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Infant vocalizing and phenotypic outcomes in autism: Evidence from the first 2 years

Samantha Plate[1,2], **Lisa Yankowitz**[1,3], **Leslie Resorla**[4], **Meghan R. Swanson**[5], **Shoba Sreenath Meera**[6], **Annette Estes**[7], **Natasha Marrus**[8], **Meredith Cola**[1], **Victoria Petrulla**[1], **Aubrey Faggen**[1], **Juhi Pandey**[1,9], **Sarah Paterson**[10], **John R. Pruett Jr.**[8], **Heather Hazlett**[11], **Stephen Dager**[7], **Tanya St. John**[7], **Kelly Botteron**[8], **Lonnie Zwaigenbaum**[12], **Joseph Piven**[11], **Robert T. Schultz**[1,9], **Julia Parish-Morris**[1,9] **IBIS Network**

[1]Center for Autism Research, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA

[2]Department of Psychology, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

[3]Department of Psychology, University of Pennsylvania, Philadelphia, Pennsylvania, USA

[4]Bryn Mawr College, Bryn Mawr, Pennsylvania, USA

[5]University of Texas at Dallas, Richardson, Texas, USA

[6]National Institute of Mental Health and Neurosciences, Bangalore, India

[7]Department of Speech and Hearing Sciences, University of Washington, Seattle, Washington, USA

[8]Department of Psychiatry, Washington University School of Medicine, Saint Louis, Missouri, USA

[9]Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

[10]The James S. McDonnel Foundation, Saint Louis, Missouri, USA

[11]University of North Carolina, Chapel Hill, North Carolina, USA

[12]Department of Pediatrics, University of Alberta, Edmonton, Alberta, USA

Abstract

Infant vocalizations are early-emerging communicative markers shown to be atypical in autism spectrum disorder (ASD), but few longitudinal, prospective studies exist. In this study, 23,850 infant vocalizations from infants at low (LR)- and high (HR)-risk for ASD (HR-ASD = 23, female = 3; HR-Neg = 35, female = 13; LR = 32, female = 10; 80% White; collected from 2007 to 2017 near Philadelphia) were analyzed at 6, 12, and 24 months. At 12 months, HR-ASD infants produced fewer vocalizations than HR-Neg infants. From 6 to 24 months, HR-Neg infants demonstrated steeper vocalization growth compared to HR-ASD and LR infants. Finally, among HR infants, vocalizing at 12 months was associated with language, social phenotype, and

Correspondence Samantha Plate, Department of Psychology, University of Pittsburgh, 3309 Sennott Square, 201 South Bouquet St, Pittsburgh, PA 15213, USA. snp52@pitt.edu.

diagnosis at age 2. Infant vocalizing is an objective behavioral marker that could facilitate earlier detection of ASD.

Autism spectrum disorder (ASD) affects an estimated 1 in 54 U.S. school children (Maenner et al., 2020) and is characterized by social communication challenges and the presence of restricted and repetitive patterns of behaviors and interests (American Psychiatric Association, 2013). Prompt diagnoses are critical for ensuring that children and families receive behavioral interventions shown to improve long-term outcomes in ASD (Green et al., 2015, 2017; Landa, 2018; Noyes-Grosser et al., 2018), but many children experience significant delays between the onset of measurable autism symptoms and formal diagnosis. For example, while infants later diagnosed with ASD demonstrate behavioral differences as early as 6 months of age (Estes et al., 2015; Landa, 2007; Zwaigenbaum et al., 2007), and can be reliably diagnosed by age two (Kleinman et al., 2008; van Daalen et al., 2009), the median age of diagnosis in the United States remains over 4 years (Maenner et al., 2020). Disparities in age at diagnosis highlights the need for novel and objective methods for quantifying early risk that could help inform providers. One promising way to assess early autism risk is by analyzing infant vocalization patterns (Yankowitz et al., 2019). Despite calls for increased reliance on ecologically valid natural language sampling methods in ASD (Barokova & Tager-Flusberg, 2018; Swanson, 2020), relatively few studies have used this approach to chart vocalization development prospectively in high-risk (HR) cohorts. In this study, we compare vocalization patterns among infants at high familial risk of ASD (referred to as HR) who go on to develop ASD (HR-ASD), HR infants not diagnosed with ASD (HR-Neg), and infants without a familial history of ASD (referred to as low-risk or LR), with the goal of identifying objective risk markers that are relatively inexpensive to measure, non-invasive, and easily acquired during infancy.

Language development in ASD

Early language delays are often the primary motivation for parents seeking clinical assessments for their children who are later diagnosed with ASD (Wetherby et al., 2004), and by school age, language ability in ASD is widely variable (Eigsti et al., 2011). Recent estimates suggest that approximately 15% of school-aged children with ASD remain nonverbal, while 10% are described as minimally verbal (Norrelgen et al., 2015). The abilities of verbally fluent children with ASD (~75%) range from low, to average, to gifted (Luyster et al., 2008). However, the developmental pathways that precede such a stunning diversity of outcome are only beginning to be understood. Infant vocalizations, such as babbles, coos, and cries, lay the framework for later social communication development, and have been shown to be tightly linked to brain development (Marschik et al., 2017). Thus, analyzing early vocalization trajectories could be the key to identifying elevated risk for ASD before age 2, especially in a sample already at increased familial risk due to the presence of first-degree relatives with ASD. Earlier identification of heightened risk of ASD could lower the age of intervention and ultimately improve long-term outcomes.

A wide range of vocal and social communication differences in infants later diagnosed with ASD are evident between 12 and 24 months of age. These differences include atypical affective expressions (e.g., higher pitched cries), delayed babbling onset, and disrupted contingencies in caregiver–child communication (for a review, see Yankowitz et al., 2019). Word acquisition is similarly delayed; children with ASD produce fewer single words than typically developing (TD) peers at 18 months (Mitchell et al., 2006) and fewer consonants, words, and word combinations at 24 months compared to TD infants (Landa et al., 2007). Studies of expressive and receptive language abilities using the Mullen Scales of Early Learning (MSEL; Mullen, 1995) at 12 months of age report differences with large effects between HR-ASD and LR infants (Estes et al., 2015; Landa & Garret-Mayer, 2006; Lazenby et al., 2016; Macari et al., 2012; Ozonoff et al., 2010; Young et al., 2011; Zwaigenbaum et al., 2005), and with medium-to-large effects between HR-ASD and HR-Neg infants (Lazenby et al., 2016; Macari et al., 2012; Ozonoff et al., 2010; Young et al., 2011; Zwaigenbaum et al., 2005). Studies utilizing parent report of infant expressive and receptive language have similarly found slower growth in vocabulary development from 8 to 24 months in HR-ASD infants (Iverson et al., 2018) and smaller receptive vocabularies at 12 and 18 months (Mitchell et al., 2006). Despite these delays, it has been suggested that children with ASD experience the same expressive language acquisition *sequence* as TD children, learning the same common set of first words (Rescorla & Safyer, 2013). However, other research suggests that infants who go on to be diagnosed with ASD may demonstrate an atypical lexicon (Lazenby et al., 2016). HR-Neg infants may also experience significant language delays, particularly in the receptive domain (Marrus et al., 2018).

Natural vocal sampling

Research on early language and communication development in ASD often relies on parent report measures (e.g., the Macarthur-Bates Communicative Development Inventories; Fenson et al., 1993) and standardized assessments (e.g., The MSEL; Mullen, 1995). However, recent studies have also used naturalistic language sampling approaches to assess vocalization production (Barokova & Tager-Flusberg, 2018; Luyster et al., 2008; Ozonoff et al., 2010; Patten et al., 2014; Paul et al., 2011; Swanson et al., 2017). Naturalistic early vocalization patterns are important to study in part because infant verbal communication creates a social feedback loop between infants and their caregivers such that when children vocalize, parents respond (Warlaumont et al., 2014). Additionally, caregivers differentially respond to infant vocalizations, with preference for more developed, communicative, and socially directed vocalizations (Gros-Louis et al., 2006, 2014; West & Rheingold, 1978). This pattern of contingent responding improves child language outcomes (Goldstein & Schwade, 2008). Thus, infants who produce fewer vocalizations at a young age may receive less feedback from parents, resulting in fewer learning opportunities and slower language development (Swanson et al., 2019; Warlaumont et al., 2014). Conversely, infants who vocalize more may receive greater parent feedback, with positive downstream effects on language outcomes.

A handful of studies suggest that infants who ultimately develop ASD vocalize less than infants who develop typically, but results are mixed. One large study of children aged 8–48 months reported reduced vocalization by children diagnosed with ASD compared to their TD peers (Warlaumont et al., 2014). Similarly, Ozonoff et al. (2010) found that infants later diagnosed with ASD showed decreased socially directed vocalizations when compared to

LR infants from 12 to 36 months, but not at 6 months; however, this study did not examine vocalizing by infants at high familial risk who were not later diagnosed with ASD. Other studies have shown no differences in overall vocalization rates in younger infants (9–12 months) later diagnosed with ASD (both HR and LR) when compared with LR and HR TD peers, nor infants later diagnosed with intellectual disability (Northrup & Iverson, 2015; Osterling et al., 2002; Pokorny et al., 2017).

Research on infant vocalizations has also utilized Language ENvironment Analysis (LENA), a small wearable device paired with software that identifies infant and caregiver vocalizations (LENA Research Foundation, 2014). This software can reduce the time and effort needed to turn a recording of naturalistic interactions into usable data. Previous research has found LENA and automated vocal analysis are stable and valid measures of language development in preschoolers with ASD (Woynaroski et al., 2017). Research utilizing LENA with infants at HR for ASD is limited. One recent study reported greater vocalizing in HR infants compared to LR infants at 9 months (Swanson et al., 2017). Specifically, they found elevated vocalization rates in a subset of infants at HR of developing ASD, but did not report diagnostic outcomes (Swanson et al., 2017) leaving open the possibility that “hyper-vocalizing” could either be a risk marker or a protective factor.

Taken together, prior research may be inconclusive due to cross-study differences in vocalization sampling procedures (e.g., archival home videos, naturalistic interactions in the home, parent–child play sessions in the lab). Additionally, these studies employed variable definitions of “vocalization.” One promising method of parsing vocalizations in a way that could relate meaningfully to later language ability is by categorizing them as speech-like or not speech-like.

Speech-like vocalizing

Vocal activity in infancy is diverse, containing grunts, cooing, single consonants, babbles, word approximations, and words. For eliciting verbal responses from parents, however, research suggests that not all infant vocalizations are created equal. Caregivers are more likely to respond to their child's speech-like vocalizations (i.e., sounds that are found in adult speech and are precursors to language, such as words, babbles, and phonemes) than to non-speech vocalizations (e.g., crying, laughing, growling, squealing; Warlaumont et al., 2014). This is important given emerging evidence that infants at high familial risk of ASD produce fewer speech-like sounds and more non-speech sounds than LR comparison infants across the first 2 years of life (Paul et al., 2011; Warlaumont et al., 2014; Winder et al., 2013). There is also evidence to suggest that, within the HR population, diagnostic group differences in speech-like utterances are present beginning at 12 months (Chenausky et al., 2017; Warren et al., 2010), with no group differences in speech-like vocalizing at 9 months (Talbott et al., 2016). Thus, early social communication development opportunities for HR infants may be adversely impacted by infant differences in speech-like vocalizing rates.

The current study

In this study, we examine longitudinal trajectories of early vocalization development in a sample of infants at high familial risk of developing ASD by virtue of having an older sibling with the condition (HR; *N* = 58), and LR (*N* = 32) controls, drawn from a multi-site network sample. Some infants in the HR group received an ASD diagnosis at 24 months (HR-ASD; *N* = 23) and others did not (HR-Neg; *N* = 35). Audio–video recordings of social communication assessments conducted in the lab at 6, 12, and 24 months of age were coded for infant vocalizations, which were subcategorized as speech-like or not. Based on prior research identifying delays in various measures of vocalization production in infants later diagnosed with ASD (Yankowitz et al., 2019), we predicted that HR-ASD infants would produce fewer total vocalizations than LR infants over time (Warlaumont et al., 2014), as well as fewer speech-like vocalizations, particularly at 12 months (Paul et al., 2011). We did not have specific a priori hypotheses about HR-Neg infants' vocalization behavior as compared to HR-ASD and LR participants. Given prior research, it was possible that a subgroup of HR infants would vocalize more than LR infants (Swanson et al., 2017). On the other hand, recent research shows that HR-Neg infants are at higher risk of language delays than LR peers (Marrus et al., 2018), and are often reported to have sub-clinical symptoms of ASD (Ozonoff et al., 2014); thus the vocalization behaviors of HR-Neg infants at the group level may be more similar to HR-ASD than LR infants. Therefore, these models were considered exploratory. To parse behavioral heterogeneity in the HR sample, we conducted exploratory analyses to the assess relation between 12-month vocalizations and 24-month language skills, social symptoms, and diagnostic outcomes.

METHOD

Participants

Infants were assessed at 6, 12, and 24 months of age as part of a multi-site study of infant siblings. The study was approved by Institutional Review Boards at all sites, and families provided written informed consent to participate. Inclusion and exclusion criteria, as well as study procedures, can be found in Estes et al. (2015).

The current study included a subset of participants who were seen at a single study site in the greater Philadelphia area from 2007 to 2017. Participants were selected based on complete data at 24 months for the following measures: Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000), MSEL (Mullen, 1995), Diagnostic and Statistical Manual, 4th edition, text revision (DSM-IV-TR; American Psychiatric Association, 2000) ratings by an expert clinician, and a videotaped administration of the Communication and Symbolic Behavior Scales (CSBS; see Vocalization samples section, below). Of the 170 participants seen at the study site, 144 had DSM-IV-TR ratings at 24 months. Of those 144 infants, 117 had a CSBS assessment at 24 months. One participant was missing 24-month MSEL administration. Additionally, some participants did not have assessment videos at all three time points due to missing a visit, not completing an assessment, or equipment failure (see Vocalization samples section, below). Only participants with usable videos from two or more assessment visits were included in the current sample. This resulted in 98 infants. Infants with non-ASD diagnoses or signs of delay were not excluded, except for one

HR-Neg participant for whom selective mutism was listed in the study's diagnostic notes, and was therefore excluded from this study focused on vocalization patterns during social interaction, resulting in 97 possible participants.

Statistical control has been identified as a problematic method for handling groups that differ on variables such as race, ethnicity, socioeconomic status (SES), maternal education, and sex (Dennis et al., 2009; Miller & Chapman, 2001), so we chose to match groups on these characteristics. Starting with HR-ASD infants (to ensure sufficient power for group comparisons) from the sample of 97 infants with usable data, subgroups of participants without ASD were matched on sex ratio at the group level (7 HR-Neg females were dropped randomly using R). The resulting 90 infants did not differ by group on key demographic variables (race, ethnicity), nor on SES measures that covary with language development (maternal education and household income; Dollaghan et al., 1999). The sample, drawn from the Northeastern United States, was primarily White with a high rate of highly educated mothers. Because previous research has shown that maternal education is related to language development (Dollaghan et al., 1999), we confirmed that maternal education in our selected sample was representative of the larger multi-site sample (Fisher's exact test for count data, $p > .05$). Thus, the final sample included 90 infants enriched for ASD status (see Table 1), of 170 infants seen at the study site. Due to matching processes that prioritized the HR-ASD group, the rate of ASD in HR infants in this subsample is elevated compared to rates that might be expected by chance (typically ~20% in HR infant studies; Ozonoff et al., 2011).

Of the 90 infants selected for these analyses, 58 had an older sibling with a diagnosis of ASD. Twenty-three of these HR children met criteria for Autistic Disorder or Pervasive Developmental Disorder-Not Otherwise Specified at 24 months, based on clinical best estimate—by applying DSM-IV-TR criteria to all available information (HR-ASD group)—and 35 did not (HR-Neg group). Assessment at 24 months was used because many infants did not return for an optional follow-up at 36 months; however, research has shown that diagnosis from 24 to 36 months is relatively stable, with high specificity (Ozonoff et al., 2015). Throughout the paper, HR-ASD diagnosis refers to being classified as having ASD for research purposes by virtue of meeting DSM-IV-TR criteria. All but one HR-ASD family was given a clinical diagnosis of ASD. The LR group consisted of 32 children with an older sibling who did not have ASD, no first-degree relatives with ASD, and who were not later diagnosed with ASD themselves. LR infants underwent all of the same study procedures and assessments as HR infants.

Vocalization samples

At 6 and 12 months of age, participants completed the Autism Observation Scale for Infants (AOSI; Bryson et al., 2008), which is a 10- to 15-min, clinician-infant, semi-structured play session including activities intended to assess verbal (e.g., vocalizations) and non-verbal (e.g., eye-contact, gestures) infant communication, social, and play behaviors. At 12 and 24 months of age, participants were administered the CSBS (Wetherby & Prizant, 1993), which is an approximately 20- to 30-min play session with a clinician or research assistant. The CSBS includes a series of activities intended to elicit specific social-communication behaviors including requests for help from children by giving them objects that they cannot open or use (e.g., bubbles, jar with cereal, deflated balloon), free play, joint attention tasks, imitation tasks, and identifying objects, body parts, and people. Caregivers are present for both assessments and instructed to avoid prompting infants but encouraged to respond as they naturally would if their infants engaged with them.

At 12 months, most infants were administered the AOSI and the CSBS. CSBS videos were longer, and were therefore analyzed when available; AOSI videos were analyzed when children did not have a usable CSBS recording at 12 months (due to recording failure or the assessment not being administered fully or at all). The final sample included 81 AOSI videos at 6 months (HR-ASD: 20, HR-Neg: 31, and LR: 30), 73 CSBS videos at 12 months (HR-ASD: 14, HR-Neg: 31, and LR: 28), and 8 AOSI videos at 12 months (HR-ASD: 5, HR-Neg: 1, LR: 2). There was a significant difference in the proportion of AOSI videos versus CSBS videos at 12 months by group, where HR-ASD infants had more AOSI videos than the other two groups ($\chi^2 = 7.75$, $p = .021$). Total recording durations were shorter for the AOSI videos ($M = 13.29$ min, $SD = 4.94$) than the CSBS videos ($M = 20.16$, $SD = 3.81$) at 12 months ($t(7.94) = -3.81$, $p = .005$), but there were no differences in average recording duration by diagnostic group at 12 months or the other two timepoints (Table 2). Research suggests that even brief vocalization samples (e.g., 6 min) can be used to identify group differences in vocalizing in toddlers with and without ASD (Tenenbaum et al., 2020). Our primary analyses were re-run without 12-month AOSIs included and the pattern of results did not change. Results for the entire sample (CSBS and AOSI) are included here. All 90 participants had videos of the CSBS at 24 months.

Coding procedure

A team of reliable coders segmented and annotated assessment videos using ELAN audio–video coding software (Figure 1; Sloetjes & Wittenburg, 2008). All coders were naïve to infant risk group and diagnostic outcome. First, one trained coder used the video, audio, and visual waveform to identify all sounds created by the child and mark vocalization onsets and offsets (segments). Coders split segments when the child changed vocalization type (e.g., speech to cry), changed topic or type of utterance (e.g., statement to question), or clearly changed the vocalization target (e.g., examiner to caregiver). A second trained coder then checked each file to confirm the accuracy of the segments and to assure that no sounds were missed.

Two coders then individually annotated vocalization segments by assigning them to one of three main categories: speech-like, non-speech, and vegetative. Definitions were derived from previous descriptions of coding procedures in the literature (Oller & Lynch, 1992; Paul et al., 2011; Plumb & Wetherby, 2013; Schoen et al., 2011; Sheinkopf et al., 2000). Speech-like segments were defined as vocalizations characterized by the production of consonants and/or vowels that could be represented by phonetic symbols and contain speech-like vocal quality (e.g., cooing “ooo,” single phonemes “mmm,” babbling “baba”). Non-speech sounds were defined as vocalizations characterized by resonance and vocal quality not typical of speech, often without recognizable phonemes. Non-speech sounds included the following categories: crying, fussing, whining, laughing growling, squealing, grunting, yelling (Oller & Lynch, 1992; Paul et al., 2011; Plumb & Wetherby, 2013; Schoen et al., 2011; Sheinkopf et al., 2000). Sounds that were clearly both speech and non-speech (e.g., talking while crying) were included in both categories, but counted as one vocalization for the purposes of calculating the total number of vocalizations produced (dual-coded segments comprised <1% of vocalizations). Vegetative sounds were defined as sounds produced naturally without linguistic or semantic intent, such as burping or coughing. After making individual annotations, the two coders conducted consensus coding where they jointly listened to every sound for which there was a coding discrepancy and came to consensus. Consensus codes were used for final analyses. Annotation reliability was defined as pre-consensus agreement between coders for labeling a sound as speech, non-speech, or vegetative for each file. Intercoder agreement based on Cohen's κ was 85.70%, $\kappa = .65$, which is considered substantial agreement (Landis & Koch, 1977). Sounds identified as vegetative or uncodable were not included in these analyses or in variable calculations.

Dependent variables

Although the entire videotaped recording was coded, due to differing assessment lengths for each infant, dependent variables were normalized per 10 min of recording time. Raw means and standard deviations for total number of vocalizations and total recording time are presented in Table 2. Two primary dependent variables were calculated: total vocalization rate (speech-like vocalizations + non-speech vocalizations divided by the length of the recording in minutes, multiplied by 10 and rounded to the nearest whole number) and speech-like vocalization rate (speech-like vocalizations divided by the length of the recording in minutes, multiplied by 10 and rounded to the nearest whole number).

Statistical approach

To assess trajectories of growth, generalized linear mixed-effects regressions (GLMER) with a Poisson distribution and a log link function were fitted using R packages “lme4” and “lmerTest” (Bates et al., 2014). GLMER with a Poisson distribution was chosen to model growth trajectories due to the nature of our variables, which are positive count data with multiple (longitudinal) values per participant. Models were fitted using maximum likelihood (Laplace Approximation). Individuals were treated as random effects to account for the longitudinal design of the study. Models controlled for sex of the infant (male = 1, female = 0), because previous studies of infants have shown differences in language development by sex (Messinger et al., 2015). Based on hypotheses that growth trajectories would differ by diagnostic group, we included the interaction between age and diagnostic group as a fixed effect. Exact age was used as a continuous variable in the models and was *z*-scored (mean centered across the entire sample) to satisfy model assumptions. GLMER provides embedded pairwise tests to assess group differences when group by time interactions are found. We report *z*-values which represent the regression coefficient divided by the standard error, and are approximately analogous to a *t*-value from a *t*-test. Given a two-sided hypothesis and α level of .05, a *z*-value >2 is considered significant. We rotated the reference group to assess all comparisons. Conditional main effects of diagnostic group and age are not reported in the presence of an interaction. To assess cross-sectional differences in group means at each time point, we compared Tukey-corrected estimated marginal effects of diagnosis at each timepoint using R package “emmeans” (Lenth, 2019).

To assess heterogeneity in the HR group, we used three separate GLM to model diagnosis, autism symptom severity, and language ability at 24 months as a function of vocalization rates at 12 months, after controlling for sex.

RESULTS

Total vocalization growth rates from 6 to 24 months

There was a significant interactive effect of age and diagnosis on total vocalization growth rates, such that the HR-Neg group showed a greater increase in vocalizations over time than the HR-ASD ($z = 3.20$, $p = .001$) and LR groups ($z = 5.30$, $p < .001$; Figure 2). Vocalization growth rates for the HR-ASD and LR groups did not differ ($z = 1.05$, $p = .29$). Cross-sectional analyses at each time point revealed no significant group differences in overall vocalization rate at 6 months (Tables 3 and 4). By 12 months, the HR-Neg group produced significantly more vocalizations than the HR-ASD group (z ratio = 2.62, $p = .024$). There was no significant difference between the LR and the two HR groups at 12 months ($p > .05$). At 24 months, the HR-Neg group produced significantly more vocalizations than both the HR-ASD group (z ratio = 4.20, $p < .001$) and the LR group (z ratio = 3.21, $p = .004$). Total vocalization rates at 24 months did not differ for HR-ASD and LR infants ($p > .05$). This pattern of results suggests vocalization is delayed in the HR-ASD group relative to HR-Neg at 12 months, with a relative surge in vocalizations by the HR-Neg group between 6 and 24 months.

Speech-like vocalization growth rates

We examined rates of speech-like vocalizations over time, given their theoretical importance to later language and communication in ASD (Warlaumont et al., 2014). An interactive effect of age and diagnosis on speech-like vocalizations was found, such that the growth trajectory of the HR-Neg group was steeper than both the HR-ASD group ($z = 5.01$, $p < .001$) and the LR group ($z = 6.10$, $p < .001$) from 6 to 24 months (Figure 3). Growth in speech-like vocalization rates did not distinguish LR and HR-ASD groups ($z = 0.06$, $p = .950$). Cross-sectional analyses revealed no significant group differences in speech-like vocalizing at 6 and 12 months (Tables 3 and 4). At 24 months, the HR-Neg group produced significantly more speech-like vocalizations than the HR-ASD group (z ratio = 3.75, $p = .001$) and the LR group (z ratio = 2.78, $p = .015$). There was no group difference in speech-like vocalization rates between HR-ASD and LR infants at 24 months ($p > .05$), despite differences in Mullen Expressive Language scores (Table 5), suggesting that the speech-like sounds produced by the ASD group may consist of non-canonical babbles, echolalia, or other kinds of speech-like vocal activities that do not correlate with higher expressive language scores on standardized tests. Overall, speech-like vocalization patterns for HR-Neg infants partially mirrored our total vocalization findings—HR-Neg infants demonstrated steeper speech-like vocalization growth than HR-ASD and LR infants, with higher-than-expected rates of speech-like vocalizing at 24 months.

Exploratory analysis: Heterogeneity in HR outcomes

To assess the clinical significance of 12-month total vocalization differences in HR-ASD compared to HR-Neg infants, we conducted GLM to see if 12-month total vocalizations were associated with 24-month diagnosis, symptom severity, and language abilities in the HR group only. A logistic regression controlling for sex revealed that 12-month vocalization rate was significantly related to diagnostic outcome at 24 months. An examination of odds ratios revealed that every additional vocalization per 10 min was associated with a 6% *decrease* in risk for autism diagnosis (OR = .94, relative risk ratio = .96, $b = -.06$, $SE = .02$, $p = .006$). In other words, an HR infant who produced 40 vocalizations per 10 min at 12 months was 60% less likely to receive an ASD diagnosis at 24 months than an HR infant who produced 30 vocalizations per 10 min. Additionally, 12-month total vocalization rate was significantly related to 24-month ADOS Social Affect calibrated severity scores ($b = -.04$, $t = -2.47$, $p = .017$), such that infants with higher vocalization rates at 12 months demonstrated reduced ASD symptom severity 1 year later. This effect was specific to Social Affect domain scores, as 12-month vocalization rates did not significantly predict ADOS Restricted and Repetitive Behaviors calibrated severity scores ($p > .05$). Lastly, infants with higher total vocalization rates at 12 months had higher expressive language ($b = .15$, $t = 2.02$, $p = .049$) and receptive language ($b = .25$, $t = 2.71$, $p = .009$) abilities at 24 months as measured by MSEL *t*-scores. Sex was significantly related to expressive language *t*-scores ($b = -7.07$, $t = -2.17$, $p = .035$) with males having lower expressive language at 24 months; however, this result should be interpreted with caution given our small sample of females with ASD. Taken together, these results suggest that infant vocalization patterns might be especially informative for predicting a variety of 2-year outcomes in samples already at high familial risk of ASD. Specifically, reduced vocalizing in HR infants at 12 months is a concerning risk marker that warrants a referral to early intervention services.

DISCUSSION

In this study, we explored trajectories of early vocalization development in infants at high and low familial risk of developing ASD, who were matched on key demographic variables that are known to affect environmental vocabulary exposure (e.g., parent education). Our findings add to a growing literature that uses naturalistic or semi-naturalistic sampling to characterize vocalization development in infancy (Dykstra et al., 2012; Swanson et al., 2017) and could have implications for the focus and timing of early intervention.

The two primary results of this study are as follows: First, we found a pattern of reduced vocalizing in HR-ASD infants that was distinct from HR-Neg infants at 12 months of age. However, vocalization rates did not just differ cross-sectionally; in fact, they predicted long-term outcomes including diagnosis, social affect symptom severity, and expressive and receptive language abilities at 24 months. Therefore, low rates of vocalizing at 12 months may be a key early indicator of heightened ASD risk in HR infants. If infants at known familial risk of ASD show a pattern of reduced vocalizing at 12 months, our results suggest that they are at especially HR of developing ASD and may benefit from *pre-diagnostic early intervention for social and/or communication delays*.

Second, we found accelerated growth in vocalization rates by HR-Neg infants from 6 to 24 months, a pattern which distinguished them from HR-ASD infants and LR controls. This longitudinal pattern held in speech-like vocalizations and resulted in significantly higher rates of vocalizing by HR-Neg infants at 24 months. However, a standardized test of language abilities in the HR-Neg group did not reveal above-average scores (Table 5) and total vocalization rates in the HR-Neg group relate only weakly to 24-month MSEL expressive language *t*-scores ($r = .29$, $p = .096$). Thus, greater vocalizing by HR-Neg infants may not reflect better language skills *per se* and may instead index a third variable, such as greater underlying motivation to engage socially. Overall, our pattern of results is consistent with prior research suggesting that HR-Neg children—as a group—demonstrate a phenotype that is distinct from both LR and HR-ASD infants (Ozonoff et al., 2014). This finding is also consistent with one prior study reporting hyper-vocalization in a subset of HR infants (Swanson et al., 2017).

Hyper-vocalizing by HR infants is a recently described phenomenon. Swanson et al. (2017) first described hyper-vocalization after identifying a cluster of HR infants who vocalized over two standard deviations more than their LR counterparts during daylong audio recordings at 9 months of age. While Swanson et al. (2017) pondered whether this subsample of HR infants might be more likely to develop ASD due to reduced proportions of conversational turn-taking, the authors also considered whether hyper-vocalization may be a protective factor. Indeed, although the percentage of vocalizations that elicited a parental response was lower in the hyper-vocalizing group (Swanson et al., 2017), the raw number of conversational turns with adults was higher in hyper-vocalizing infants than any other subgroup. By adding critically important information about diagnostic outcome, our study confirms that hyper-vocalizing infants largely fall into the HR-Neg group at 24 months. This finding sheds light on the two competing hypotheses outlined in Swanson et al. (2017), and suggests that active vocalizing may be a "protective effect" or otherwise indicate lower risk for developing ASD. Additionally, recent research has shown that mothers of HR-Neg infants provide more gestural communication than mothers of LR and HR-ASD infants, suggesting that caregivers also contribute to the hyper-communicative social feedback loop (Talbott et al., 2015). If HR-Neg dyads are engaging in more back and forth communication with parents by virtue of increased vocalizing, this may enable HR-Neg infants to gain more experience with social communication early on, providing the opportunity to develop critical skills that may insulate them from an ASD diagnosis. Heterogeneity in HR infants may therefore be understood—in part—by identifying hypo- and hyper-vocalizing behaviors across the first 2 years of life; a critical time period for communication development and window for early intervention.

The cause-and-effect relation between early vocalizing and diagnostic outcome remains unclear, and complicated by wide phenotypic heterogeneity in HR-Neg infants. For instance, it is possible that HR infants who do not develop ASD are naturally more vocally active, perhaps due to the same genetic protective factors that prevent them from developing ASD. Alternatively (or simultaneously), it is possible that increased vocalizing drives a positive social feedback loop, creating additional opportunities for social communication and thus protecting against ASD (Goldstein & Schwade, 2008; Warlaumont et al., 2014). Conversely, hypo-vocalizing results in fewer opportunities for social communication, which may have downstream effects on later language and social skills development, and is associated with heightened risk of ASD. Regardless of the etiology, it appears that vocal activity during infancy signals differential likelihood of receiving an ASD diagnosis at 24 months in HR infants—but critically, is not necessarily indicative of overall language abilities as measured by standardized tests at age 2 (Table 5).

Limitations

To date, this study is one of the largest longitudinal analyses of vocalization development focused on infants at high familial risk of developing ASD. However, several limitations should be considered when interpreting the results reported here. First, there are many ways to conceptualize, measure, and analyze vocalization data. For the purposes of this study, we chose to focus on vocalization rates (number of vocalizations per 10 min of recording). It is possible that the length of utterances or total time spent vocalizing may be important for understanding later language development, which are not fully captured by the dependent variables analyzed here. Additionally, there was significant overlap in the distribution of vocalization rates across groups at each time point. This calls into question the utility of using vocalization rates alone to identify infants who will go on to be diagnosed with ASD, and suggests that combining vocalization trajectories with other data sources (e.g., standardized tests, parent report) could maximize the value of this approach. The potential utility of understanding early vocalization trajectories should be interpreted in light of the fact that our HR-Neg group was quite heterogeneous and we did not include comparison groups such as infants with specific language delay or developmental delay. However, it is important to note that, despite overlap between groups, vocalization pa-terns at 12 months nonetheless distinguished HR-Neg and HR-ASD groups. In fact, within the HR group alone, vocalizing at 12 months predicted the likelihood of an ASD diagnosis at 24 months, as well as social affect scores and language ability. Thus, further research is urgently needed to determine whether early vocalization patterns could be used to characterize homogeneous subgroups (i.e., biotypes) within a pre-diagnosis HR sample. The data presented here show that particularly quiet infants with known familial risk are more likely to go on to have ASD and may benefit from early intervention targeting language and social communication before an ASD diagnosis can be made. It may also be important to consider longitudinal trajectories of vocalization development rather than cross-sectional differences. If HR infants are quiet at 12 months and do not show huge gains during the second year of life, they should be referred for an ASD evaluation.

It is important to note that for this study we analyzed pre-existing videos that were not collected for the purpose of naturalistic vocalization analyses. Infants were engaged in play-based assessments with a clinician or research assistant and parent during vocalization sampling. Thus, the testing environment may have caused some children to produce vocalization patterns that do not generalize well to everyday behavior with parents alone. This highlights the importance of analyzing home-based daylong recordings (as in Swanson et al., 2017). Another limitation is that while both the CSBS and the AOSI are structured tasks, assessments proceeded slightly differently for each child. For instance, some parents were more involved in the assessment tasks than others. It is possible that parents of HR infants were more participatory due to the experience of having an older child with ASD, and thus provided more language input and social feedback for their subsequent children (potentially eliciting more infant vocalizations), which may explain why the HR-Neg participants were more vocal than even the LR participants. This may also explain why infants in the HR-ASD group appear to “catch up” to their LR peers in vocalizing by 24 months. Infants may be vocalizing more in response to increased input by caregivers who have heightened awareness that their infants are at risk for ASD. These results differ from previous studies that show continued group differences in infant vocalizing over time (Ozonoff et al., 2010; Winder et al., 2013); however, methodological variability between studies, including how infant vocalizations are conceptualized, coded, and/or elicited, could also cause these discrepancies.

As is often the case in ASD research, our subgroups did not statistically differ in sex distribution, but nonetheless had fewer girls in the HR-ASD group. Given research suggesting that early language development differs by sex (Messinger et al., 2015), this may have affected our results and warrants future research. However, we note that girls in the HR-Neg group produced highly variable vocalization rates (distributed across the range of the group as a whole), and we controlled for sex in our models. Our groups also lacked diversity in race, ethnicity, and maternal education. This limited sample, therefore, does not tell us whether vocalization rates may be predictive of diagnostic risk in the general population. However, for families who experience diagnostic disparities (e.g., children of color and female children), vocalization rates could be a more objective measure of development that is less susceptible to clinical biases, thus reducing barriers to diagnosis. This is an important future research direction that requires prospective studies of HR infants from diverse family backgrounds.

Finally, consistent with previous reports of comparable standardized language scores at 6 months (Brian et al., 2014; Chawarska et al., 2013; Ozonoff et al., 2010), we did not detect group differences in vocalizing at this age. This may be due to a lack of sensitivity in our count-based measurement of vocalizations (e.g., acoustic measurements of vocalization might be more sensitive to early group differences than counts; Sheinkopf et al., 2012). Alternatively, the table-top-based AOSI may not effectively elicit vocal behavior at 6 months (i.e., free play or home-based recordings might work better). There also seems to be a floor effect at 6 months, with all three groups being pretty quiet. Lack of differences may be driven by the fact that 6-month samples were shorter than 12- and 24-month samples (approximately 10 min vs. 20 min). There also may truly be no group differences in vocalizing at this age.

Future directions

In this study, we grouped all speech and speech-like sounds together. In future efforts, we will code infant speech-like utterances to identify canonical babbling and use these results to inform classification models predicting current and later phenotype. We also plan to analyze non-speech vocalizations—including laughing, crying, and atypical sounds—in the future, which may allow us to identify group differences at 6 months. We have begun efforts to code socially directed versus non-socially directed infant vocalizations. These data will help us determine if increased growth rates of speech-like vocalizing in the HR-Neg group are related to social communication per se. Future research would benefit from a non-ASD language delay clinical contrast group, as well as a group with global developmental delay but no ASD. Given the amount of effort and time needed to code infant vocalizations, future research should explore utilizing automated methods such as LENA (LENA Research Foundation, 2014). In the future, related coding efforts by members of the larger network (e.g., initiation of joint attention) will be aligned with the vocalization metrics described here to look for associations and to better describe HR infant behavior. In an important extension of this research, we aim to generate acoustic measures of the infant vocalizations identified in this study (see Bedoya et al., 2020 for an example of acoustic differences in infants with ASD), and combine those features with our coded metrics to predict diagnostic outcome, language, and social symptom severity. Finally, we plan to relate vocalization properties and patterns to structural and functional brain development metrics that have already been collected over the first 2 years of life. This will allow us to better understand the utility of using early vocalization patterns as a biobehavioral marker for ASD that is indicative of differences in brain development.

CONCLUSIONS AND IMPLICATIONS

Semi-naturalistic vocalization sampling is a promising tool for ASD researchers (Barokova & Tager-Flusberg, 2018). This study adds to the literature by analyzing vocalization development in a longitudinal sample of infants at high and low familial risk of developing ASD. Our sample, which includes multiple time points and diagnostic outcome assessments at 24 months, allowed us to comprehensively examine longitudinal patterns of vocalization development over the first 2 years, and identify whether vocalization trajectories differed between risk and diagnostic groups. Our two main findings add to the literature by demonstrating distinct profiles of vocalizations in infants at high familial risk of ASD that do and do not develop the condition. Given that language delays are one of the first concerns reported by parents of children who are later diagnosed with ASD (De Giacomo & Fombonne, 1998; Kozlowski et al., 2011), and early intervention focused on communication deficits in ASD is effective (Green et al., 2013; Kasari et al., 2014; Yoder et al., 2021) and improves outcomes in a variety of areas such as social skills (Landa, 2007; Zwaigenbaum et al., 2007), identifying distinctive vocalization patterns before age two has significant potential for lowering the age of diagnosis, guiding early intervention, and optimizing long-term functioning for children and families.

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Abbreviations:

ADOS	Autism Diagnostic Observation Schedule
AOSI	Autism Observation Scale for Infants
ASD	autism spectrum disorder
CSBS	Communication and Symbolic Behavior Scales
DSM-IV-TR	Diagnostic and Statistical Manual 4th edition, text revision
GLMER	generalized linear mixed-effects regressions
HR	high-risk
LENA	Language ENvironment Analysis
LR	low-risk
MSEL	Mullen Scales of Early Learning
RRR	relative risk ratio
SES	socioeconomic status
TD	typically developing

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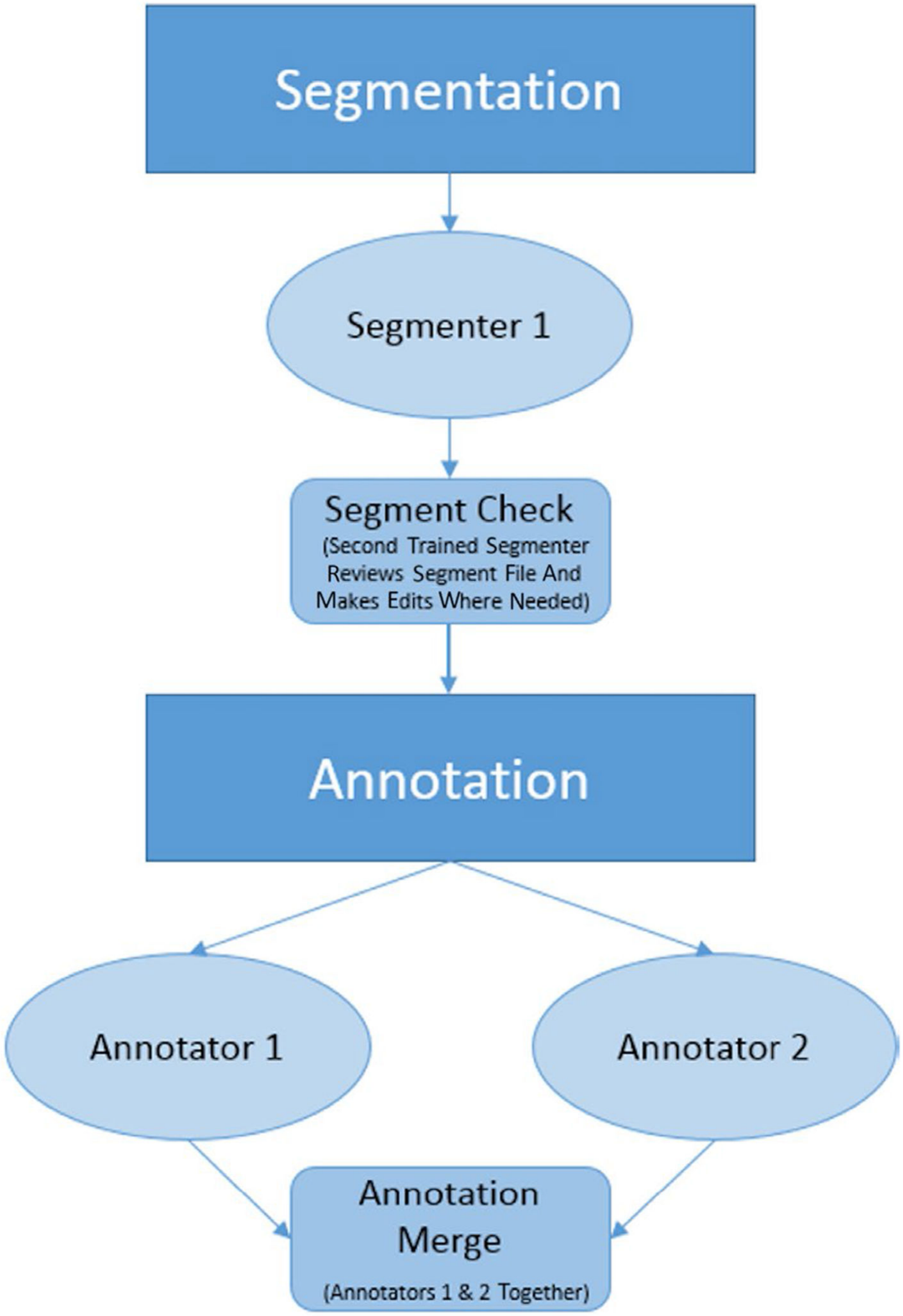

FIGURE 1.

Video coding process including consensus coding (annotation merge)

FIGURE 2.

Growth in the estimated marginal mean number of total infant vocalizations produced per 10 min of recording time by age and diagnosis, controlling for sex. Age was entered as a continuous variable in our primary statistical models, and individual participant ages are shown as hollow points. Average estimated marginal means for each visit time point (6, 12, 24) are shown as diamonds. HR-Neg infants showed significantly steeper growth in vocalizations over time than LR ($p < .001$) and HR-ASD ($p = .001$) infants. The LR and HR-ASD groups did not differ in growth over time ($p > .05$). Cross-sectional comparisons are indicated on the graph where “a” and “b” are significantly different. Specific pairwise comparisons can be found in Table 4. Abbreviations: ASD, autism spectrum disorder; HR, high-risk; LR, low-risk

FIGURE 3.

Growth in estimated marginal mean number of speech-like vocalizations per 10 min of recording time by age and diagnosis, controlling for sex. Age was entered as a continuous variable in our primary statistical models, and individual participant ages are shown as hollow points. Average estimated marginal means for each visit time point (6, 12, 24) are shown as diamonds. HR-Neg infants showed significantly steeper growth in speech-like vocalizations over time than LR ($p < .001$) and HR-ASD ($p < .001$) infants. The LR and HR-ASD groups did not differ in growth over time ($p > .05$). Cross-sectional comparisons are indicated a on the graph where “a” and “b” are significantly different. Specific pairwise comparisons can be found in Table 4. ASD, autism spectrum disorder; HR, high-risk; LR, low-risk

TABLE 1

Participant demographic information

	LR (N = 32)	**HR-Neg (N = 35)**	**HR-ASD (N= 23)**	**Difference**
Sex (M, F)	22, 10	22, 13	20, 3	*n.s.*, $p > .10$
Race	N = 32	N = 35	N = 22	*n.s.*, $p > .10$
White	24	27	20	
Black	3	6	1	
Multiracial	5	2	1	
Ethnicity	N = 32	N = 35	N = 21	*n.s.*, $p > .10$
Hispanic	1	2	0	
Non-Hispanic	31	33	21	
Mother's education	N = 32	N = 35	N = 22	*n.s.*, $p > .10$
High school	2	0	1	
Some college	8	5	2	
College degree	9	16	8	
Some graduate	1	2	0	
Graduate level	12	12	11	
Income	N = 30	N = 34	N = 21	*n.s.*, $p > .10$
<$25,000	2	1	0	
$25,000–$35,000	2	0	3	
$35,000–$50,000	4	2	2	
$50,000–$75,000	4	2	3	
$75,000–$100,000	4	6	4	
$100,000–$150,000	10	7	6	
$150,000–$200,000	3	8	1	

Note: Demographic variable differences calculated using Fisher's exact tests for count data.

Abbreviations: ASD, autism spectrum disorder; HR, high-risk; LR, low-risk.

TABLE 2

Means and standard deviations of total recording time (in minutes) and total number of vocalizations by visit and diagnostic group

	LR	HR-Neg	HR-ASD	Difference
6 Months				
Total recording time	11.47 (2.65)	11.77 (2.52)	13.06 (2.93)	*n.s.*, $p > .10$
Total number of vocalizations	32.96 (23.83)	34.75 (21.80)	40.16 (30.11)	*n.s.*, $p > .10$
12 Months				
Total recording time	19.67 (3.44)	19.57 (3.72)	19.04 (6.57)	*n.s.*, $p > .10$
Total number of vocalizations	95.60 (32.26)	99.37 (43.09)	56.26 (32.20)	$F(2, 78) = 8.69^{***}$ HR-ASD < (HR-Neg = LR)
24 Months				
Total recording time	19.97 (4.18)	21.57 (3.57)	22.03 (4.64)	*n.s.*, $p > .10$
Total number of vocalizations	133.71 (58.40)	183.65 (62.36)	143.21 (66.73)	$F(2, 81) = 5.80^{**}$ (HR-ASD = LR) < HR-Neg

Abbreviations: ASD, autism spectrum disorder; HR, high-risk; LR, low-risk.

* $p < .05$

** $p < .01$

*** $p < .001$.

TABLE 3

Estimated marginal mean number of vocalizations per 10 min and standard errors by timepoint and group

	LR	HR-Neg	HR-ASD
6 Months			
Total vocalizations	31.36 (1.76)	30.24 (1.61)	26.21 (1.87)
Speech-like vocalizations	20.16 (1.30)	17.62 (1.09)	17.94 (1.47)
12 Months			
Total vocalizations	39.85 (2.08)	41.95 (2.07)	34.05 (2.24)
Speech-like vocalizations	27.96 (1.67)	27.52 (1.56)	24.85 (1.87)
24 Months			
Total vocalizations	64.35 (3.41)	80.73 (3.98)	57.45 (3.88)
Speech-like vocalizations	53.82 (3.21)	67.21 (3.74)	47.69 (3.64)

Abbreviations: ASD, autism spectrum disorder; HR, high-risk; LR, low-risk.

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TABLE 4

Pairwise comparisons of estimated marginal means

	Estimate (*SE*)	*z*-Ratio	*p*-Value
6 Months			
Total vocalizations			
LR versus HR-Neg	.04 (.08)	0.48	.881
HR-Neg versus HR-ASD	.14 (.09)	1.65	.224
LR versus HR-ASD	.18 (.09)	2.06	.099
Speech-like only			
LR versus HR-Neg	.13 (.09)	1.53	.276
HR-Neg versus HR-ASD	−.02 (.10)	−0.18	.982
LR versus HR-ASD	.12 (.10)	1.16	.477
12 Months			
Total vocalizations			
LR versus HR-Neg	−.05 (.07)	−0.73	.745
HR-Neg versus HR-ASD	.21 (.08)	2.62	.024*
LR versus HR-ASD	.16 (.08)	1.96	.121
Speech-like only			
LR versus HR-Neg	.02 (.08)	0.12	.979
HR-Neg versus HR-ASD	.10 (.09)	1.12	.502
LR versus HR-ASD	.12 (.09)	1.29	.402
24 Months			
Total vocalizations			
LR versus HR-Neg	−.23 (.07)	−3.21	.004**
HR-Neg versus HR-ASD	.34 (.08)	4.20	<.001***
LR versus HR-ASD	.11 (.08)	1.39	.349
Speech-like only			
LR versus HR-Neg	−.22 (.08)	−2.78	.015*
HR-Neg versus HR-ASD	.34 (.09)	3.75	.001**
LR versus HR-ASD	.12 (.09)	1.31	.39

Abbreviations: ASD, autism spectrum disorder; HR, high-risk; LR, low-risk.

* $p < .05$

** $p < .01$

*** $p < .001$.

TABLE 5

Means and standard deviations for Mullen Scales of Early Learning (MSEL) scores and Autism Diagnostic Observation Schedule (ADOS) severity scores at 24 months by diagnostic group

	LR	**HR-Neg**	**HR-ASD**	**Difference**
MSEL composite standard score	109.34 (11.78)	99.37 (13.63)	79.74 (18.47)	$F(2, 87) = 28.45^{***}$ HR-ASD < HR-Neg < LR
MSEL expressive language *T*-score	52.19 (9.63)	49.49 (11.27)	37.17 (11.39)	$F(2, 87) = 14.24^{***}$ HR-ASD < (LR = HR-Neg)
MSEL receptive language *T*-score	56.78 (6.56)	53.09 (7.66)	34.35 (17.00)	$F(2, 87) = 33.33^{***}$ HR-ASD < HR-Neg < LR
ADOS severity score	1.59 (1.43)	1.71 (0.99)	6.39 (1.67)	$F(2, 87) = 105.5^{***}$ HR-ASD > (LR = HR-Neg)

Abbreviations: ASD, autism spectrum disorder; HR, high-risk; LR, low-risk.

* $p < .05$

** $p < .01$

*** $p < .001$.