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Social skills and autism spectrum disorder symptoms in children with neurofibromatosis type 1: evidence for clinical trial outcomes

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ABBREVIATIONS

ASD	Autism spectrum disorder
NF1	Neurofibromatosis type 1
SRS-2	Social Responsiveness Scale, Second Edition
SSIS-RS	Social Skills Improvement System – Rating Scales

AIM We examined key features of two outcome measures for social dysfunction and autism spectrum disorder traits, the Social Responsiveness Scale, Second Edition (SRS-2) and the Social Skills Improvement System – Rating Scales (SSIS-RS), in children with neurofibromatosis type 1 (NF1). The aim of the study was to provide objective evidence as to which behavioural endpoint should be used in clinical trials.

METHOD Cross-sectional behavioural and demographic data were pooled from four paediatric NF1 tertiary referral centres in Australia and the United States (N=122; 65 males, 57 females; mean age [SD] 9y 2mo [3y], range 3–15y).

RESULTS Distributions of SRS-2 and SSIS-RS scores were unimodal and both yielded deficits, with a higher proportion of severely impaired scores on the SRS-2 (16.4%) compared to the SSIS-RS (8.2%). Pearson's product-moment correlations revealed that both questionnaires were highly related to each other (r=–0.72, p<0.001) and to measures of adaptive social functioning (both p<0.001). Both questionnaires were significantly related to attention-deficit/hyperactivity disorder symptoms, but only very weakly associated with intelligence.

INTERPRETATION The SRS-2 and SSIS-RS capture social dysfunction associated with NF1, suggesting both may be suitable choices for assessing social outcomes in this population in a clinical trial. However, careful thought needs to be given to the nature of the intervention when selecting either as a primary endpoint.

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What this paper adds

- The Social Responsiveness Scale-2 yielded a large deficit relative to population norms.

- The Social Skills Improvement System – Rating Scales yielded a moderate deficit relative to population norms.
- Both scales were highly correlated, suggesting that they are measuring a unitary construct.

[main text]

Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic condition that puts children at increased risk of various clinical manifestations involving the central and peripheral nervous systems, including benign and malignant nerve sheath tumours, optic pathway gliomas, and cognitive deficits.[1] Recent research has focused on social outcomes for children with NF1, with a growing body of literature, summarized in a systematic review and meta-analysis,[2] reporting a significantly higher prevalence of social dysfunction in children with the condition. In brief, studies using child-direct assessments have highlighted weaknesses in social perception, including evidence of reduced emotion and face recognition in school-aged children with NF1.[3,4] Deficits in higher-level social information processing, such as theory of mind and perspective taking, have similarly been reported. For example, 26 children with NF1 aged 4 to 12 years demonstrated difficulties in sequencing mental state stories that required them to take the perspective of a character in the story, while control stories that did not require mentalizing were sequenced normally.[5] Poor social competency is also evident at the behavioural level, with a number of studies reporting significant social difficulties in school-aged children on the Social Skills Rating System.[6,7] Children with NF1 also demonstrate higher rates of peer rejection, difficulties forming friendships, and fewer friendships compared to unaffected siblings.[8] Further, there is evidence that 40% to 56% of individuals with NF1 demonstrate problem behaviours that broadly resemble those seen in autism spectrum disorder (ASD),[9,10] and a recent meta-analysis demonstrated a large effect size for ASD symptomatology across eight individual studies (Hedges' g=0.9).[2] While there is some variability in estimates of prevalence rates, up to 25% may meet the DSM-5 diagnostic criteria for ASD,[2] which is significantly higher than the general population (1–2%).[11]

As a single gene disorder, NF1 allows detailed insights into the molecular mechanisms and neuropathology contributing to the clinical phenotype. Unlike social problems or ASD in the general population, where the cause is unclear, understanding the contributing mechanisms in NF1 allows the identification of potential disease-specific targets for treatment. To date, most of this research has been performed using *Nf1*$^{+/-}$ knockout mice, which have been used to model the human condition.[12] Within these various preclinical models, targeted therapies have corrected the underlying pathophysiology within the neural circuitry and normalized the behavioural phenotype, such as rescuing social learning deficits by blocking *Pak1* function within the amygdala.[13] These findings have led to expectations that targeted pharmacological intervention may similarly treat neurodevelopmental impairments in children with NF1. However, results of translational proof-of-concept trials in children with NF1 have so far been variable.[14]

A methodological challenge when designing clinical trials is selecting appropriate outcome measures. Outcome measures should be valid and reliable, relevant to the patient population (i.e. capturing a high base rate of deficits), and be able to capture meaningful clinical improvement that genuinely reflect real-world problems and concerns.[15] These issues are especially relevant for cognitive and behavioural outcomes in clinical samples such as NF1, where study measures may be particularly unreliable,[16] and where much baseline data published to date has been from small samples.[2] The importance of this issue has resulted in the establishment of the Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) working groups, whose aims are to systematically evaluate outcome measures and make recommendations for clinical trials in NF1 to the scientific community.[17] In order to optimize the design of future clinical trials directed at improving the broader social phenotype/ASD symptoms in children with NF1, acquiring condition-specific baseline data from larger samples on potential outcome measures is crucial. Furthermore, comparison of the utility of multiple measures in the same sample is needed.

The overall aim of this study was to examine parent-reported rating scales of ASD symptoms and social behaviours to provide information about participants' social functioning. Data were sampled from individuals across different international sites to maximize sample heterogeneity and ensure a wide representation of the condition. The specific objectives of this study were to: (1) establish mean effect sizes and the base-rates of deficits on two candidate outcomes, one measuring prosocial skills, the Social Skills Improvement System – Rating Scales (SSIS-RS), and the other measuring the nature and severity of autism-related symptoms, the Social Responsiveness Scale, Second Edition (SRS-

2); (2) determine the direct relationships between these key outcome measures, as well as other salient features of the NF1 behavioural phenotype; and (3) examine relationships between ASD symptoms and social behaviours and social adaptive abilities in children with NF1.

METHOD

Participants

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Deidentified participant data were pooled from NF1 clinics at four tertiary referral centers: The Royal Children's Hospital/Murdoch Children's Research Institute; The Children's Hospital at Westmead; the Children's Hospital of Wisconsin; and the Children's National Health System (USA). The data presented here originate from two independent studies: (1) an international, multisite, prospective cross-sectional study investigating ASD and social functioning in children with NF1 conducted at the Murdoch Children's Research Institute, The Children's Hospital at Westmead, and the Children's National Health System,[18] and (2) a cross-sectional study investigating the behavioural phenotype during the school-age years of children with NF1, conducted at the Children's Hospital of Wisconsin. All participants were diagnosed at respective clinics by an expert neurologist or clinical geneticist using clinical criteria.[19] Data were collected from 122 unique children (65 males, 57 females) aged from 3 to 15 years (mean age [SD] 9y 2mo [3y]). There was no statistically significant difference in the proportion of males across the sites.

Data collection at each site was approved by the respective Human Research Ethics Committees at the Royal Children's Hospital (HREC/16/RCHM/137), the Sydney Children's Hospitals Network (HREC/16/SCHN/42), and the Children's National Health System (Pro00007045), and the University of Wisconsin-Milwaukee Institutional Review Board (IRB 15.171). Written informed consent was obtained for each participant.

Procedure and measures

Primary outcomes

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ASD symptom severity was assessed using the parent report version of SRS-2 (mean [SD] 50 [10]), which is a well-validated, 65-item questionnaire designed to ascertain the nature and severity of the reciprocal social interaction difficulties and restricted interests/repetitive behaviours that characterize ASD.[20] Each item is rated on a 4-point Likert scale (not true, sometimes true, often true, almost always true), which contributes to a total score. While this is not a diagnostic measure, higher T-scores represent more elevated ASD symptoms.

Social skills were assessed with the Social Skills scale (mean [SD] 50 [15]) from the parent rated SSIS-RS,[21] a 79-item questionnaire designed to quantify positive social skills. Each item is rated on a 4-point Likert scale (never, seldom, often, almost always), which contributes to a total standard score across two scales. Of these, the Social Skills scale is reported here, with higher scores reflecting more positive social skills.

At the Murdoch Children's Research Institute, The Children's Hospital at Westmead, and Children's National Health System sites, social adaptive behaviour was measured via the parent-rated Social domain score from the Adaptive Behavior Assessment System, Third Edition (mean [SD] 100 [15]), which assesses functional impairment within social daily living skills.[22] Each item is rated on a 3-point Likert scale (almost never when needed, sometimes when needed, almost always when needed) with higher scores reflecting stronger adaptive social skills. At the Children's Hospital of Wisconsin, social adaptive behaviour was measured by the parent-rated Social Interaction and Communication Skills domain from the Scales of Independent Behavior – Revised (mean 100 [15]),[23] which assesses functional impairment within social daily living skills. Each item is rated on a 4-point scale (never or rarely, does but not well, does fairly well, does very well). Higher scores reflect stronger adaptive social skills. Adaptive Behavior Assessment System, Third Edition and Scales of Independent Behavior – Revised social domain variables were pooled into a single 'social adaptive functioning' variable.

Secondary outcomes

Attention-deficit/hyperactivity disorder (ADHD) symptoms were measured with the Conners' ADHD/DSM-IV Scales for children aged 3 to 5 years (n=24),[24] and the Conners-3 for children aged 6 years or above (n=98). These parent-rated questionnaires yield hyperactive/impulsive and inattentive scale T-scores, with higher scores reflecting elevated ADHD symptoms (mean [SD] 50 [10]). For children aged 6 years or above at the Murdoch Children's Research Institute, Children's Hospital at Westmead, and Children's National Health System sites, intellectual functioning was assessed using the full-scale IQ from the Wechsler Intelligence Scale for Children, Fifth Edition (n=59). Children aged 3 to 5 years at these sites were assessed using the full-scale IQ from the Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (n=24). At the Children's Hospital of Wisconsin, intelligence was assessed with the General Conceptual Ability score from the Differential Ability Scales, Second Edition, School-Age Form (n=39). For all these measures, higher scores indicate better performance (mean [SD] 100 [15]). Since correlated coefficients (r)

between full-scale IQ on the Wechsler Intelligence Scale for Children, Fifth Edition and Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition are high (r=0.84),[25] as are Pearson's correlation coefficients between the Wechsler Intelligence Scale for Children, Fifth Edition full-scale IQ and the Differential Ability Scales, Second Edition, General Conceptual Ability score (r=0.84),[26] these variables were pooled to represent a single intellectual functioning variable.

Statistical analysis

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Data were analyzed with SPSS version 22 (IBM Corp., Armonk, NY, USA). Normality of data distribution was assessed using visual inspection as well as Shapiro–Wilk and Kolmogorov–Smirnov tests. Analysis of variance was used to examine site differences on key demographic and outcome data. Post hoc tests identified the source of any significant main effects. Differences between the NF1 group and normative reference data were tested using one-sample t-tests for normally distributed data and one-sample Wilcoxon signed-rank tests for asymmetrically distributed data. χ^2 analyses were performed to determine whether one social functioning questionnaire was more likely to capture a higher base-rate of deficit than another. Pearson's product-moment correlations or Spearman's rank order correlation (for asymmetrically distributed variables) were then used to determine the relationships between SRS-2 and SSIS-RS Social Skills scores and full-scale IQ, ADHD symptom ratings, and adaptive functioning.

RESULTS

Demographic, intellectual functioning, and behavioural data for all 122 study participants are shown in Table 1. All variables met the assumptions for parametric analyses except the ADHD-inattentive and ADHD-hyperactive/impulsive symptoms, which were not normally distributed. The effects of site were compared on key demographic and outcome data. There was a main effect of age (p<0.01), with The Children's Hospital at Westmead site enrolling younger children than the Murdoch Children's Research Institute and Children's Hospital of Wisconsin (both p<0.001). There was a main effect of site for the SRS-2 total score, with post hoc comparisons revealing a trend for the Murdoch Children's Research Institute site to have more elevated symptoms than the Children's Hospital of Wisconsin (p=0.06). SSIS-RS, full-scale IQ, and ADHD ratings were comparable across sites (all p>0.08).

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Compared to population norms, children with NF1 performed more poorly on all primary and secondary outcomes (all p<0.001). For ease of cross-questionnaire comparisons,

we defined levels of severity in the manner outlined in the SRS-2 manual:[20] a mild level of deficit was defined as at least 1 SD or more below population mean (16th centile); a moderate level of deficit was defined as at least 1.5 SD or more below population mean (6th centile); and a severe deficit was defined as 2.5 SD or more below the population mean (1st centile).

Distribution of SRS-2 total T-scores were unimodal with a slight positive skew (Fig. 1a). Mean SRS-2 total scores were elevated by 0.99 SD relative to population norms indicating a large effect;[27] and there were no differences between males (mean [SD] 60.5 [12.7]) and females (mean 59.3 [15.2]; mean difference 1.3; 95% confidence interval [CI]:–3.87 to –6.13, p=0.66). In total, 45.1% of patients fell within or above the mild range for SRS-2 total scores, 35.2% fell within or above the moderate range, and 16.4% scored within the severe range. Distribution of mean SSIS-RS Social Skills scores were also unimodal and reduced by 0.65 SD relative to population norms indicating a medium effect (Fig. 1b).[27] Again, there was no difference between males (mean 88.4 [15.8]) and females (mean 92.2 [17.9]; mean difference 3.78; 95% CI:–9.82 to 2.27, p=0.22). A total of 36.9% of children were rated in or above the mild range for SSIS-RS total scores, 24.6% fell within or above the moderate range, and 8.2% were rated as severe.

We then examined whether there were any differences between the SRS-2 total score and SSIS-RS Social Skills score in their ability to identify at least a mild deficit, at least a moderate deficit, or a severe deficit in the study sample. There was no difference between questionnaires in identifying at least a mild (χ^2=1.69, p=0.19) or moderate deficit (χ^2=3.30, p=0.07); however, there was a trend for the SRS-2 to capture a higher base-rate of severe deficits than the SSIS-RS (χ^2=3.80, p=0.05).

Next, we performed a Pearson's product-moment correlation to determine the relationship between the SRS-2 total scores and SSIS-RS Social Skills scale. Parent ratings on these two scales were strongly and negatively correlated, r=–0.72, p<0.001 (Fig. 2). Pearson's product-moment correlations or Spearman's rank order correlation (for asymmetrically distributed variables) were then used to determine the relationships between SRS-2 scores and SSIS-RS Social Skills scores and full-scale IQ and ADHD symptom ratings. As shown in Table 2, both SRS-2 scores and SSIS-RS scores were moderately correlated with ADHD-inattentive symptoms. SRS-2 scores were also moderately associated with ADHD-hyperactive/impulsive symptoms, while the SSIS-RS scores were weakly correlated. There was a very weak correlation between SRS-2 scores and full-scale IQ, and no significant relationship between full-scale IQ and SSIS-RS scores. There were no significant correlations between age and SRS-2 scores or SSIS-RS scores (both p>0.25). Last,

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Pearson's product-moment correlations were used to examine relationships between ASD symptoms and social skills and social adaptive functioning. Both SRS-2 and SSIS-RS scores were moderately-to-strongly correlated with social adaptive functioning (Table 2).

DISCUSSION

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Advances in modelling the neurobiological mechanisms of social dysfunction in NF1 are providing the rationale for proof-of-concept clinical trials targeting social outcomes and atypical development in children with the condition. For these trials to translate into clinically meaningful outcomes, there is a pressing need to evaluate outcome measures that are representative of real-world settings and reflect functional concerns. At present, there is little consensus regarding which outcomes to use as social functioning endpoints in clinical trials. To address this gap, this study evaluated two widely used parent-rated questionnaires of social dysfunction, the SRS-2 and the SSIS-RS, in a paediatric NF1 sample.

First, we established prevalence rates of deficits on the two candidate measures. Scores on both measures were significantly and pathologically shifted relative to population norms, consistent with previous studies.[2,7] The effect size of the shift on the SRS-2 was large compared to population norms, while the SSIS-RS yielded a medium effect.[27] The base-rate of deficits identified by the SRS-2 in our study aligned with those from the comprehensive pooled data from the International NF1-ASD Consortium Team (INFACT) cohort, in which 39.2% of individuals with NF1 scored in the mild-to-moderate range for ASD symptoms on the SRS-2, while 13.2% scored in the severe range.[9]

While our data demonstrated no statistically significant difference between these two questionnaires in identifying the number of children reported with mild or moderate deficits, there was a trend for the SRS-2 to capture a higher base-rate of severe deficits relative to the SSIS-RS. This suggests the SRS-2 may capture a higher proportion of individuals with severe impairment. A possible explanation for this trend relates to the underlying constructs assessed by each tool. While it is important to acknowledge that social skills and autism symptoms are interrelated, there are distinctions that can be made. The SSIS-RS rates children on socially acceptable behaviours that enable positive interactions with others, including communication skills (e.g. turn taking, eye contact), co-operation (sharing, helping others), assertion (initiating behaviours), responsibility (showing regard for property/work), empathy, engagement (joining activities in progress/inviting others to join), and self-control (responding appropriately in situations of conflict).[21]

On the other hand, the SRS-2 captures a broader range of problem behaviours associated with ASD. While it includes some subscales that conceptually converge with the SSIS-RS, including reciprocal social communication and interactions, it also extends into other behaviours that align with autism that are not specifically social in nature. These restricted interest and repetitive behaviour symptoms include items measuring rigid and inflexible patterns of behaviour, unusual sensory interests, and motor co-ordination skills. While it is intuitive that the two measures would be strongly related, as our analyses indicate, it is important to acknowledge the different theoretical frameworks underpinning each tool. While both appear to be appropriate choices for measuring social functions impacted by NF1, careful thought should be given to the nature of the intervention when selecting the outcome for a given trial. For example, if the intervention under examination is a social skills training programme specifically designed to enhance prosocial behaviours, then the SSIS-RS may be a superior endpoint. However, if the investigational product is a pharmacological agent hypothesized to impart more generalized neurodevelopmental benefits, then the SRS-2 may be the superior endpoint, particularly given the larger effect size and the greater proportion of cases identified as severe with that tool. Further research about the amount of change needed on each measure to capture clinically significant improvement is needed.

Interestingly, we observed no significant sex difference in symptom burden on either the SRS-2 or SSIS-RS. This finding provides further support for the attenuation of the female protective ASD effect in the NF1 population,[28] and is congruent with data from the INFACT cohort.[9] Further, we did not observe significant associations between age and severity of SRS-2 or SSIS-RS scores, suggesting that social skills and autism traits do not greatly vary by age in children with NF1. This observation is consistent with some previous research,[29] but not with other studies that report elevations in social difficulties with increasing age across paediatric NF1 samples.[9,10] While longitudinal analyses are required to truly evaluate the patterns and prevalence of deficits assayed by the SRS-2 and SSIS-RS over time, our data suggest both measures adequately identify deficits across childhood in NF1.

Second, this study investigated relationships between the SRS-2 and SSIS-RS candidate outcome measures, together with other salient features of the NF1 clinical phenotype. These social outcomes were highly correlated with each other, suggesting that they are measuring a unitary construct. While this finding suggests that the social skills deficits in NF1 resemble the types of social competency problems observed in ASD, inclusion of an idiopathic ASD comparison sample would provide more definitive evidence for this. Our analyses revealed that both social outcomes were significantly related to

symptoms of ADHD-inattentive and ADHD-hyperactive/impulsive. These findings support converging evidence to suggest that ADHD symptoms tend to coexist with ASD symptoms in NF1,[9,29] and that ADHD symptoms are more likely to be present in children with social skills deficits.[7] While there has been some speculation that cognitive impairments may explain the behavioural and social problems that children with NF1 experience,[6] our data indicate only weak relationships between general intellectual functioning and autism traits on the SRS-2, and no relationship between IQ and social skills on the SSIS-RS. This is not dissimilar to evidence from the literature on idiopathic ASD, which suggests a complicated, non-linear relationship between autism traits, IQ, and adaptive functioning,[30] as well as NF1-specific literature that indicates minimal-to-no relationships between IQ and social attention skills,[31] facial emotion recognition, theory of mind, and ASD symptomatology.[2] Ultimately, the weak relationships between IQ and SRS-2 and SSIS-RS in the current study suggest these questionnaires are not simply measuring general cognitive deficits in NF1, but a fairly unrelated social-behavioural phenotype.

Third, this study examined relationships between ASD symptoms and prosocial behaviours and functional impairments in children with NF1. This was achieved by examining associations between our key social outcomes and social adaptive behaviour measures. Adaptive measures themselves may not make ideal primary outcomes in clinical trials as they are chiefly designed for diagnostic and prognostic purposes and may be less sensitive to treatment effects over shorter-term treatments.[32] However, because they assess the effectiveness and degree to which an individual meets social/cultural standards of personal independence, they are considered to genuinely reflect clinical concerns and impairments observed in real-world settings.[15,16] While there is a strong body of research highlighting the clinical utility of autism rating scales such as the SRS-2,[33] the literature is perhaps less clear about the clinical value of social functioning scales such as the SSIS-RS.[34] Importantly, our data suggest moderate-to-strong relationships between adaptive social functioning and both SSIS-RS and SRS-2 outcomes, advocating the real-world utility of both outcome measures as clinical endpoints in randomized controlled trials.

In summary, we showed in a pooled, international, cross-sectional sample that both the SRS-2 and SSIS-RS capture elevated rates of social dysfunction in NF1, that are accompanied by social adaptive deficits. There was a trend for the SRS-2 to identify a higher proportion of severely impaired scores compared to the SSIS-RS. Ultimately, no single instrument will capture all aspects of a complex construct such as social function. As such, careful thought is required when deciding which measure is best suited to various research

paradigms and intervention studies. Nonetheless, both instruments analyzed here capture social dysfunction across sex and age, and do not appear to reflect the well-established cognitive dysfunction associated with NF1 in childhood, suggesting both are suitable choices for assessing social outcomes in this population.

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Table 1: Participant demographics and behavioural data

Characteristics	MCRI	CHW	CNHS	UWM	Total
Sample size, (*n*)	44	27	12	39	122
Sex, *n* (%)					
Male	24 (55)	12 (44)	7 (58)	22 (56)	65 (53)
Female	20 (45)	15 (56)	5 (42)	17 (44)	57 (47)
Age, y:mo	9:8 (3:0)	6:7 (2:10)	7:8 (2:10)	10:11 (1:7)	9:2 (3:0)
ADHD-inattentive[a]	71.3 (14.8)	63.2 (18.8)	71.1 (16.6)	67.6 (13.0)	68.2 (15.6)
ADHD-hyperactive/impulsive[a]	67.0 (17.6)	62.5 (16.8)	73.4 (16.3)	61.8 (13.8)	64.9 (16.3)
Full-scale IQ[b,c]	87.9 (13.4)	93.2 (10.9)	86.7 (6.1)	93.8 (13.4)	90.9 (12.6)
SRS-2 total[a]	63.7 (14.6)	57.6 (15.7)	64.4 (13.9)	55.9 (10.3)	59.9 (13.9)
SRS-2 total <60, *n* (%)	19 (43.2)	16 (59.3)	6 (50)	26 (66.7)	67 (54.9)
SRS-2 total ≥60, *n* (%)	25 (56.8)	11 (40.7)	6 (50)	13 (33.3)	55 (45.1)
SRS-2 total ≥65, *n* (%)	21 (47.7)	8 (29.6)	5 (41.7)	9 (23.1)	43 (35.2)
SRS-2 total ≥75, *n* (%)	11 (25.0)	4 (14.8)	3 (25.0)	2 (5.1)	20 (16.4)
SSIS-RS total[b]	85.6 (15.0)	95.6 (18.9)	89.8 (20.3)	91.7 (15.4)	90.2 (16.9)
SSIS-RS total >85, *n* (%)	22 (50.0)	20 (74.1)	8 (66.7)	27 (69.2)	77 (63.1)
SSIS-RS total ≤85, *n* (%)	22 (50.0)	7 (25.9)	4 (33.3)	12 (30.8)	45 (36.9)
SSIS-RS total ≤77, *n* (%)	13 (29.5)	5 (18.5)	4 (33.3)	8 (20.5)	30 (24.6)
SSIS-RS total ≤63, *n* (%)	4 (9.1)	1 (3.7)	2 (16.7)	3 (7.7)	10 (8.2)
Social adaptive functioning[b,d]	85.9 (11.6)	94.3 (14.6)	86.8 (13.2)	94.9 (12.0)	90.7 (13.2)

Data are mean (SD) unless otherwise stated. [a]*t*-score (mean [SD] 50 [10]). [b]Standard score (100 [15]). [c]Full-scale IQ (FSIQ), Wechsler Intelligence Scale for Children, Fifth Edition (Murdoch Children's Research Institute [MCRI], Children's Hospital at Westmead [CHW], Children's National Health System [CNHS]) or General Conceptual Ability, Differential Ability Scale, Second Edition

(Children's Hospital of Wisconsin [UWM]). [d]Social domain, Adaptive Behavior Assessment System, Third Edition (MCRI, CHW, CNHS) or Social Interaction and Communication Skills Cluster, Scales of Independent Behavior-Revised (UWM). Categorical definitions for the Social Responsiveness Scale, Second Edition (SRS-2) and the Social Skills Improvement System – Rating Scales (SSIS-RS) are equivalent and correspond to the 'normal range' (top 83%), 1 SD lower than population mean (16th centile), 1.5 SD lower than population mean (6th centile), 2.5 SD lower than population mean (1st centile). ADHD, attention-deficit/hyperactivity disorder.

Table 2: Correlation coefficients between the Social Responsiveness Scale, Second Edition (SRS-2) and the Social Skills Improvement System – Rating Scales (SSIS-RS) and attention-deficit/hyperactivity disorder (ADHD) symptom severity, full-scale IQ, and social adaptive functioning

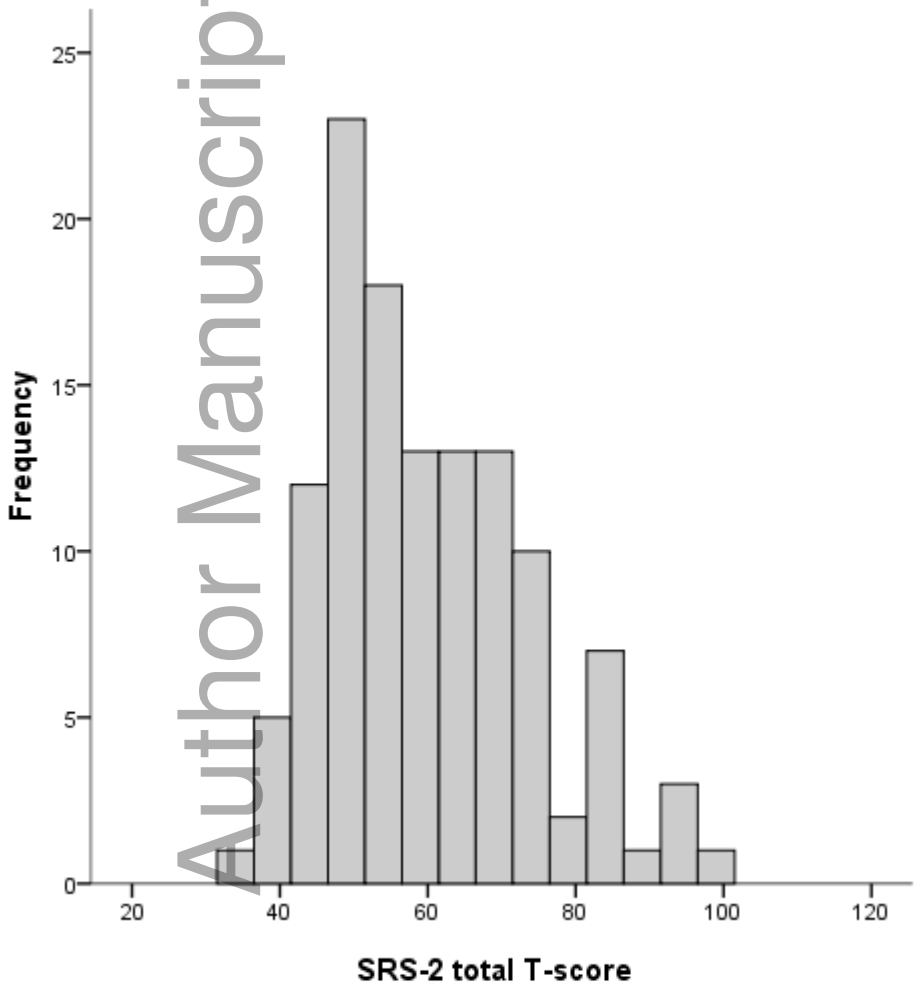
	ADHD-inattentive	ADHD-hyperactive/impulsive	Full-scale IQ	Social adaptive functioning
SRS-2 total	0.63[a]	0.63[a]	0.13	–0.69[a]
SSIS-RS, Social Skills	–0.55[a]	–0.44[a]	–0.23[b]	0.72[a]

[a]$p<0.01$, [b]$p<0.05$.

Figure 1: Distribution of participant scores on (a) the Social Responsiveness Scale, Second Edition (SRS-2) and (b) the Social Skills Improvement System – Rating Scales (SSIS-RS).

Figure 2: Scatter plot demonstrating relationship between total autism spectrum disorder symptoms, as measured by parental report on the Social Responsiveness Scale, Second Edition (SRS-2), and social skills, as measured by parental report on the Social Skills Improvement System – Rating Scales (SSIS-RS).

(a)



(b)