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The Autism Parent Screen for Infants: Predicting risk of autism spectrum disorder based on parent-reported behavior observed at 6–24 months of age

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Abstract

This study examined whether a novel parent-report questionnaire, the Autism Parent Screen for Infants, could differentiate infants subsequently diagnosed with autism spectrum disorder from a high-risk cohort (siblings of children diagnosed with autism spectrum disorder (n = 66)) from high-risk and low-risk comparison infants (no family history of autism spectrum disorder) who did not develop autism spectrum disorder (n = 138 and 79, respectively). Participants were assessed prospectively at 6, 9, 12, 15, 18, and 24 months of age. At 36 months, a blind independent diagnostic assessment for autism spectrum disorder was completed. Parent report on the Autism Parent Screen for Infants was examined in relation to diagnostic outcome and risk status (i.e. high-risk sibling with autism spectrum disorder, high-risk sibling without autism spectrum disorder, and low-risk control). The results indicated that from 6 months of age, total score on the Autism Parent Screen for Infants differentiated between the siblings with autism spectrum disorder and the other two groups. The sensitivity, specificity, and positive and negative predictive validity of the Autism Parent Screen for Infants highlight its potential for the early screening of autism spectrum disorder in high-risk cohorts.

Keywords

autism spectrum disorder, high-risk siblings, parent report, prospective, screening

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that is characterized by impairments in social communication and the presence of repetitive or restricted behavior (American Psychiatric Association, 2013). ASD frequently goes undiagnosed until 4 years of age or later (Daniels and Mandell, 2013); however, parents often report that they were concerned about their child's development before their second birthday (Chakrabarti and Fombonne, 2005). Identifying early signs in children with ASD is crucial to ensure timely access to needed services that have the potential to improve functional outcomes (Dawson et al., 2010; Perry et al., 2008; Sallows and Graupner, 2005). One method for gaining information about early development is to collect information from parents using questionnaires or interviews. Such measures aid in obtaining information about behavioral features to assist with early identification of developmental disorders (Eisert et al., 1991). Surveillance, as part of a more comprehensive process in which referral decisions are based

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on clinical judgment, or screening at check-ups, either universal (level 1, regardless of pre-existing concerns) or targeted (level 2, based on concern or risk status), can assist with the diagnostic process and monitoring changes in behavior over time (Glascoe et al., 2007).

Parents provide uniquely valuable information from the perspective of their everyday observations of infants' usual behavior across varied contexts. Siegel et al. (1986) reported high agreement between parent reports of childhood behavior in the home and clinical impressions derived from diagnostic play sessions used to elicit specific ASD-related behavior. Furthermore, Glascoe (2000) (Glascoe et al., 1997) reported that developmental diagnoses generally correspond with parent reports of their concerns about children's development. A recent examination of parent concerns in a longitudinal examination of children at risk of an ASD diagnosis indicated that parents recognize atypical behavior in their children, in broad agreement with directly observed behavioral signs emerging in the first 2 years (Sacrey et al., 2015).

The currently available parent-questionnaire screening tools for signs of ASD in children under 36 months of age with published evaluation data are presented in Table 1. The First Year Inventory (FYI; Ben-Sasson and Carter, 2012; Reznick et al., 2007; Watson et al., 2007) is a 63-item measurement tool for signs of ASD in 12-month olds. The current version of the Modified Checklist for Autism in Toddlers, the M-CHAT-Revised with Follow-up (M-CHAT-R/F; Robins et al., 2014), consists of a 20-item questionnaire administered between 18 and 30 months and a follow-up interview for positive screens. The Qualitative Checklist for Autism in Toddlers (Q-CHAT; Allison et al., 2008) covers a broad range of ASD symptoms, each rated on a 5-point scale, and is completed when target children between the ages 18 and 24 months. The Parent Observation of Early Markers Scale (POEMS; Feldman et al., 2012) is a parent-report measure designed to monitor the behavioral development of infants at risk for ASD (because they have older siblings diagnosed with ASD). The Early Screening of Autistic Traits Questionnaire (ESAT; Dietz et al., 2006) is a 14-item parent questionnaire for detecting ASD in young children in the general population (Swinkels et al., 2006). The Infant Toddler Checklist (ITC; Wetherby et al., 2008) is a broadband screener to identify children with ASD in the general population. The Brief Infant-Toddler Social and Emotional Assessment (BITSEA; Kruizinga et al., 2014) is a 43-item questionnaire that measures both developmental problems and acquisition of competencies in children aged 1–3 years and includes items designed to measure ASD symptoms (Briggs-Gowan et al., 2004). The Parent's Observational Screen of Social Interactions (POSI; Smith et al., 2013) is a brief, 7-item screen of ASD-specific behaviors assessed for children between the ages of 16 and 48 months. There is a need for a reliable and valid screening instrument targeting a high-risk sample that covers a range of behaviors emerging during early development (6 months+).

The purpose of this study was to assess the potential for the Autism Parent Screen for Infants (APSI) to identify ASD in a high-risk cohort. Items were selected based on behaviors measured by the Autism Observation Scale for Infants (AOSI; Bryson et al., 2008), which has predictive validity as an observational tool by 12 months of age in infant siblings of children diagnosed with ASD (Bryson and Zwaigenbaum, 2014; Zwaigenbaum et al., 2005). Unique features of the AOSI include its use with infants as young as 6 months of age and being specifically designed for use in high-risk cohorts. Adapting the AOSI into a parent questionnaire (the APSI) may yield broader clinical applicability to community settings where trained observers are not readily available. Thus, the APSI could complement existing screening tools, particularly with respect to being potentially informative for children under 18 months of age and its application in high-risk infants (a need highlighted by the American Academy of Pediatrics (Johnson and Myers, 2007)).

In this study, the APSI was completed by two groups of parents. The first group had at least one (older) child diagnosed with ASD (high-risk; HR) and the second had no family history of ASD (low-risk; LR). The primary caregiver completed the APSI at 6, 9, 12, 15, 18, and 24 months of age. Infants underwent a diagnostic assessment for ASD at 36 months of age. Our main objective was to examine whether scores on the APSI distinguished among HR infants who were diagnosed with ASD at 36 months, other HR infants, and comparison LR infants. We hypothesized that the total score on the APSI would differentiate HR infants subsequently diagnosed with ASD at 36 months from non-diagnosed HR infants and LR infants by 12 months of age. An additional objective was to assess the predictive ability of the APSI total score across the age range studied, that is, the sensitivity and specificity of APSI scores relative to 3-year ASD diagnoses, assessed at an individual level.

Methods

Participants

Infant siblings of children with ASD were recruited between the ages of 6 and 12 months from families attending one of five multidisciplinary ASD diagnostic and treatment centers in Canada: (locations blinded). The research ethics board at each institution approved this study and all families gave written informed consent during initial enrollment into the study.

For the HR group, diagnosis of ASD in the older sibling (i.e. proband) was confirmed by a clinical assessment or a review of diagnostic records, using *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text rev.;

Table 1. Currently available ASD screens with evaluation data.

Author	Assessment	Ages assessed	Outcome for ASD
Reznick et al. (2007)	First Year Inventory (FYI)	12 months	FYI identified 44% of infants at 12 months (n = 699) who were diagnosed with ASD at 3 years (Turner-Brown et al., 2012) Children who met FYI 95th percentile cutoff had higher AOSI scores and lower MSEL scores (Ben-Sasson et al., 2012)
Robins et al. (2013)	Modified Checklist for Autism in Toddlers–Revised with follow-up (M-CHAT-R/F)	18–30 months	PPV in community sample of 0.51 (i.e. 51% of children referred for ASD would receive a diagnosis of ASD; Robins et al., 2014)
Allison et al. (2008)	Qualitative Checklist for Autism in Toddlers (Q-CHAT)	18–24 months	High sensitivity and specificity (91% and 89%, respectively) when scoring the 10 items that best discriminated ASD from other diagnostic groups, but further evaluation is warranted (Allison et al., 2012)
Feldman et al. (2012)	Parent Observation of Early Markers Scale (POEMS)	1–24 months	Parents of HR infants (n = 108) completed POEMS at multiple times between 1 and 24 months; resulted in an overall sensitivity of 0.74 (range, 0.25–1.00) and overall specificity of 0.73 (range, 0.65–0.84) from outcomes at 3 years of age (Feldman et al., 2012)
Dietz et al. (2006)	Early Screening of Autistic Traits Questionnaire (ESAT)	14–15 months	Only 25% of children with ASD screened positive on ESAT, although the remaining children did not show typical development (Dietz et al., 2006)
Wetherby et al. (2008)	Infant Toddler Checklist (ITC)	6–24 months	Only 6.1% of children who screened positive for ASD were diagnosed with ASD at 3 years (Wetherby et al., 2008)
Kruizinga et al. (2014)	Brief Infant-Toddler Social Emotional Assessment (BITSEA)	12–36 months	In a community sample of 2-year olds who screened positive showed good sensitivity and specificity for the problem scale (0.83 and 0.84, respectively) and competence scale (0.85 and 0.89, respectively; Briggs-Gowan et al., 2004)
Smith et al. (2013)	Parent's Observational Screen of Social Interactions (POSI)	16–48 months	Sensitivity and Specificity compared to M-CHAT in clinical sample and community referred sample showed higher sensitivity (but comparable specificity; 0.89 and 0.54) in clinical sample compared to M-CHAT (0.71 and 0.62, respectively) and higher specificity (but comparable sensitivity 0.74 and 0.83) in community sample compared to M-CHAT (0.84 and 0.50, respectively)

AOSI: Autism Observation Scale for Infants; ASD: autism spectrum disorder; HR: high risk; MSEL: Mullen Scales of Early Learning; PPV: positive predictive value.

DSM-IV-TR) criteria. Neither the high-risk (HR) infant siblings nor the probands had identifiable neurological or genetic conditions, or severe sensory or motor impairments. The LR controls, recruited from local communities, were included on the basis of having no first- or second-degree relatives with an ASD diagnosis. All participants were born at 36–42 weeks gestation and had a birth weight greater than 2500 g.

Children from our larger HR cohort were included in this study if (1) they had undergone a 3-year diagnostic assessment and (2) had at least one completed APSI. Of the 279 HR children with 3-year follow-up, 75 did not have any completed APSI forms and were excluded from further analyses. Of the 90 LR children who had completed 3-year follow-up, 10 did not have any completed APSI forms (including one child who was diagnosed with ASD at age 3 years). These children were recruited and completed their 3-year assessment prior to inclusion of the APSI in the larger longitudinal study and thus were excluded from further analyses. Therefore, a total of 204 HR infant siblings and 79 LR controls participated in the study. Table 2 presents detailed participant characteristics.

Measures

Participants were assessed at 6, 9, 12, 15, 18, and 24 months of age, with the initial time point between 6 and 12 months, depending on the age of recruitment. Parent report of early signs was measured by the APSI, early behavior and development was measured using the AOSI, Mullen Scales of Early Learning (MSEL), and Vineland Adaptive Behavior Scale (VABS), and the diagnostic assessment was completed using the Autism Diagnostic Observation Schedule (ADOS) and the Autism Diagnostic Interview–Revised (ADI-R).

The APSI is a 26-item forced-choice parent-report questionnaire with content and format similar to the AOSI (Bryson et al., 2008; Bryson and Zwaigenbaum, 2014). It thus covers a wide range of pre-diagnostic behavioral symptoms, including impairments in eye contact, visual tracking, responding to name, imitation, language, social

Table 2. Participant characteristics.

Characteristic	LR	HR-N	HR-ASD
N			
6 months	51	67	21
9 months	56	83	37
12 months	74	104	54
15 months	68	104	53
18 months	72	122	56
24 months	61	58	28
36 months	79	139	66
Sex	43M:36F	69M:69F	50M:16F[a,b]
MSEL ELC	M (SD)	M (SD)	M (SD)
6 months	92.3 (9.4)	91.3 (11.1)	92.2 (10.3)
12 months	98.2 (16.1)	94.0 (18.7)	89.1 (18.1)[a]
24 months	116.1 (20.0)	99.0 (17.1)[a]	88.7 (16.4)[a]
36 months	111.0 (14.0)	104.31 (21.1)	93.3 (15.4)[a,b]
VABS ABC	M (SD)	M (SD)	M (SD)
12 months	104.8 (6.7)	103.8 (8.7)	99.1 (8.5)[a]
18 months	97.7 (7.1)	93.0 (7.2)[a]	85.2 (8.8)[a,b]
24 months	93.8 (8.7)	90.0 (9.3)	83.1 (10.6)[a,b]
36 months	99.0 (10.5)	95.1 (13.2)	81.3 (12.8)[a,b]
AOSI	M (SD)	M (SD)	M (SD)
6 months	7.6 (3.8)	7.3 (3.2)	9.7 (3.7)
9 months	5.2 (3.6)	5.3 (3.0)	5.2 (3.9)
12 months	3.2 (3.2)	5.1 (3.4)[a]	7.3 (4.8)[a,b]
15 months	3.2 (2.8)	4.9 (3.8)	7.6 (4.8)[a,b]
18 months	3.3 (3.0)	5.1 (3.9)[a]	8.3 (4.2)[a,b]
ADOS Severity Score	M (SD)	M (SD)	M (SD)
36 months	1.6 (1.1)	2.6 (1.7)[a]	6.2 (2.0)[a,b]
ADI-R	M (SD)	M (SD)	M (SD)
36 months	4.4 (3.9)	5.9 (4.6)	22.4 (10.3)[a,b]

LR: low risk; HR-N: high-risk infants not diagnosed with autism spectrum disorder; HR-ASD: high-risk infants diagnosed with autism spectrum disorder; MSEL ELC: Mullen Scales of Early Learning Early Learning Composite; SD: standard deviation; VABS ABC: Vineland Adaptive Behavior Scales Adaptive Behavior Composite; AOSI: Autism Observation Scale for Infants; ADOS: Autism Diagnostic Observation Schedule; ADI-R: Autism Diagnostic Interview–Revised.

[a]Different from LR.

[b]Different from HR-N.

development, joint attention, gestures, play, visual examination of objects, and emotional regulation (see Table 3 for items). For example, to the question, "Does your child use gestures, such as waving good-bye, nodding his or her head, or blowing a kiss?" response choices are "definitely," "possibly," or "no," which are scored "0," "1," and "2," respectively. The APSI was designed to monitor putative signs of ASD in infants aged 6–24 months and takes approximately 10–15 min to complete. The primary caregiver completed the APSI. More items with scores indicating the presence of ASD-like behavior resulted in a higher score. Table 4 displays reliability analyses for internal consistency and split-half reliability of the APSI in the sample of children who received an ASD diagnosis at 36 months.

AOSI. The AOSI (Bryson et al., 2008) is a semi-structured direct observational measure designed to identify early behavioral markers of ASD in infants/toddlers (e.g. atypicalities in social communication, engagement, affect sharing, attention, and behavioral regulation). The AOSI is designed for use with 6- to 18-month olds, and administration takes approximately 15–20 min. Each behavior is rated on a scale from 0 to 2 or 3, where 0 implies typical function, and higher values indicate increasing atypicality. The AOSI has excellent inter-rater reliability (0.93 for total score at 12 months), fair-to-good test-retest reliability at 12 months (0.61 for total score: Bryson et al., 2008), and good predictive validity at 12 months for its original 16 items (Brian et al., 2008; Zwaigenbaum et al., 2015). We used a total score cutoff of $\geqslant 7$ to indicate risk, based on the evidence of good positive predictive value (0.75) and negative predictive value (0.98–0.99) in earlier work (Bryson and Zwaigenbaum, 2014). The AOSI was administered at 6 (where applicable), 9, 12, 15, and 18 months of age.

The MSEL. The MSEL (Mullen, 1995) consists of five scales, four of which (Visual Reception, Receptive Language, Expressive Language, and Fine Motor) assess nonverbal, cognitive, and language ability, while the fifth scale measures gross motor development (from 0 to 29 months only). An Early Learning Composite is calculated based on scores from the first four scales for children aged 0–69 months. Inter-rater and test–retest reliability are excellent (Mullen, 1995). The MSEL was administered at 6 (where applicable), 12, 24, and 36 months of age.

VABS. The VABS (Sparrow et al., 1984) is a semi-structured parent interview designed to assess adaptive behavior across four subdomains—Communication, Daily Living, Socialization, and Motor skills (the last domain limited to children younger than 30 months), outlined by typical developmental milestones that are anchored to specific ages. The scale has excellent reliability and concurrent validity and is sensitive to impairments experienced by children with ASD (Carter et al., 1998; Volkmar et al., 1993). The VABS was administered at 12, 18, 24, and 36 months of age.

Table 3. Items queried on the Autism Parent Screen for Infants.

1—Difficulty visually tracking a moving object
2—Visual fixation, or stare, at certain objects
3—Fail to respond to name
4—React to changes in facial expression
5—Anticipate the pleasure of social games
6—Imitation of sounds or actions of others
7—Vocalize back-and-forth with you
8—Difficulty in establishing eye contact
9—Smile in response to your smiles
10—Coordinate actions with eye gaze
11—Tend to be over-reactive or under-reactive
12—Cuddle into your body when holding them
13—Difficult to soothe
14—Show sustained interest and pleasure in interacting
15—Have difficulty with change
16—Difficulty using hands/holding objects
17—Unusual repetitive motor behaviors
18—Use another person's hand as a tool
19—Have unusual sensory behaviors
20—Difficulty focusing attention on objects
21—Insist on holding/playing with certain toys
22—Resist others joining in play/have fixed play routines
23—Share interests in object/event with others
24—Point to objects/event at a distance
25—Use gestures
26—Loss of skill over past 2–3 months

ADOS. The ADOS (Lord et al., 2000) includes standardized activities and "presses," which are used to elicit communication, social interaction, imaginative use of play materials, and repetitive behavior (Lord et al., 1989). Inter-rater reliability for the ADOS is excellent (Lord et al., 2000). The scoring algorithm was recently revised to optimize discrimination of ASD from other developmental disabilities and is organized into two domains, Social Affect (including Communication and Social items) and Restricted Repetitive Behaviors (Gotham et al., 2007). The ADOS consists of four modules, each of which is appropriate for individuals of differing language levels (Module 1 = minimal or no language, Module 2 = regular use of non-echoed 3-word phrases, Module 3 = child with fluent language, and Module 4 = adolescent or adult with fluent language), the first three of which were used to assess participants in this study; Module 1 alone was administered at the 18-month assessment. To optimize comparability across modules (and thus, across language levels), we used the 36-month ADOS severity metric (Gotham et al., 2009).

ADI-R. The ADI-R (Lord et al., 1994) is an investigator-directed interview that elicits information regarding social development, verbal and non-verbal communication skills, and the presence of repetitive, stereotyped interests and behavior required to make an International Classification of Diseases (10th ed.; ICD-10) or DSM-IV-TR diagnosis of ASD. The questions are designed to distinguish qualitative impairments from developmental delays. The ADI-R discriminates well between ASD and other forms of developmental disability, and inter-rater reliability is excellent (Lord et al., 1994). The ADI-R was administered at 36 months of age.

Diagnostic procedure

At 3 years of age, each participant underwent an independent diagnostic evaluation, conducted by an expert clinician blind to results from previous study visits. ASD diagnoses

Table 4. Reliability of the APSI.[a]

Age (months)	6	9	12	15	18	24
Internal consistency (α)	0.77	0.90	0.83	0.89	0.87	0.92
Split-half reliability (α)	0.35	0.89	0.82	0.91	0.91	0.94

APSI: Autism Parent Screen for Infants; HR-ASD: high-risk infants diagnosed with autism spectrum disorder.
[a]Reliability calculated on HR-ASD sample only.

were assigned using DSM-IV-TR criteria, based on the best judgment of the clinician (developmental pediatrician, child psychiatrist, or clinical psychologist, all with at least 10 years of diagnostic experience), taking into account information from the ADI-R and ADOS, as well as concurrent developmental assessment using the MSEL and VABS.

Statistical analysis

Group membership was determined from the 3-year outcome assessments: high-risk infants diagnosed with ASD (HR-ASD), high-risk infants not diagnosed with ASD (HR-N), and low-risk infant not diagnosed with ASD (LR). Clinical characteristics of the groups were compared using linear mixed modeling with Group (LR, HR-N, HR-ASD) and Age (6, 9, 12, 15, 18, 24 months) as independent measures and scores on the various assessments as the dependent measures. Performance on the APSI was compared using linear mixed modeling with Group and Age as independent measures and scores on the questionnaire as the dependent measure. Total scores were compared and group by age interactions were explored using Benjamini and Hochberg corrections (Benjamini and Hochberg, 1995). In this method, the p-values are ordered smallest to largest. The alpha level for each test is then set at $(k * \alpha)/m$ with k corresponding to the p-value's rank (e.g. lowest p-value = 1) and m corresponding to the number of comparisons, which in this case was 18. The comparisons stop once one of the t-tests is rejected. Thus, this method decreases the chance of false positives. Our main objective was to determine when differences appeared among the three groups of children, therefore planned comparisons were completed on all group by age interactions. Effect sizes were calculated for group differences between the two HR groups using Cohen's *d*, with 0.2–0.49 = small effect, 0.5–0.79 = medium effect, and 0.8 + = large effect.

To provide a preliminary assessment of the predictive utility of the APSI, we used receiver operator characteristic (ROC) analyses to assess the sensitivity and specificity of the APSI at each age with respect to ASD diagnosis at age 3. Analyses were limited to the HR cohort, to examine specifically the potential properties of the APSI within that context. To determine the optimal cut-point for the total score, Youden's index was used, which is defined as the maximum vertical distance between the ROC curve and the diagonal or chance line (Youden's index (*J*) = sensitivity + specificity − 1 (Akobeng, 2007)). Other determinants of screening accuracy were (1) sensitivity, the proportion of children with ASD correctly classified by the APSI; (2) specificity, the proportion of children not diagnosed with ASD correctly classified by the APSI; (3) positive likelihood ratio (LHR+), the ratio of the probability of identifying a child as having ASD if the child does have ASD (true positive) relative to the probability of identifying the child as having ASD if the child does not have ASD (false positive) (*sensitivity*/(1 − *specificity*)); (4) negative likelihood ratio (LHR−), the ratio of the probability of not identifying the child as ASD if the child does have ASD (false negative) to the probability of not identifying the child as ASD if the child does not have ASD (true negative) ((1 − *sensitivity*)/*specificity*); (5) odds ratio (OR), the ratio of the odds of a correctly identifying a child as ASD when having the "disorder" relative to the odds of a identifying a child as ASD when not having the "disorder" ((*sensitivity***specificity*)/((1 − *sensitivity*)*(1 − *specificity*)); (6) positive predictive validity (PPV), the child with ASD is correctly identified as a child with ASD ((*true positive*/(*true positive* + *false positive*))); and (7) negative predictive validity (NPV), the child without ASD is incorrectly identified as a child with ASD ((*true negative*/(*true negative* + *false negative*))) (Fischer et al., 2003).

Results

Completers versus non-completers

A chi-square analysis was completed to determine if there were differences in the clinical characteristics of the children who have parents compete versus not complete APSI forms. There were no differences in the proportion of parents in each group who completed APSI forms ($\chi(2) = 3.56$, $p = 0.107$). As well, there were no differences between the completers versus non-completers for the child's severity score on the ADOS at 24 ($t = .74$, $p = 0.46$) and 36 months ($t = 1.28$, $p = 0.20$), nor the total score on the ADI at 36 months ($t = 1.33$, $p = 0.18$).

Respondent characteristics

The respondent who completed an APSI at each age assessed is presented in Table 5 as mother, father, both parents, or unidentified. Group differences for the respondent were assessed using chi-square analyses at each age. There were no group differences, except for age 18 months, where the difference was driven by the number of "unidentified" respondents in the HR-N group. The vast majority of respondents (78% or greater) were identified as "mother" across all groups and ages assessed.

The average age of the mother at study enrollment was significantly different between groups, with older mothers in the HR-ASD (34.35 ± 4.15 years) and HR-N (33.91 ± 4.25 years) groups compared to mothers in the LR group (31.72 ± 3.97 years; $ps < .001$). Similarly, the average age of the father at study enrollment was significantly different between groups, with older fathers in the HR-ASD (37.31 ± 5.83 years) and HR-N (36.35 ± 5.34 years) groups compared to the LR group (33.64 ± 4.09 years; $ps < 0.001$).

Table 5. Respondents for each group at each age assessed.

Age	HR-ASD				HR-N				LR				Significance	
	M	F	B	U	M	F	B	U	M	F	B	U	X	p
6 months	84.85	6.06	6.06	3.03	88.17	1.08	5.38	5.38	93.55	0.00	4.84	1.61	7.01	0.32
9 months	89.47	2.63	7.89	0.00	82.29	1.04	6.25	10.42	94.12	0.00	4.41	1.47	11.29	0.08
12 months	86.57	1.49	5.97	5.97	80.85	2.13	5.67	11.35	93.10	0.00	5.75	1.15	10.79	0.09
15 months	86.00	2.00	4.00	8.00	81.03	1.72	4.31	12.93	85.71	2.86	7.14	4.29	4.89	0.56
18 months	85.07	4.48	7.46	2.99	78.21	3.21	4.49	14.10	90.59	1.18	5.88	2.35	15.34	0.02*
24 months	88.89	0.00	3.70	7.41	92.98	1.75	5.26	0.00	90.16	1.64	6.56	1.64	5.74	0.45

M: mother; F: father; B: both parents; U: unidentified; HR-N: high-risk infants not diagnosed with autism spectrum disorder.
Values are percentages.
*Difference is driven by the number of unidentified respondents in the HR-N group.

Child characteristics

From the results of the 36-month diagnostic assessments, three groups were identified for comparison: (1) HR infant siblings who received a diagnosis of ASD ("HR-ASD"; n = 66; 50 boys and 16 girls); (2) HR infant siblings who did not receive a diagnosis of ASD ("HR-N"; n = 138; 69 boys and 69 girls); and (3) LR controls who did not receive a diagnosis of ASD ("LR"; n = 79; 43 boys and 36 girls). As shown in Table 2, a significant sex difference ($\chi = 11.26$, $p = .004$) showed a higher boy-to-girl ratio in the HR-ASD group than in the LR and HR-N groups, who did not differ ($ps < 0.01$), as anticipated from previous analyses on this sample (citation blinded). The groups differed in age at initial assessment ($F(2,284) = 7.64$, $p < 0.01$). The HR-ASD group was slightly older than the HR-N and LR groups, resulting from a lower proportion of first assessments at 6 months in the HR-ASD group, relative to the other two groups. The groups did not differ in age at the 36-month diagnostic assessment ($F(2,283) = 0.20$, $p = 0.50$). Descriptive data on developmental and behavioral features are also summarized for the three groups in Table 2. There were group differences for the MSEL, VABS, and AOSI at 12 months of age and older.

Total APSI scores

For each infant at each age, scores on each APSI item were computed and summed to yield a total score (n = 26; maximum score = 52). To determine group differences for the total score, a mixed model analysis was performed. Overall, there were significant effects of Group ($F(2, 1153) = 121.72$, $p < 0.001$), Age ($F(5, 1153) = 34.38$, $p < 0.001$), and a Group × Age ($F(10, 1153) = 1.81$, $p < 0.05$) interaction. Post hoc analyses were run on the interaction effect using a Benjamini and Hochberg correction ($q < .036$). As shown in Figure 1, the total score was higher for HR children with ASD compared to the other two groups *beginning at 6 months* and continuing to 24 months. Only 12-month APSI scores were higher for the HR-N group compared to the LR group. Effect sizes were computed for comparisons between the two HR groups at 6–24 months, resulting in ds of 4.13, 7.25, 8.11, 10.64, 8.01, and 10.21, respectively.

Group comparisons were also completed on individual APSI questions for ages 6, 12, and 18 months. As shown in Table 6, item-level differences between the two HR groups at 6 months were detected on questions related to visual tracking and back-and-forth vocalizations. At 12 months, item-level group differences between the two HR groups were detected on 14 of 26 items, as detailed in Table 7. Finally, item-level group differences between the HR groups at 18 months were detected on 21 of 26 questions, as presented in Table 8. Comparisons were corrected for multiple testing using the Benjamini and Hochberg (1995) correction.

ROC curve analyses

ROC curve analyses were completed to identify cutoff scores at each age that optimized the predictive utility of the APSI (total score), with respect to subsequent ASD diagnosis. The HR groups (HR-ASD vs HR-N) were compared using a series of ROC analyses at 6, 9, 12, 15, 18, and 24 months of age. The area under the curve (AUC) for the total score was significant at each age (i.e. the overall "area under the curve" was different from 0.5, the value expected by chance). Sensitivity, specificity, PPV, and NPV for the total scale score were 0.67, 0.86, 0.47, and 0.83, respectively (cutoff = 15), at 6 months, 0.59, 0.72, 0.65, and 0.76, respectively (cutoff = 10), at 12 months, and 0.65, 0.72, 0.68, and 0.77, respectively (cutoff = 9), at 18 months. Table 9 displays the results of the ROC analyses at each age. Youden indices indicated different optimal cutoffs for the total scale score at each age, with highest cutoffs at the youngest ages. When comparing the optimal parameters, discrimination between those HR children who would and would not be diagnosed with ASD was achieved at the youngest ages assessed, as determined by the highest sensitivity and specificity.

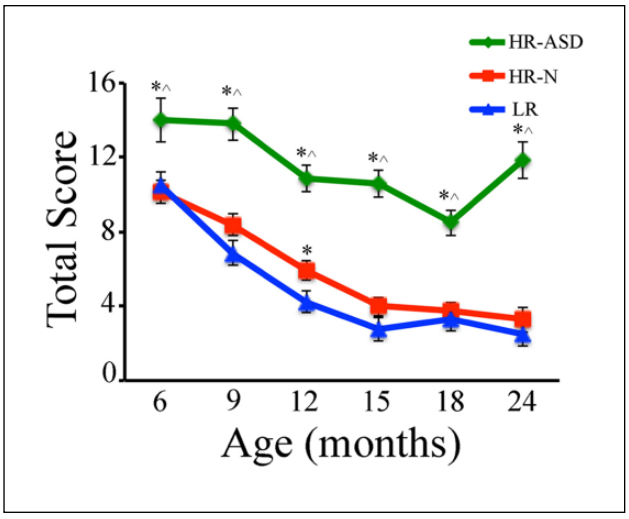

Figure 1. Total score on the APSI (all questions combined) for ages 6–24 months.
*Different from LR; ^different from HR-N.

Discussion

In this study, we described a parent-report questionnaire analogue of the AOSI, the APSI, which was completed by the primary caregivers of HR and LR infants at multiple time points from 6 to 24 months of age. Overall, the HR-ASD group had a higher mean APSI total score than the LR and HR-N groups at each time point between 6 and 24 months of age. Importantly, ROC analyses indicated that the APSI predicted group status beyond chance at the earliest age point assessed (6 months), differentiating between HR infants who would and would not receive an ASD diagnosis.

The earlier identification of high-risk siblings who would later be diagnosed with ASD reported here was based on differences in sensory behavior, imitation, responding to changes in facial emotion, back-and-forth communication, and sharing interests with others. This finding is consistent with those of the Avon Longitudinal Study of Parents and Children, a prospective investigation

Table 6. Group differences for individual questions at 6 months of age.

APSI at 6 months	HR-ASD (n = 21)		HR-non-ASD (n = 67)		LR-non-ASD (n = 52)		HR-ASD versus HR-N	HR-ASD versus LR	HR-N versus LR
Item	% 1	% 2	% 1	% 2	% 1	% 2	p value	p value	p value
1—Visual tracking	19	5	–	2	–	2	0.001*	0.001*	0.65
2—Visual fixation	43	10	33	44	33	44	0.61	0.002*	0.001*
3—Respond to name	48	14	37	8	37	8	0.44	0.12	0.26
4—Response to facial emotion	35	45	48	19	48	19	0.02	0.05	0.75
5—Anticipatory social response	40	5	21	6	21	6	0.093	0.22	0.56
6—Imitation	24	62	53	13	54	14	0.02	0.001*	0.19
7—Vocalize with you	52	29	25	4	25	4	0.001*	0.001*	0.53
8—Eye contact	10	5	6	4	6	4	0.38	0.58	0.68
9—Reciprocal social smile	5	0	2	–	2	–	0.36	0.45	0.87
10—Coordinate actions with eye gaze	19	10	35	–	35	–	0.59	0.90	0.59
11—Reactivity	38	5	14	4	14	4	0.09	0.05	0.61
12—Cuddle with you	24	–	19	4	19	4	0.97	0.83	0.72
13—Difficult to soothe	24	5	10	4	10	4	0.66	0.23	0.28
14—Social interest and affect	24	–	4	–	4	–	0.66	0.07	0.05
15—Difficulty with change	5	–	10	–	10	–	0.48	0.42	0.87
16—Hand use/holding objects	19	–	12	–	12	–	0.43	0.50	0.05
17—Repetitive motor behaviors	5	10	10	6	10	6	0.16	0.86	0.09
18—Another person's hand as tool	5	–	4	–	4	–	0.42	0.80	0.46
19—Unusual sensory behaviors	19	5	8	4	8	4	0.09	0.24	0.52
20—Focusing attention on objects	10	5	10	2	19	2	0.65	0.77	0.84
21—Insistence on particular object	–	–	4	–	4	–	0.73	0.18	0.16
22—Resist play/fixed play routines	–	5	–	–	–	–	0.08	0.05	0.67
23—Share interests with others	33	38	35	13	35	13	0.02	0.02	0.99
24—Distal point	–	100	4	96	4	96	0.26	0.40	0.72
25—Use gestures	5	95	2	98	2	98	0.62	0.41	0.07
26—Loss of skill	5	–	2	–	2	–	0.37	0.46	0.86

APSI: Autism Parent Screen for Infants; HR-ASD: high-risk infants diagnosed with autism spectrum disorder; LR: low risk; HR-N: high-risk infants not diagnosed with autism spectrum disorder; "–": no code at that score for item.
*$p < 0.006$.

Table 7. Group differences for individual questions at 12 months of age.

APSI at 12 months	HR-ASD (n = 54)		HR-non-ASD (n = 104)		LR-non-ASD (n = 75)		HR-ASD versus HR-N	HR-ASD versus LR	HR-N versus LR
Item	% 1	% 2	% 1	% 2	% 1	% 2	p value	p value	p value
1—Visual tracking	6	7	1	2	1	3	0.02*	0.04	0.74
2—Visual fixation	28	9	14	2	20	4	0.003*	0.10	0.19
3—Respond to name	20	19	14	2	11	3	0.001*	0.001*	.73
4—Response to facial emotion	54	13	56	5	36	4	0.24	0.003*	0.02*
5—Anticipatory social response	13	9	8	2	4	–	0.005*	0.001*	0.19
6—Imitation	35	7	22	4	11	–	0.024*	0.001*	0.006*
7—Vocalize with you	33	11	22	3	8	–	0.001*	0.001*	0.009*
8—Eye contact	19	15	10	1	3	1	0.001*	0.001*	0.32
9—Reciprocal social smile	19	–	4	–	–	–	0.001*	0.001*	0.28
10—Coordinate actions with eye gaze	20	4	7	2	8	1	0.03*	0.05	0.88
11—Reactivity	22	17	11	4	5	1	0.001*	0.001*	0.10
12—Cuddle with you	31	13	18	3	19	–	0.001*	0.001*	0.57
13—Difficult to soothe	9	7	13	5	4	4	0.83	0.18	0.18
14—Social interest and affect	13	7	8	3	5	–	0.05	0.003*	0.17
15—Difficulty with change	20	7	16	2	16	3	0.10	0.22	0.73
16—Hand use/holding objects	9	9	9	3	4	–	0.07	0.002*	0.09
17—Repetitive motor behaviors	15	11	14	1	1	–	0.002*	0.001*	0.02*
18—Another person's hand as tool	11	2	14	2	17	11	0.84	0.005*	0.002*
19—Unusual sensory behaviors	13	4	7	2	9	–	0.10	0.09	0.88
20—Focusing attention on objects	35	6	24	3	19	1	0.11	0.01*	0.21
21—Insistence on particular object	15	7	8	1	9	4	0.02*	0.13	0.46
22—Resist play/fixed play routines	9	–	2	1	–	–	0.11	0.01*	0.24
23—Share interests with others	28	17	21	5	9	3	0.007*	0.001*	0.06
24—Distal point	19	54	25	41	28	36	0.35	0.10	0.38
25—Use gestures	19	24	28	11	4	5	0.06	0.001*	0.001*
26—Loss of skill	2	6	3	2	1	–	0.23	0.04	0.27

APSI: Autism Parent Screen for Infants; HR-ASD: high-risk infants diagnosed with autism spectrum disorder; LR: low risk; HR-N: high-risk infants not diagnosed with autism spectrum disorder; "–": no code at that score for item.
*$p < 0.03$.

of 14,541 families. The authors reported that differences in social skills and communication were evident by 6 months of age in those children who were later diagnosed with ASD (n = 68; Bolton et al., 2012).

The sensitivity and specificity of the APSI total score (derived from the Youden index) ranged from 0.58 to 0.67 for sensitivity and from 0.72 and 0.87 for specificity. Although moderate, the sensitivity and specificity estimates of the APSI are comparable to those of other ASD screening instruments. For example, recent evaluative data on the M-CHAT-R/F report sensitivity and specificity data (0.73 and 0.89, respectively) for a cutoff score of 3 (Robins et al., 2014). Similarly, the positive and negative predictive value of the APSI are similar to those of the ITC, which reports lower PPV at the lowest ages (0.43 at 6–8 months) and higher PPV at the highest ages examined (0.79 at 21–24 months) and NPV ranging between 0.87 and 0.99 across the ages examined (Wetherby et al., 2008). Although sensitivity and specificity are comparable, the APSI has some unique strengths. For example, the M-CHAT/R (Robins et al., 2013) is administered between 18 and 30 months of age and requires a clinician-led follow-up interview in most cases to confirm positive screens. Although there are several screeners available, the APSI may fulfill a unique role, as it is informative as early as 6 months of age, and as a stand-alone instrument. Moreover, the APSI is particularly well suited for research with high-risk siblings because of its relationship and possible convergence with the AOSI. Indeed, there is a need for early detection tools suited to infants who have an older child with autism, as this group has been identified as in need of intensified surveillance by Johnson and Myers (2007).

Current observational data suggest that social communication differences in ASD may not be evident until around 12 months (Landa et al., 2012; Landa and Garrett-Mayer, 2006; Ozonoff et al., 2010; Sacrey et al., 2013; Zwaigenbaum et al., 2005). Prodromal features of ASD,

Table 8. Group differences for individual questions at 18 months of age.

APSI at 18 months	HR-ASD (n = 56)		HR-non-ASD (n = 122)		LR-non-ASD (n = 73)		HR-ASD versus HR-N	HR-ASD versus LR	HR-N versus LR
Item	% 1	% 2	% 1	% 2	% 1	% 2	p value	p value	p value
1—Visual tracking	2	–	–	2	–	1	0.46	0.84	0.57
2—Visual fixation	18	4	8	1	5	1	0.01*	0.02*	0.96
3—Respond to name	32	13	10	1	11	–	0.001*	0.001*	0.83
4—Response to facial emotion	41	7	39	6	27	–	0.46	0.008*	0.02*
5—Anticipatory social response	9	4	1	1	1	–	0.002*	0.002*	0.78
6—Imitation	21	5	14	–	8	–	0.002*	0.001*	0.23
7—Vocalize with you	20	7	14	1	3	–	0.002*	0.001*	0.03*
8—Eye contact	21	5	7	2	5	3	0.002*	0.003*	0.95
9—Reciprocal social smile	16	–	4	–	1	–	0.001*	0.001*	0.43
10—Coordinate actions with eye gaze	18	–	3	1	10	–	0.03*	0.33	0.25
11—Reactivity	23	11	8	3	5	–	0.001*	0.001*	0.14
12—Cuddle with you	16	5	7	1	7	–	0.002*	0.002*	0.80
13—Difficult to soothe	18	9	14	1	5	4	0.02*	0.009*	0.61
14—Social interest and affect	14	13	10	1	–	1	0.001*	0.001*	0.17
15—Difficulty with change	25	7	25	–	27	–	0.10	0.21	0.77
16—Hand use/holding objects	11	4	1	1	1	1	0.003*	0.05	0.37
17—Repetitive motor behaviors	16	9	15	2	3	–	0.02*	0.001*	0.01*
18—Another person's hand as tool	16	18	18	11	22	21	0.39	0.33	0.03*
19—Unusual sensory behaviors	7	9	6	–	3	4	0.001*	0.03*	0.40
20—Focusing attention on objects	25	9	16	–	14	5	0.001*	0.02*	0.34
21—Insistence on particular object	18	13	14	3	16	10	0.04*	0.57	0.11
22—Resist play/fixed play routines	13	2	2	–	–	1	0.003*	0.004*	0.89
23—Share interests with others	30	2	20	2	11	3	0.09	0.03*	0.45
24—Distal point	25	18	16	9	15	4	0.007*	0.001*	0.31
25—Use gestures	14	11	5	–	–	1	0.001*	0.001*	0.50
26—Loss of skill	7	4	1	–	–	–	0.001*	0.001*	0.63

APSI: Autism Parent Screen for Infants; HR-ASD: high-risk infants diagnosed with autism spectrum disorder; LR: low risk; HR-N: high-risk infants not diagnosed with autism spectrum disorder; "–": no code at that score for item.
*$p < 0.04$ highlighted.

such as atypical visual orienting and face processing, have been detected by electroencephalogram (EEG) and eye tracking by 6–8 months, yet such technology-based methods are expensive and time-consuming (Chawarska et al., 2013; Cohen et al., 2013; Elison et al., 2013; Elsabbagh et al., 2012; Jones and Klin, 2013). Although eye tracking may ultimately be adapted for application in clinical settings, specialized equipment and technical skills will be needed. The APSI findings suggest that parents of high-risk siblings are detecting differences at around the same time as the technology measures and possibly earlier than laboratory- or clinic-based behavioral observations.

Our findings are promising, but not without limitations. We did not obtain inter-rater agreement, but rather requested responses from informants identified as the primary caregiver. We did record who identified himself or herself as the primary caregiver (e.g. father, mother) and although the overwhelming majority were identified as "mother," it is possible that the different respondents may have added variability to the responses recorded. Additionally, children included in the analyses did not have had an APSI completed at each age assessed. To be included, children only needed to have one APSI completed, reducing potential bias from parents who chose to participate versus non-participants. Finally, parents received feedback concerning their child's performance at each visit. This in turn may have affected how the parent scored later APSIs. In line with this, parental ratings could also be influenced by their experience with the older sibling, affecting how the APSI was scored. As such, ratings reported in this research context, which provided the parents of high-risk children with ongoing feedback, might be fundamentally different from parental experiences when completing the APSI as part of a universal screen at general wellness visits. We also acknowledge that the APSI may perform differently in infants who are at increased risk of ASD for reasons other than family history. Previous research using the AOSI to

Table 9. ROC characteristics for total score on the APSI for the high-risk sample only.

Total scale score										
Age	AUC (CI)	Cutoff	Sensitivity	Specificity	LHR+	LHR−	OR	J	PPV	NPV
6	0.78 (0.62–0.94)	14	0.67	0.77	2.93	0.34	6.80	0.44	0.45	0.82
		15[a]	0.67	0.86	4.89	0.20	12.67	0.53	0.47	0.83
		16	0.5	0.89	4.40	0.23	7.80	0.39	0.60	0.84
9	0.8 (0.69–0.92)	13	0.62	0.84	3.92	0.26	8.67	0.46	0.68	0.80
		14[a]	0.62	0.87	4.70	0.21	10.73	0.49	0.70	0.79
		15	0.52	0.9	4.98	0.20	9.35	0.42	0.74	0.78
12	0.66 (0.53–0.79)	9	0.59	0.67	1.76	0.57	2.86	0.26	0.63	0.79
		10[a]	0.59	0.72	2.09	0.48	3.64	0.31	0.65	0.76
		11	0.5	0.74	1.95	0.51	2.90	0.24	0.67	0.76
15	0.74 (0.61–0.87)	9	0.61	0.75	2.34	0.41	4.75	0.36	0.69	0.77
		10[a]	0.58	0.83	3.48	0.29	6.92	0.41	0.73	0.76
		11	0.45	0.88	3.61	0.28	5.76	0.33	0.80	0.75
18	0.68 (0.51–0.84)	8	0.74	0.6	1.85	0.54	4.25	0.34	0.63	0.78
		9[a]	0.65	0.72	2.33	0.43	4.82	0.37	0.68	0.77
		10	0.61	0.72	2.17	0.46	4.00	0.33	0.69	0.75
24	0.72 (0.55–0.90)	11	0.58	0.77	2.52	0.39	4.58	0.35	0.72	0.78
		12[a]	0.58	0.85	3.76	0.27	7.56	0.43	0.79	0.77
		13	0.53	0.85	3.42	0.29	6.11	0.37	0.85	0.77

AUC: area under the curve; CI: confidence interval (95%); LHR+: positive likelihood ratio; LHR−: negative likelihood ratio; OR: odds ratio; J: Youden's Index; PPV: positive predictive value; NPV: negative predictive value.
[a]Shading indicates the optimal cutoff (via Youden's J).

assess early signs of ASD in other at-risk groups indicates overlapping findings with early signs in younger siblings, but also important differences that may relate to underlying differences in biology and cognitive profiles (Jeste et al., 2016; Roberts et al., 2016; Yaari et al., 2016). Nevertheless, the strengths of our study include the large high-risk sibling sample, which included 66 children diagnosed with ASD, and availability of outcome data on the full sample, including "screen-negative" HR and LR children. Future work could assess the validity of the APSI in other high- and low-risk samples to assess potential generalizability beyond the high-risk context.

Based on the current findings, the APSI has potential to differentiate, starting at 6 months of age, high-risk siblings who will be diagnosed with ASD at 3 years of age from both high-risk siblings who do not have ASD and community controls. Although additional research is needed, the APSI shows promise as a simple, low-cost parent-report monitoring system. The use of the APSI may lead to earlier identification of children who could benefit from increased monitoring and/or early intervention to remediate problematic behavior in children at risk for an ASD diagnosis.

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