Title

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Journal

Journal of Intellectual Disability Research, 66(3)

ISSN

0964-2633

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Publication Date

2022-03-01

DOI

10.1111/jir.12910

Peer reviewed

HHS Public Access

Author manuscript

J Intellect Disabil Res. Author manuscript; available in PMC 2023 March 01.

Published in final edited form as:

J Intellect Disabil Res. 2022 March ; 66(3): 265–281. doi:10.1111/jir.12910.

Latent Profiles of Autism Symptoms in Children and Adolescents with Down Syndrome

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Abstract

Down syndrome (DS) is associated with elevated rates of autism spectrum disorder (ASD) and autism symptomatology. To better characterise heterogeneity in ASD symptomatology in DS, profiles of caregiver-reported ASD symptoms were modeled for 125 children and adolescents with DS. Participants were recruited through several multi-site research studies on cognition and language in DS. Using the Social Responsiveness Scale-2 (SRS-2; Constantino & Gruber, 2012), two latent profile analyses (LPA) were performed, one on the broad composite scores of Social Communication and Interaction and Restricted Interests and Repetitive Behavior, and a second on the four social dimensions of Social Communication, Social Motivation, Social Awareness, and Social Cognition. A 3-profile model was the best fit for both analyses, with each analysis yielding a Low ASD Symptom profile, an Elevated or Mixed ASD Symptom profile, and a High ASD Symptom profile. Associations were observed between profile probability scores and IQ, the number of co-occurring biomedical conditions reported, sex, and SRS-2 form. Characterising heterogeneity in ASD symptom profiles can inform more personalised supports in this population, and implications for potential therapeutic approaches for individuals with DS are discussed.

Keywords

Down syndrome; social relatedness; autism spectrum disorder; mixture modeling

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The authors have no conflict of interest in the publication of this article.

The study of social development in children with Down syndrome (DS) has led to divergent findings. In some studies, aspects of social development are reported to be areas of relative strength (Fidler et al., 2008; Kasari et al., 2003). Other studies report that people with DS are at elevated risk for autism spectrum disorder (ASD; DiGuiseppi et al., 2010), a condition that is associated with delays in social and communication development (Davis & Carter, 2014). Recent prevalence estimates of ASD in DS (DS+ASD) range as high as 42% (Oxelgren et al., 2017), and even conservative estimates (16%; Richards et al., 2015) are notably elevated relative to the general population (~2%; Baio et al., 2018). These findings suggest the presence of some degree of heterogeneity in outcomes among individuals with DS that is not currently captured in group-level study designs. Further clarification of the variability in social and ASD symptom presentation in DS is vital for more personalized educational planning and supports.

ASD in Down Syndrome

ASD is a lifelong condition that can impact well-being and adaptation. The diagnostic criteria for ASD include symptoms in two areas: (1) social communication and (2) restricted, repetitive patterns of behaviour, interests, or activities (American Psychiatric Association, 2013). Social presentation has long been identified as an important aspect of ASD (see Davis & Carter, 2014 for a review; Rutter, 1978). Relative to those with DS only, individuals with DS+ASD often demonstrate increased difficulties with social or emotional reciprocity, lower levels of spontaneous sharing of affect or interests with others, and challenges with developing age-appropriate peer relationships (Capone et al., 2005). Other features observed in DS+ASD include more pronounced delays in symbolic play and stereotyped and restricted patterns of interest and motor behavior (Capone et al., 2005). Expressive language challenges are also found in DS+ASD (Capone et al., 2005), though these are often observed in DS in general (Abbeduto et al., 2007).

Recent studies have examined the nature of autism screening measures and the characteristics of children with DS who screen positively (Warner et al., 2017) or negatively for ASD (Channell, 2020; Channell et al., 2015). Interestingly, children with DS who screen positively for ASD show fewer social symptoms than those who screen positively in the general population (Warner et al., 2017). In addition, children and adolescents with DS who screen negatively for ASD nonetheless demonstrate some ASD symptoms (Channell, 2020; Channell et al., 2015). These complementary findings suggest a degree of complexity in the co-occurrence of DS and ASD.

Critical next steps for researchers include understanding the heterogeneity of ASD symptom presentations among individuals with DS, whether symptoms are yoked to one another, and how this information can inform educational and support planning. The aim of this study is to address these issues using a mixture modeling analytic approach that will characterise latent profiles of ASD symptoms in children and adolescents with DS and identify key predictors of probability of profile membership.

Social development in DS

Informative distinctions within the domain of social functioning have made it possible to characterise social presentations with increasing precision and nuance (Constantino & Gruber, 2012). According to one framework, the social relatedness skills that are most relevant to ASD can be categorised into Social Motivation, Social Awareness, Social Communication, and Social Cognition (Constantino & Gruber, 2012). *Social Motivation* involves the drive to engage in social interaction, *Social Awareness* involves the ability to attend to social cues, *Social Communication* involves the ability to send communicative signals to others, and *Social Cognition* involves the ability to think about social cues once they are identified (Constantino & Gruber, 2012).

In several of these social functioning categories, nomothetic patterns of social performance in DS during childhood have been partially characterised. There has been theoretical discussion regarding the social motivation of children with DS (Fidler, 2006), and empirical studies report a tendency to select social versus instrumental/goal-directed strategies (Pitcairn & Wishart, 1994). Kasari and Freeman (2001) demonstrated increased task-related social behaviours in DS, and Kasari et al. (1990) reported increased visual attention toward social versus nonsocial stimuli. Other studies have reported increased social motivation in DS relative to children with other neurogenetic conditions, like Smith-Magenis syndrome (Wilde et al., 2016). Thus, when measured in a variety of ways, there is evidence for relatively strong social motivation among youth with DS at the group level.

Several aspects of social awareness in DS have been examined over the past several decades. Challenges are reported among children with DS in interpreting emotional cues, including a greater propensity for confusing a positive emotion for a negative one (Kasari et al., 2001) and difficulties with interpreting neutral or surprised emotional displays (Hippolyte et al., 2008). Another study reported that although happiness was commonly interpreted correctly, children with DS demonstrated a range of incorrect interpretations for the dimensions of disgust, surprise, fear, and sadness (Williams et al., 2005).

Studies on social communication in DS date back to earlier characterisations of joint attention and nonverbal requesting conducted in the 1990s (Kasari & Sigman, 1996) and there has been continued examination of these early communicative behaviours in recent years (see Hahn et al., 2018 for a review). Language delays are common among young children with DS (Abbeduto et al., 2007), however, early aspects of social communication seem to emerge with competence in many young children with DS, particularly in the area of joint attention (Hahn et al., 2018). Other early social communication skills, like nonverbal requesting, appear to be more delayed and possibly linked to underlying problem-solving skills (Fidler et al., 2005; Kasari & Sigman, 1996).

The social cognitive performance observed in DS at the group level also involves some degree of complexity. Kasari et al. (2003) found that in observable (not hypothetical) scenarios, children with DS attended to another person's demonstration of distress and offered more comfort than developmentally matched counterparts with and without intellectual disability (ID), suggesting increased capacity to think about someone else's

emotional state and react accordingly. However, other studies that examine more advanced aspects of theory of mind using methods such as false belief tasks have demonstrated greater challenges among individuals with DS relative to developmentally equated counterparts (Abbeduto et al., 2001; Neitzel & Penke, 2021). Overall, then, a mixed pattern of relative strengths and challenges has been identified at the group level in DS in studies of social motivation, awareness, communication, and cognition.

Restricted interests and repetitive behaviour in DS

Less is known regarding the repetitive behaviour features associated with ASD in children with DS. Children with DS tend to demonstrate more repetitive behaviour than children with disabilities at similar developmental levels (Evans et al., 2014). These repetitive behaviours are relatively stable over time in this population and are also associated with greater challenges in adaptive behaviour (Evans et al., 2014). It is notable that children with DS+ASD show higher levels of repetitive behaviour than children with DS-only (Hepburn & MacLean, 2009; Moss et al., 2013). In idiopathic ASD, repetitive motor behaviours and insistence on sameness are associated with social and communication challenges (Lam et al., 2008), but the presence of a co-occurring condition, like DS, may modify this association, and the association between repetitive behaviours and social relatedness in DS has not been well-characterised.

Addressing within-DS heterogeneity

Taken together, the literature suggests group-level patterns of competence and challenge in social development among individuals with DS, as well as elevated risk for varying degrees of ASD symptomatology. With these multi-layered findings, a shift from group-level approaches is warranted to better explicate the social and ASD symptom profiles observed among individuals with DS. More recent studies have examined within-DS differences in ASD symptoms using several strategies delineated below.

One recent approach to studying ASD symptom heterogeneity in DS has aimed to identify children with co-occurring DS+ASD and compare their presentations to those with DS-only and those with ASD-only. Godfrey et al. (2019) found that children with DS+ASD demonstrated ASD symptom presentations that were distinct from children with ASD-only and DS-only, with a profile involving elevated social communication and repetitive behaviour difficulties in children with DS+ASD relative to children with DS-only. However, when verbal mental age was controlled for, these differences were not observed. Another recent study reported that lower IQ scores, lower adaptive behaviour scores, and higher levels of maladaptive behaviour were associated with ASD symptoms in DS (Channell et al., 2019) as measured by the Social Communication Questionnaire (SCQ; Rutter et al., 2003).

Because the approach to current work has primarily focused on dichotomous groupings within DS samples (those with and without ASD; high risk vs. low risk), it is difficult to ascertain the degree of overlap and complexity in ASD symptom presentation that is observed among individuals with DS. Channell et al. (2015; Channell, 2020) addressed this by screening for ASD in individuals with DS and then analysing ratings for the individuals

who presented as low risk for ASD based on a clinical risk cutoff on the SCQ. They reported that the SRS-2 Social Cognition and Repetitive Behaviors domains were elevated even in children with DS who were at low risk for ASD, whereas Social Awareness and Social Motivation were less impacted (Channell et al., 2015). Similar findings were reported with a follow up younger sample of participants with DS at low risk for ASD, although Social Awareness symptoms were also elevated in this group (Channell, 2020). These findings speak to the potential complexity of ASD presentation among individuals with DS, which implies that it may not be useful to rely on a dichotomy of those with and without ASD presentations. Additional investigation is needed into the nuance of ASD presentation within samples of individuals with DS to identify the varying ways that symptoms may present themselves.

To build on these contributions, an important next step is to use a person-centered and data-driven approach to identifying symptom presentation profiles in youth with DS without any a priori information regarding ASD risk or diagnoses. An ideal quantitative approach to address this question is mixture modeling (cf. McLachlan et al., 2019), which allows researchers to examine whether symptom profiles in a sample fall along one distribution of outcomes, or whether there are several distributions that constitute specific profiles of presentation within a larger sample. Based on the existing literature, a mixture modeling approach is likely to reveal that a dichotomous categorisation into high and low ASD symptoms is inadequate and that there is greater complexity within DS, which can help guide the diagnostic process for clinicians and clinical researchers.

In this study, we examine the patterns of reported autism symptoms in 125 children and adolescents with DS. Participants were recruited through community-based research studies on cognition and language in DS, with no specific emphasis on ASD, and therefore, a reduced likelihood of sampling bias related to ASD presentation. Using caregiver-report SRS-2 data, we conducted latent profile analysis (LPA) on the DSM-5 composite scores for Social Communication and Repetitive Behaviors, and then a second LPA that included the four scores on the Social Communication and Interaction dimension: Social Motivation, Social Awareness, Social Communication, and Social Cognition. After identifying the model with the best fit for the data in each analysis, we then conducted auxiliary analyses to examine the role of biomedical risk, IQ, sex, and SRS-2 form on profile probability scores. Based on the work conducted by Channell et al. (2020; 2015) and others reviewed above, we hypothesise that the best model fit for our data will involve more than two profiles of ASD symptom presentation and that factors such as biomedical risk, IQ, and sex will likely predict probability of profile membership.

Method

Participants.

Participants were 125 children and adolescents with DS and their caregivers. The chronological age (CA) range for this study was intentionally wide (2.57 to 18.00 yrs; mean = 9.51 yrs, SD = 4.95) to examine the nature of ASD profiles across childhood and adolescence in DS (see Table 1 for demographics).

Procedure.

All procedures were approved by the Institutional Review Boards (IRBs) at the participating institutions or a professional external IRB. Study procedures conformed to the ethical standards of the US Federal Policy for the Protection of Human Subjects. Participants were recruited into multi-site studies of cognition and communication in children and adolescents with DS. Recruitment took place in Colorado, Ohio, and California in the United States and involved publicizing the larger studies through parent advocacy groups, social media, DS clinics, and regional events, as well as through university-based research registries. Participants took part in cognitive and communication assessment visits, and caregivers completed proxy-report measures and provided demographic/medical information either via paper and pencil or via a secured, online portal.

Though CA inclusion criteria varied from study to study, all studies required parental confirmation of a documented DS diagnosis. All studies had inclusion criteria involving no more than a mild documented hearing loss and no uncorrected vision problems and involved language-related criteria wherein participants should be able to understand simple instructions in English. In the two studies that included younger children, inclusion criteria involved independent sitting. None of the studies excluded participants with a co-occurring ASD diagnosis.

Study data were collected and managed using REDCap electronic data capture tools hosted at the Colorado Clinical and Translational Sciences Institute. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

Measures

The Social Responsiveness Scales, Second Edition (SRS-2; Constantino & Gruber, 2012).—Caregivers completed the SRS-2, a proxy-report measure of ASD symptoms that contains 65 items scored on a Likert-type scale from 1 (not true) to 4 (almost always true). Composite scores for the SRS-2 include overarching scores based on the DSM-5 diagnostic criteria for ASD (here referred to as the “DSM-5 Domains”), with a Social Communication and Interaction scale and a Restrictive Interests and Repetitive Behavior scale. Social symptoms (here referred to as the “Social Domains”) are further broken down into subscales measuring Social Motivation (e.g., “Does not join group activities unless told to do so”), Social Awareness (e.g., “Knows when he or she is talking too loud or making too much noise”), Social Cognition (e.g., “Is able to understand the meaning of other people’s tone of voice or expressions”), and Social Communication (e.g., “Is able to communicate his or her feelings to others through words and gestures”). The SRS-2 has demonstrated convergent validity with the Autism Diagnostic Observation Schedule-2 (ADOS-2; Lord et al., 2012) and the ICD-10 ASD symptom count (*r*s ranging from .48 to .59; Charman et al., 2007). The SRS-2 was selected because it has been used in previous studies and has strong psychometric properties for use in DS, including

strong internal consistency, moderate-to-excellent test-retest reliability, and a high degree of feasibility (Channell et al., 2015; Schworer et al., 2021). It has also been used in recent studies of ASD-symptoms in DS (Channell, 2020; Channell et al., 2015), and the use of converging measures facilitates the interpretation of findings across studies.

There are three forms of the SRS-2, corresponding to phases of the lifespan. For this study, we report data from the Preschool Form (ages 2.5 to 4.5 yrs) and the School-Age Form (ages 4 to 18 yrs; See Table 1 for demographic comparisons). SRS-2 data are reported using T-scores with a mean of 50 (SD = 10) that are sex-adjusted for the School Age Form. Clinically severe levels of ASD symptoms are denoted by T-scores that are 76 or higher, moderate symptom presentations fall in the range between 66 and 75, and mild symptoms range between 60 and 65. Scores below 60 generally denote the absence of ASD symptoms. All participants who were administered the School Age form were 4.5 years or older. However, five participants who were between the ages of 4.6 and 5.0 were administered the Preschool form because of the study design at one site, wherein parents were given the option to take the Preschool form or the School Age form if their child was between 4.0 and 5.0 yrs. Internal consistency for both SRS-2 forms in this sample was strong overall (Cronbach's alpha for the Preschool form = .93; School Age form = .99).

Cognition.—Cognition was measured via one of two standardised assessments, the Stanford-Binet, Fifth Edition (SB-5; Roid, 2003a) or the Differential Ability Scales–Second Edition (DAS-II; Elliott, 2007). The SB-5 measures intelligence and cognitive ability for individuals ages 2 to 85+ years. The SB-5 Abbreviated Battery (ABIQ) was used in this study and is comprised of two subtests: Nonverbal Fluid Reasoning (Object Series/Matrices) and Verbal Knowledge (Vocabulary). The ABIQ demonstrates high reliability with the other IQ scales on the SB-5 (above .90; Roid, 2003b). The DAS-II is a measure of cognitive ability for children 2 years 6 months to 17 years 11 months. Similar to the construction of the SB-5, it is comprised of core subtests that are used to calculate a General Conceptual Ability (GCA; similar to IQ) score. The Early Years administration of the DAS-II was used for this study, and is split into *lower*, for children 2:6–3:5 years, and *upper*, for children 3:6 years up to 8:11 years. There are four core subtests that contribute to the GCA in the lower Early Years administration, including Verbal and Nonverbal Ability. The six core subtests that comprise the upper Early Years GCA include Verbal Ability, Nonverbal Reasoning Ability, and Spatial Ability. Reliability has been demonstrated for the Early Years GCA (0.95; Elliott, 2007) and alpha coefficients reported for a subsample with ID were above 0.80 (Elliott, 2007). In the present sample, 42 participants completed the DAS-II instead of the SB-5. Thirteen of the 42 completed the lower Early Years assessment and 29 were administered the upper Early Years. These participants ranged in age from 2:6 to 7:11 years.

Standard scoring for the SB-5 and DAS-II is similar, but not identical. The SB-5 provides standard scores only as low as 47, which biases the scores of the participants who were administered this measure, and overrepresents the number of participants in the moderate ID category, as the assessment is not normed low enough to differential severe ID from moderate ID. To address this issue, IQ scores were treated as a dichotomous variable, as per Channell et al. (2019). Any participant with an IQ score of 55 or higher was designated as

having higher cognitive functioning, and any participant with a score of 54 or lower was designated as having lower cognitive functioning. Four participants had missing IQ data.

Medical History Questionnaire.—Caregivers were asked to provide information regarding their child's medical history, including DS type, vision and hearing, and additional biomedical diagnoses. For 7 participants, the answer "Don't Know" was provided for questions about hearing status, and for one participant, no answer was provided for vision status. A biomedical composite estimate was calculated, which involved computing the total number of the following conditions: congenital heart defect, prematurity, sleep disorder, gastrointestinal concerns, thyroid problems, diabetes, a history of head injury, and seizures.

Analytic Approach.—To address the study goals, we first conducted latent profile analysis (LPA; cf. Berlin et al., 2014 for an overview of latent variable mixture modeling) on both DSM-5 Scales (Social Communication and Interaction; Restricted Interests and Repetitive Behaviors) of the SRS-2. We then conducted a second LPA that included the four Social domains (Social Communication, Social Motivation, Social Awareness, and Social Cognition). We ran both sets of models with and without controlling for CA to assess whether including CA would substantially change the profile characteristics. The models were nearly identical with and without controlling for CA and because of the limitations of current software to conduct auxiliary tests with predictors of the categorical latent class variable, we elected to move forward with the models without controlling for CA. We further examined a range of within-class variance-covariance structures per recommendations by Masyn (2013) and Pastor et al. (2007), which all resulted in similar fit and class structure. Therefore, we retained the most parsimonious model in which the variances were held equal across classes and the covariances among the latent class indicators were fixed at zero. This choice resulted in a model that required the estimation of the fewest parameters, which is advisable with a relatively small sample. Results of models controlling for CA and with varying within-class variance-covariance structures are available in a supplementary file.

After identifying the model with the best fit for the data in each analysis, we conducted auxiliary analyses (described below) to examine differences in the distribution of biomedical risk, IQ, sex, and SRS-2 form (SRS-2 Preschool vs. School Age form) across profile probability scores. By using a person-centered analysis, we were able to examine heterogeneity among individuals and group together individuals similar to each other such that within- group homogeneity and between group heterogeneity were maximised (Jung & Wickrama, 2008).

Model Selection.—*Mplus* version 8 was used to test 1- through 4- profile models (Muthén & Muthén, 1998–2017) to determine the best-fitting model. Model fit was examined, and the best-fitting models were chosen based on recommendations from simulation studies (Muthén & Muthén, 2000; Nylund et al., 2007). We used the following criteria for model selection: 1. The Lo–Mendell–Rubin likelihood ratio test of model fit (LMR; Lo et al., 2001) is a statistical test that was used to compare the fit of the current model to a model with one fewer profile.; 2. The sample size adjusted Bayesian Information Criterion (aBIC; Schwarz, 1978) was used to compare model fit across nested models, with values

closer to zero indicating better model fit (Muthén & Muthén, 2000); 3. Entropy values were used as an index of classification quality with values closer to 1 indicating better fit (Jung & Wickrama, 2008); and 4. Average latent class probabilities (ALCPs) were used to determine how well participants belonged to the profile for which they had the highest probabilistic membership by latent class discrimination. ALCP values range from 0 to 1, with values closer to 1 indicating good fit. In addition to these criteria, we also considered the substantive interpretation of the model and parsimony.

Auxiliary Testing.—To compare latent profiles across pertinent participant characteristics, we added the biomedical risk composite, IQ, sex, and age group (Preschool vs School Age SRS-2 form) to the model as categorical auxiliary distal outcomes utilizing the DCAT method (Asparouhov & Muthén, 2014; Lanza et al., 2013). Results of the auxiliary distal outcomes provide global and pairwise comparisons between latent profiles using Wald chi-square tests. These analyses were conducted simultaneously with LPAs and allowed consideration of the probabilistic profile membership of participants to control error.

Results

Model selection.

Preliminary analyses were conducted for the association between hearing/visual impairments and SRS-2 total T scores using *t* tests. They were found not to be significantly related to SRS-2 total T scores and were not included in subsequent analyses (hearing impairment $t(117) = .42$; $p = .68$; visual impairment $t(122) = .09$; $p = .93$).

The best fitting LPAs for both the DSM-5 Domain model and the Social Domain model were 3-class solutions (see Table 2). In the DSM-5 Domain model, the 3-class solution had similar entropy and ALCP values to the 2-class solution, a relatively lower aBIC than the 1-, and 2-class models, and the LMR test confirmed that the 3-class solution was a better fitting model than the 2-class solution. Although the 4-class model did have a slightly lower aBIC, the LMR test revealed that it did not fit statistically better than the 3-class solution. A similar pattern held for the LPA with SRS-2 Social Domain scores. More specifically, the 3-class solution had the best classification quality, a relatively lower aBIC than the 1-, and 2-class models, and the LMR test was significant indicating that the 3-class solution was a better fitting model than the 2-class solution ($p = .02$). While the 4-class model did have a slightly lower aBIC, the LMR test revealed that it did not fit statistically better than the 3-class solution ($p = .26$). In both the DSM-5 Domain and Social Domain models, the smallest latent class accounted for 6% of the sample based on assigning participants to their most likely latent class.

Model interpretation.

Tables 3 and 4 present the means and standard errors for each of the DSM-5 domains and Social domains estimated in each latent profile as well as results of the auxiliary tests. Figures 1 and 2 depict the means across latent profiles. In the final best-fitting model for the DSM-5 Domain model, the three classes are best described as: a Low ASD Symptom Profile, an Elevated ASD Symptom Profile, and a High ASD Symptom Profile.

The Low ASD Symptom Profile had mean T scores for both Social Communication and Interaction and Restricted Interests and Repetitive Behavior at approximately 50 (the mean for the general population), the Elevated ASD Symptom Profile had mean T scores for both domains around 65, and the High ASD Symptom Profile had mean T scores for both domains greater than 80.

Results for the Social Domain model involved a greater degree of complexity. The three classes are best described as: a Low ASD Symptom Profile, a Mixed ASD Symptom Profile, and a High ASD Symptom Profile. There was little variability in the mean T scores for the Low ASD Symptom Profile. However, there was variability in the mean T scores for the Mixed ASD Symptom Profile, which had a value for Social Motivation in the 50s and all other social domains in the mid-60s. There was also variability in the High Symptom Profile, which had mean T scores ranging from the high 60s (Social Motivation) to the mid-80s (Social Cognition).

In LPA, all participants are assigned a probability of profile membership score to each profile. When considering the most likely profile membership for each participant (i.e., the profile with the highest probability score), 7 of the 8 participants who would be assigned to the High ASD symptoms profile in the DSM-5 model also would be assigned to the High ASD profile in the Social Domain model, and vice versa. In addition, of the four participants who were reported to have a formal ASD diagnosis, two demonstrated the greatest likelihood of membership in the High ASD symptoms profile in each model, and two demonstrated the greatest likelihood of membership in the Elevated and Mixed ASD profiles.

Auxiliary testing results.

Results of the auxiliary testing are presented in Tables 3 and 4. In the DSM-5 Domain model, the Low ASD symptom profile differed significantly from the High ASD symptom profile on IQ, X^2 (1) = 16.85, $p < .0001$; sex, X^2 (1) = 5.39, $p < .02$; and biomedical composite variables, X^2 (5) = 12.96, $p < .03$, with all participants in the High ASD symptom profile having IQs less than 55 and the High ASD symptom profile including a significantly higher proportion of female participants and significantly more co-occurring biomedical conditions compared to those in the Low ASD symptom profile. The Low ASD and Elevated ASD symptom profiles differed significantly on IQ and SRS-2 form, with the Elevated ASD symptom profile having a higher proportion of participants with an IQ less than 55, X^2 (1) = 5.26, $p < .02$ and a significantly higher proportion of participants who were scored on the School-Age form, X^2 (1) = 12.15, $p < .0001$. The Elevated ASD symptom profile and the High ASD symptom profile differed significantly on sex, X^2 (1) = 8.69, $p < .003$; and biomedical composite variables, X^2 (5) = 21.65, $p < .001$, with those most likely to be in the High ASD symptom profile more likely to be female, and more likely to have a higher number of co-occurring biomedical conditions.

Results from the Social Domain model auxiliary tests were similar to those from the DSM-5 Domain model. More specifically, the Low ASD symptom profile differed significantly from the High ASD symptom profile on IQ, X^2 (1) = 39.58, $p < .0001$; sex, X^2 (1) = 4.92, $p < .03$; and biomedical condition composite variables, X^2 (5) = 13.70, $p < .02$, with the High ASD

symptom profile having 100% of participants with an IQ less than 55, a higher proportion of female participants, and more co-occurring conditions compared to those in the Low ASD symptom profile. The Low ASD and Mixed ASD symptom profiles differed significantly on IQ, X^2 (1) = 16.86, p < .0001, and SRS-2 form, X^2 (1) = 3.99, p < .05, with the Mixed ASD symptom profile having a higher proportion of participants with an IQ less than 55 and a higher proportion of participants rated on the School Age Form. The Mixed ASD symptom profile and the High ASD symptom profile differed significantly on IQ, X^2 (1) = 6.35, p < .01; sex, X^2 (1) = 8.75, p < .003; and co-occurring biological conditions, X^2 (5) = 30.52, p < .0001, with those most likely to be in the High ASD symptom profile having a greater probability of having an IQ less than 55, more likely to be female, and more likely have a high number of co-occurring conditions.

Discussion

The aim of this study was to discern latent patterns of ASD features among children and adolescents with DS. Caregivers rated ASD symptoms for 125 participants with DS ranging from early childhood through late adolescence. A mixture modeling analytic approach was applied to characterise the latent profiles of ASD symptoms. For the DSM-5 related domains of the SRS-2, a three-profile model was determined to be the best fit, including a Low ASD symptom profile, an Elevated ASD symptom profile, and a High ASD symptom profile. Based on profile probability scores, most participants with DS best fit the Low and Elevated profiles, with a small percentage of participants demonstrating the greatest likelihood of being assigned to the High ASD symptom profile.

Subsequent mixture modeling that focused only on the Social Domains similarly demonstrated a best fit for a three-profile model. In this case, however, findings were more nuanced. Although a Low Symptom profile was again observed, the intermediate profile demonstrated a combination of elevated difficulties in the areas of Social Communication, Social Awareness, and Social Cognition, but lower symptom levels in Social Motivation. A similar pattern of fewer Social Motivation symptoms was observed in the High Symptom profile in this model. Across all three profiles, Social Motivation mean T scores were substantially less impacted than the remaining social domain scores. These findings have important implications for interpreting ASD symptom presentations among those with DS in clinical settings. In particular, effective educational and intervention approaches for individuals with uniformly high levels of ASD symptoms likely differ from approaches for those with relatively preserved social motivation, but challenges in the remaining areas of social functioning.

A notable finding from this study is that the best model fit for both mixture models involved three, rather than two, profiles. This finding suggests that a simple bimodal approach to ASD evaluation involving a dichotomous yes or no for the presence or absence of co-occurring ASD does not reflect the actual distribution of caregiver-reported ASD symptomatology in this sample of individuals with DS. There is a range of symptom presentations observed in this sample with DS that corresponds to the DSM-5 conceptualization of autism as a spectrum disorder. Thus, it may be important to consider the profile findings presented here

in the larger conversation regarding best practices for diagnostic procedures and educational planning for children with DS (Hepburn & Moody, 2011).

Auxiliary analyses also demonstrated that factors like IQ and co-occurring biomedical conditions vary along with ASD symptoms. These findings align with previous reports of the connection between ASD and severity of intellectual disability in DS (Channell et al., 2019; Hepburn et al., 2008) and the interplay between biomedical risk and ASD presentation in both DS (e.g., Hoffmire et al., 2014) and the general population (Croen et al., 2015; Vohra et al., 2017). Future work is needed to clarify the interplay between IQ and ASD symptoms in DS and in neurogenetic conditions more broadly. In addition, participants who were evaluated by their caregivers using the Preschool form were represented more in the Low ASD symptom profile than the Elevated and Mixed profiles in both models. This difference could be attributed to several possible factors. First, it may be the case that the norming for the two versions of the SRS-2 differed in systematic ways that would lead one form to generate lower versus higher T-scores. However, the specifications in the SRS-2 manual suggest similar norming procedures for the Preschool and School Age forms. It may be the case, instead, that young children in this sample demonstrated fewer ASD symptoms, which was accurately captured in the Preschool form. This explanation is plausible when considering that ASD presentation in DS may become more pronounced with age as the cognitive demands of social interactions increase. Alternatively, it may be that caregivers did not detect the ASD symptoms in younger children, as early ASD presentation in the presence of an already existing neurogenetic condition may be difficult for a caregiver to identify and interpret. Despite these possible issues and explanations, there is utility in presenting the combined dataset to obtain a comprehensive account of ASD symptoms from early childhood through the later stages of adolescence. Future studies should continue to examine the intersection between age, symptom detection, and symptom severity when studying ASD presentation in young children with DS.

An unexpected finding of this study is the greater representation of females than males in the High ASD Symptom profiles for both models, a pattern that directly contradicts previous work on DS+ASD and ASD research in general. These findings could be an artefact of the sex-based norming of the School Age form of the SRS-2, which assigns higher T-scores to females than males for the same symptom presentation. Indeed, follow up exploration of raw scores demonstrated that females who were scored on the School-Age form had (non-significantly) lower mean raw total scores than males (57.75 vs 59.93), but (non-significantly) higher mean T-scores (62.06 vs 60.51). We also note that this pattern of more females than males was observed only in the small group of participants with the most pronounced ASD symptoms, as the moderate ASD symptom profile (“Elevated”) in the DSM-5 Domain model involved a higher proportion of males than females, as did the Mixed ASD symptom profile of the Social Domain model.

The issue of ASD diagnostic patterns in males versus females has garnered increased research attention, with less convergent findings reported in the literature. Recent work in another neurogenetic condition, Smith-Magenis syndrome, has demonstrated greater risk for ASD symptoms among females (Nag et al., 2018), and the increased ratio of males to females among those with ASD is less pronounced in some previously-reported samples of

individuals with DS (Channell et al., 2019; Naerland et al., 2017). These findings relate to the larger contemporary conversation regarding the underdiagnosis of females with ASD, possibly due to differential presentation between males and females (Kreiser & White, 2014). In the context of this important issue, the results from this person-centered analytic approach suggest that there may be a small subgroup of females with DS who demonstrate very pronounced ASD symptoms, while more moderate symptom presentations may be more frequently observed in males with DS. This finding warrants further replication, but it may be the case that the analytic approach taken in this study uncovered a subtle pattern of sex-related findings.

This study builds on a growing body of work that aims to characterise ASD symptom heterogeneity in individuals with DS. The findings presented in this study converge with the literature in identifying Social Motivation as a key dimension of interest, as it was the dimension that demonstrated the lowest levels of symptom presentation in each Social Domain profile, which echoes previous findings from the SRS-2 (Channell, 2020; Channell et al., 2015). The models presented here also align with the latent profiles reported in another recent study that also identified a three-profile model as the best fit for cognitive, behavioural, and ASD data collected on a large sample of individuals with DS (Channell et al., 2021). The complex presentation of ASD reported in the present study appears to also be captured in Channell et al. (2021), providing further evidence that a bimodal approach to understanding the presence or absence of ASD in DS is not the most appropriate representation of the ASD symptom data for children with DS.

Though this study provides a novel contribution to a growing area of clinical research, several limitations should be noted. First, as described above, this project draws SRS-2 data from several multi-site studies that involve community-based samples, but not epidemiological samples. Thus, the proportion of participants designated for each profile should be interpreted cautiously and warrants replication in a larger sample. Second, to adequately represent the childhood and adolescent years, we used both the Preschool and the School-Age forms of the SRS-2. The measures are very similar along many dimensions (number of items, DSM-5 Domains, Social Domains). However, they are normed on samples with different CAs and, therefore, there may be systematic ways that the Preschool and the School Age versions impacted the T-scores reported. As a result, the SRS-2 form-related findings reported here should be interpreted with these caveats in mind. Relatedly, there were five participants between the ages of 4;6 and 5;0 years who were rated using the Preschool form. Though these participants were within the Preschool form range in terms of overall developmental status, and SRS-2 Preschool T-scores are not age dependent, this should nonetheless be noted as a further limitation of the use of different forms. Third, although the sample size is relatively large for a study of this nature, the mixture modeling approach taken in this study is often used with larger samples, and future work should seek to replicate these findings on a larger scale. Furthermore, diversity in demographic dimensions such as race and ethnicity was limited in this sample, which impacts the generalisability of the findings.

Another set of limitations relate to the type of measures used. The findings reported here are based on caregiver report, not direct assessment of ASD symptoms using gold-standard

measures. Replication studies that model symptom presentation using direct observation will be important for advancing this area of clinical research. This study also included two measures of IQ, which resulted from the use of data from multiple studies at different sites. To address this issue, IQ was dichotomised into mild (55+) and moderate-to-severe (54 and lower). Though the IQ-related findings are not at the center of the outcomes reported here, this is a limitation of the auxiliary findings reported in this study.

These limitations should be acknowledged when interpreting the findings presented. Despite these issues, however, this research makes a novel contribution to the study of the heterogeneity in ASD features in children and adolescents with DS. Rather than reporting a bimodal, two-profile model, the mixture modeling approach demonstrated that the best representations of ASD symptoms in this sample of participants with DS were three-profile models for both the DSM-5 Domains and the Social Domains. Both models included low symptom profiles, high symptom profiles, and an intermediate profile that either had uniformly moderate symptom presentation (DSM-5 Domains) or a mixed symptom presentation (Social Domains). Social Motivation appears to be the domain that is least impacted within ASD profiles, and biomedical risk, sex, IQ, and age grouping appeared to predict probability of profile membership to some degree. This work can inform future interventions, as a greater understanding of the complex presentation of ASD symptoms in DS provides a basis for more personalised and informed educational approaches and supports.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding Acknowledgements:

Research reported in this article was supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the National Institutes of Health under award numbers R01HD099150-0, 1 R21 HD101000-01, P50HD103526, UL1TR000002, R01 HD093654, and 1R01HD093754-01A1).

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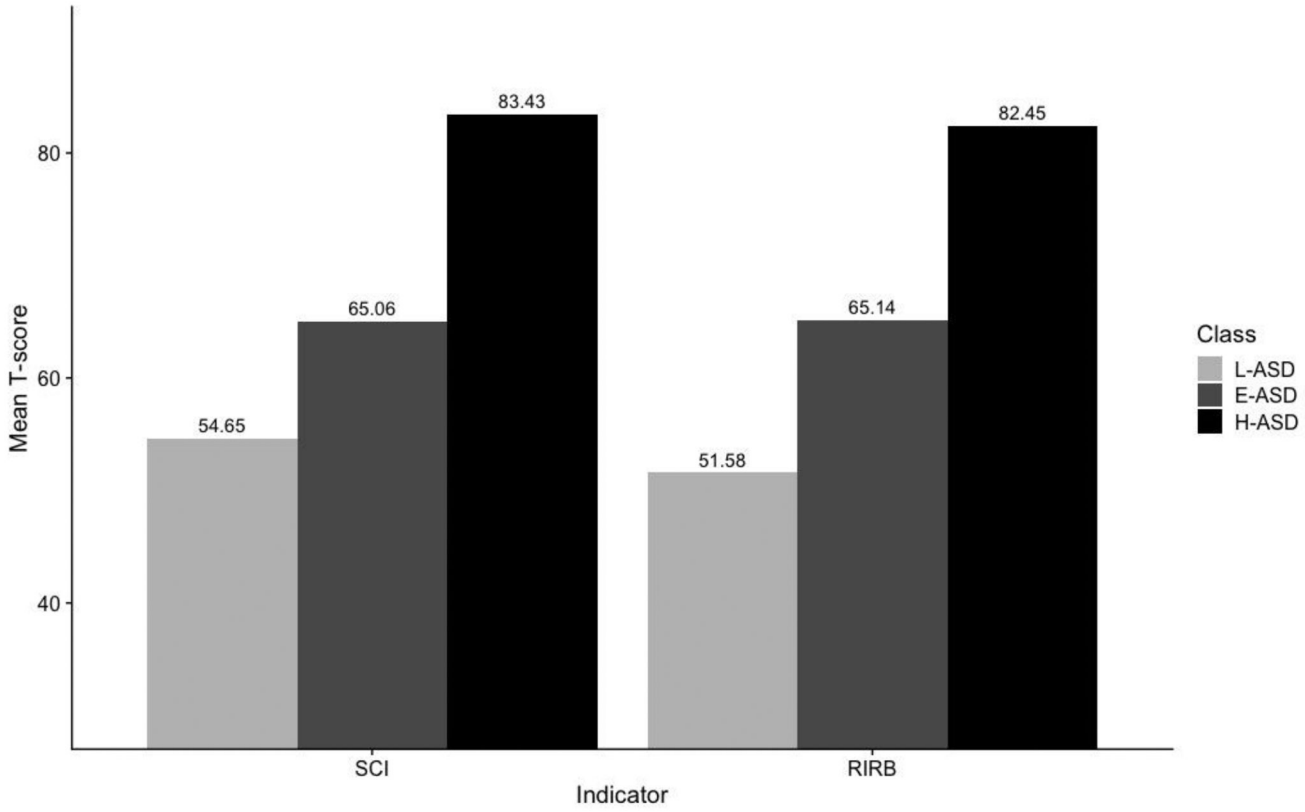

Figure 1.

Visualizations of the Social Responsiveness Scale-2 DSM-5 Domains LPA.

Note: SCI = Social Communication & Interaction; RIRB = Restricted Interests & Repetitive Behavior; L-ASD = low autism spectrum disorder symptom profile; E-ASD = elevated autism spectrum disorder symptom profile; H-ASD = high autism spectrum disorder symptom profile.

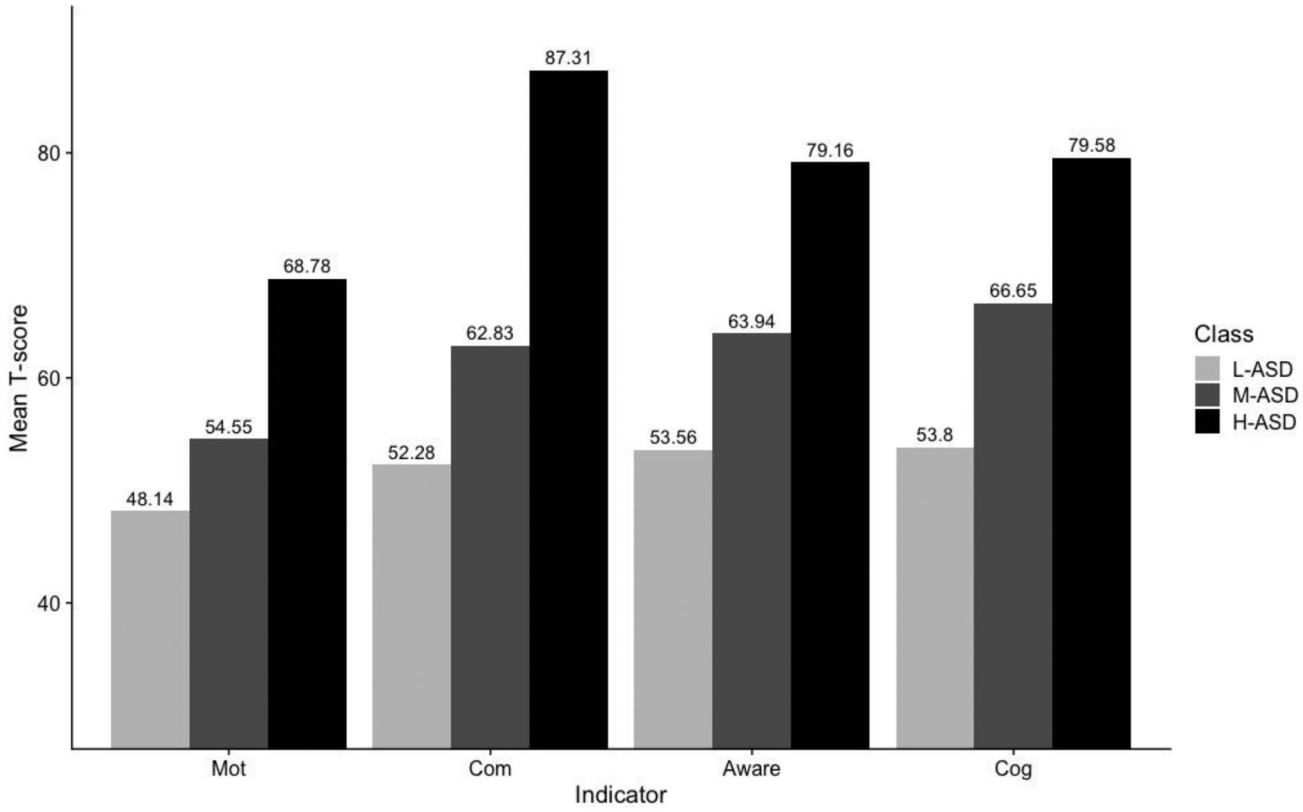

Figure 2.

Visualizations of the Social Responsiveness Scale-2 Social domains LPA.

Note: Mot = Social Motivation; Com = Social Communication; Aware = Social Awareness; Cog = Social Cognition; L-ASD = low autism spectrum disorder symptom profile; M-ASD = mixed autism spectrum disorder symptom profile; H-ASD = high autism spectrum disorder symptom profile.

Table 1.

Demographic Information (Total and by SRS-2 form)

	Preschool Form N = 32	School Age Form N = 93	Total N = 125
Child variable	**% (n)**	**% (n)**	**% (n)**
% Male	46.9 (15)	48.4 (45)	48.0 (60)
Child/Adolescent age (years)	3.90 (.70)	11.44 (4.27)	9.51 (4.95)
IQ under 55 (n = 4 missing)	38.7 (12)	84.4 (76)	72.7 (88)
Race (n = 2 missing)			
Asian-American	3.1 (1)	6.5 (6)	5.6 (7)
Black/ African-American	0 (0)	2.2 (2)	1.6 (2)
White	87.5 (28)	84.9 (79)	85.6 (107)
Other	9.4 (3)	4.3 (4)	5.6 (7)
Ethnicity (n = 1 missing)			
Hispanic	12.5 (4)	8.7 (8)	9.7 (12)
Not Hispanic	87.5 (28)	90.2 (83)	89.5 (111)
DS Type (n = 15 missing)			
Trisomy 21	84.4 (27)	88.5 (69)	87.3 (96)
Mosaicism	3.1 (1)	3.8 (3)	3.6 (4)
Translocation	0 (0)	3.8 (3)	2.7 (3)
Not sure	12.5 (4)	3.8 (3)	6.4 (7)
Premature Birth (% yes; n = 16 missing)	28.1 (9)	20.8 (16)	22.9 (25)
Congenital Heart Defects (% yes)	84.4 (27)	40.9 (38)	52.0 (65)
Caregiver variable			
Primary Caregiver Age (Mean/SD years; n = 1 missing)	37.78 (4.86)	47.65 (7.68)	44.10 (8.27)
% Primary Caregiver Education at least 1 year of college/tech training (n; n = 1 missing)	100 (32)	92.4 (85)	94.4 (117)
% Annual Income (n)			
Below $50,000	3.1 (1)	14.0 (13)	11.2 (14)
$50,000–100,000	31.3 (10)	24.7 (23)	26.4 (33)
Above $100,000	62.5 (20)	48.4 (45)	52.0 (65)
Did not wish to provide	3.1 (1)	12.9 (12)	10.4 (13)

Table 2.

Comparative Fit and Classification Quality for LPA Models

	SRS-2 DSM-5 Domain Models			
	1-Class	**2-Class**	**3-Class**	**4-Class**
aBIC	1873.915	1804.476	1766.996	1753.227
Entropy	-	0.843	0.821	0.796
ALC-Probabilities	-	.92 to .97	.89 to .94	.86 to .95
LMR Test (value, p-value)	-	69.63, .043	39.74, .026	17.55, .08
	Number in most likely class Count (Proportion)			
Class 1	125 (100%)	97 (78%)	75 (60%)	32 (26%)
Class 2		28 (22%)	42 (34%)	62 (50%)
Class 3			8 (6%)	24 (19%)
Class 4				7 (5%)
	SRS-2 Social Domain Models			
	1-Class	**2-Class**	**3-Class**	**4-Class**
aBIC	3702.897	3566.635	3460.589	3430.336
Entropy	-	0.88	0.878	0.851
ALC-Probabilities	-	.87 to .98	.94 to .98	.89 to 1.00
LMR Test (value, p-value)	-	138.84, .61	109.83, .0152	37.05, .26
	Number in most likely class Count (Proportion)			
Class 1	125 (100%)	103 (82%)	64 (51%)	41 (33%)
Class 2		22 (18%)	8 (6%)	20 (16%)
Class 3			53 (42%)	57 (46%)
Class 4				7 (5%)

Note: SRS = Social Responsiveness Scale-2; aBIC = sample size adjusted Bayesian Information Criterion; ALC-Probabilities = Average Latent Class Probabilities for Most Likely Latent Class Membership; LMR = Vuong-Lo-Mendell-Rubin Likelihood Ratio Test. Bold indicates the selected best fitting model.

Table 3.

Best fitting model means by class and auxiliary variable testing summary.

	SRS-2 DSM-5 Domain Models		
	Low ASD n = 75 M (SE)	**Elevated ASD n = 42 M (SE)**	**High ASD n = 8 M (SE)**
Social Communication & Interest	54.65 (1.20)	65.06 (1.54)	83.43 (2.01)
Restricted Interests & Repetitive Behavior	51.58 (.99)	65.14 (2.64)	82.45 (4.60)
	Auxiliary Testing Proportion in each class		
IQ category [a, b]:			
≤54	0.59	0.90	1.00
≥55	0.41	0.10	0.00
SRS-2 Form [a]:			
Preschool	0.46	0.10	0.46
School-Age	0.54	0.90	0.54
Sex [b, c]:			
Male	0.46	0.58	0.13
Female	0.54	0.42	0.87
Biomedical Composite (# of comorbid conditions) [a,b,c]:			
0	0.10	0.08	0.00
1	0.40	0.25	0.22
2	0.41	0.30	0.52
3	0.07	0.27	0.00
4	0.00	0.08	0.26
5	0.02	0.02	0.00

Note: SRS-2 = Social Responsiveness Scale-2; ASD = autism spectrum disorder symptoms; M = mean; SE = standard error; n = approximate sample size based on participants' most likely class membership.

a = significant difference between Low ASD and Elevated ASD Classes;

b = significant difference between Low ASD and High ASD Classes;

c = significant difference between Elevated ASD and High ASD Classes.

Table 4.

Best fitting model means by class and auxiliary variable testing summary.

	SRS-2 Social Domain Models		
	Low ASD n = 53 M (SE)	**Mixed ASD n = 64 M (SE)**	**High ASD n = 8 M (SE)**
Social Awareness	53.56 (1.05)	63.94 (1.31)	79.16 (4.51)
Social Cognition	53.79 (1.19)	66.65 (1.23)	79.58 (1.59)
Social Communication	52.28 (1.24)	62.83 (.98)	87.31 (2.67)
Social Motivation	48.14 (1.14)	54.55 (1.08)	68.78 (5.64)
	Auxiliary Testing Proportion in each class		
IQ category *d, e, f*:			
≤54	0.49	0.88	1.00
≥55	0.51	0.12	0.00
SRS-2 Form *d*:			
Preschool	0.47	0.27	0.40
School-Age	0.53	0.73	0.60
Sex *e, f*:			
Male	0.42	0.58	0.12
Female	0.58	0.42	0.88
Biomedical Composite (# of comorbid conditions) *e, f*:			
0	0.10	0.08	0.00
1	0.41	0.26	0.28
2	0.38	0.34	0.44
3	0.08	0.23	0.00
4	0.00	0.07	0.29
5	0.02	0.02	0.00

Note: SRS-2 = Social Responsiveness Scale-2; ASD = autism spectrum disorder; M = mean; SE = standard error; n = approximate sample size based on participants' most likely class membership;

d = significant difference between Low ASD and Mixed ASD Classes;

e = significant difference between Low ASD and High ASD Classes;

f = significant difference between Mixed ASD and High ASD Classes.