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## Autism Spectrum Disorder-Associated Behaviour in Infants with Down Syndrome

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### Abstract

**Background**—Individuals with Down syndrome (DS) are at high risk for autism spectrum disorder (ASD) with ~20% of individuals meeting diagnostic criteria for ASD. Despite the high risk, there is no research documenting early signs of ASD in infants with DS or potential prodromal ASD-associated behaviors.

**Aim**—This preliminary case-control study described ASD-associated behaviors in infants with DS contrasted to typically developing (TD) infants.

**Patients and Methods**—The Autism Observation Scale for Infants (AOSI) was used to describe ASD-related behaviors in 18 infants with DS (7–18 months) and 18 TD infants (9–14 months).

**Results**—Thirty nine percent (7 out of 18) of infants with DS in our sample were designated “at risk” for ASD on the AOSI with 100% of infants with DS demonstrating at least one feature of ASD. In contrast, only 11% (2 out of 18) of TD infants were designated “at risk” for ASD on the AOSI. Social and communication impairments appear to represent early signs of elevated ASD-associated behavior in infants with DS.

**Conclusions**—Early signs of ASD-associated behavior appear present and detectable in infants with DS. These early signs mirror findings of other populations at risk for ASD with social communication as the primary behavioral impairment to signal elevated risk for the emergence

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Author Contribution Statement:

LJH and JER conceived of the study and participated in its design. LJH had the primary role in coordination of the study, overseeing data collection, preparation for analysis, performed the formal statistical analyses, interpretation of the data, and drafted, reviewed, and edited the manuscript. JER, LRH, and BLK assisted with interpretation of the data and helped to review and edit the manuscript. JER also provided mentorship throughout the project.

Conflict of Interest

The authors declare that they have no conflict of interest.

of ASD. This study contributes to the refinement of the DS behavioral phenotype and identifies important next steps to help improve the identification, diagnosis, and treatment of ASD in DS.

### Keywords

Down syndrome; Autism Spectrum Disorder; Infants

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### Background

Autism spectrum disorder (ASD) is a common and lifelong disorder affecting 1:59 in the general population [1]. Early treatment of ASD leads to improved outcomes [2, 3]; thus, early detection is critical. Examining ASD in neurogenetic syndromes at high risk for ASD, such as Down syndrome (DS), helps establish the shared phenomenology between disorders [4] and advance our understanding of the specific needs of children with neurogenetic syndromes.

DS is caused by the presence of an overexpression of genes on chromosome 21 and is the most common genetic (chromosomal) abnormality associated with intellectual disability (affecting 1 in 691 individuals [5]). While not extensively researched, existing work suggests that ~20% (7–42%) of children with DS meet diagnostic criteria for ASD [6–8]. As such, ASD is highly expressed in DS at a rate much higher than the general population. The limited research is likely due to diagnostic challenges given the presence of intellectual disability because clinicians need to differentiate ASD-like behaviors from similar behaviors associated with intellectual disability [9, 10] and a historical bias that the “social strengths” in DS represent a protective factor against ASD [11]. Also, many children with DS may not be eligible for ASD diagnostic tools depending on the level of their motor skills (e.g., the toddler module of the Autism Diagnostic Observation Schedule-2 requires a minimum mental age of 12 months and that the child is walking or “cruising” [12]). These challenges have led to reluctance in making a diagnosis of ASD in DS resulting in delays or misdiagnoses [10, 11, 13]. Whereas, the average age of diagnosis in non-syndromic ASD (nsASD) is 3–4 years [1].

Research identifying early signs of nsASD has primarily focused on developmental trajectories of infants with older siblings with nsASD suggesting that early behavioral signs include impaired visual attention [14], delays in language and gesture [15], and motor difficulties [16]. To date, no research has described signs of ASD in children with DS younger than 2 years-of-age with only a handful of studies conducted at preschool-age and older [17]. In a longitudinal study with 20 2-to-3-year-olds with DS, 15% (3 children) met ASD diagnostic criteria (mean age 34 months [17]). Diagnostic stability was high over time, and all three children with DS+ASD demonstrated impairments in communication and social skills with more severe difficulties in communication than social skills and had greater developmental delays than those with DS without ASD. These data provide initial evidence that ASD symptoms emerge within the second year of life and remain stable in DS.

Despite the high prevalence of ASD in DS and the importance of early identification, no research has examined behavioral signs of ASD in infants with DS.

## Aim

This preliminary case-control study aims to describe ASD-associated behaviors in infants with DS contrasted to typically developing (TD) infants. This is accomplished by reporting those who score above risk cut-offs on the Autism Observation Scale for Infants [18, 19], identifying potential ASD risk markers, and describing the relationship of ASD-associated behavior to chronological age and developmental level.

## Patients and Methods

### Participants

Participants were 18 infants with DS (14 males, 4 females) between 7–18 months and 18 TD infants (14 males, 4 females) between 9–14 months (see Table 1). TD infants were included to represent typical variation in development (i.e., the control group). Infants with DS were from three pilot studies examining the infant phenotype in neurogenetic syndromes from the University of South Carolina (USC; n = 11), the University of Illinois (UIUC; n = 3), and Purdue University (PU; n = 4). Across all three sites, infants with DS were recruited through flyers shared with local parent groups, DS clinics, and ongoing research studies in Georgia, Illinois, Indiana, Missouri, and South Carolina. TD infants were recruited as part of a study on the emergence of ASD in fragile X syndrome at USC. As part of this larger study, TD infants were followed until they were 3 years of age and were determined not to have ASD or another developmental disability. TD infants were matched to infants with DS on sex at an individual level and age at a group level, no significant differences between groups (see Table 2 for matching statistics).

### Tools

**Autism Observation Scale for Infants (AOSI)**—The AOSI is a semi-structured, play-based observation to identify early signs of ASD from 6–18 months [18, 19]. The infant's behavior is ranked on 19 items as either “typical” (score 0), “inconsistent, partial or questionable” (score 1), or “atypical” (score 2–3). ASD risk is defined as the Number of Markers Score (tally of the number of items scored 1), with a score of >7 indicating ASD risk [20]. Test-retest reliability at 12 months is .61 for the Total Score [19]. The AOSI has been used with other neurogenetic syndromes, but not with DS [21, 22]. All examiners were research reliable on the AOSI.

### Mullen Scales of Early Learning (MSEL)

The MSEL is a standardized assessment of development from birth to 68 months [23]. We used the Early Learning Composite and calculated a nonverbal (visual reception + fine motor), and verbal (expressive language + receptive language) composite using the average T-scores, which account for age effects. Several infants with DS scored at the floor on the different domains of the MSEL (expressive language = 1, receptive language = 2, fine motor = 4, visual reception = 3). No TD infants in our sample scored at the floor. The MSEL has well-established validity and reliability [23].

## Ethical Considerations

All study procedures were approved by the Institutional Review Board (IRB) for each site (UIUC, USC, PU). In addition, each IRB had approved a data sharing plan, which allowed for data from USC and PU to be shared with the lead author (Hahn) at UIUC. Participant's mothers consented for their child to participate. Family-friendly procedures were used to reduce stress and promote a positive experience (e.g., taking frequent breaks, scheduling visits at a time that is best for the family, asking mothers for input, etc.).

## Procedure

Informed consent was provided by the parents of all infants. As part of a larger assessment battery, the MSEL and AOSI were administered to all infants at either their home (UIUC, USC) or the lab (USC, PU). Two infants with DS were not administered the MSEL because the Bayley Scales of Infant Development [24] was used instead.

## Analytical Plan

Given the descriptive nature of this study, results include descriptive results and a report of the proportion of infants with DS who met criteria for ASD-risk using the AOSI Number of Markers Score. The proportion of individual AOSI items scored for infants with DS is reported to reflect potential discreet ASD-associated behaviors that might signal risk. In addition, an independent samples *t*-test was conducted to examine differences between groups on the AOSI Number of Markers Score. Pearson correlations were conducted to assess the relationship between the AOSI Number of Markers Score to age and developmental variables for infants with DS and TD infants. A partial correlation was conducted as a follow up analysis to examine whether the effect between the AOSI Number of Markers Score and expressive language remained when covarying age and Early Learning Composite. For all inferential statistics, our *p*-value was set at .05.

## Results and Discussion

### Results

**ASD Risk**—Of the 18 infants with DS, 7 (39%) met criteria for ASD-risk. Of note, 2 infants with DS had a total of 6 markers indicating a sub-threshold score, while no infants with DS had an AOSI score of 0 (see Table 1). For each site, a range of AOSI scores were observed (USC = 3–17, UIUC = 9–13, PU = 3–20); no significant differences between sites on AOSI scores existed,  $F[2,15] = .29, p = .75$ ). The proportion of AOSI item scores for infants with DS (i.e., 0, 1, 2+) are displayed in Figure 1.

In contrast, only 2 TD infants (11%) met criteria for ASD-risk. As a follow-up analysis, we compared AOSI scores between infants with DS and TD. Results indicated that infants with DS had significantly higher AOSI scores than TD infants (see Table 2).

**Relationship Between AOSI Number of Marker Scores and Developmental Variables**—For infants with DS, a large and statistically significant effect was found between the AOSI and expressive language (See Table 3 for correlation matrix). While not significant, a small to medium effect was observed between the AOSI and age, overall verbal

abilities, overall nonverbal abilities, Early Learning Composite, and receptive language for infants with DS. For both the verbal abilities composite and the Early Learning Composite, these relationships may be driven by the relationship between the AOSI and expressive language. To explore this possibility, we conducted a follow-up analysis to investigate if the relationship between the AOSI and expressive language was still observed when covarying age and Early Learning Composite. Results indicated that the large, and statistically significant, effect between the AOSI and expressive language remained when covarying age and Early Learning Composite ( $r_p = -.62, p = .02$ ).

For TD infants, no statistically significant relationships were evident between the AOSI and developmental variables (See Table 4 for correlation matrix); however, several small to medium effects were observed for age, verbal abilities, expressive language, and receptive language. For the Early Learning Composite and nonverbal abilities, the correlations with the AOSI were very small.

## Discussion

Despite being at an increased risk for ASD, no reports of early signs or prodromal features of ASD in infants with DS exist. To address this gap, we present descriptive findings from our preliminary case-control pilot study on ASD-associated behaviors in infants with DS. Our results indicate that whereas only 2 of our TD infants (11%) were designated as “at risk,” 39% of our DS sample (7 of 20 infants) was designated “at risk” for ASD. This is somewhat higher than the consensus of ~20% but falls within the range of existing prevalence studies in DS (7–42% [5–7]). The somewhat higher incidence of DS infants “at risk” for ASD likely reflects that the AOSI is a screener, and elevated false-positive rates are expected<sup>19</sup>. It is also possible that children with neurogenetic syndromes, such as DS, are “over-identified”, and, a higher “risk” cut-off score may provide better sensitivity and specificity for later ASD outcomes, as has been suggested for other neurogenetic samples [21, 22]. Answers to these questions require empirical study with longitudinal studies that track the trajectories of infant development through to diagnoses, which is beyond the scope of this study.

None of our sample with DS received an AOSI Markers or Total score of 0, indicating that all infants demonstrated either inconsistent/questionable or atypical behavior on one or more AOSI items. While these items are designed to detect ASD risk, they may also be sensitive to areas of difficulty associated with the broader DS phenotype. The two items scored with the highest rating (item score of 2+) for infants with DS were Visual Disengagement (55%) and Orients to Name (61%; see Figure 1). Difficulties with visual attention have been noted in DS starting in infancy [25]. Also, the ability to orient to name involves disengaging from the current attentional focus and shifting attention to the person speaking to indicate a response. If infants with DS are having difficulty with visual disengagement, they may be less likely to shift their attention when their name is called. Thus, visual disengagement may not be an early indicator of ASD, but instead, capture early impairments associated with the DS behavioral phenotype. This highlights the difficulty of identifying ASD in infants as some early behavioral signs are present in those who are not later diagnosed with

ASD, and simply represent variability in early development, or who are at risk for other neurodevelopmental disorders (i.e., developmental delay, language disorders, etc. [26, 27]).

The majority of infants with DS received atypical scores (item score of 2+) in key areas of social functioning—Orients to Name (61%), Social Babbling (50%), Eye Contact (39%), Imitation (22%)—despite social function being an area of noted strength in infants and young children [28]. In preschoolers with DS, elevated severity of social and communication impairments was associated with an ASD diagnosis [17]. However, there are also social and communication AOSI items that many infants with DS received typical behavior scores on (item scores of 0; see Figure 1), such as Response to Facial Emotion (83%), Coordination of Eye Gaze & Action (72%), Engagement of Attention (83%), and Sharing Interest (72%). Within the context of our preliminary findings, it seems that infants with DS are showing subtle impairments in select social and communication skills. These subtle impairments may represent a typical pattern for infants with DS depending on their level of developmental delay or they may be an early indicator of ASD in DS, similar to other populations at risk for ASD [17, 29]. More research is needed to explore the potentially nuanced social and communication profiles of those with DS and ASD.

Due to our small sample size, correlations between ASD risk and most of the developmental variables did not reach statistical significance, but the strength of these associations range from small to medium in infants with DS. A significant and large effect was observed indicating that those with higher AOSI Marker Scores had lower expressive language abilities. This pattern is similar to previous studies suggesting that higher ASD risk is related to lower verbal abilities in DS [17, 26, 29], and this pattern was also observed in our sample of TD infants.

### Limitations of the Study

While the AOSI is designed to detect early signs of ASD in infants, this is the first study to use this measure with infants with DS; therefore, the validity of the AOSI indicators for detecting ASD in DS is not yet clear. However, our results provide initial evidence that ASD-associated behaviors can be identified in DS using the AOSI. Our sample was primarily male, and we were not able to examine sex effects. Future research is needed to examine sex differences in ASD-associated behavior in DS. Further examination of the developmental impact of ASD on DS is important because those with DS and ASD may require different approaches and unique supports than those with DS only.

### Conclusion

In summary, 39% of infants with DS displayed a high degree of ASD-associated behaviors with 100% displaying at least one feature of ASD-associated behavior. The diagnostic relevance of these early features of ASD in predicting either intellectual disability, ASD, or both is unclear, and further research is needed to examine these important developmental trajectories. While we are the first to describe ASD-associated behavior in infants with DS using the AOSI, the small size of our sample and our lack of data on outcomes are limitations. The results of this study contribute to the refinement of the DS behavioral

phenotype and identify important next steps to help improve the identification, diagnosis, and treatment of ASD in DS.

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## Abbreviations

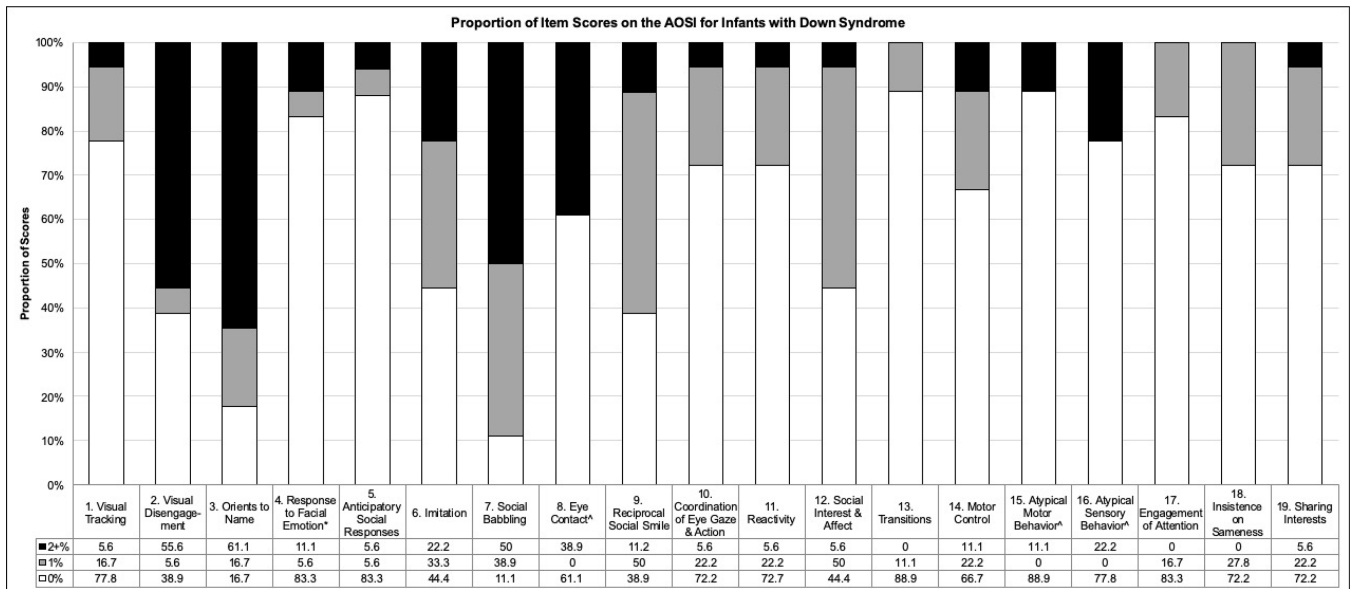
<b>DS</b>	Down syndrome
<b>ASD</b>	autism spectrum disorder
<b>TD</b>	typically developing
<b>nsASD</b>	non-syndromic ASD
<b>AOSI</b>	Autism Observation Scale for Infants

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Notes. One participant received a score of 8, “not applicable”, on this item because a good press was not achieved. <sup>^</sup>These items can only be scored as either “0” or “2+”

**Table 1**

## Participant Characteristics

Characteristic	Down syndrome			Typically developing		
	M/%	SD	Range	M/%	SD	Range
Child						
Chronological Age (in months)	11.67	3.29	7–18	11.54	1.71	9–14
AOSI Total Score	9.28	4.91	3–20	4.72	3.41	1–15
AOSI Markers Score	5.89	2.49	3–10	3.33	1.97	1–8
Early Learning Composite	68.31	12.40	49–93	96.44	13.01	71–115
Overall Mental Age (in months)	8.03	2.41	4.25–13.00	11.79	3.39	7–21.75
Nonverbal Abilities Composite	32.25	9.45	20–48.50	51.22	10.02	32.50–65.50
Verbal Abilities Composite	33.09	7.24	20.50–46.50	44.92	6.51	36–57.50
Expressive Language T-Score	34.81	8.07	20–45	47.22	9.88	29–66
Receptive Language T-Score	31.38	8.28	20–49	42.61	7.37	34–58
Child Race/Ethnicity (%)						
White	55.5			77.8		
African American	5.6			16.7		
Hispanic	5.6			-		
More than One Race/Ethnicity	5.6			5.6		
Unknown/Choose Not to Respond	27.8			-		

**Table 2**

Independent Samples t-test Comparing Age and AOSI Markers Score between Groups

	Down Syndrome		Typically Developing		<i>t</i> (34)	<i>p</i>	Cohen's <i>d</i>
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>			
Age	11.67	3.29	11.54	1.71	-0.51	0.88	0.05
AOSI Markers Score	5.89	2.49	3.33	1.97	-3.41	0.002	1.14

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**Table 3**

Correlations between AOSI Number of Marker Scores and Developmental Variables for the DS group

	1	2	3	4	5	6	7
1. AOSI Markers Score	-	-0.08	-0.28	-0.12	-0.42	-0.59 <sup>*</sup>	-0.17
2. Age	-	-	-0.53 <sup>*</sup>	-0.40	-0.59 <sup>*</sup>	-0.33	-0.71 <sup>**</sup>
3. Early Learning Composite	-	-	-	0.92 <sup>***</sup>	0.85 <sup>***</sup>	0.68 <sup>**</sup>	0.83 <sup>***</sup>
4. Nonverbal Abilities Composite	-	-	-	-	0.58 <sup>*</sup>	0.40	0.63 <sup>**</sup>
5. Verbal Abilities Composite	-	-	-	-	-	0.88 <sup>***</sup>	0.89 <sup>***</sup>
6. Expressive Language T-Score	-	-	-	-	-	-	0.57 <sup>*</sup>
7. Receptive Language T-Score	-	-	-	-	-	-	-

<sup>^</sup>  
 $p < 0.10$ 
<sup>\*</sup>  
 $p < 0.05$ 
<sup>\*\*</sup>  
 $p < 0.01$ 
<sup>\*\*\*</sup>  
 $p < 0.001$

**Table 4**

Correlations between AOSI Number of Marker Scores and Developmental Variables for the TD group

	1	2	3	4	5	6	7
1. AOSI Markers Score	-	-0.23	-0.06	0.02	-0.13	-0.35	0.24
2. Age	-	-	-0.08	-0.08	0.27	0.09	0.35
3. Early Learning Composite	-	-	-	0.88 **	0.68 **	0.56 *	0.45 ^
4. Nonverbal Abilities Composite	-	-	-	-	0.25	0.20	0.18
5. Verbal Abilities Composite	-	-	-	-	-	0.83 ***	0.66 **
6. Expressive Language T-Score	-	-	-	-	-	-	0.12
7. Receptive Language T-Score	-	-	-	-	-	-	-

^  
 $p < 0.10$ \*  
 $p < 0.05$ \*\*  
 $p < 0.01$ \*\*\*  
 $p < 0.001$