinnebusch et al., 2017; Woodman et al., 2015). Our results are also in line with those of studies depicting higher adaptive abilities for individuals that decrease in symptoms over time (Charman et al., 2011; Gotham et al., 2012; Harstad et al., 2023; Perry et al., 2009).

Concerning mental health challenges, the association we identified between decrease in RRBs severity and higher anxiety levels do not replicate those of previous studies. These studies showed increasing RRBs severity to be associated with higher anxiety (Baribeau et al., 2022), and that individuals with decreasing core symptoms are characterized by reduced levels of mental health challenges (Orinstein et al., 2015). Performing certain types of RRB has been reported by

autistic adults to act as a self-regulation mechanism (Kapp et al., 2019), supporting the hypothesis that some RRBs can reduce anxiety and the increased arousal brought on by it (Spiker, Lin, Van Dyke, & Wood, 2012; Stratis & Lecavalier, 2013; Wood & Gadow, 2010). If this is the case, then elimination of this form of self-expression could lead to increased anxiety. This position has previously been suggested (Jiujias, Kelley, & Hall, 2017), and could explain why we found that children who decreased in the severity of their RRBs experienced heightened anxiety levels later in childhood.

Last, our findings confirm those of previous studies, that children's symptom severity levels early on are not necessarily a good predictor of future change in core symptom levels (Bal et al., 2019; Pellicano et al., 2019; Sutera et al., 2007).

Concerning environmental factors, other longitudinal studies have also found that, similar to our results, having less educated parents increases the likelihood of symptom severity increase and reduces the likelihood of severity decrease (Fountain et al., 2012; Fountain et al., 2023; Georgiades et al., 2021). Finally, caution must be taken when evaluating intervention history in relation to gains over time. While our results are in line with those of studies (Giserman-Kiss & Carter, 2019; Gotham et al., 2012; Harstad et al., 2023) finding no association between these two, it might be that this relationship is more subtle and complex and thus requires further, nuanced investigation into its different aspects. For example, we found that children who decreased in symptom severity across childhood actually did receive more intense early intervention during their toddler years compared to children that increased in severity. Yet, their having received more intense early intervention was strongly associated with the fact that their parents were more educated compared to parents of children that increased in severity. Thus,

intervention history may indeed be associated with symptom severity change, but the relationship is mediated through other factors.

Summary – what do these results tell us about change in autism symptom severity?

Combined, these results advance the field in several ways. First, by showing that autism symptoms can change during childhood, and to a much higher extent than previously considered. A substantial proportion of children experienced change, some having very large increases or decreases in the severity of their symptoms. Second, by suggesting that change is not consistent and can differ within person across time. That means children can show increasing autism challenges followed by marked improvement at later ages. Third, our results indicate that evaluating change in the severity of autism symptom domains separately can be highly informative. Social-communication challenges and RRBs have unique developmental trajectories and relationships with other factors during childhood. For instance, both domains were more strongly associated with the emergence of mental health challenges compared to change in overall autism severity. Collectively, these points also attest to the large variability (both between-person and within-person over time) characterizing autism symptom severity change. Importantly, this variability also makes measuring and analyzing severity change longitudinally a complex task (Waizbard-Bartov & Miller, 2023).

Across the three studies, we identified several groups of children characterized by distinct developmental profiles during childhood. For instance, the Increasing Severity Group identified in study 1 is characterized by intellectual disability, lower-and-stable adaptive functioning and increasing autism severity during early childhood. The Social-Affect-Increasing-Severity-group

identified in study 3, in comparison, is characterized by average IQ and low social-communication severity at age 3, but increasing social-communication challenges during middle childhood and relatively higher psychopathology at age 11. Both these groups were characterized by increase in the severity of their core symptoms, yet during different periods and with very different developmental profiles. All children are born with an inherent, biological potential concerning behavioral traits, including autism symptom severity (Tunc et al., 2019). Yet, it is likely that different factors characterizing these children (e.g., their cognitive ability and mental health challenges) interacted with each other to impact children's overall developmental trajectory as it unfolded across childhood (Duvekot, van der Ende, Verhulst, & Greaves-Lord, 2018; McGowan et al., 2022; Waizbard-Bartov, Ferrer, et al., 2023). Adding to the complexity, behavioral and environmental changes can, in turn, affect children's biological potential for autism symptom severity through epigenetic changes (Andari et al., 2020). Our results emphasize the fact that development happens in a cascading way (Waddington, 1957), with bidirectional and interactive links not yet properly understood.

Limitations

There are several limitations to these studies. First, the need for longitudinal data reduced our sample to 75-182 participants across studies. This is a relatively modest sample size and future studies should replicate our findings with larger cohorts. Furthermore, our sample is a convenience sample collected at a center associated with a large university campus. A more diverse sample reflecting all levels of Socioeconomic stances and education levels would be needed to comprehensively evaluate the relationships identified in these studies, especially between sociodemographic features and severity change patterns. Second, our sample included

a total of 55 girls and only addressed birth-assigned sex (and not gender identity). Ideally, the sex differences we identified in symptom severity change should be replicated and further investigated with larger numbers of girls of diverse gender identities evaluated longitudinally. Third, assessment of IQ was conducted using the MSEL and the DAS-II, two measures that are relatively suitable to assess cognitive ability in autistic children. The use of two different measures across time points, however, might have contributed to IQ scores being artifactually higher or lower at different time periods. In addition, several children in our cohort did not achieve basal scores in cognitive assessments. There is ongoing work in the field of cognitive assessments for children with ASD and future studies would do well to evaluate this structure using the same measure across time and a range of abilities. Last and importantly, the work described above shows patterns of associations which will need to be empirically tested in order to determine causality, the possibility that a third factor might be impacting associations identified, and of course the mechanisms leading to these results.

Conclusions & implications

Throughout this work, we evaluated autism symptom severity and severity change based on core autism symptoms alone. We did this because that is the way autism severity is currently defined, in both research settings as well as in clinical practice. But, as evident in our findings, the way core symptoms present and change over time is impacted by additional factors such as unique developmental periods, individual characteristics and environmental factors. And, most importantly, core symptoms alone do not capture or account for the multitude of challenges faced by autistic individuals in their everyday lives. Having intellectual disability, language delays (or being non-verbal), dealing with anxiety, having gastrointestinal (GI) symptoms or sleep

problems are all factors that impact autistic people's everyday lives as well as the trajectory of their core symptoms (Waizbard-Bartov, Fein, et al., 2023a; Waizbard-Bartov, Fein, Lord, & Amaral, 2023b). Thus, a main conclusion of our work is that in order to evaluate trajectories of autism severity, severity level must be defined and measured across development, based on core symptoms as well as developmental characteristics and co-occurring conditions (and their interactions), and how all these translate into a person's actual support needs in daily life.

These interactions between different factors characterizing autistic people, as well as varying biological potentials, likely contribute to the enormous heterogeneity described in ASD (Waterhouse, 2022; Waterhouse & Gillberg, 2014). Individuals with autism vary widely in their developmental features (e.g., cognitive and language ability), clinical presentations (e.g., core and mental health symptoms), the challenges they face in daily life (e.g., adaptive functioning levels) and of course how all of these aspects develop across the life span (Waizbard-Bartov, Fein, et al., 2023a). Naturally, such differences also impact outcomes, which range greatly between autistic individuals, from being fully independent and needing minimal support to needing full-time care and substantial support (i.e., "profound autism"; Lord et al. (2022)). In fact, we now know that the autistic population is so heterogenous that it begs the question: is it one cohesive diagnostic group at all (Green, 2023; Whitehouse, 2023)? This discourse is evident in the field today, with some advocates emphasizing the restricting, impairing aspects of having autism (Singer, 2022, November 11), as is evident in individuals considered to have "profound autism" (Lord et al., 2022), while others, many of them autistic self-advocates, endorse the neurodiversity movement that views autism as a diverse expression of human existence rather than a disorder

(Baron-Cohen, 2017; Leadbitter, Buckle, Ellis, & Dekker, 2021). This debate challenges the field to grow, but care must be taken so that all sides of the discussion are heard, and their needs met.

While the heterogeneity of autism challenges terminology and socio-cultural aspects of the field, it also provides promising opportunities for more accurate, individualized care. Our collective work has shown that core symptoms, as well as other developmental characteristics, are much more malleable than previously considered. This malleability can be harnessed through intervention. Understanding how people with autism develop differently over time can help shed light on differential susceptibility to risk factors. For instance, knowing that decreasing RRBs during middle childhood is a risk factor for developing an anxiety disorder, children on this trajectory may benefit from interventions aimed at developing self-regulation tools to mitigate the risk for onset of anxiety (Waizbard-Bartov, Ferrer, et al., 2023). Individualized care targeting an autistic person's unique (and changing) support needs, that considers the overall developmental profile impacting functioning and daily life, can help promote gains over time (Waizbard-Bartov, Fein, et al., 2023a, 2023b).

Future research

In two of the three studies, we found that girls decreased more and increased less than boys in the severity of their symptoms during childhood (study 3 likely did not have sufficient power to evaluate sex differences). This is in line with previous literature concerning sex differences in symptom trajectories (Harstad et al., 2023; Lai & Szatmari, 2019; Szatmari et al., 2015), as well as works indicating autistic girls show more gains compared to boys in various other developmental areas such as cognition (Lai et al., 2012), sociability (Head, McGillivray, &

Stokes, 2014), communication (Conlon et al., 2019) and social functioning (Mahendiran et al., 2019). We do not know, however, *which* specific behaviors are driving this sex difference. Since autism symptoms are comprised of two core domains and many different types of behavior, future research should attempt to evaluate in which specific behaviors girls are improving over time, and which behaviors remain static.

Furthermore, it is not clear *why* girls reduce in the severity of their symptoms with time. One possibility is that these girls truly are becoming less symptomatic, and the ADOS is capturing that. Another possibility, however, is that girls in our cohort have developed the ability to mask their symptoms with age. Camouflage of autism symptoms is a coping strategy used by autistic individuals in order to mask their symptoms in social situations and appear less autistic to others (Hull et al., 2017; Perry, Mandy, Hull, & Cage, 2020; Seers & Hogg, 2022). Camouflaging has been shown to be more prevalent among autistic girls (Dean, Harwood, & Kasari, 2017; Ratto et al., 2018) and adult women (Lai et al., 2017; Schuck, Flores, & Fung, 2019) compared to autistic males. In our studies, we evaluated autism symptoms using the ADOS which is a socially-based assessment that has been shown to be susceptible to camouflage behavior (Lai et al., 2017; Rynkiewicz et al., 2016). In light of this, it remains unclear whether the sex difference in symptom severity change evident in our cohort is the result of girls truly improving, or rather, that they are learning how to mask their symptoms with time. This is a question that should be further explored in future studies.

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Appendix A:

Clinical Psychology Review 99 (2023) 102230

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Clinical Psychology Review

Review

Does the severity of autism symptoms change over time? A review of the evidence, impacts, and gaps in current knowledge

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ABSTRACT

Studies evaluating change in autism symptom severity across the lifespan have yielded inconsistent results, making it difficult to assess the prevalence of meaningful change in autism symptom severity, and what characterizes it. Better understanding the ways in which autism symptoms change over time is crucial, with important implications for intervention. Synthesizing information across past studies, autism symptom severity change (especially decreases) appears common, though stability of symptoms is also frequent. Symptom severity change is characterized by variability in patterns of change *between different individuals* (between-person), variability in change *within a person's trajectory* across time (within-person), and variability in change *patterns across symptom domains* (i.e., social-communication, restricted/repetitive behaviors). Variability in severity change is likely impacted by differences in person-level characteristics (e.g., sex, IQ, sociodemographic factors) as well as developmental processes across time. Numerous methodological issues may impact our ability to understand how common change in symptom severity is, including varying measurement tools, analytic approaches, and change patterns between symptom domains across time. Potential implications of better understanding and characterizing symptom severity change include incorporation of severity change patterns and predictors of change into research on biomarkers, and consideration of such predictors as moderators or mediators of change in clinical practice.

1. Introduction

In 1943, Leo Kanner first identified a unique behavioral phenotype (Kanner, 1943), now known as autism spectrum disorder (ASD). In this initial work, Kanner described eleven children (eight boys, three girls) between the ages of 2 to 8, all of whom exhibited a common set of symptoms. From early childhood, these children did not relate to others as expected, failed to use language to communicate, showed an obsessive tendency to maintain sameness, a restricted repertoire of behaviors, and limited spontaneity. In 1971, Kanner outlined the long-term outcomes of 9 of these 11 children: Two gained independence skills and were fully employed adults, one lived on a farm with his adoptive parents, five experienced worsening symptoms and lived in state hospitals or institutions, and one had died (Kanner, 1971).

Kanner's depictions of longer-term outcomes and change in behavioral phenotype were an important first step for evaluating developmental trajectories. They lacked in methodology, however, as they were mainly based on letters from family members and reports of treating physicians or educational staff at institutions. Since then, the rigor of longitudinal studies to evaluate outcomes has considerably increased. This is due to several advancements made in the field including early identification of large samples of autistic children followed prospectively across development (Georgiades et al., 2021; Waizbard-Bartov et al., 2022), individuals of diverse backgrounds being included in research samples (Giserman-Kiss & Carter, 2019), use of innovative analytic techniques for analysis of longitudinal data (Gotham, Pickles, & Lord, 2012; Kim, Macari, Koller, & Chawarska, 2016), and most importantly the development of standardized tools for assessment of autism symptoms (Lord et al., 2000; Lord et al., 2012; Lord, Rutter, & Le Couteur, 1994).

Although the diagnostic definitions of ASD have changed over time, the *DSM-5* currently separates the core symptoms into two domains: deficits in social communication and social interaction (SC symptoms), and restricted, repetitive patterns of behavior, interests, and activities (RRB) (American Psychiatric Association, 2013). In the 1980s, initial standardized assessment measures were developed to evaluate autism

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symptoms, informing clinical judgment and assisting clinicians in determining whether an individual met criteria for an autism diagnosis. The development of such tools changed the state of both autism research and clinical practice, providing a common framework and a valid, reliable way to measure autism symptomatology across researchers and clinicians (Lord et al., 2022).

Two measures, in particular, are now viewed as the "gold standard" assessment tools for autism symptoms: The Autism Diagnostic Interview-Revised (ADI-R) (Lord et al., 1994) and the Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 2000; Lord et al., 2012). The ADI-R is a semi-structured caregiver interview conducted by a clinician trained to a reliability standard on this tool. It assesses both current and early childhood (ages 4–5 years) autism symptoms, and yields three subdomain scores, with the "Reciprocal Social Interaction" and "Communication" (verbal and nonverbal) subdomains assessing SC symptoms and a "Restricted, Repetitive, and Stereotyped Patterns of Behavior" subdomain for assessing RRB symptoms (Lord et al., 1994). In contrast, the ADOS is a semi-structured assessment based on direct observation of autism symptoms in a standardized setting by a trained clinician. The current version (2nd edition; ADOS-2) includes five modules, each adapted for use with individuals of a specific age and/or language development level, from pre-verbal to fluent speech. The ADOS-2 yields algorithm scores for two subscales: the Social Affect subscale (SC symptoms) and the RRB subscale, as well as an overall total algorithm score. In addition, the ADOS-2 allows for ascertainment of a Calibrated Severity Score (CSS), which is a standardized, 10-point severity metric that transforms algorithm scores into standardized scores relatively independent of individual characteristics such as age and language ability (Gotham, Pickles, & Lord, 2009). The CSS are available for the overall total algorithm score (ADOS CSS) as well as for the Social Affect (SA CSS) and RRB (RRB CSS) algorithms, separately (Hus, Gotham, & Lord, 2014). The CSS allows researchers and clinicians to use the ADOS-2 to measure autism symptom severity in a standardized way across modules, time, and developmental abilities. Most studies evaluating core autism symptom trajectories across time have incorporated the ADI-R, the ADOS, or both (Gotham et al., 2012; Pellicano, Cribb, & Kenny, 2019; Shattuck et al., 2007).

Several other standardized tools have been developed for the purpose of measuring autism symptoms. These include questionnaires based on parental report such as the Autism Behavior Checklist (ABC) (Krug, Arick, & Almond, 1980), the Social Responsiveness Scale (SRS) (Constantino & Gruber, 2005), and the Social Communication Questionnaire (SCQ) (Rutter, Bailey, & Lord, 2003); the Childhood Autism Rating Scale (CARS), a combination of clinician-rated observation informed by parent report (Schopler, Reichler, & Renner, 1986); and clinical interviews with parents such as the Diagnostic Interview for Social and Communication Disorders (DISCO) (Wing, Leekam, Libby, Gould, & Larcombe, 2002).

The ADI-R, ADOS, and these other standardized measures were not developed with the purpose of evaluating change in autism symptom severity over time. But, as they have been used repeatedly for diagnostic purposes with the same individuals, longitudinal studies have utilized them to examine individuals' symptom trajectories across the lifespan and to evaluate the possibility of change in symptom levels.

Several large studies have indicated that, for most individuals, autism symptom severity tends to remain stable across the lifespan (Gotham et al., 2012; Szatmari, et al., 2015; Venker, Ray-Subramanian, Bolt, & Ellis Weismer, 2014). In contrast, a recent study examined patterns of autism symptom trajectories in a large sample of children (*N* autism symptoms are prone to change across time is not yet clear. In addition, once change does occur, little is understood about what accounts for, or predicts, such change. Better understanding the ways in which autism symptoms change in severity over time could have important implications for intervention.

1.1. Aims and methods of the current review

The current paper reviews and synthesizes the literature focused on autism symptom severity trajectories over the lifespan. We evaluate 2 key questions: (1) How common is autism symptom severity change, and what characterizes it? and (2) What factors (individual/developmental characteristics as well methodological factors) influence findings concerning symptom severity change?

As the goal of this review is to both characterize symptom severity change as well as to identify factors that impact the inconsistent findings in the area, we describe a range of different aspects for each of the studies surveyed including main results, measure(s) used, analytic approach, sample characteristics and developmental period evaluated. We do this in order to identify factors that can help unpack different underlying causes that might contribute to the variability in findings in the area of symptom severity change.

Studies included in the current review were selected based on the following inclusion criteria: A) Study evaluated samples incorporating only individuals diagnosed with autism, B) Study participants were assessed repeatedly at multiple time points across development, C) Study used standardized assessment tools at each of the assessment time point (with the same tool used repeatedly at 2 or more time points), D) Study analyses assessed change in the severity of autism symptoms for the sample (either for total symptoms or both symptom domains separately). Since the ADI-R and ADOS-2 are considered to be the gold-standard, most widely used assessment tools for autism symptoms, we focus mainly on studies employing these measures across time. A detailed account of studies reviewed can be found in Table 1. The current review incorporates studies published by April 2022.

The term "autism symptom severity" includes a broad range of possible definitions. In the current review, we define autism symptom severity level based on scores on a standardized assessment tool for autism symptoms. We use the term "change in autism symptom severity" to mean statistically significant change in such severity levels across time. The authors recognize that traditional medical model terms related to autistic traits/characteristics, such as "symptom" and "severity", have the potential of contributing to stigmatization and marginalization of autistic individuals. These terms are used in the current review in order to maintain consistency with the studies surveyed (and the measures they rely on) and so the use of these terms was unavoidable.

2. Does autism symptom severity change across time? Assessing change using standardized measures

2.1. Parent/caregiver report

2.1.1. ADI-R

In this section, we describe studies employing the ADI-R across childhood, from childhood into adulthood and prospectively from childhood, through adolescence and into adulthood, to identify autism symptom trajectories across time. All studies are detailed in Table 1

Two studies have employed the ADI-R to identify short-term change in autism symptom severity across childhood, between 2 and 7 years of age. During this period, some children were found to remain stable while others decreased in severity, and to different degrees (Charman et al., 2005). Severity change has also been shown to differ between toddlerhood (from 2 to 3 years of age) and early childhood (from 3 to 7 years) (Charman et al., 2005), as well as between symptom domains based on childrens' symptom levels and other characteristics (Starr, Szatmari, Bryson, & Zwaigenbaum, 2003).

Table 1
Summary of studies reviewed.

	Study	Sample description	Measures	Analytic approach	Summary of results
1	Starr et al. (2003)	Autism and Asperger Syndrome Trajectories Study sample: 58 children diagnosed with autistic disorder or Asperger's syndrome, evaluated at ages 4–6 and again after a 2-year follow-up (ages 6–8).	Parent report: ADI & ADI-R	Mean change in ADI-R subdomain scores (communication, social, and repetitive behaviors) was evaluated for both diagnostic groups.	The autistic disorder group exhibited a larger decrease in communication symptoms while the Asperger's group demonstrated a larger increase in social symptoms. RRBs remained stable for both groups across time.
2	Charman et al. (2005)	Newcomen Centre, Guy's Hospital London, UK sample: 26 children evaluated at ages 2, 3, and 7.	Parent report: ADI-R	Mean change in ADI-R subdomain scores (verbal or nonverbal communication, social, and repetitive behaviors) was evaluated for the sample.	Autism symptoms changed across childhood for the three subdomains, but change was highly variable in pattern, rate and across childhood periods. Some children's scores remained stable while others decreased in severity, and to different extents (differences that increased as children grew older). Change also differed between the two periods evaluated (ages 2–3 and 3–7).
3	Lord et al. (2015)	Early Diagnosis Study sample (EDX): 85 individuals evaluated in early childhood at ages 2, 3, and 5, middle childhood at age 9, and late adolescence at age 19.	Parent report: ADI-R	Three groups were derived based on age 19: ASD-Less Cognitively-Able (VIQ	All three groups showed decreases in the social-communication domain and in one subtype of RRB (repetitive sensorimotor). Only the ASD-Less Cognitively-Able group increased in one RRB type (Insistence on Sameness). Rate of change differed between the groups. For social-communication symptoms, the ASD-Less Cognitively-Able group decreased in a linear way while both other groups showed quadratic decreases.
4	Fecteau et al. (2003)	H sample: 28 verbal children and adolescents between 7 and 20 years of age.	Parent report: ADI-R; comparing past/lifetime and current scores	Mean change in ADI-R subdomain scores (communication, social, and repetitive behaviors) & the proportion of participants who either decreased, increased, or remained stable in subdomain items across time.	On average, participants showed significant severity reductions in all subdomains over time. Evaluating severity change patterns individually at the item level, symptoms tended to either decrease in severity or remain stable, with few instances of increasing severity.
5	Piven et al. (1996)	University of Iowa Child Psychiatry Clinic sample: 38 individuals with nonverbal IQ	Parent report: ADI-R; comparing past/lifetime and current scores	Mean change in ADI-R subdomain scores (communication, social, and ritualistic/repetitive behavior) between past/lifetime and current scores, and the proportion of participants showing decreases in each subdomain across time.	The full sample decreased in both social and communication symptoms and remained stable in ritualistic, repetitive behaviors. Individually, significant decreases in severity were seen in 82% of participants for the social and communication subdomains and for 55% of individuals in ritualistic, repetitive behaviors.
6	Boelte and Poustka (2000)	Frankfurt University site, International Molecular Genetic Study of Autism Consortium sample (IMGSAC): 76 individuals aged 15–37 (and an additional 17 characterized with broader autism phenotype).	Parent report: ADI-R; comparing past/lifetime and current scores	Correlations between ADI-R subdomain scores (communication, social, and restricted, repetitive behaviors) for past/lifetime and current scores for the full combined sample.	On average, there was a moderate tendency for symptom severity to decrease across time, with symptoms being milder at later ages.
7	Seltzer et al. (2003)	Adolescents and Adults with Autism Study sample (AAA):405 individuals divided into two cohorts: adolescents (*N*	Parent report: ADI-R; comparing past/lifetime and current scores	Compared current and past/lifetime scores for the ADI-R subdomains (communication, social, and repetitive behaviors) for the adolescent and adult cohorts, and percentage of individuals showing symptom decrease at the item level across time.	Average decreases in symptom severity were evident across time, predominantly for social and communication symptoms, for both adolescents and adults. More individuals decreased in items related to social and communication symptoms compared to RRB. Severity change patterns varied between the two age cohorts, with adolescents and adults showing different symptom manifestations across time.
8	McGovern and Sigman (2005)	Marian Sigman's UCLA Longitudinal Autism Project sample: 48 individuals evaluated at middle childhood (age 12) and late adolescence (age 19).	Parent report: ADI-R; comparing past/lifetime and current scores at middle childhood and adolescence	Analyzed ADI-R subdomain scores (verbal and nonverbal communication, social, and repetitive behaviors) across 3 time points: past/lifetime, middle childhood and adolescence, using single factor repeated measures GLM in the full sample.	On average, current scores (at both middle childhood and adolescence) showed a decrease in symptom severity for all subdomains compared to early childhood. Social symptoms and RRB also decreased in severity from middle childhood to adolescence.
9	Gillespie-Lynch et al. (2012)	Marian Sigman's UCLA Longitudinal Autism Project sample: Extended the work of McGovern and Sigman (2005)	Parent report: ADI-R; comparing past/lifetime and current scores	Compared scores for the ADI-R subdomains (social, nonverbal communication, and repetitive	No change was evident across adolescence and adulthood for non-verbal communication symptoms and

(*continued on next page*)

Table 1 (*continued*)

	Study	Sample description	Measures	Analytic approach	Summary of results
		to include an additional time point in adulthood (12, 18 and 26.6 years) for a subgroup of 20 individuals.	including an additional time point in adulthood	behaviors) for past/lifetime time point and three current scores at middle childhood, adolescence, and adulthood.	RRB. Social symptoms decreased in severity across adolescence and increased in severity into adulthood.
10	Shattuck et al. (2007)	AAA sample: Symptom trajectories were evaluated prospectively at 4 time points (every 18 months) across a 4.5-year period for 241 adolescents and adults ranging from 10 to 52 years of age.	Parent report: ADI-R	Mean sample ADI-R subdomains (social, verbal and nonverbal communication, and repetitive behaviors) were compared between the first and fourth (final) time points & individual change scores were computed for each participant using a standardized mean difference in scores between first and last time points.	On average, most symptom subdomains decreased in severity across the period evaluated (except nonverbal communication symptoms, which remained stable). Symptom severity change was highly variable between individuals; many exhibited stable severity levels (22.9%–54.5% depending on subdomain), a substantial proportion decreased in severity (26.1%–58.5%), and a minority of participants increased in symptom severity (14.5%–25.7%).
11	Taylor and Seltzer (2010)	AAA sample: Extended trajectories of Shattuck et al., 2007 to include an additional 5th time point, evaluating autism symptoms across a nearly 10-year period for 242 individuals with a mean age of 16.3 years at study entry.	Parent report: ADI-R	Multilevel growth models were estimated for the full sample using all time points available for each ADI-R subdomains (social, verbal and nonverbal communication, and repetitive behaviors).	All ADI-R subdomains significantly decreased in severity across adolescence and during the transition to adulthood. The rate of decrease varied based on the developmental period being assessed. Specifically, the rate of improvement significantly slowed (reduced by half) after high school exit and during the transition to adulthood.
12	Woodman et al. (2015)	AAA sample: Extended trajectories of Shattuck et al., 2007, evaluating 313 adolescents and adults ranging in age from 10 to 49 years at Time 1 across 5 time points during an 8.5-year period.	Parent report: ADI-R	Mean sample ADI-R subdomains (social, verbal and nonverbal communication, and repetitive behaviors) were compared between the first and final time points and individual change scores were computed for each participant using a standardized mean difference in scores between first and final time points. Multilevel growth models were also estimated for the full sample using all time points available for each ADI-R subdomain.	On average, all ADI-R domains decreased in severity across the period evaluated, but severity change varied between individuals; 55% (20%–44% depending on specific subdomain) exhibited stable severity levels for total autism symptoms, 33% (35%–61%) decreased, and 12% (16%–22%) of individuals increased in total symptom severity into adolescence and adulthood.
13	Woodman et al. (2016)	AAA sample: Extended trajectories of Shattuck et al., 2007, evaluating 364 adolescents and adults ranging in age from 10 to 52 years at Time 1 across 2–6 time points during a 10-year period.	Parent report: ADI-R	Change in autism symptoms as well as other outcome variables was examined through hierarchical linear growth modeling. Then, mixture modeling was used to identify latent classes based on all outcome measures combined.	For the entire sample, autism symptoms followed a linear pattern, decreasing in a constant way across the study period. Two latent classes were observed: Class 1 (45%) had a lower initial symptom severity level and a faster rate of severity decrease. Class 2 (55%) had a higher mean initial severity level and decreased at a very slow rate across time.
14	Eaves and Ho (2004)	Sunny Hill Health Centre for Children sample: 49 children evaluated at age 2.5 and again at age 5.	Clinician observation: CARS	Mean CARS scores compared across the two time points and individual change in CARS score.	On average, mean symptom levels did not change across early childhood for the full sample. Variability in severity change was evident between children, with 33% showing change in symptom levels (either increase or decrease in severity) across this period.
15	Pellicano (2012)	University of Western Australia sample: 37 children with IQs	Parent report: SCQ	Mean symptom domain scores (social, communication, and repetitive behaviors) were compared for the entire sample combined across the period studied.	On average, ASD symptomatology improved for all symptom domains across the 3-year period, but magnitude of change differed according to the symptom domain evaluated; improvement was most evident for social interaction symptoms, more than for communication symptoms and RRB.
16	Eaves and Ho (1996)	Sunny Hill Health Centre for Children sample: 76 children assessed at an average initial age of 7.6 and again at 11.5 years.	Clinician observation: CARS	Mean sample CARS scores compared across time.	A slight decrease in symptom severity for the full sample was evident during middle childhood.
17	Mesibov et al. (1989)	North Carolina's TEACCH program sample: 89 individuals evaluated from middle childhood (mean age 8.7) into adolescence (mean age 15.9).	Clinician observation: CARS	Mean CARS scores compared across time.	A decrease in symptom severity from middle childhood into adolescence was evident for the full sample.
18	Fountain et al. (2012)	California Department of Developmental Services (DDS) records: Symptom trajectories were	Parent report: based on the Client Development Evaluation Report	Group-based latent trajectory models (for identifying subgroups in the sample) were estimated separately for	Children were characterized by six developmental trajectories for autism symptoms. Most trajectories showed

(*continued on next page*)

Table 1 (*continued*)

	Study	Sample description	Measures	Analytic approach	Summary of results
		evaluated in a large sample of 6975 children from age 2–14.	interview, conducted by trained staff at the DDS	symptom domains (social, communication, and repetitive behaviors).	change in severity, but change differed between children and symptom domains. Severity decreases were most evident for SC symptom trajectories while stability was common in RRB trajectories. Symptom trajectories exhibited variable patterns and rates of change; some children showed rapid improvement while others demonstrated slower/less marked improvement over time. Substantial decreases in symptoms were most robust before age 6, at which time the rate of severity decrease reduced compared to the rate evident during early childhood.
19	Szatmari et al. (2009)	Autism and Asperger Syndrome Trajectories Study sample: 64 individuals diagnosed with either Autism or Asperger's syndrome, without intellectual disability, evaluated 2–5 times from age 4–6 to late adolescence (age 17–19).	Parent report: ABC	Individual growth trajectories were estimated using hierarchical linear models and growth curves trajectories for both diagnostic groups (autism and Asperger's syndrome) were compared.	Both diagnostic groups decreased in severity of symptoms across the period evaluated, and at similar rates. The rate of decrease changed across time; improvement slowed or plateaued during later ages.
20	Lin et al. (2022)	Children's Mental Health Center of National Taiwan University Hospital Longitudinal Sample: 106 children (6–11, mean age 9) and 48 adolescents (12–19, mean age 14.5) with FSIQ	Parent report: SRS	Entire group trajectories for each SRS subdomain (social communication, stereotyped behavior, social awareness, social emotion) were compared from first to second measurement and modeled across time for repeated measurements.	Autistic symptoms were stable for the group of children over time. There was a modest improvement in social communication and decreased stereotyped behaviors in the adolescent group across time.
21	Simonoff et al. (2019)	Special Needs and Autism sample (SNAP): A population-based epidemiological sample of 158 individuals evaluated at ages 10–12, 15–16, and 23 years of age.	Parent report: SRS	Latent growth curve models were estimated for symptom trajectories. Trajectories were also modeled based on school placement: mainstream school (including a special unit in a mainstream school) vs specialist school (a unit or special school for intellectual disabilities, emotional / behavioral problems or autism)	Autism symptom severity remained unchanged for the entire sample over time. But symptom trajectories differed based on school placement: individuals attending specialized schools increased in severity over time compared to those attending mainstreamed schools, while those attending mainstream schools had lower symptom levels at older ages (23) compared to those attending specialist schools.
22	Kim et al. (2016)	Yale Toddler Developmental Disabilities Clinic sample: Evaluated symptom trajectories (and short -term outcomes) during very early childhood, from age 2 to 3, in a sample of 100 toddlers.	Clinical observation: ADOS CSS	Used hierarchical clustering analysis based on a set of variables assessed at age 2, including ADOS SA and RRB scores as well as additional outcome variables, to identify latent clusters.	Three out of four latent groups in the sample showed stable symptom severity trajectories (based on ADOS CSS) across the one-year period, with only one group (16%) of toddlers showing symptom severity increase.
23	Giserman-Kiss and Carter (2019)	University-based, Multi-stage Screening Project sample: 60 children of diverse backgrounds (80% racial/ethnic minorities) evaluated from a mean age of 2.4 to 4.4 years.	Clinical observation: ADOS CSS	Comparing mean ADOS CSS scores across time (and after receiving early intervention).	There was a reduction in ASD symptomology across early childhood for all children combined.
24	Gabbay-Dizdar et al., 2021	National Autism Research Center of Israel sample (NARCI): 131 children evaluated twice across early childhood; initial assessment at age 1.2–5 and follow up 1–2 years later.	Clinical observation: ADOS CSS	Individual change scores were computed for change in ADOS, SA and RBB CSS. Children were groups based on age at time of diagnosis; younger (	Children diagnosed before 2.5 years of age were nearly three times more likely (65%) to exhibit considerable reductions in the severity of social symptoms as compared with children diagnosed at older ages (23%). Reductions in autism severity resulted from decrease in SA symptoms despite increase in RRB.
25	Venker et al. (2014)	University of Wisconsin-Madison, Waisman Center, Longitudinal Study of Early Language Development sample: 129 children evaluated 1 to 4 times across early childhood from age 2.5 to age 5.5.	Clinical observation: ADOS CSS	A series of latent-class growth curve models were estimated based on symptom trajectories, identifying 4 latent classes in the sample. Intercept and growth parameters were allowed to vary between, but not within, classes.	Most children (78%) retained stable severity levels, belonging to either persistent-high (36%) or persistent-moderate (42%) trajectory groups. Some variability in severity change was demonstrated, with 8% of children showing "worsening" trajectories and 14% showing "improving" trajectories over time. There was large within-group variability (in individual trajectories) characterizing the groups.
26	Szatmari, et al. (2015)	Pathways in ASD sample: 421 children assessed at 3 time points across early	Clinical observation: ADOS CSS	A semiparametric, group-based approach was used with ADOS CSS to	Two trajectory groups were identified in the sample. A large proportion

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Table 1 (*continued*)

	Study	Sample description	Measures	Analytic approach	Summary of results
		childhood, with initial assessment between ages 2–5 and final assessment at age 6.		identify different developmental trajectory groups (distinct mixtures of trajectories) within the sample.	(89%) showed stable symptom trajectories across time, while a small group (11%) showed declining symptom severity trajectories.
27	Waizbard-Bartov et al. (2021)	Autism Phenome Project sample (APP): 125 children assessed across early childhood, from age 3 to age 6.	Clinical observation: ADOS CSS	Individual change scores were computed across early childhood, and reliable change in symptom severity was determined using the Reliable Change Index statistic. Children were grouped based on their individual tendency for change across early childhood: decreased, increased or stable severity levels in ADOS CSS.	Approximately half (54%) of children in the sample retained stable severity levels, while nearly half showed symptom severity change over this period. Severity change was highly variable between children, with almost 29% decreasing in severity and almost 17% increasing in severity during early childhood.
28	Clark et al. (2017)	Social Attention and Communication Study sample (SACS): Symptom trajectories were evaluated across 3 time points: at age 2 and again at age 4 during the preschool years, and at 7–9 during early school-age, in a sample of 48 children.	Clinical observation: ADOS CSS	Comparing mean ADOS CSS across time for two outcome groups: A Non-Stable ASD group (children who did not meet the ADOS-2 cut-off score for an autism diagnosis at ages 4 or 7–9), and a Stable ASD group (children who continued to meet the ADOS-2 cut-off score).	Both outcome groups demonstrated change in symptom severity across childhood. The Non-Stable ASD group (27%) decreased in symptom severity consistently across childhood and the Stable ASD group (73%) decreased in severity during the preschool period (age 2–4) with subsequent increases in severity during the early school years (age 4–7/9).
29	Waizbard-Bartov et al. (2022)	APP sample: Extended trajectories of Waizbard-Bartov et al. (2021) to evaluate symptom trajectories from early childhood (age 3) up to middle childhood (age 11) in a group of 182 children.	Clinical observation: ADOS CSS	Individual change scores in ADOS CSS were computed across early childhood (age 3–6) and middle childhood (age 6–11) separately, and reliable change in severity was determined using the Reliable Change Index statistic. Children were grouped based on their individual tendency for change across childhood: decreased, increased or stable severity levels.	More than half (51%) of the children changed in symptom severity across time, with 27% decreasing in severity while 24% increased in severity, and 49% remained stable across childhood. Symptom severity change also varied across time; severity decrease was more common during early childhood and severity increase equally common across both periods. But a large increase in SA was evident during middle childhood. At the individual level, most children experienced severity change during only one period and remained stable during the other period.
30	Georgiades et al. (2021)	Pathways in ASD sample: Extended trajectories of Szatmari, et al. (2015) evaluating symptom trajectories across 4 time points, from early childhood (mean age 3.5) up to middle childhood (age 10) for 187 children.	Clinical observation: ADOS CSS	Children were assigned into distinct trajectory groups and (latent clusters) were derived in the sample based on their autism symptoms across time (ADOS CSS as well as SA and RRB scores) and age at assessment.	Two trajectory groups were identified. The first group (73%) showed improvements in symptom severity during early childhood through age 6, at which point the trajectory plateaued across middle childhood. A second group (27%) exhibited reductions in severity during early childhood at a relatively faster pace than the first group and continued to experience decreases in severity during middle childhood as well, but at a slower pace relative to its early childhood improvement.
31	Zachor and Ben-Itzchak (2020)	Assaf Harofeh Medical Center, Zerifin, Israel sample: Symptom trajectories were evaluated from toddlerhood (mean age 2.2) up to adolescence (mean age 13.10) for 68 individuals.	Clinical observation: ADOS CSS	Comparing mean ADOS domain scores (SA CSS, RRB CSS) across time and three outcome groups at adolescence: a low-functioning ASD group (IQ	The group with IQ
32	Gotham et al. (2012)	EDX sample: 345 individuals were evaluated at 2–8 time points, from early childhood (initial assessment at age 2) up to adolescence (age 15).	Clinical observation: ADOS CSS	Generalized Linear Latent and Mixed Models were estimated and children were assigned to 4 latent trajectory classes based on stability or change in ADOS severity across time.	More than 80% of participants showed stable symptom severity across time, belonging to either a persistent-high (46%) or a persistent-moderate (38%) trajectory group. Small groups either "improved" (decreased in severity; 7%) or "worsened" (increased in severity; 9%) across time.
33	Pellicano et al. (2019)	University of Western Australia sample: 27 individuals were evaluated across a 9-year period from middle childhood (mean age 8.5) up to early adulthood (mean age 18).	Clinical observation: ADOS CSS	Comparing mean ADOS CSS for the entire sample across time & evaluating individual change in severity using the Reliable Change Index statistic.	For the entire sample combined, mean symptom severity remained stable across the 9-year period evaluated. At the individual level, symptom severity change was common, with more than half of participants experiencing

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Table 1 (*continued*)

Study	Sample description	Measures	Analytic approach	Summary of results
				significant change over time, either decreasing (29%) or increasing (29%) in severity.

Studies using the ADI-R to evaluate change across a longer time period, from childhood to adolescence or adulthood, have also demonstrated a tendency for symptom severity decrease, with some stability. A number of studies have evaluated symptom severity change from early childhood through adolescence or adulthood by comparing the two types of scores ascertained from the ADI-R: "past/lifetime" scores (symptom presentation at age 4–5) and "current" scores. Most of these studies have identified a decrease in symptom severity from childhood to later ages. Decreases in total symptom severity were identified at a group level (i.e., for entire samples of individuals with ASD combined) (Boelte & Poustka, 2000; Fecteau, Mottron, Berthiaume, & Burack, 2003), as well as when evaluating the different ADI-R subdomains separately. Decreases in social and communication symptoms were found at a group level from early childhood through late adolescence (McGovern & Sigman, 2005), and individually, most participants (82%) tended to decrease in these subdomains (Piven, Harper, Palmer, & Arndt, 1996). RRB have been found to either decrease in severity or remain stable at the group level, while at the individual level, about half (55%) of individuals show decreases in RRB severity (McGovern & Sigman, 2005; Piven et al., 1996). In addition to this general trend of severity decrease, these studies have also found variability in severity change patterns between individuals; most participants either decreased or retained stable severity levels from early childhood up to adulthood, with a much lower incidence of severity increase (Fecteau et al., 2003). Rates of change also differed between individuals.

The longer-term period evaluated, from childhood to adulthood, also allowed these studies to compare differences in severity change across development. While change is evident during both adolescence and adulthood, it can differ in specific pattern (decrease or increase) based on the period evaluated (Gillespie-Lynch et al., 2012), and between symptom domains both in terms of pattern and amount of change (Gillespie-Lynch et al., 2012; Seltzer et al., 2003).

Some studies have used the ADI-R prospectively at multiple time points to evaluate symptom severity change. From childhood to late adolescence, a decrease in the severity of social-communication symptoms was identified, yet the rate of decrease (linear or quadratic) varied based on participants' symptom severity levels and cognitive ability at their final assessment (Lord, Bishop, & Anderson, 2015). Severity change also differed between and within symptom domains, with RRB tending to decrease in one subtype (Repetitive Sensorimotor), and exhibit variable change patterns (including increases) in another subtype (Insistence on Sameness) for some participants. Studies evaluating change prospectively across adolescence and adulthood have shown that autism symptoms, including the majority of ADI-R subdomains, tend to decrease in severity across this period (Taylor & Seltzer, 2010). At the individual level, however, change appears highly variable between participants in this developmental period, with a substantial proportion decreasing (26–61% across the different studies and symptom domains evaluated), many remaining stable (20–55%), and a minority of participants increasing in symptom severity (12–26%) (Shattuck et al., 2007; Woodman, Smith, Greenberg, & Mailick, 2015). In addition, rate of change, specifically of decreasing severity (slower vs faster), has been found to vary during adolescence and adulthood, both between individuals with different characteristics (Woodman, Smith, Greenberg, & Mailick, 2016) as well as across age within this period (Taylor & Seltzer, 2010).

Summary: Evaluating autism symptom severity change using the ADI-R, studies focusing on short-term change across childhood (ages 2 to 7), have shown change to be common across childhood, and also varied between children with different developmental profiles, symptom domains, and across childhood periods. Studies using the ADI-R to evaluate longer-term change, from early childhood to adulthood, have identified a tendency for severity decrease, but severity change was also highly variable between individuals, between symptom domains, and across development. Finally, using the ADI-R to evaluate change prospectively from childhood and across adolescence into adulthood, autism symptoms tended to decrease in severity, with some stability identified as well. Severity change also varied between individuals, in the rate at which individuals decreased over time and change differed between adolescence and adulthood.

2.1.2. Other standardized measures (CARS, SRS, SCQ, ABC)

Some studies have employed other parent/caregiver report measures beyond the ADI-R to identify autism symptom trajectories across childhood through adolescence and up to adulthood (detailed in Table 1).

Similar to those utilizing the ADI-R to evaluate change across childhood through adolescence, studies using other standardized measures across this period have also identified substantial decrease in symptom severity (Lin, Chiu, Wu, Tsai, & Gau, 2022; Mesibov, Schopler, Schaffer, & Michal, 1989; Pellicano, 2012; Szatmari et al., 2009), as well as some evidence of stability (Eaves & Ho, 2004; Lin et al., 2022), over time. These studies have also identified high variability in severity change within samples. Subgroups of individuals (33%) within larger "stable" samples have been shown to either decrease or increase in severity (Eaves & Ho, 2004). Patterns of change seem to also differ based on the developmental period evaluated (e.g., childhood vs adolescence; Lin et al. (2022)). Moreover, rate of change (especially of decreasing severity) differs between symptom domains, with social symptoms decreasing more rapidly than RRB symptoms (Pellicano, 2012). Rate of change also varies across time, with the rate of decrease in symptom severity slowing with age (Szatmari et al., 2009). Finally, in a very large sample (*N*

Simonoff et al. (2019) evaluated autism symptom severity change prospectively across adolescence and adulthood, finding stability across time. However, the pattern of change differed based on educational placement, with individuals attending specialist schools increasing in severity over time compared to those attending mainstreamed schools.

Summary: Evaluation of symptom severity change across childhood to adolescence using a variety of standardized measures shows a tendency for decreases in symptom severity, alongside three types of variability in change: between children, between symptom domains, and in pattern and rate of change within a person across time and developmental period. Evaluation of severity change from adolescence through adulthood indicated symptom stability, but individual change patterns also varied, with some individuals showing a stronger tendency to increase in severity across time.

2.2. Assessments based on direct clinician observation

2.2.1. ADOS CSS

Since the development of the ADOS CSS (Gotham et al., 2009), many studies have used it to evaluate symptom severity change across time. Here, we describe studies employing the ADOS CSS to identify symptom severity trajectories across early childhood, from early childhood through adolescence, and from middle childhood up to adulthood (detailed in Table 1)

Evaluating symptom severity change during early childhood, several studies have identified large groups of children (ranging from 78% to 89% across samples) characterized by stable symptom trajectories (Kim et al., 2016; Szatmari, et al., 2015; Venker et al., 2014). They also showed some variability in change between children, with smaller subgroups either decreasing (11%–14%) or increasing (8%–16%) in severity. Another study, however, identified higher prevalence of change during this period, with 29% of the children decreasing and 17% increasing in severity (54% retained stable levels) (Waizbard-Bartov et al., 2021). Reduction in symptom severity has also been found for children who had received intervention during early childhood (Gisserman-Kiss & Carter, 2019), with higher rates of decreasing severity identified among children diagnosed early (65%) compared to those diagnosed at a later age (23%) (Gabbay-Dizdar et al., 2021).

The ADOS CSS has also been used to evaluate symptom trajectories beginning in early childhood and across a longer duration, up to middle childhood and adolescence. Most studies have identified high prevalence of severity change, again characterized by substantial variability. Grouping participants according to their individual severity change patterns, 7–27% of individuals have been shown to decrease in symptom severity with 9–24% showing increases in severity across this period (Georgiades et al., 2021; Gotham et al., 2012; Waizbard-Bartov et al., 2022). Other studies that have grouped participants based on their individual outcomes in adolescence or adulthood (e.g., retaining/not retaining ASD diagnosis, having typical-range IQ or intellectual disability) have found that most individuals (79–100%) show change in symptom severity levels over time, whether decreasing or increasing in severity (Clark, Barbaro, & Dissanayake, 2017; Zachor & Ben-Itzchak, 2020).

These studies also suggest that symptom severity change is characterized by variability across development. Severity change patterns appear to differ between early childhood/preschool years and middle childhood/school-age, with earlier ages having a stronger tendency toward severity decrease, and later ages being characterized by a slower rate of severity decrease, a plateauing symptom trajectory, or increasing severity (Clark et al., 2017; Georgiades et al., 2021; Waizbard-Bartov et al., 2022). A recent study found that, at the individual level, most children tend to experience severity change during either early *or* middle childhood, remaining stable during the other period (Waizbard-Bartov et al., 2022).

One study used the ADOS CSS to evaluate symptom severity change from middle childhood into adulthood. While symptom severity appeared stable across this period at a group level, at the individual level, severity change was quite common. More than half of individuals were shown to experience significant change, either decreasing (29%) or increasing (29%) in severity (Pellicano et al., 2019).

Summary: While all studies reviewed using the ADOS CSS have identified some change in symptom severity during early childhood, some have identified a strong tendency for symptom stability while others have emphasized a tendency for severity decrease during this period. Thus, the extent to which autism symptoms either change or remain stable across this period is unclear (and might also be related to other characteristics). Studies using the ADOS CSS to evaluate change from early childhood through adolescence have shown change to be common across this time, with substantial proportions of children either decreasing or increasing in severity. Severity change also differed across time and between developmental periods, with decreases being more prominent during early childhood, and middle childhood being characterized less often by symptom decreases and more often by stable trajectories or increasing symptom severity. Only one study has focused on change from middle childhood into adulthood using the ADOS CSS, showing that the majority of individuals experienced change in severity (either increasing or decreasing) rather than stability through this developmental period.

2.3. Summary: does autism symptom severity change over time, and how is change characterized?

Most of the studies reviewed above suggest that, rather than remaining stable over time, autism symptoms change in severity in a substantial proportion of individuals. Moreover, the evidence indicates that the most common pattern of change over time is decreasing symptom severity. More specifically, most studies reviewed describe decreases in the mean severity level of entire groups, or among substantial proportions of individuals within a sample, as the dominant pattern of change across time. However, findings are not consistent across all studies, and some have identified very large groups of individuals that retain stable symptom levels.

Findings also suggest symptom severity change is characterized by extensive variability. Specifically, three types of variability were identified. The first is *between*-person variability, that is, variability in patterns of change, indicating that autism symptoms change differently for different individuals or groups of individuals. Many individuals show decreases in symptoms over time, while a substantial proportion retain stable symptom levels, and a relatively smaller subgroup appears to increase in symptom severity. Even among individuals who demonstrate the same general pattern of change, rates of change across time can differ with symptoms changing at either a slower or more rapid pace. For instance, Fountain et al. (2012) identified 6 distinct trajectories of communication and of social symptoms across childhood, each of them showing different rates of symptom severity decrease.

The second type of variability identified is *within*-person variability, that is, variability in change across time/development within a specific individual. These are differences in pattern and rate of change across time and development, within a person's own trajectory. For example, Waizbard-Bartov et al. (2022) found that most children experience severity change (increase or decrease) rather than stability during either early *or* middle childhood, but not both (i.e., most retain stable severity levels during the other period). Many studies indicate that decreases tend to occur at faster rates during earlier ages, either slowing or plateauing with time (Fountain et al., 2012; Georgiades et al., 2021; Lord et al., 2015; Szatmari et al., 2009; Taylor & Seltzer, 2010; Waizbard-Bartov et al., 2022). It is important to note that these different types of variability (between and within person) are not mutually exclusive. For instance, rates of change can differ both between different individuals or groups as well as within a specific individual across various developmental periods and across symptom domains (see below).

The third type of variability identified is *between symptom domains*. Social-communication and RRB symptoms (and subcategories of RRB) appear to show different change patterns within entire samples (Pellicano, 2012), within subgroups of individuals in a given sample (Lord et al., 2015), and within specific individuals across time (Fountain et al., 2012). For example, subgroups of individuals have been found to decrease in one symptom domain (SC symptoms) and increase in the other (RRB subcategory Insistence on Sameness) (Lord et al. (2015).

3. Research gaps: contributors and implications

The significant variability characterizing symptom trajectories in autism presents a challenge to the analysis of change and the ability to draw consistent conclusions regarding its prevalence. Findings are mixed and substantial gaps in the literature are apparent. In addition, studies in this area have utilized many different methodological

approaches to identify and analyze changes in symptom severity over time. These different research approaches may have contributed to the mixed pattern of results reported in the literature. Indeed, a number of factors may contribute to such differences, including the use of diverse standardized tools for assessing autism symptoms, the variety of analytic methods employed for evaluating change, and the fact that the two symptom domains show different severity change patterns across time, yet are often lumped together.

3.1. Measurement issues

The use of different standardized assessment tools may have contributed to somewhat different results. Studies utilizing the ADI-R, a clinician-administered parent interview, have consistently identified decreases in symptom severity across development (Fecteau et al., 2003; Lord et al., 2015; McGovern & Sigman, 2005; Woodman et al., 2015). Studies employing the ADOS CSS, in contrast, have yielded more mixed results, especially concerning the prevalence of severity change during early childhood. As noted previously, several studies using the ADOS CSS have documented substantial decreases in severity across this period (Clark et al., 2017; Georgiades et al., 2021; Giserman-Kiss & Carter, 2019; Waizbard-Bartov et al., 2021), while others have emphasized symptom stability (Gotham et al., 2012; Kim et al., 2016; Szatmari, et al., 2015; Venker et al., 2014).

Most studies that have identified large groups of children with stable symptom trajectories have used the ADOS CSS. This could suggest that the ADOS CSS is better at identifying stable trajectories than other measures, or that it is less sensitive to capture change; that is, it requires relatively higher "amounts" of severity change in an individual's trajectory over time for such change to manifest in the measurement. Indeed, a meta-analysis of studies that used the ADOS CSS to evaluate symptom severity change from infancy to adolescence concluded that the ADOS CSS tends to remain stable over time across most studies (Bieleninik et al., 2017). The authors also added that, while the ADOS CSS is the most phenotypically stable measure of autism symptoms, the limited range along with the very fact that symptoms do appear stable over time might indicate they are less sensitive to change in symptom severity and thus may underestimate it. On the other hand, comparing total symptom scores across time, as with the ADI-R, leads to other serious methodological problems because it essentially compares symptom levels in an unstandardized way among individuals spanning different developmental periods, cognitive abilities, and other differentiating characteristics that might affect symptom presentation. It is critical to keep in mind that these assessment tools were not developed to measure change across time; rather, they were devised to inform clinical judgment regarding an individual's diagnosis at the time of assessment. This emphasizes the crucial need to develop a standardized, sensitive measurement tool with a wide enough range to capture change in symptom severity across time, while considering different individual characteristics. One example of such a tool is the Brief Observation of Social Communication Change (BOSCC) (Grzadzinski et al., 2016), a relatively new standardized measure aimed to quantify subtle changes in social communication skills over short-term periods (such as related to receiving specific interventions). Future longitudinal studies using this measure could explore if it may also be well-positioned and sufficiently sensitive to measure change in symptoms across time.

The fact that autism symptoms present differently across different ages (e.g., children vs. adults) could also impact the measurement of symptom severity change across time and developmental periods (Bal, Kim, Fok, & Lord, 2019). Standardized assessment tools rely heavily on symptom manifestation in childhood and early adolescence. The ADOS, for instance, was originally developed (and has been revised over time) mostly based on symptom presentation in individuals up to 16 years of age (Gotham et al., 2008; Gotham, Risi, Pickles, & Lord, 2007). The ADI-R includes diagnostic cut-off scores for past behaviors only, not accounting for parent-reported current symptom presentation (the Current Behavior Algorithm). To reliably measure and consider symptoms at later ages, however, diagnostic instruments must be sensitive to, and adapted for, symptom presentation across the lifespan (Bal et al., 2019). Several efforts have been made in this direction. For example, an adult self-report version of the SRS-2 was developed (Constantino & Gruber, 2012), symptom presentations on the DISCO were compared between children and recently-diagnosed adults to understand age impacts (Carrington et al., 2019), and the ADOS has been adapted for use with both verbally fluent adults (i.e., Module 4) (Hus & Lord, 2014), and minimally verbal adolescents and adults (i.e., Adapted ADOS) (Bal et al., 2020). As measurement becomes adapted to age-dependent symptom presentations, it is important to determine whether symptom severity change evident across later ages results from true change or, rather, from less reliable assessments of symptoms at these ages.

Differences between rates of change identified using either the ADI-R or the ADOS CSS might also result from the different informants used with each measure. For example, the higher prevalence of symptom severity change, especially severity decrease, identified using the ADI-R might suggest that parents, who are involved in most aspects of their child's life, have more information and are in a better position to *accurately* identify change in symptoms over time compared to clinicians conducting a short assessment in a specific context with a more restricted amount of information. Alternatively, parental-reports of severity change on the ADI-R might be *inflated* compared to those on the ADOS, as parental report is potentially subject to more biases relative to clinical judgment made using direct observation. For instance, scores on the parent-report based ADI-R have been shown to be affected by parental concerns regarding ASD (Havdahl et al., 2017), and parental report reliant on memory have been previously identified as a serious problem in longitudinal studies (Ozonoff, Li, Deprey, Hanzel, & Iosif, 2018). A third possibility is that a gap between the symptom severity level ascertained based on parent report vs clinician observation might express the fact that symptoms can manifest to different degrees in various contexts for the same individual (i.e., day-to-day experience with familiar others compared to a limited, structured setting with an unfamiliar adult). These are several potential explanations for gaps in severity levels established using different informants, and it remains difficult to sort out the true impact of informant on study findings. This is, of course, exactly the reason why a rigorous clinical assessment of individuals referred for possible ASD, as well as evaluations of severity change over time, should include both parent report as well as direct clinical observation (Havdahl et al., 2017; Lord et al., 2022), allowing for comparison and combination of multi-informant data to create a more representative symptomatic presentation across contexts and perspectives.

3.2. Analytic approaches

A variety of analytic approaches have been used to define, analyze, and interpret symptom severity change. Such differences in methodological approaches may also impact results and contribute to the inconsistent findings in the area. For example, as a result of the large variability in change patterns between individuals, evaluating means (aggregated scores) across entire samples could potentially mask changes occurring across individual participants comprising the samples. For instance, mean scores showing symptom severity decreases for an entire sample might indeed reflect the fact that most individuals decrease in severity to some degree, or rather, that a specific *group* of individuals within the sample substantially decreases in severity, thereby lowering the mean for the entire sample. On the other hand, mean scores showing symptom stability (i.e., no change) over time might be masking the fact that some individuals decrease in severity while others increase. Several studies reviewed herein identified no change in symptom severity levels across time when averaging across entire samples, but once change was analyzed within individuals, between 33 and 58% demonstrated significant symptom severity change

across time (Eaves & Ho, 2004; Pellicano et al., 2019; Waizbard-Bartov et al., 2022). It would thus be highly informative, when evaluating means of entire samples, to also consider and interpret the variability around mean levels and mean changes in symptom severity in order to understand the extent of individual differences within the overall trend.

In an attempt to deal with the widely prevalent between-person variability in severity change, many studies have separated participants into subgroups that show different patterns of change. The different analytic methods used for this purpose, however, might have also contributed to inconsistencies in results across studies. One such approach is mixture modeling (Muth
probability-based latent groups are derived based on the symptom trajectories of all individuals in the sample across time. These groups are characterized by a "shared" pattern of severity change across time points. Many studies utilizing this approach have identified large subgroups that show stable trajectories (Gotham et al., 2012; Venker et al., 2014). Other studies have taken a different approach, evaluating significant change in an individual's severity by comparing levels across time points and often assigning participants into subgroups based on these patterns of individual change (Pellicano et al., 2019; Shattuck et al., 2007; Waizbard-Bartov et al., 2021). Studies employing this latter approach tend to identify larger subgroups of individuals who experience significant symptom severity change across time. In addition, many subgroups in studies of autism severity change are characterized by high within-group variability, as manifested in variability in the direction of change, rate of change, and individual-level deviance from the group trajectory (Georgiades et al., 2021; Georgiades, Bishop, & Frazier, 2017). That is, groups that are described using a cohesive label such as "improving" (Venker et al., 2014), "worsening" (Gotham et al., 2012), or "improving then plateauing" (Georgiades et al., 2021) actually include different patterns of individual change, which "average out" within the group. This within-group variability is especially evident in groups identified using mixture modeling. For instance, Gotham et al. (2012) described a "worsening" (increased severity) group, but about a third of these individuals showed wide variability in change across time, some having lower severity levels in their final measurement compared to previous ones. Similarly, one-fifth of the individuals in Venker et al.'s (2014) "worsening" group showed the same levels of symptom severity from initial to final measurement. A third of the participants in the "Improving" class (decreased severity) remained stable over time (and one participant worsened). This phenomenon also characterizes very large subgroups labeled as "stable severity". Within the two large stable classes identified by Venker et al. (2014), comprising 78% of the sample, roughly 40% of participants evidenced decreases in symptoms, along with 23–33% of participants who increased in symptoms across childhood. The mixture modeling approach requires sufficiently large samples to reliably detect latent subgroups with a shared symptom trajectory (Ram & Grimm, 2009). It may be that the high variability characterizing autism symptom trajectories, in combination with the relatively smaller samples used in longitudinal studies of ASD, impact the ability of statistical models to identify symptom severity change, especially at the individual level. This might contribute to the identification of subgroups with high within-group variability and/or large subgroups interpreted as having stable trajectories. Adding to the challenge is that often it is not clear how different studies specified the models used to identify subgroups. In order to better understand the subgroups yielded by any model, especially concerning within-group variability in the parameters (e.g., initial severity level, change over time), it is important to report how the model was specified. Thus, when evaluating the conclusions of different studies regarding the prevalence of severity change, the method for assigning participants into subgroups must also be considered.

While studies have tried to tackle the between-person variability characterizing symptom trajectories in the ways mentioned above, the within-person variability presents a challenge for analysis as well. Studies evaluating symptom severity change across several developmental periods have identified differences in individuals' change patterns across different ages (Georgiades et al., 2021; Gillespie-Lynch et al., 2012; Szatmari et al., 2009; Taylor & Seltzer, 2010; Waizbard-Bartov et al., 2022), as well as between entire groups evaluated at different developmental periods (Lin et al., 2022; Seltzer et al., 2003). Such differences highlight a potential problem when attempting to define an individual's longitudinal symptom trajectory across age (spanning several periods of time) using a single severity change pattern to represent them all in a combined way. Such a trajectory might not be representative of actual severity change. Rather, it could inadvertently mask different severity change patterns occurring across time and development of clinical importance (Seltzer, Shattuck, Abbeduto, & Greenberg, 2004). Evaluating change across specific developmental periods, however, would provide a more precise portrayal of symptom severity change as well as a meaningful context through which change can be understood (Nordin & Gillberg, 1998).

Last, due to the costly and effortful nature of longitudinal data collection, many of the studies reviewed describe repeated reporting and re-analyses of the same samples as additional data waves are collected with time (see Table 1 for an account of specific samples repeatedly used in different studies). In some cases, these follow up analyses yield somewhat different results compared to previous publications (Shattuck et al., 2007; Taylor & Seltzer, 2010). This issue, typical of longitudinal studies, requires further investigation concerning effects on findings, and specifically on inconsistent findings, in the area of symptom severity change. It is clear, however, that different results reported using the same samples provide additional evidence to the mix of findings when evaluating change patterns across shorter vs longer periods, as well as by using various analytic approaches.

3.3. Symptom-domain trajectories

Differences in change patterns between the two autism symptom domains could affect the combined trajectory in several ways. For instance, ADOS CSS scores are biased toward SC symptoms, as items measuring this domain account for roughly two thirds of the items scored in the ADOS severity algorithms (Lord et al., 2000). This could lead to unequal domain-representation within the combined symptom trajectory. Similar to the fact that different severity change patterns can be averaged-out (increase/decrease) between individuals, this can also occur between the two symptom domains. That is, different (or even opposite) severity change patterns demonstrated by SC symptoms compared to RRB symptoms might average-out within the overall symptom trajectory, masking change occurring in each individual domain. Indeed, SC and RRB symptoms have repeatedly been shown to follow different trajectories across time. SC symptoms, for the most part, show a consistent tendency to decrease in severity (Bal et al., 2019; Fecteau et al., 2003; Fountain et al., 2012; Lord et al., 2015; McGovern & Sigman, 2005) while RRB trajectories tend to either remain stable (Fountain et al., 2012; Gillespie-Lynch et al., 2012; Piven et al., 1996; Starr et al., 2003), decrease (Lin et al., 2022; McGovern & Sigman, 2005; Pellicano, 2012; Shattuck et al., 2007; Woodman et al., 2015), or increase in severity for specific individuals, items, or periods (Charman et al., 2005; Fountain et al., 2012; Lord et al., 2015). This potential pitfall can be difficult to identify as most studies evaluate either the combined symptom trajectory or separate domain trajectories, but not both. One way of preventing these issues would be to analyze symptom domains separately, interpreting change patterns for each domain in addition to their combined presentation in the overall symptom trajectory. This could prove highly informative for understanding which of the processes is propelling change (for instance, in response to intervention) and implications of that change (Hus et al., 2014).

3.4. Summary: methodological impacts on findings in the area of symptom severity change

The variability characterizing autism symptom trajectories renders findings relatively susceptible to, or even biased by, the various research methodologies employed. First, different standardized tools for assessing autism symptoms can contribute to the inconsistent results in this area due to distinct ways of scoring and measuring symptom change, a limited ability to adequately evaluate symptom presentations among adults, and the use of different types of informants (parent-report versus clinician observation), which can lead to conflicting information. Second, various analytic approaches for evaluating change have been used across studies, some of which may inadvertently obscure the between- and within-person differences in change. This can occur by analyzing sample means without considering the variability in change between participants, by dividing individuals into subgroups characterized by high within-group variability that might obscure individual change patterns, and by evaluating change across long durations of time without considering differences across development. In addition, many of the studies reviewed have repeatedly reported on the same cohorts with additional timepoints as these are added to the sample. The impact of repeated analyses of the same data and its effect on findings in the area of symptom severity change requires further investigation. Third, as the two symptom domains show different severity change patterns across time, their composite (overall) symptom trajectory might primarily reflect change in a single symptom domain (usually SC symptoms), and/or fail to genuinely reflect either of these change patterns. Finally, there is currently no consistent criteria across studies to determine how much change, or proportion of individuals experiencing change, is needed for change to be considered present within a given sample (and clinically meaningful for individuals' everyday life). While interpretation of findings is always subjective to some extent, the use of varied measures and analytic approaches in this area also contributes to inconsistencies in the literature; different aspects of similar results can be highlighted or interpreted in contradicting ways.

4. Factors associated with symptom severity change

While the high variability characterizing symptom severity change presents a challenge for analysis, the fact that change does not happen uniformly creates an opportunity to evaluate predictors and impacts associated with specific types of change. For example, what factors may account for the different severity change patterns evident between individuals? And why do distinct change patterns seem to characterize specific periods of development? Several factors may impact the main trends identified concerning symptom severity change.

An overall decrease in symptom severity over time appears to be a robust pattern across many studies (Fecteau et al., 2003; Giserman-Kiss & Carter, 2019; Lord et al., 2015; McGovern & Sigman, 2005; Szatmari et al., 2009; Woodman et al., 2016). Specifically, studies reporting on more recently ascertained cohorts (Clark et al., 2017; Georgiades et al., 2021; Waizbard-Bartov et al., 2022) have also identified higher proportions of individuals that decrease in symptom severity compared to those reporting on older cohorts (Gotham et al., 2012). This can be understood in several ways. First, an increasing appreciation of the heterogeneity characterizing individuals with autism (Harris, 2019) has contributed to more diversity in samples' symptom presentations, capturing individuals with less severe symptom presentations (Hertz-Picciotto & Delwiche, 2009) as well as more females, and those without cognitive or language impairments (Seltzer et al., 2003). This change in sample composition could impact findings in the areas of symptom severity change, as it has been shown that decrease in symptom severity, and a faster rate of decrease, are associated with both having lower initial symptom severity during early childhood as well as belonging to a more-recently born cohort (Clark et al., 2017; Fountain et al., 2012; Georgiades et al., 2021; Szatmari, et al., 2015; Woodman et al., 2016). In addition, an increasingly higher proportion of individuals have access to intensive early intervention, services, and treatments that are specific to autism (Seltzer et al., 2004; Zwaigenbaum et al., 2015). Some studies have documented reductions in symptom severity following early interventions aimed at core symptoms, in both short-term (Giserman-Kiss & Carter, 2019) as well as longer-term (Pickles et al., 2016) outcomes. But this relationship is not consistent across the literature (Gotham et al., 2012; Waizbard-Bartov et al., 2021). Future studies would do well to evaluate how differential types and intensity levels of early intervention associate with symptom severity change across the life span. These factors, however, could result in a high and increasing number of individuals experiencing decrements in severity over time, even more so as individuals with milder symptom presentations and higher cognitive, developmental, and language abilities at a young age have been shown to decrease more in autism severity via early interventions (Bentenuto, Bertamini, Perzolli, & Venuti, 2020; Hudry et al., 2018).

Symptom severity change is also characterized by variability. Differences in other participant-level characteristics might be related to the variability *between*-person–the different severity change patterns demonstrated by individuals. For instance, symptom trajectories have been shown to vary according to sex, with girls more likely to exhibit decreases in symptom severity compared to boys. This sex difference has been found during early childhood (Szatmari, et al., 2015; Waizbard-Bartov et al., 2021) and middle childhood (Waizbard-Bartov et al., 2022), and a recent review concluded that autistic females are more likely to have less intense symptoms and to experience reductions in symptom severity during childhood (Lai & Szatmari, 2019).

Higher cognitive/developmental abilities or not having intellectual disability have also repeatedly been associated with decreases in symptom severity during childhood and into adolescence and adulthood, as well as faster rates of decrease (Clark et al., 2017; Fountain et al., 2012; Georgiades et al., 2021; Gotham et al., 2012; McGovern & Sigman, 2005; Waizbard-Bartov et al., 2021;Woodman et al., 2016; Zachor & Ben-Itzchak, 2020). Increases in severity, however, have been linked with both lower (Simonoff et al., 2019; Waizbard-Bartov et al., 2021) and higher cognitive ability (Gotham et al., 2012; Kim et al., 2016; Venker et al., 2014), showing a less consistent relationship.

The literature indicates the initial severity level at a young age is not necessarily a good predictor of the future severity change an individual will undergo across life. Symptom severity decrease has been documented for children with either higher (Waizbard-Bartov et al., 2021) or lower (Szatmari, et al., 2015; Venker et al., 2014) initial severity levels compared to other children. Increasing severity, on the other hand, has more consistently been shown to occur from initially lower severity levels, at the group level (Gotham et al., 2012; Kim et al., 2016; Venker et al., 2014; Waizbard-Bartov et al., 2021). This does not rule out, however, increased severity that occurs from moderate or high initial severity levels, which might be harder to identify due to ceiling effects in measurement.

Family-related and sociodemographic factors have also been associated with differences in symptom severity change, illustrating how environments can affect individual outcomes, often in an unequal way. Decreases in symptom severity (and faster rates of decreases) have been linked with higher parental education levels (Fountain et al., 2012; Waizbard-Bartov et al., 2022), not belonging to a family of lower socioeconomic status (Georgiades et al., 2021), positive comments made by mothers during a structured task (Woodman et al., 2016), and improvement in mother-child relationship quality (Woodman et al., 2015). In contrast, belonging to a minority group (not being White and/or having a foreign-born mother) (Fountain et al., 2012), parents being younger at the time of child's birth (Fountain et al., 2012; Waizbard-Bartov et al., 2022), parents with lower educational attainment (Fountain et al., 2012; Waizbard-Bartov et al., 2022) and greater neighborhood deprivation (Simonoff et al., 2019) have been associated with increases in severity (or a lower likelihood for fast decreases in severity). It is possible that caregivers who have abundant resources are more

easily able to advocate for their children concerning receiving high quality and intensity of services, and/or to create enriching home and educational environments that promote skill development and support symptom reduction over time (Fountain et al., 2012), and that children who are exhibiting decreases in symptom severity may engage more readily with their parents resulting in improvements in relationship quality. However, it is important to note that the literature is not consistent regarding these environmental factors and other studies have not identified such associations with symptom severity change.

Several studies have also found that educational placement differs based on symptom severity change. While specialist school attendance predicts greater relative increase in symptom severity (Simonoff et al., 2019), individuals that decrease in symptom severity have a higher likelihood of attending inclusive (full or partial) educational settings (Woodman et al., 2016; Zachor & Ben-Itzchak, 2020). It has also been suggested that the relationship between higher IQ and symptom severity improvement might be exerted through educational placement. Mainstream, inclusive settings associated with higher abilities can expose individuals to new experiences, opportunities for engagement and sophisticated interactions with neurotypical peers who serve as role models (Pellicano, 2012; Simonoff et al., 2019), and to inclusive practices and environments (Woodman et al., 2016) that can impact symptom trajectories and outcomes in general (Lord et al., 2022).

The core symptoms of autism have also been suggested to manifest differently across different periods of development (Nordin & Gillberg, 1998). This likely contributes to the variability *within*-person–differences in severity change in an individual's trajectory across time (Georgiades et al., 2014). This is part of the concept Georgiades et al. (2017) termed "chronogeneity: the study of autism heterogeneity in relation to the dimension of time." Varied stages in life are characterized by unique influences, both opportunities as well as challenges, and could thus affect symptom severity in unique ways. Early childhood, usually the time at which children are first diagnosed, is a period characterized by high family involvement and relatively high prevalence of intervention, support, and resources (Lord et al., 2022; Towle, Vacanti-Shova, Higgins-D'Alessandro, Ausikaitis, & Reynolds, 2018). While severity change is variable during early childhood, most studies indicate symptom severity either decreases (Giserman-Kiss & Carter, 2019) or remains stable (Venker et al., 2014) across this time, with lower rates of severity increases. Fountain et al. (2012), for instance, showed substantial decreases in symptoms were most robust before age 6, at which time the rate of severity decrease slowed compared to the rate evident during early childhood. Significant decreases in symptoms, especially in SC symptoms, across early childhood have been suggested to be associated with a parallel development in language ability during this time (Bal et al., 2019).

During middle childhood, children face a significant transition, entering the school system. Multiple challenges characterize this phase including heightened anxiety, increased social pressure, the need to communicate and form relationships with teachers, adjust to a new schedule, actively engage in the classroom, and various attention and sensory challenges (Bolourian, Stavropoulos, & Blacher, 2019; Nuske et al., 2019; Sanz-Cervera, Pastor-Cerezuela, Gonzalez-Sala, Tarraga-Minguez, & Fernandez-Andres, 2017; Sparapani, Morgan, Reinhardt, Schatschneider, & Wetherby, 2016). Services and support are usually provided by the school at these ages and are often less accessible compared to early childhood, depending on the child's characteristics (Lord et al., 2022; Towle et al., 2018). Several studies have identified a turning point in symptom trajectories at the start of middle childhood. While symptom severity tends to decrease in these studies across early childhood, during middle childhood it either continues to reduce but at a slower rate (Fountain et al., 2012; Waizbard-Bartov et al., 2022), plateaus resulting in symptom stability (Georgiades et al., 2021), or shifts altogether to increasing severity (Clark et al., 2017).

As children grow, and especially during the transition to adolescence, they face heightened social intensity and complexity that leads to greater social demand. Such challenges could potentially contribute to the manifestation of new symptoms or exacerbate existing ones (Picci & Suzanne Scherf, 2015; Starr et al., 2003). Surprisingly, most studies find that many individuals exhibit declines in symptom severity across adolescence and into adulthood (Lin et al., 2022; McGovern & Sigman, 2005; Pellicano et al., 2019; Seltzer et al., 2003; Shattuck et al., 2007; Szatmari et al., 2009; Woodman et al., 2015, 2016), in addition to others that maintain stable severity levels (Pellicano et al., 2019; Shattuck et al., 2007; Simonoff et al., 2019) or increase (Pellicano et al., 2019). Change, however, is not uniform in rate and seems to slow over time (Szatmari et al., 2009). Taylor and Seltzer (2010) identified a second turning point in symptom trajectories as individuals face another major transition at the time of exiting the school system. While individual trajectories continued to improve in symptom severity across both adolescence and adulthood, the rate of symptom decrease reduced substantially after leaving school and upon entering young adulthood. Interestingly, the slowing of improvement was most pronounced for those without intellectual disability. In addition to dealing with the change itself, this slowing of improvement might reflect the loss of stimulating educational activities and added difficulties brought on by change or reduction in services received (Taylor & Seltzer, 2010). The decrease in services rendered at the entrance to adulthood (Roux, Shattuck, Rast, Rava, & Anderson, 2015), known as the 'services cliff', could potentially impact individual outcomes such as symptom severity change patterns (Lord et al., 2022).

4.1. Summary: Individual, environmental and developmental impacts on symptom severity change

Several factors could impact symptom severity change across the life span including broadening the definition of ASD which now incorporates less severe behavioral presentations, as well as the increasing rates of early intervention in the community, both associated with severity decreases. Differences in severity change patterns *between*-individuals could be impacted by differences in other characteristics, as decreases in symptom severity have been associated with being female and having higher IQ and/or not having an intellectual disability. Familial and sociodemographic factors might also impact symptom trajectories including parental education level, familial income, and quality of environment. Educational placement (specialized or inclusive) has also been associated with differing severity change patterns. Symptom severity change is also characterized by *within*-person variability, demonstrating different change patterns within the same person across time/developmental periods. Early childhood is a period in which symptoms tend to either (relatively rapidly) decrease in severity or remain stable for most children. During middle childhood, however, symptom trajectories tend to slow in rate of improvement, plateau, or begin increasing in severity, suggesting that a turning point in symptom trajectories may exist at around age 6. During adolescence and adulthood, symptom severity has been shown to decrease for many individuals. However, a second potential turning point has been suggested around the time of school exit/entrance to young adulthood, at which point the rate of symptom improvement declines (despite the general trend for decrease to continue). These "turning points" may be impacted by increasing challenges and more limited resources and services as individuals grow older.

5. Implications and future directions

Understanding the ways in which symptom severity progresses over time is a first step. It must be followed by translating this knowledge to impact and support the lives of those in the ASD community. From a research perspective, groups of individuals with different symptom severity trajectories are of interest for genetic and imaging studies (Hus, Pickles, Cook Jr., Risi, & Lord, 2007; Lord et al., 2015; Szatmari et al., 2007). Such studies may seek to identify biological mechanisms

responsible for changes in severity or resulting from them. For instance, Andrews et al. (2021) identified an association between trajectories of white matter development and children's differential symptom severity change patterns across early childhood. Such biology-behavior links, if identified, could be used as biomarkers for expected symptom severity change in an individual over time. Biological features associated with specific severity change patterns at a young age could be used as potential predictors of expected change. Once identified, they can suggest a child's potential for either symptom severity decrease with time, or, for severity increase and highlight the importance of early intervention to try and prevent this from happening. Biological processes that are found to occur in parallel to specific severity change patterns across time could help in the attempt to uncover biological mechanisms underlying behavioral change.

Although autism symptom severity often changes over time, it remains difficult to predict such change at an individual level. If specific individual traits or environmental factors can be identified that modulate the course of severity change, such factors could be taken into account by professionals as risk and resilience indices of future change and its consequences. For example, being female, having higher IQ (or no intellectual disability), having parents with higher educational attainment, and having a higher-quality environment have all been associated with symptom severity decreases. Experiencing major life transitions and facing social inequities, in comparison, have been associated with worsening change patterns in an individual's symptom trajectory. While facing such challenges should automatically entitle an individual to more support and resources (regardless of other factors), in reality, that is often not the case. In fact, going through major transitions has been associated with a decline in available resources (Roux et al., 2015), and recent evidence suggests non-white autistic students receive less special education services compared to white autistic students (Sturm, Williams, & Kasari, 2021). Understanding the full extent of risk these factors pose for an individuals' outcomes, including their impact on symptom severity change, is relevant for planning support across development. Specifically, they can help create a "road map", marking potential pitfalls ahead for families, service providers, and case managers supporting an individual across their life. Transition planning, for instance, would do well to consider the potential for different life phases to act as turning points for symptom severity change and plan individualized intervention, adaptations, and additional supports accordingly to mitigate the risk of symptom increase and maintain or improve functioning (Bolourian et al., 2019; Georgiades et al., 2021; Taylor & Seltzer, 2010). In addition, the socio-environmental risk factors described for severity increases stress the importance of providing equal access to resources and intervention for all individuals early on (Fountain et al., 2012; Zwaigenbaum et al., 2015).

In addition to implementation of current findings, future research could also expand the assessment of autism symptom severity and change over time through various methodological advances. While the current paper reviews studies utilizing standardized *behavioral* tools alone, novel quantitative, observer-independent measures for assessing autism symptoms and social behavior in general are emerging. Examples include the use of motion tracking to evaluate social symptoms and reciprocity of social interaction (Budman et al., 2019; Lahnakoski, Forbes, McCall, & Schilbach, 2020), and the use of eye-tracking to analyze visual attention style to social and non-social stimuli as an indicator of autism symptom severity (Frazier et al., 2018; Wen et al., 2022). Another advancement made is the broadening diagnostic criteria for ASD, most recently manifested in the new *DSM-5* (American Psychiatric Association, 2013). The majority of samples described in the current review were diagnosed using the *DSM-IV* or *DSM-IV-TR*. Nonetheless, more recently-ascertained samples (Georgiades et al., 2021; Waizbard-Bartov et al., 2021) include higher proportions of individuals that change in symptom severity compared to earlier-ascertained samples (Gotham et al., 2012). Future cohorts which rely exclusively on *DSM-5* diagnostic criteria for study eligibility, may further emphasize the heterogeneity of symptom trajectories and severity change over time. Comparing findings reported from cohorts diagnosed under *DSM-IV* with those diagnosed under *DSM-5* could also be informative regarding the impact of sample diversification on prevalence of symptom severity change. Finally, previous work has shown that specific symptoms change differently across time at an item level. For instance, evaluating change in social-communications symptoms, Bal et al. (2019) found that the severity of the ADI-R item "Shared enjoyment" tends to decrease over time, while the severity of "Inappropriate Facial Expressions" tends to remain stable. Advances in analysis methods, such as the ongoing development of longitudinal network-model approaches (Borsboom et al., 2021), could help identify which symptoms are leading processes of change, or stability, over time.

The complex development of autism severity change across time suggests symptom trajectories are highly unique, formed in a cascading way through interactions between biological predispositions, individual phenotypes, and inputs from the environment. However, if identified, these unique profiles have great potential for both clinical and research purposes. While high variability in severity change presents a challenge for determining prognosis, it also opens a window for potential gains across time.

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Contributors

The first author conceptualized the review, conducted the literature search, provided summaries of past studies, wrote the original draft of the manuscript, reviewed and edited the manuscript. The senior author reviewed and edited the manuscript and provided editorial comments. All authors have approved the final manuscript.

Declaration of Competing Interest

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COMMENTARY

Appendix B:

Autism severity and its relationship to disability

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Abstract

Autism severity is currently defined and measured based exclusively on the severity levels of the two core symptom domains: social-communication and restricted or repetitive patterns of behaviors and interests. Autistic individuals, however, are often diagnosed with other medical, developmental, and psychological co-occurring conditions. These additional challenges such as intellectual disability, limited expressive and/or receptive language, and anxiety disorders, can have a tremendous impact on the day-to-day lives of autistic individuals, for both their adaptive functioning as well as their sense of wellbeing. Furthermore, the initial presentation of core symptoms and their likelihood of changing over time are influenced by the presence of such co-occurring conditions. In order to truly understand how a person

as other challenges should be considered. This approach was recently taken by *The Lancet Commission on the future of care and clinical research in autism*, which proposed the term "profound autism" for a subgroup of individuals presenting with high core symptom severity, co-occurring intellectual disability, and little or no language, who require extensive long-term care. Considering other individual factors such as daily living skills, specific support needs and environmental resources would also enhance the evaluation of disability in autistic individuals. As currently employed in the assessment of intellectual disability, a multidimensional approach to autism could provide a more comprehensive system for classification of impairment. At present, however, there is no formal way to designate the combined effect of these different aspects of autism on a person

sive outlook tha acknowledges impairments capabilities co-occurring conditions, and environmental factors would be useful for identifying subgroups of individuals as well as for determining individual needs and strengths in clinical assessments.

Lay Summary

The severity of a person

core autism symptoms: impaired social-communication and the presence of restricted or repetitive patterns of behaviors and interests. But autistic people often face additional challenges such as intellectual disability, epilepsy, and anxiety disorder, that considerably impact their everyday life, wellbeing, and the need for support. A more complete view of autism severity, one that includes core symptoms as well as additional challenges, could help identify meaningful subgroups of autistic individuals and could be useful in clinical care.

KEYWORDS

ADOS calibrated severity score, autism severity, autism spectrum disorder, autism symptoms, profound autism, symptom severity change

INTRODUCTION

Autism has historically been considered an impairing condition. Based on current DSM5 criteria (APA, 2013), autism includes three levels of severity ranging from "requiring support" to "requiring very substantial support." Judgments of severity are based solely on the characteristics of the two core domains that make up the diagnostic criteria. The first domain comprises deficits in social and communication abilities (social affect). These can manifest, for instance, in failure to use eye contact to initiate communication with others, as well as in social interactions that lack a natural, "back and forth" reciprocal quality. The second core domain is the presence of restricted or repetitive patterns of behavior and interests (RRBs). These can range from engaging in repetitive movements, such as hand flapping, to having an intense preoccupation with highly specific objects or topics. The underlying assumption is that the way neurotypical individuals seek out, initiate and maintain social interactions represents a basic human behavior, and lack of interest or ability to participate in this behavior is considered to be a disability. Moreover, the presence of circumscribed or repetitive behaviors can limit an autistic individual experience of the varied human activities and is again, therefore, considered to be a disability. While clinicians also specify if there is accompanying intellectual or language impairment, these features are not commonly integrated into the overall judgment of autism severity. Moreover, other common, co-occurring conditions in autism such as sleep difficulties, gastrointestinal distress and epilepsy are also not usually considered in evaluating the level of autism severity. This is due to the fact that, as stated above, the DSM-5 specifies levels of autism severity based solely on the core symptom domains and three levels of needed supports, regardless of other individual characteristics.

The severity levels of social affect and repetitive behaviors are described with some specificity in DSM-5. For example, level 3 social communication entails "very limited initiation of social interactions, and minimal response to social overtures from others" while level 1 social communication entails "difficulty initiating social interactions, and clear examples of atypical or unsuccessful response to social overtures of others." Furthermore, these severity levels are explicitly posited to correspond to different levels of functional impairment: Level 1, "without supports in place, deficits in social communication cause noticeable impairments"; Level 2 "social impairments apparent even with supports in place"; and Level 3, "severe deficits in verbal and nonverbal social communication skills cause severe impairments in functioning." Thus, the DSM-5 attaches to the severity levels specific behaviors, degrees of impairment and required support resulting *only from autism-specific symptoms* rather than associated conditions.

Writing a commentary on autism severity at this time is fraught with potential controversy. The autism community is becoming increasingly polarized with some seeing little or no "disability" associated with autism (Kapp et al., 2013) while others view limited social ability as disabling in itself, and/or highlight the significant associated medical issues that cause substantial disability and limit daily functioning (Singer, 2022, November 11). This diversity of opinion on the level of disability associated with autism results, in part, from the enormous heterogeneity in how the core and co-occurring conditions present in individual autistic persons. It goes beyond this, however, since the level of disability is often moderated by environmental factors such as amount and efficacy of intervention, socioeconomic level and availability of quality support services.

In this commentary, we will first review how autism severity is evaluated in a research context. We will then briefly summarize evidence that autism severity in an individual is changeable during development and mention some of the factors that may be associated with severity changes. We conclude with a discussion of why a research estimation of autism severity that corresponds to the DSM-5 levels is not sufficient to closely map on to an individual
riences and challenges. We describe the evolution of classification systems in intellectual disability that now use criteria that go well beyond IQ. In autism, we favor the use of such multidimensional classification systems to determine not only severity levels and concomitant impairment, but also to lead to an understanding of the individual based on his or her support needs. Such a system is consistent with the use of terms such as "profound autism" for those individuals who have not only severe autism symptoms per se but also significant challenges beyond the core symptoms of autism, such as intellectual disability. A multidimensional approach to defining autistic subgroups would undoubtedly achieve a more balanced picture of the impairments and capabilities which are both features of the autistic individual and promote better clinical characterization. It would probably also promote fundamenta biologica research As pointed out by Waterhouse and Gillberg (2014), studying autism spectrum disorder (ASD) as a single syndrome and attempting to find a single underlying brain dysfunction has led research away from directions that may be more productive, specifically individual variation and existence of micro-subgroups.

HOW IS AUTISM SEVERITY ASSESSED IN A RESEARCH CONTEXT?

Autism assessment in a research context is done in diagnostic settings and includes standard assessment tools for evaluation of core symptoms. There are different standardized tools available for this purpose, such as the

Childhood Autism Rating Scale (CARS) (Schopler et al., 1986), the Autism Behavior Checklist (ABC) (Krug et al., 1980) and others. However, the gold standard measures for evaluation of autism symptoms are the Autism Diagnostic Interview-Revised (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS). The ADI-R (Lord et al., 1994) is an in-depth clinical interview conducted with caregivers regarding the individuals current and past behavior. The ADOS (Lord et al., 2000) is a relatively short clinical observation in which a clinician directly assesses the presence of autism symptoms in the individual

2015; Gotham et al., 2009; Hus & Lord, 2014). The CSS yields a symptom severity rating that is standardized relative to individuals of the same age and language abilities. The strength of this approach is that it deliberately limits the impact of other characteristics when evaluating symptom presentation, allowing a non-biased assessment of autism core symptoms.

WHAT IS THE EVIDENCE THAT AUTISM SEVERITY CAN CHANGE DURING DEVELOPMENT?

An autism assessment provides a snapshot of the individual at a specific moment in time. A person
sentation, however, is not constant across the lifespan. Just as people develop in every area of functioning, so does their autism change and develop with time. Studies evaluating this question have shown that for a substantial number of individuals, autism symptoms can significantly change in severity (Elias & Lord, 2022; Waizbard-Bartov & Miller, 2023). The percentage of autistic individuals showing change depends, in part, on which cohort of autistic individuals are described. More recent studies tend to show higher percentages of individuals demonstrating severity change. The tendency for change, however, differs among individuals; some decrease while others increase in severity. There is also change within individuals across different periods of their life; some decrease in severity during early childhood but increase in school years. Moreover, in the same way that developmenta characteristics and co-occurring conditions impact autism presentation at a given period, they also affect its change over time.

Estimates of change in the severity of autism symptoms over time range from 11% to 58% depending on the cohort evaluated and the measures used (Waizbard-Bartov & Miller, 2023). Cohorts identified some time ago (such as the early-diagnosis sample) tend to report lower percentages of change (Gotham et al., 2012). More recently evaluated cohorts (such as the Pathways in ASD sample and the Autism Phenome Project sample) observe higher proportions of individuals that change in symptom severity (Georgiades et al., 2021; Waizbard-Bartov et al., 2022). Decrease in symptom severity ranges from 7% to 29% across differen cohorts (Georgiades et al., 2021; Pellicano et al., 2019; Szatmari et al., 2015; Venker et al., 2014; Waizbard-Bartov et al., 2020).

The tendency to decrease in severity, however, is not uniform across development. Severity decrease tends to be more common during the preschool years compared to later in childhood (Fountain et al., 2012; Lord, Luyster, et al., 2012), when, at school-age, it can either decrease (Waizbard-Bartov e al., 2022) plateau (Georgiades et al., 2021) or increase in severity (Clark et al., 2017). Sex differences also exist, with young autistic girls showing a higher likelihood of reductions in severity than young autistic boys (Szatmari et al., 2015; Waizbard-Bartov et al., 2020, 2022). Conversely, between 8% and 29% of autistic individuals increase in autism symptom severity over time (Gotham et al., 2012; Kim et al., 2016; Pellicano et al., 2019; Waizbard-Bartov et al., 2020). It is not yet clear why some individuals increase in symptom severity across development while others do not. It has been repeatedly found that groups of autistic children increase in severity from an initially low average severity level at the beginning of early childhood (Gotham et al., 2012; Kim et al., 2016; Venker et al., 2014; Waizbard-Bartov et al., 2020). But, for individuals, levels of autism severity at a young age on their own are not strong predictors of future change, highlighting the crucial need for further investigation into this issue.

WHAT INFLUENCES WHETHER AUTISM SEVERITY CHANGES OVER TIME?

Different factors can potentially impact change in core symptom severity levels. Many of these include developmental characteristics as well as the presence of co-occurring conditions. The fact that decrease in severity, especially in social-communication symptoms, is more common during younger ages suggests that reduction in symptoms involves rapid development of language, which tends to occur during the preschool years (Bal et al., 2019). Indeed, children who experience speech delays or remain minimally verbal are less likely to decrease in severity during early childhood (Bal et al., 2019). IQs within the normal range also characterize individuals who decrease in autism symptoms (Georgiades et al., 2021; Gotham et al., 2012; Waizbard-Bartov et al., 2020; Woodman et al., 2015). Conversely, autistic children around age 2 who were functioning

below the developmental age of 12 months showed minimal developmental gains in the next 2 years, especially in the area o socia communication (Hinnebusch et al., 2017). Cognitive ability is associated with other lifestyle factors that can influence changes in autism symptom severity. For example, children with typical range IQ are more likely to attend inclusive schools. By doing so, they are exposed to neurotypical peers who can serve as models for complex social interactions and learning experiences (Pellicano, 2012; Simonoff et al., 2019; Woodman et al., 2016). In fact, those individuals that "lose" their autism diagnosis, (i.e., decrease in symptom severity to no longer meeting the diagnostic criteria for autism

2022)), tend to have typical-range IQ and attend inclusive educational settings (Elias & Lord, 2022; Fein et al., 2013; Lord & Jones, 2012). In some studies, these children with LAD, also had significantly more behavioral therapy between ages 2 and 3 (Orinstein et al., 2014) and showed a reduction in RRBs over the same period (Anderson et al. (2014)). Moreover, having relatively strong cognitive skills can also support a child

and to practice and generalize the tools received (e.g., social skills) in real-life settings (Hudry et al., 2018). Children with intellectual disability, in contrast, often attend special education settings and are not afforded the same exposure to neurotypical environments though they may receive other kinds of needed support. Finally, facets of the social psychology of being a girl might convey specific advantages for symptom severity decrease. Girls environments tend to put a higher emphasis on, and present more opportunities for, social interaction compared to boys (Bargiela et al., 2016; Dean et al., 2017), serving as inherent learning opportunities for social and communication skills and perhaps experiencing higher expectations from others. It is important to note, however, that attempting to meet such social demands might also lead autistic females to "camouflage," that is, mask their autism symptoms in social settings (Hull et al., 2017), which can be experienced as stressful and can lead to detrimental effects for mental health (Hull et al., 2021). It is also possible that biological differences between boys and girls that contribute to sex differences in typical children also contribute to social symptom decrease in autistic girls, but this has not yet been rigorously investigated.

Often, individuals who increase in symptom severity also increase in other types of mental health problems (Baribeau et al., 2022; Waizbard-Bartov et al., n.d.; unpublished observations). Conversely, individuals who show marked decreases in symptom severity may also show decrease in comorbid psychopathology (e.g., anxiety, depression, oppositional defiant disorder; Orinstein et al. (2015)). These parallel increases and decreases make it hard to tease apart behaviors resulting from autism symptoms from those resulting from other psychopathology Fo instance bot social-communication deficits as well as anxiety and depression can lead to impaired social functioning and social withdrawal (Duvekot et al., 2018; Hunsche et al., 2022). This makes it difficult to distinguish which condition is the cause for behaviors such as social isolation and avoidance. Another example is that having co-occurring anxiety is associated with higher levels of RRBs (Cashin & Yorke, 2018; Kim et al., 2020; Rodgers et al., 2012). Furthermore, RRBs and anxiety can also impact each other trajectorie acros developmen (Waizbard-Bartov et al., n.d.; unpublished observations). When experiencing distress, autistic individuals may use some forms of RRBs in order to regulate their anxiety level (Jaffey & Ashwin, 2022). Sensory sensitivities, a type of RRBs, can also lead to specific phobias focused on that sensory stimulus (Green & Ben-Sasson, 2010). Regardless of the diagnosis driving it, behaviors such as social withdrawal and avoidance (of people or stimuli) illustrate how the challenges associated with autism can impact a person

tioning and well-being in daily life Socioeconomic factors might also have an influence on whether a child increases or decreases their autism symptoms. Thus, living in an impoverished neighborhood (Simonoff et al., 2019) or having more poorly educated parents (Fountain et al., 2012; Waizbard-Bartov et al., 2022) are associated with increases in autism severity over time. Lai and Baron-Cohen (2015) discuss the theoretical and clinical difficulties in distinguishing true co-morbidities, overlapping symptoms, and differential diagnosis when considering ASD symptoms in relation to Obsessive-compulsive disorder (OCD), anxiety, depression and other conditions.

WHAT IS THE LIMITATION IN RESEARCH EVALUATIONS OF AUTISTIC SEVERITY IN DETERMINING FUNCTIONAL IMPAIRMENT?

While we have indicated that autism symptom severity, and how it changes developmentally, is important and can be reliably measured, we now turn to the point that autism severity does not provide a complete understanding of the ramifications on quality of life of having autism. Perhaps the major reason that this is true is that the majority of individuals with autism are also diagnosed with other co-occurring condition (Lai et al., 2019) such as intellectual disability, language delays, sleep disorders, gastrointestinal symptoms, anxiety, depression, aggression, and so forth. The DSM definition of autism severity and the ADOS CSS, were not designed to measure autism severity in relation to these co-occurring characteristics. Rather, they were intentionally designed to evaluate autism symptoms *independent* of them (though not perfectly, see Gotham et al., 2009). But, in the context of functional outcomes and well-being, these co-occurring conditions can greatly impact

the way the core symptoms are manifest in an individual

Consider, for example, an individual that received an ADOS CSS of 9 and a second individual that received an ADOS CSS of 5. The first individual would have showed more core-symptom-like behaviors during their ADOS assessment than the second. Comparing specific behaviors, it could mean, for example, that the first individual did not engage in any reciprocal interaction with the assessor, while the second did engage in conversation, but one characterized by poor "back and forth" quality. Similarly, the first individual (ADOS CSS 9) may have played during the ADOS but in a restricted, inflexible way, while the second individual (ADOS CSS 5) played in a more flexible manner that also included the assessor as an active participant in the play. Their behaviors during the ADOS session determined their severity level. But, what if the individual with ADOS CSS of 9 also had average IQ and fluent language, while the second individual, with ADOS CSS of 5, had cognitive disability and minimal speech? Wouldn

ences would affect the degree to which their autism impacts their everyday functioning in real life? In addition, emotional and behavioral issues, such as anxiety or agitation, that appear during the ADOS do affect the CSS and the same issues as reported in standardized measures are related to higher scores on caregiver-report autism measures such as the ADI-R or SRS (Havdahl et al., 2017). These differences, however, are not captured under the research definition of autism severity, based on core symptoms alone. This issue has been more exhaustively discussed in Pickles et al. (2020).

HOW DOES HAVING AUTISM IMPACT A PERSON

Defining and evaluating autism severity based solely on the presentation of core symptoms has the benefit of being specific and measurable. Yet, it does not consider many other meaningful aspects of having autism and thus does not provide a full picture of the challenges and strengths faced by autistic individuals. To understand how autism impacts a person

and everyday life, we must understand how the different aspects of autism interact with each other at specific periods and across development. This cascading trajectory determines the way having autism manifests in a person

that addresses the core symptoms as well as other influential aspects of an autistic person

mensional outlook could prove significant for clinical work, that is, identifying needs, planning intervention, assigning support, and creating future goals.

One imperfect but important type of measure for understanding an individual

ing (Kanne et al., 2011) is a measure that places adaptive skills in communication, socialization, self-care, and motor abilities on an absolute age equivalence scale as well as a standardized score relative to age-matched peers. Examples of such instruments are the Vineland Adaptive Behavior Scale (Sparrow et al., 2017), the Adaptive Behavior Assessment System (Harrison & Oakland, 2015), and the Inventory for Client and Agency Planning (Bruininks et al., 1986), all frequently used with autistic individuals from very early childhood to adulthood (Losada-Puente & Bana, 2022). Several studies find that adaptive skills as measured on these instruments may be more highly correlated with cognitive functioning than with autism symptom severity and that adaptive skills tend to be lower than might be predicted by IQ in autistic individuals (Kanne et al., 2011 Weitlauf et al., 2014).

Another approach to assessing an individual

life challenges is by using instruments focused on support needs in everyday life. These include, for example, the Support Intensity Scale (Thompson et al., 2004) and the Instrument for the Classification and Assessment of Support Needs (Arnold et al., 2009). Both of these tools provide a standardized approach to support needs by measuring, profiling and describing the types and amount of support needed for an individual to successfully engage in daily activities. In addition to objectively measured adaptive skills and support needs, intrapsychic well-being and quality of life are equally important in understanding how autism impacts a person

for the development and use of measures of mood, self-esteem, and life satisfaction for individuals with autism and different levels of cognitive ability. Particular attention should be paid to developmental periods of physical and social transition, such as transition into adolescence and into early adulthood, when coping skills may need to be modified and when social demands and physical changes may place moods under particular stress. Core symptom severity levels have been repeatedly shown to influence quality of life: having higher or more severe autistic traits is associated with lower quality of life for adults (Capp et al., 2022), children and adolescents (Oakley et al., 2021) and preschoolers (as reported by their caregivers) (Lopez-Espejo et al., 2021). However, other factors related to having autism, particularly associated mental health conditions such as anxiety and depression, have also been shown to impact quality of life, even after accounting for core autism traits (Oakley et al., 2021).

There is a multitude of factors and dimensions along which the implications of having autism can be evaluated for impact on an individual

proposed by McCauley et al. (2020) of *autonomy*, *daily*

living skills, *relationships and employment/activities outside the home*, in forms that are consistent with the individual

"profound autism."

THE BENEFITS OF THE TERM PROFOUND AUTISM AND OF DEFINING DIFFERENT SUBTYPES OF AUTISM

The Lancet Commission on the future of care and clinical research in autism (Lord et al., 2022) provided a comprehensive overview of current diagnostic and intervention practices for ASD. Among many proposals to improve the lives of autistic individuals in the next 5 years, was the suggestion for the use of the term "profound autism." This term highlights a clinical presentation of autism that includes high severity of core symptoms, co-occurring intellectual disability, little or no language and requiring extensive long-term care. For these individuals (and their caretakers), the challenges brought on by having autism are substantial and go well beyond the core characteristics. Having profound autism is impairing to functioning and independence and greatly impacts outcomes A major advantage of this term is that it integrates both core and co-occurring conditions to represent the real-life challenges of an individual. Caution must be used, however, not to view individuals with profound autism as inferior or less deserving of their needed supports, due to the high severity of their challenges and disability compared to others on the spectrum. While there are reasonable concerns that providing a term associated with the greatest needs may stigmatize a group, almost all terms, no matter how gentle can be used to stigmatize. The onus is on us to challenge this stigmatization in whatever form it occurs.

The term profound autism, however, pertains to only a subgroup of individuals on the autism spectrum. Other individuals, those, for example, with intact cognitive and language abilities, have the potential for needing reduced, specific supports while leading independent lives. Recent work evaluating outcomes for 232 late-diagnosed autistic adults without intellectual disability in Germany reported that 50.4% had acquired university-entrance qualifications, 21.6% graduated from university and 74.8% were employed (Espeloer et al., 2022). Most importantly, findings from the EU-AIMS study suggest that 36%
autistic individuals *do not* experience a reduced quality of life (Oakley et al., 2021). Such strengths do not imply that these individuals completely escape the struggles and challenges due to having autism. What might also characterize individuals in this group are well-developed coping skills that support their resilience. Skills such as self-advocacy (Kapp, 2020), the ability to compensate for symptoms in social settings (Livingston & Happe, 2017), creating strategies to restrict debilitating aspects of autism fo example sensory overload (Clement et al., 2022) can all help to mitigate the challenges of autism in everyday life. Living in beneficial environments is also a strength that characterizes some individuals on the spectrum. This can be done, for example, by finding a peer group with similar interests, creating social connections that suit them (Tesfaye et al., 2022) and seeking out socia and emotiona suppor (Ghanoun & Quirke, 2022). Another example for establishing beneficial environments is engaging in employment that is suited to their own unique skills and abilities (Cheriyan et al., 2021), for instance, having abundant knowledge about specific topic areas. Some autistic individuals show impressive strengths *associated with* their autism, in areas such as memory, computation, music, visual learning (Bal et al., 2022), attention to details, and the ability to understand reasoning rules and systemizing (Baron-Cohen et al., 2009). For this group of individuals, their autism leads to a complex mixture of struggles and strengths, both of which are relevant when evaluating autism severity and how it impacts impairment in daily life. It would seem valuable to assign a specific name to this portion of the autism spectrum although members of this group might be the best to establish a self-referential terminology. At one point, the term "Asperger syndrome" was closely associated with this group though it was excluded from the latest Diagnostic and Statistical Manual because its use was so inconsistent and the opposite of stigmatization occurred in which families and individuals sought out an Asperger
sounded superior to autism, sometimes to find that they were then excluded from services because the diagnosis implied fewer needs (Lord & Jones, 2012; Lord, Petkova, et al., 2012).

The two subgroups described above represent two extreme ends of a highly heterogenous spectrum of autistic individuals who differ not only on autism severity but also concerning their needs, challenges and abilities. It would appear that most autistic individuals are somewhere in between these two extremes. These individual differences are what makes defining the way autism impacts people
from being severely impairing to promoting a diverse, enriching sense of identity (Cooper et al., 2021). Using this overarching perspective on autism, other clinically meaningful subgroups could be identified, with the goal of encouraging each group to reach its fullest potential in adaptive functioning and subjective wellbeing and to generally flourish in life.

The two defined subgroups discussed above differ on many dimensions. In order to be able to classify all of the intermediate individuals, an attempt could be made to identify the most useful dimensions for both clinical characterization and research progress. Attempts at classifying autism subtypes have been many and varied; perhaps the first attempt at subgrouping by social functioning was as early as 1979 (Wing & Gould, 1979), classifying autistic children
and Active but Odd.

Using a genetic approach, (Zhou et al., 2022) recently identified five new risk alleles in the very large SPARK database of autistic volunteers
genes associated with autism, these new risk alleles do not appear to cause profound autism with intellectual disability. The authors suggest that there are many more single genes of large effect that can cause severe autism that remain to be discovered, but also that additional risk alleles will be discovered in very large samples, that confer a moderate likelihood of autism with intact cognition, potentially with higher intellectual, adaptive, and outcome status. Such approaches, using genetics, neuroanatomy, or neurophysiology as well as behavioral response to intervention and co-occurring conditions, may allow progress in accurate subgrouping of autistic individuals. However, Rapin (2014) discusses the three levels of understanding a developmental disorder like autism (genetic or environmental etiology, pathophysiology, and phenomenology) and cautions that relating categories or dimensions on one level to categories or dimensions on another has not been very successful to date, although it needs to be a goal for the future. The more attainable goal for the near future may be a more universally accepted dimensional characterization of behavior.

A promising model of such characterization was proposed fo individual with intellectua disability (Schalock & Luckasson, 2015). These dimensions are (a) intelligence (b) adaptive behavior (c) health, (d) participation in social activities, and (e) the personal and environmental context in which individuals live their daily lives. For autism, obviously, severity of social and RRB symptoms would have to be added. Fortunately, severity of autism symptoms, intelligence (verbal and nonverbal), and adaptive behavior already have available operationalized, standardized measures. Description of health issues for the autism population would probably benefit from two divisions: conditions that are primarily physical (but may have psychological consequences) such as epilepsy and GI disorders, and conditions that are primarily psychologica (e.g. anxiety depression and obsessionality). Schalock and Luckasson (2015) suggest that their classification system of ID could serve four purposes: describing functional levels, operationalizing the level of supports needs, defining health status, and determining legal status, in relation to specific areas and contexts. Such purposes are very relevant and appropriate for the clinical needs of the autism population, and may promote accurate research into statistically determined subtypes, type and intensity of supports needed, and outcomes of intervention research, although basic biological research might have to involve more finely detailed characterization (Waterhouse and Gillberg "micro-groups" (2014)).

ENVIRONMENTAL INFLUENCES ON AUTISM SEVERITY

It will be obvious that the dimensions proposed by Schalock and Luckasson (2015), plus autism severity, will not be independently developing domains. Beyond the severity of core symptoms and the occurrence of co-occurring health or intellectual conditions, the environment plays a meaningful role in the way autism impacts a person
Having access to more resources in the parental and home environment (Fountain et al., 2012; Simonoff et al., 2019; Waizbard-Bartov et al., 2022) as well as to early diagnosis (Gabbay-Dizdar et al., 2021) and intervention (Pickles et al., 2016) can help promote gains and mitigate impairments over time. Moreover, the environment in which a person lives is not static, but rather changes with time. Some aspects of autism can have differential impacts, meaning they are impairing to different degrees during various developmental stages, depending on the challenges, demands and support available during that stage (Bal et al., 2019). For example, increased social complexities along with decreased resources and support characterize the transition from adolescence to young adulthood, potentially leading the same level of autistic symptoms to have more impairing outcomes for everyday life (Taylor & Seltzer, 2010). With age, enhancing person-environment fit can contribute to an individual
to promoting individual skills (Lai & Szatmari, 2019). There are different ways in which environments can support better fit. Providing adequate services across the duration of development is one example (Laxman et al., 2019). Creating opportunities to engage with non-autistic peers, such as growing up with neurotypical siblings or attending inclusive educational settings (Pellicano, 2012; Woodman et al., 2016) are naturalistic learning opportunities for social modeling and to practice social interaction. On the other hand, autistic individuals and stakeholders repeatedly indicate how environmental stressors such as social biases, negative attitudes, and stigmatization toward people with autism lead to detrimental outcomes and play a major role in their real-life challenges (Cohen et al., 2022; Ghanouni & Quirke, 2022).

CONCLUSIONS AND FUTURE DIRECTIONS

The current definition of autism severity, and the way it is measured in research, is based solely on the severity

levels of the two core symptom domains, controlling for age and language level. The challenges faced by autistic individuals in real life, however, go far beyond core symptoms. Common, co-occurring conditions such as intellectual disability, language delays, and anxiety disorders are as impairing to functioning and wellbeing for many individuals as are the core symptoms themselves. Moreover, core symptoms and co-occurring conditions can interact across development, each influencing the other

approach promoted fo ID (Schalock & Luckasson, 2015), encompasses the impact of IQ scores, but adds other important factors, including adaptive behavior and support needs. In the DSM-5, the severity levels for the core symptoms of autism are already posited to correspond to levels of functional impairment. This further supports the idea that in autism, as is the case for intellectual disability, characterizing autistic individuals for both clinical and research purposes should include not only severity level but should take into account other impactful dimensions that are part of the condition and influence people

If created, a multidimensional, measurable definition of autism severity could potentially be useful for identifying unique subgroups of individuals for clinical purposes, for determining individual needs and strengths in clinical assessments, and for developing intervention goals and plans that involve all the different aspects and challenges relevant to the life of a person with autism. Fein and Helt (2017) also suggest several approaches that could be included in classifying research "micro-groups" (Waterhouse & Gillberg, 2014), such as noting behaviors that seem relatively impervious to environmental differences (e.g., high pain thresholds, social improvement with fever), studying emergence of autism in the first 2 years of life, before intervention has started, and including longitudinal course as a classifier (improving, worsening, and response to intervention, as described above).

One caution is that dimensions and specific variables that are used to characterize individuals with autism are not necessarily the best "outcome" variables. In many cases, baseline characterization will serve to describe the individual at one point in time, while outcome variables may assess change in that variable over time or because of an intervention.

Given this caution, however, one promising avenue in this regard is the development of a core outcome set (COS) for autism. A COS identifies the domains of a condition that are most relevant to clinicians, caregivers and individuals with autism. Recently, a COS for autism was developed by The International Consortium of Health Outcome Measurement in an attempt to calibrate severity along multiple dimensions and with different assessment tools (Patient-centered outcome mesasures, 2022). This system lists published instruments that can characterize core symptoms (social communication and RRBs), as well as adaptive skills, family functioning, sleep and anxiety, other neurodevelopmental disorders (as measured by the Child Behavior Checklist) and general quality of life. This is one promising attempt to conceptualize autism severity based on different components of the clinical presentation, authored primarily by clinicians and researchers with expertise in autism phenomenology. Hopefully, others will take up this system which will allow researchers and clinicians to have a comprehensive characterization of the individual, as well as to select dimensions that are most relevant to their basic biological and intervention studies.

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CONFLICT OF INTEREST STATEMENT

David G. Amaral is on the Scientific Advisory Boards of Stemina Biomarkers Discovery, Inc. and Axial Therapeutics. Catherine Lord receives royalties from Western Psychological Services for diagnostic instruments, including the ADOS and is on Scientific Advisory Boards for Child Mind, Kyo, Springtide, Autism Speaks and the Autism Science Foundation and collaborates with Jazz Pharmaceuticals and GW. Deborah Fein and Einat Waizbard-Bartov have no relevant conflicts of interests to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICS STATEMENT

There is no original human or animal subject data reported in this paper. Therefore, there is no need for an ethics statment.

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