Can Parents' Concerns Predict Autism Spectrum Disorder? A Prospective Study of High-Risk Siblings From 6 to 36 Months of Age

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Objective: This prospective study characterized parents' concerns about infants at high risk for developing autism spectrum disorder (ASD; each with an older sibling with ASD) at multiple time points in the first 2 years, and assessed their relation to diagnostic outcome at 3 years.

Method: Parents of low-risk controls (LR) and high-risk infant siblings (HR) reported any concerns that they had regarding their children's development between 6 and 24 months of age regarding sleep, diet, sensory behavior, gross/fine motor skills, repetitive movements, communication, communication regression, social skills, play, and behavioral problems, using a parent concern form designed for this study. At 3 years of age, an independent, gold-standard diagnostic assessment for ASD was conducted for all participants.

Results: As predicted, parents of HR children who received an ASD diagnosis reported more concerns than parents of LR and HR children who did not have ASD. The total number of concerns predicted a subsequent diagnosis of ASD as early as 12 months within the HR group. Concerns regarding sensory behavior and motor development predicted a subsequent diagnosis of ASD as early as 6 months, whereas concerns about social communication and repetitive behaviors did not predict diagnosis of ASD until after 12 months.

Conclusion: Parent-reported concerns can improve earlier recognition of ASD in HR children.

Key Words: autism spectrum disorder, parent concern, high-risk siblings, prospective

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Autism spectrum disorder (ASD) is 1 of the most prevalent developmental disorders, with a current estimate of 1 in 68 children.[1] ASD is generally diagnosed at age 4 years or later,[2] but retrospective parental concerns and home videos suggest that symptoms appear earlier, even prior to the child's first birthday.[3-8] That said, retrospective parent reports have potential limitations. Parents' recollection of early symptoms may be influenced by perceptions of what behaviors are linked to ASD, such as language delay or reduced eye contact. Less attention may be given to differences not typically recognized as part of ASD, such as motor delays or sensory sensitivities. This is unfortunate, as a growing literature suggests that early sensory and motor differences form a prodrome of ASD that manifests in the latter half of the first year of life[9-12] before the appearance of social communication and restrictive behavioral differences more directly related to ASD diagnostic criteria (reviewed in Zwaigenbaum *et al.*[13]). Although there are limitations of retrospective inquiry, parents generally describe having concerns before signs of ASD are detected by other mechanisms (including community surveillance and screening)[14]; thus, parental concerns can index clinically significant behavioral differences.[15]

Prospective studies of infants considered to be at high risk (infant siblings of children diagnosed with ASD[16]) or children ascertained by screening for communication delays[17] have provided a window into the emergence of ASD and a unique opportunity to track parents' concerns in relation to subsequent ASD diagnoses. Using this method, parents of children with ASD report concerns as early as 12 to 14 months,[18,19] the most frequent related to delayed communication.[17-19] Although promising, these studies' findings are limited in scope. For example, Wetherby *et al.*[17] informed parents that the researchers were examining communication, potentially limiting the range of concerns reported. Hess and Landa[13] lacked a control group of LR children and did not collect parent reports before 14 months. Ozonoff *et al.*[19] collected parent reports at 3 time points in the first 18 months but focused on the total number of concerns rather than specific areas as potential predictors of later diagnosis.

The present study examined parent concerns between 6 and 24 months of age across multiple domains of

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development and their relation to ASD risk. We used a structured interview that included questions regarding concerns in 10 domains: sleep, diet, sensory interests, motor development, repetitive movements, communication, communication regression, social skills, play, and behavioral problems. Parents of infants who were LR and HR were interviewed at ages 6, 9, 12, 15, 18, and 24 months. Our primary objective was to identify parent-reported concerns in the first 24 months that distinguished HR infants who were diagnosed with ASD at 36 months from other HR and LR infants.

METHOD

Study Participants

Parent concerns were analyzed in respect to infants at HR and LR who were participating in a longitudinal study of early behavioral markers of ASD at 1 of 4 sites in Canada (Glenrose Rehabilitation Hospital in Edmonton, Alberta; Holland Bloorview Kids Rehab in Toronto, Ontario; Offord Centre for Child Studies in Hamilton, Ontario; IWK Health Centre in Halifax, Nova Scotia).[20] All infants were enrolled between 6 and 12 months and underwent comprehensive assessment of their cognitive, communication, social, and motor abilities, as well as ASD-related symptoms, at 6, 9, 12, 15, 18, 24, and 36 to 42 months (hereafter, 3 years).

Infants at LR and HR who were followed to at least 3 years were included in the study if they underwent an ASD diagnostic assessment and if parents had completed our parent concern form at a minimum of 2 time points between 6 and 24 months. As a result, 10 of 79 infants at LR and 49 of 217 infants at HR (28 of 134 HR without ASD and 21 of 83 HR with ASD at 3 years) were excluded. The diagnosis of the older sibling (or proband) was based on evaluation by a multidisciplinary team and expert clinical review using *DSM-IV-TR* criteria, supported by a comprehensive developmental history and the Autism Diagnostic Observation Schedule (ADOS).[21] Infants at LR were recruited from the local community at each site on the basis of having no first- or second-degree relatives with an ASD diagnosis. All participants were born at 36 to 42 weeks' gestation, had a birth weight greater than 2,500 g, and had no known genetic or neurological disorders. The institutional review boards at each of the 4 sites approved the research protocol, and parents provided written informed consent after receiving a detailed description of the study.

Measures

Several assessments were administered to track cognition, adaptive behavior, and ASD-specific characteristics over time. The Mullen Scales of Early Learning (MSEL[22]) is a direct measure of development, consisting of 4 scales that, together, form the Early Learning Composite (ELC). The ELC of the MSEL was calculated at 12, 24, and 36 months. The Vineland Adaptive Behavior Scales (VABS)[23] is a semistructured parent interview designed to assess adaptive behavior, notably communication, daily living, socialization, and motor skills. The Adaptive Behavior Composite (ABC) of the VABS was calculated at 12, 18, 24, and 36 months of age. The first version of the VABS was used as the longitudinal study was implemented before the release of the second edition.[24]

ASD symptoms were measured using the ADOS[21] and the Autism Diagnostic Interview–Revised (ADI-R).[25] The ADOS uses standardized activities and presses to elicit communication, social interaction, imaginative play, and repetitive behavior, allowing the examiner to observe the occurrence or nonoccurrence of behaviors diagnostic of ASD. The ADOS was administered at 24 and 36 months, and ADOS severity scores were calculated.[26] The ADI-R is an investigator-directed interview used to elicit information about social development, verbal/nonverbal communication, and repetitive interests and behavior required to make an *ICD-10* or *DSM-IV* diagnosis of ASD. The ADI-R was administered at 3 years.

Assessment of Parent Concerns

We developed an interview to collect information about parent concerns during the first 2 years in children at LR and HR of ASD. The interview is semistructured, with the interviewer asking parents questions in 10 developmental domains in a standardized order (see Supplement, available online, for the interview). Parents were asked if they had current concerns in each of 3 broad areas: general concerns (sleep, diet, sensory, motor); behavioral concerns (social, play, behavioral problems, repetitive behaviors/restricted interests); and communication concerns (verbal/nonverbal, regression). Responses were digitally transcribed into a master file using Microsoft Excel (Microsoft Excel for Mac 2011, Version 14.4.1). Participants were identified using a unique number, and other identifying information was removed. A coder blinded to group membership (L.R.S.) coded the data file using a binary system of "0" and "1," with "0" representing the absence of a concern and "1" the presence of a concern. If a domain was left blank or if parents indicated "None" or "N/A," this was coded as "0." A second coder (C.N.), also blinded to group status, coded 30% of all of the parent concern forms. Analysis of interrater reliability was completed using Cohen's κ, with an overall reliability of 0.71. Reliability was analyzed for each domain using the criteria of Fleiss[27] and ranged from 0.60 (good) to 1.0 (excellent) at sleep: 0.91; diet: 0.94; sensory: 0.60; gross/fine motor: 0.69; repetitive motor: 0.69; communication: 0.60; communication regression: 1.0; social: 0.64; play: 0.76; and behavioral problems: 0.64.

Diagnostic Outcome Assessment

At 3 years, each participant underwent an independent diagnostic evaluation conducted by an expert clinician blinded to the results of all previous assessments. ASD diagnoses 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 with ASD), taking into account information from the concurrent ADI-R, ADOS, and assessments of cognitive, language, and adaptive skills. Some children with a clinical diagnosis of ASD had subthreshold algorithm scores on the ADOS and/or ADI-R but met *DSM-IV-TR* criteria based on expert review of all available 3-year data. Infants at HR were stratified by 3-year status into those diagnosed with ASD (HR-ASD) and those not diagnosed with ASD (HR-N).

Statistical Analyses

Children who were HR-ASD, HR-N, and LR were compared using the Statistical Package for the Social Sciences (SPSS) version 19, using group and age (6, 9, 12, 15, 18, and 24 months) as fixed factors, with α (i.e., overall type I error) set at 0.05. Groups were compared using mixed-model analyses. Group differences and group-by-age interactions were explored using Benjamini and Hochberg corrections.[28] In this method, the p values are ordered from smallest to largest. The α level for each test is then set at $\frac{k*\alpha}{m}$, 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 1 of the t tests is rejected. Our main objective was to determine when differences appeared among the 3 groups of children, and therefore planned

comparisons were completed on all group-by-age interactions. Effect sizes were calculated using Cohen's d, with 0.2 to 0.49 indicating a small effect, 0.5 to 0.79 a medium effect, and ≥0.8 a large effect.[29]

RESULTS

Participant Characteristics by Outcome Group

Participant characteristics are presented in Table 1. Three groups based on 3-year diagnostic outcomes were compared: 69 LR (31 boys); 106 HR-N (55 boys); and 62 HR-ASD (48 boys). There was a group difference for sex, with fewer girls in the HR-ASD group compared to HR-N and LR groups ($F_{2,218} = 5.3$, $p = .006$). There was a group difference for exact age at 6 months ($F_{2,136} = 3.3$, $p = .04$), with HR-N (mean ± SD = 6.27 ± 0.35 months) being younger than LR (mean ± SD = 6.46 ± 0.37 months), but HR-ASD (mean ± SD = 6.46 ± 0.65 months) did not differ from the 2 other groups. There were no other group differences in age at any of the remaining 6 time points (all $p > .05$). Group comparisons on developmental and ASD symptom measures are shown in Table 1.

Group Comparisons: Parental Concerns

Group and age differences for each domain were explored using a series of mixed-methods analyses. The percentages of concerns reported for children in the LR, HR-N, and

TABLE 1 Participant Characteristics

Characteristic	LR, n (Total = 69)		HR-N, n (Total = 106)		HR-ASD, n (Total = 62)		F test	p
Sex (M:F)	31:28		55:45		48:14 [ab]		χ^2=10.26	<.01
Age, mo								
6	52		64		22			
9	60		76		34			
12	69		102		57			
15	56		95		55			
18	67		106		58			
24	69		106		62			
Age, mo	**Mean**	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**		
6	6.5	(0.3)	6.3	(0.4)	6.3	(0.3)	3.3	<.05
9	9.2	(0.4)	9.2	(0.4)	9.2	(0.3)	0.93	>.05
12	12.4	(0.5)	12.4	(0.4)	12.3	(0.2)	0.19	>.05
15	15.3	(0.3)	15.3	(0.4)	15.3	(0.4)	0.21	>.05
18	18.5	(0.4)	18.4	(0.4)	18.4	(0.3)	0.29	>.05
24	24.6	(0.6)	24.5	(0.5)	24.5	(0.6)	0.5	>.05
36	41.8	(7.4)	40.6	(3.9)	39.6	(3.2)	0.04	>.05
Mullen ELC, mo	**Mean**	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**		
12	108.4	(12.1)	100.0	(15.9)	98.0	(16.9)[abc]	8	<.001
24	117.9	(15.3)	105.1	(15.0)[a]	89.3	(18.9)[ab]	42.84	<.001
36	118.8	(15.9)	106.7	(18.1)[a]	93.8	(20.7)[ab]	26.5	<.001
VABS ABC, mo	**Mean**	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**		
18	97.3	(7.0)	92.2	(7.8)[a]	85.5	(9.0)[ab]	30.85	<.001
24	94.9	(9.3)	91.0	(9.9)[a]	83.5	(10.1)[ab]	20.47	<.001
36	99.0	(9.9)	94.4	(12.8)	80.6	(12.4)[ab]	35.68	<.001
ADOS Severity, mo	**Mean**	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**		
24	1.5	(0.8)	2.7	(1.8)[a]	5.5	(2.2)[ab]	79.46	<.001
36	1.7	(1.2)	2.7	(1.8)[a]	6.3	(1.7)[ab]	139.47	<.001
ADI-R, mo	**Mean**	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**		
36	3.9	(3.3)	7.2	(4.9)[a]	22.2	(10.6)[ab]	126.73	<.001

Note: ADI-R = Autism Diagnostic Interview-Revised Total Score; ADOS = Autism Diagnostic Observation Schedule Severity Score; ASD = autism spectrum disorder; ELC = Early Learning Composite Score; F = female; HR-ASD = high-risk infant sibling diagnosed with ASD; HR-N = high-risk infant sibling without ASD; LR = low-risk infant without ASD; M = male; VABS ABC = Vineland Adaptive Behavior Scale Adaptive Behavior Composite Score.

[a]*Different from LR; significant at p < .0167.*

[b]*Different from HR-N; significant at p < .0167.*

[c]*Difference between HR-N and HR-ASD is not clinically relevant.*

TABLE 2 Reported Concerns in Each Domain by Group

Domain	6 Months % Reported			9 Months % Reported			12 Months % Reported			15 Months % Reported			18 Months % Reported			24 Months % Reported		
	LR	HR-N	ASD	LR	HR-N	ASD	LR	HR-N	ASD	LR	HR-N	ASD	LR	HR-N	ASD	LR	HR-N	ASD
Sleep	19	33	35	12	27	30	7	27	30^{ab}	5	23	30^{a}	9	22	26^{a}	6	26^{a}	32^{a}
Diet	17	14	20	15	18	15	11	17	16	9	16	11	13	21	26	20	28	23
Sensory	6	12	35^{ab}	15	16	33^{ab}	6	11	38^{ab}	4	15	33^{ab}	13	13	47^{ab}	14	21	39^{ab}
Motor	15	26	50^{ab}	23	29	45^{a}	14	22	30^{a}	7	27^{a}	37^{a}	7	20	46^{ab}	4	9	44^{ab}
RRB	4	12	10	2	22^{a}	24^{a}	0	17	32	2	14	22^{a}	4	20^{a}	37^{ab}	3	13	37^{ab}
Communication	6	11	20	7	18	30^{a}	9	37^{a}	41^{a}	13	36^{a}	57^{ab}	16	35^{a}	63^{ab}	19	32	47^{a}
Comm reg.	2	6	10	0	6	6	0	9^{a}	9	0	7	13^{a}	0	6	11^{a}	0	3	13^{ab}
Social	8	6	25	3	9	15	3	14	29^{ab}	4	17	26^{ab}	7	14	42^{ab}	4	17^{a}	48^{ab}
Play	0	2	10	0	3	15^{ab}	0	7	16^{ab}	0	5	13^{a}	0	5	23^{ab}	4	4	32^{ab}
Behavioral problems	8	3	15	8	8	21	7	18	32^{a}	13	27	30	16	38^{a}	49^{ab}	13	33^{a}	57^{a}
Total concerns, n	0.9	1.2	2.3^{a}	0.9	1.6	2.4^{a}	0.6	1.8^{a}	2.7^{ab}	0.6	1.9^{a}	2.7^{ab}	0.9	1.9^{a}	3.7^{ab}	0.9	1.9^{a}	3.7^{ab}

Note: ASD = autism spectrum disorder; Comm. reg. = communication regression; HR-ASD = high-risk infant sibling diagnosed with ASD; HR-N = high-risk infant sibling without ASD; LR = low-risk infant without ASD; Motor = gross and fine motor; RRB = repetitive behaviors and restricted interests.

[a]*Different from LR; based on their corrected t tests as reported in the text.*

[b]*Different from HR-N; based on their corrected t tests as reported in the text.*

HR-ASD groups for each domain are presented in Table 2. A complementary analysis of parent concerns, which subdivides the HR-N group based on the presence or absence of the broader autism phenotype as per Ozonoff *et al.*,[30] can be located in the Supplement, available online.

General Concerns. The number of reported sleep-related concerns differed significantly by group ($F_{2,1196} = 25.6$, $p < .001$), but not age ($F_{5,1196} = 1.1$, $p > .05$) or group-by-age ($F_{10,1196} = 0.2$, $p > .05$). Overall, the LR group had fewer concerns than both HR groups ($q < .033$; $d = 0.5$), who did not differ ($d = 0.08$). As shown in Figure 1A (also see Figure S1, available online), group differences appeared by 12 months between LR and both HR groups, which did not differ.

As illustrated in Figure 1B, a significant age difference was found for the number of reported diet concerns ($F_{5,1196} = 2.5$, $p < .05$) but no group ($F_{2,1196} = 1.7$, $p > .05$) or group-by-age ($F_{10,1196} = 0.5$, $p > .05$) effects. Post hoc analyses showed no resultant age differences ($d < 0.2$).

The number of reported sensory concerns differed significantly by group ($F_{2,1196} = 44.4$, $p < .001$) but not by age ($F_{5,1196} = 1.7$, $p > .05$) or group-by-age ($F_{10,1196} = 0.7$, $p > .05$). Overall, HR-ASD had more concerns than LR and HR-N groups ($q < .033$; $d = 0.5$ and 0.7 respectively), which did not differ ($d = 0.2$). Post hoc analyses (Figure 1C) indicated that group differences emerged at 6 months between HR-ASD and both LR and HR-N groups, which did not differ (all $q \leq .032$).

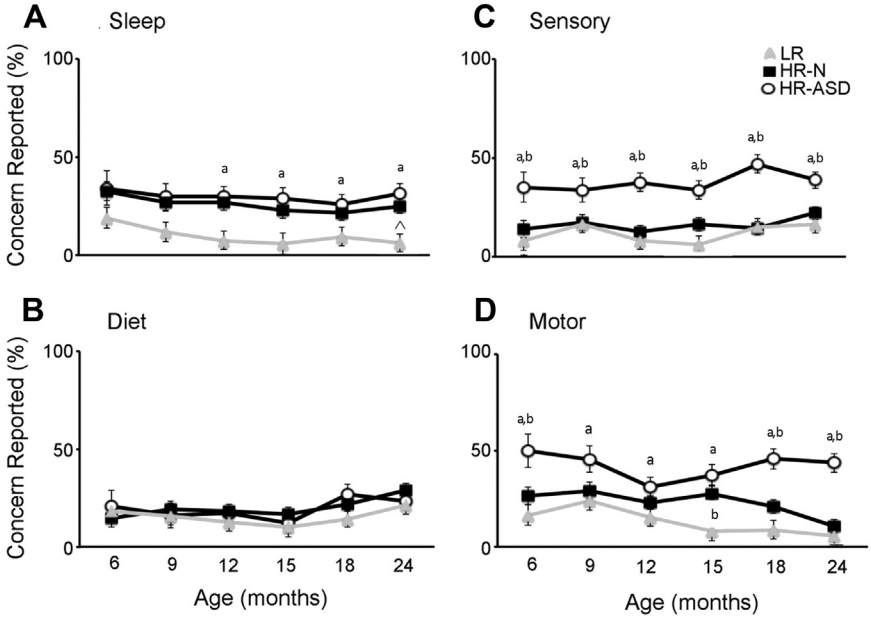
Significant group ($F_{2,1196} = 40.1$, $p < .001$) and age ($F_{5,1196} = 2.5$, $p < .05$) differences were observed for the number of reported motor concerns, but no group-by-age ($F_{10,1196} = 1.5$, $p > .05$) effect. Overall, HR-ASD had more concerns than LR ($d = 0.7$) and HR-N ($d = 0.4$), and HR-N had more concerns than LR ($d = 0.3$; $q < .05$). Post hoc analyses indicated that group differences emerged at 6 months between HR-ASD and both LR and HR-N, and between HR-N and LR at 15 months (Figure 1D; all $q \leq 0.28$).

Behavior Concerns. Significant group ($F_{2,1196} = 42.7$, $p < .001$), age ($F_{5,1196} = 4.2$, $p < .001$), and group-by-age ($F_{10,1196} = 2.2$, $p < .01$) differences were found for the number of reported social concerns. Overall, HR-ASD had more concerns than HR-N ($d = 0.5$) and LR ($d = 0.8$), who also differed ($d = 0.3$). Post hoc analyses, shown in Figure 2A (also see Figure S2, available online), indicated that group differences emerged at 12 months between HR-ASD and both LR and HR-N, who also differed beginning at 15 months (all $q \leq .025$).

Significant group ($F_{2,1196} = 40.8$, $p < .001$), age ($F_{5,1196} = 3.5$, $p < .01$), and group-by-age ($F_{10,1196} = 2.1$, $p < .05$) differences were found for the number of reported play concerns. Overall, HR-ASD had more concerns than HR-N ($d = 0.5$) and LR ($d = 0.7$), who also differed ($d = 0.2$; $q < .05$). Post hoc analyses indicated that group differences emerged at 9 months between HR-ASD and both LR and HR-N, who did not differ (Figure 2B; all $q \leq .025$).

Significant group ($F_{2,1195} = 24.7$, $p < .001$), age ($F_{5,1195} = 12.3$, $p < .001$), and group-by-age ($F_{10,1195} = 2.1$, $p < .01$) differences were found for the number of reported behavioral problem concerns. Overall, HR-ASD had more

FIGURE 1 General concerns. Note: Mean ± standard error of the mean (SEM) for percentage of concerns is reported for each group by each age for (A) sleep, (B) diet, (C) sensory, and (D) motor. ASD = autism spectrum disorder; HR-ASD = high-risk infant siblings diagnosed with ASD; HR-N = high-risk infant siblings without ASD; LR = low-risk infants without ASD; [a]Different from LR. [b]Different from HR-N.



concerns than LR (d = 0.7) and HR-N (d = 0.3), who also differed (d = 0.3; q < .05). Post hoc analyses, shown in Figure 2C, indicated that group differences emerged at 12 months between the HR-ASD and LR groups, at 24 months between the HR groups, and at 18 months between HR-N and LR (all q ≤ .017).

Significant group ($F_{2,1195}$ = 39.4, p < .001) and age ($F_{5,1195}$ = 2.2, p < .05) differences were found for the number of reported repetitive motor/restrictive behavior (RRB) concerns, but no group-by-age ($F_{10,1195}$ = 1.4, p > .05) effect. Overall, HR-ASD had more concerns than both LR (d = 0.8) and HR-N (d = 0.3), and HR-N had more concerns than LR (d = 0.5; q < .05). Post hoc analyses, as shown in Figure 2D, indicated that group differences emerged at 9 months between HR-ASD and LR, and at 18 months between HR-ASD and HR-N. Differences between the HR-N and LR groups emerged at 9 months (all q ≤ .03).

Communication and Total Concerns. Significant group ($F_{2,1196}$ = 41.8, p < .001) and age ($F_{5,1196}$ = 8.4, p < .001) differences were found for the number of reported communication concerns, but no group-by-age ($F_{10,1196}$ = 1.5, p > .05) effect. Overall, the HR-ASD group had more concerns than both LR (d = 0.8) and HR-N (d = 0.4), and HR-N had more concerns than LR (d = 0.5; q < .05). Post hoc analyses, as shown in Figure 3A (also see Figure S3, available online), indicated that group differences emerged at 9 months between HR-ASD and LR and at 15 months between the HR groups. Differences between the HR-N and LR groups emerged at 12 months (all q ≤ .028).

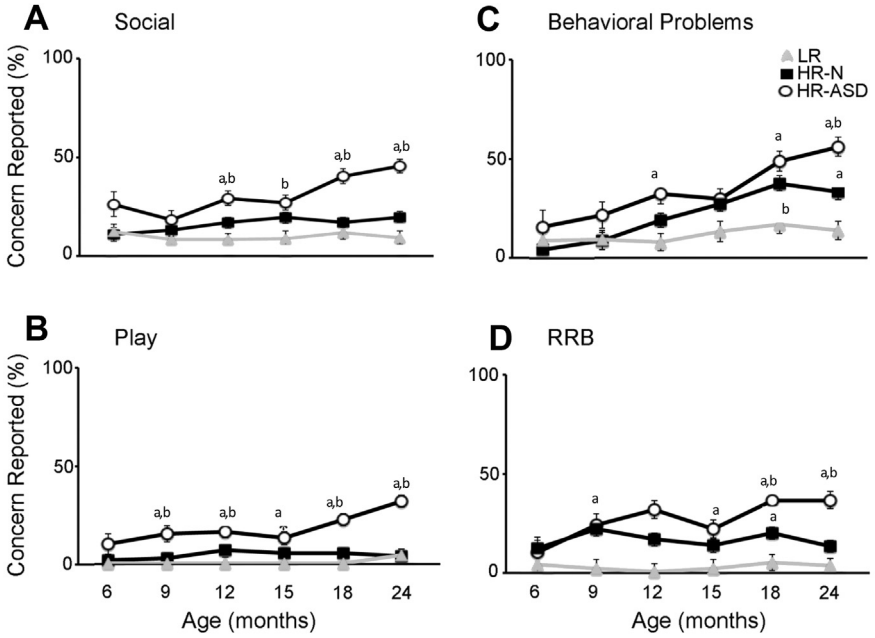
A significant group difference was found for the number of reported communication regression concerns ($F_{2,1196}$ = 15.4, p < .001), but no age ($F_{5,1196}$ = 0.2, p > .05) or group-by-age ($F_{10,1196}$ = 0.6, p > .05) effects. Overall, LR had fewer concerns than HR groups (d = 0.3 [HR-N], 0.5 [HR-ASD]), and HR-ASD had more concerns than HR-N (d = 0.2; q < .05). Post hoc analyses, shown in Figure 3B, indicated that more group differences emerged at 15 months between HR-ASD and LR, at 24 months between HR-ASD and HR-N, and at 15 months between HR-N and LR (all q ≤ .014).

Analyses of total number of concerns (sum of all domains) resulted in an overall effect of group ($F_{2,1196}$ = 129.1, p < .001), age ($F_{5,1196}$ = 5.9, p < .001), and a group-by-age interaction ($F_{10,1196}$ = 2.5, p < .01), with HR-ASD having more concerns compared to the LR (d = 1.3) and HR-N (d = 0.7) groups, which also differed (d = 0.7; q < .05). Post hoc analyses, shown in Figure 3C, indicated that group differences emerged at 6 months between HR-ASD and LR, at 12 months between HR groups, and at 12 months between HR-N and LR.

DISCUSSION

This study provides the most detailed description of prospectively examined parental concerns to date, comparing rates of concerns in multiple domains in infants at LR and HR for ASD from 6 to 24 months. Overall, parents of children with ASD recognize very early developmental differences in their later-born infants who develop ASD that distinguish them from other infants. Notably, the relative rates of types of concerns reported over time were remarkably similar across risk and outcome groups, in that parents of children in all groups were more likely to report sleep and

FIGURE 2 Behavioral concerns. Note: Mean ± standard error of the mean (SEM) for percentage of concerns is reported for each group by each age for (A) social, (B) play, (C) behavioral problems, and (D) repetitive behavior. ASD = autism spectrum disorder; HR-ASD = high-risk infant siblings diagnosed with ASD; HR-N = high-risk infant siblings without ASD; LR = low-risk infants without ASD; RRB = restricted interests and repetitive behaviors. [a]Different from LR. [b]Different from HR-N.



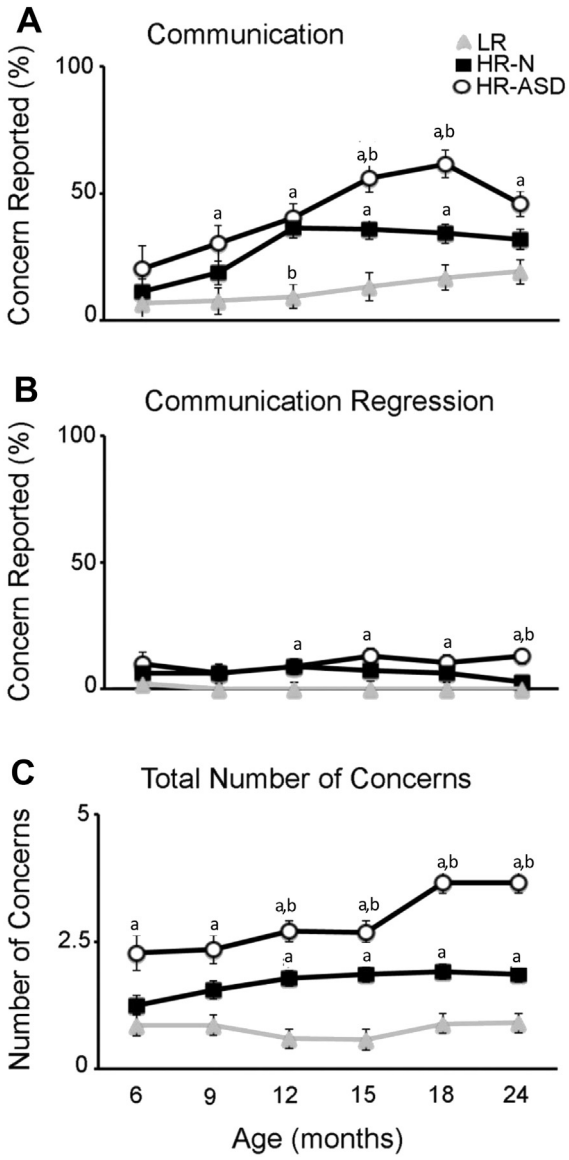
motor concerns during the first year, and communication and behavioral concerns in the second and third years, even though parents of children with ASD reported more concerns overall than their LR and HR-N counterparts.

The total number of concerns at 12 months predicted which children at HR would likely receive an ASD diagnosis, consistent with the prospective findings of Ozonoff *et al.*[19] However, group differences were apparent even earlier when looking at individual domains. Differences in sensory and motor skills at 6 months and in sensory and play skills at 9 months differentiated between children at HR who did and did not receive a diagnosis of ASD at 3 years. In contrast, differences in rates of concerns in other domains differentiated between groups at later ages. For example, group differences between the children at HR with and without ASD did not appear until 12 months for social concerns, 15 months for communication concerns, and 18 months for repetitive behaviors/restricted interests. The finding that parents report restricted and repetitive behaviors in the 2 HR groups is consistent with findings by Chawarska *et al.*[39] and highlights the challenges of diagnosing infants with ASD by 18 months, as a subsample of the children at HR exhibit such behaviors but do not go on to be diagnosed with ASD by age 3 years. The sequencing of concerns reflects a growing literature that suggests that early sensory and motor differences form a prodrome of ASD that manifests in the latter half of the first year of life,[9-12] preceding social communication and restrictive behavioral differences more directly related to ASD diagnostic criteria (reviewed by Zwaigenbaum *et al.*[13]).

Group differences between children at LR and children diagnosed with ASD emerged earlier than differences between children at HR without ASD versus those with ASD. This is most apparent for communication, regression, and repetitive behaviors/restricted interests, those domains most associated with ASD. Two potential factors may account for the later emergence of group differences between the HR groups. First, parents of children at HR have at least 1 child with an ASD diagnosis, and may be sensitized to detecting developmental differences in their younger child and thus report a higher number of concerns than parents without a child with ASD. Second, a subgroup of the HR-N group is at a heightened risk for developmental and behavioral challenges related to ASD, that is, the broader autism phenotype,[30,31] potentially resulting in their parents reporting more concerns. Despite these factors, parents' total number of concerns differentiated the HR-ASD and HR-N groups by age 12 months.

These and other recent findings[17-19] argue for a renewed attention to the content and timing of parental concerns. Historically, parents' descriptions helped inform the development of early detection and screening strategies (e.g., Robins *et al.*[32]), but have received less attention with the shift to direct observation in prospective studies of high-risk infants. In community-based surveillance contexts, parental concerns correlate highly with a broad range of developmental delays and emotional–behavioral problems.[15,32] Indeed, in the current study, the pattern and time course of parental concerns related to subsequent ASD diagnoses mirror findings from laboratory-based

FIGURE 3 Communication and total concerns. Note: Mean ± standard error of the mean (SEM) for percentage of concerns is reported for each group by each age for (A) communication, (B) communication regression, and (C) total number of concerns. ASD = autism spectrum disorder; HR-ASD = high-risk infant siblings diagnosed with ASD; HR-N = high-risk infant siblings without ASD; LR = low-risk infants without ASD. [a]Different from LR. [b]Different from HR-N.



observational studies of infants at high risk (reviewed by Zwaigenbaum *et al.*[13]). Moreover, although technology-based indices of underlying brain structure,[33] function,[34] and visual orienting differences[33-37] predict ASD in pre-symptomatic infants, differences on these measures generally emerge no earlier than 6 months. This corresponds to the age at which parental concerns begin to differ between HR-ASD and LR groups, perhaps driven primarily by concerns regarding sensory and motor behavior. This suggests that parents recognize developmental differences related to ASD very early. Indeed, parents' ability to recognize such differences could support intensified efforts for surveillance of early signs of ASD in these children at HR, as recommended by the American Academy of Pediatrics.[38]

Unique strengths of this study include the large sample size, prospective design, and systematic analysis of parental concerns across a broad range of domains, conducted blind to outcome and risk status. However, the study also has a number of limitations. First, parents of children at HR already have at least 1 child with a diagnosis of ASD and may be aware of the early problems associated with ASD and more sensitive to developmental or behavioral differences than other parents, limiting generalizability beyond a high-risk context. Second, although the HR-N group includes some children with developmental delays, we have not specifically compared parental concerns in ASD to those of parents of children with developmental delays outside the ASD context. Supplemental analyses of participants who met criteria for the broader autism phenotype[30] noted that parental concerns for these children also indicate earlier recognition of developmental abnormalities when compared to an LR sample. Third, findings from this HR cohort may not generalize to nonfamilial cases of ASD (i.e., multiplex versus simplex families) or to clinically referred children with ASD of similar age. Fourth, this study also does not take into account the differences between clinically referred samples and our high-risk family sample. There is the potential risk that families who chose to participate in longitudinal research are not representative of children with ASD from nonfamilial samples. Fifth, although interrater reliability for sleep, diet, communication regression, and play were quite strong, other domains were fair to good, representing the difficulty when teasing apart age-related concerns, and highlight the importance of clinical experience when categorizing parent concerns as clinical concerns.

In summary, our findings indicate that the presence of parent concerns can predict later diagnostic outcomes in children at high risk for ASD. ASD screening tools are designed to elicit parents' observations regarding early ASD-related behaviors, with evidence of increased sensitivity relative to open-ended questions about parental concerns.[41] Uptake into clinical practice remains modest despite current practice guidelines[38] but could be improved if perceived barriers were addressed, including streamlined referral systems to ensure that children with identified concerns are assessed in a timely way, and training for support staff to facilitate referrals and to track follow-through and outcomes. Although these findings may not generalize to families who do not already have a child with ASD, retrospective research would suggest that these families are aware of red flags from an early age.[3] Although ambiguity about the clinical interpretation of behavioral signs can cause uncertainty for both clinicians and families, increased access to early interventions for children at risk

due to early signs, regardless of familial risk, may help encourage buy-in and ultimately improve outcomes. &

CG Clinical Guidance

- Parent reports provide important information concerning the development of their child as early as the first year of life.
- Parent reports reflecting motor, sensory, and play concerns in the first year are predictive of an outcome of ASD.
- Reports of communication and social concerns in the second year are predictive of an outcome of ASD.

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REFERENCES

1. Centers for Disease Control and Prevention. Prevalence of autism spectrum disorder among children aged 8 years—Autism and Developmental Disabilities Monitoring Network, 11 sites, United States, 2010. MMWR. 2014;63:1-22.
2. Daniels AM, Mandell DS. Explaining differences in age at autism spectrum disorder diagnosis: a critical review. Autism. 2013;18:583-597.
3. De Giacomo A, Fombonne E. Parental recognition of developmental abnormalities in autism. Eur Child Adolesc Psychiatry. 1998;7:131-136.
4. Mars AE, Mauk JE, Dowrick PW. Symptoms of pervasive developmental disorders as observed in prediagnostic home videos of infants and toddlers. J Pediatr. 1998;132:500-504.
5. Ohta M, Nagai Y, Hara H, Sasaki M. Parental perception of behavioral symptoms in Japanese autistic children. J Autism Dev Disabil. 1987;17:549-563.
6. Osterling J, Dawson G. Early recognition of children with autism: a study of first birthday home videotapes. J Autism Dev Disabil. 1994;24:247-257.
7. Volkmar FR, Stier DM, Cohen DJ. Age of recognition of pervasive developmental disorder. Am J Psychiatry. 1985;142:1450-1452.
8. Werner E, Dawson G, Osterling J, Dinno N. Brief report: recognition of autism spectrum disorder before one year of age: a retrospective study based on home videotapes. J Autism Dev Disabil. 2000;30:157-162.
9. Baranek GT. Autism during infancy: a retrospective video analysis of sensory-motor and social behaviours at 9-12 months of age. J Autism Dev Disabil. 1999;29:213-224.
10. Libertus K, Sheperd KA, Ross SW, Landa RJ. Limited fine motor and grasping skills in 6-month-old infants at high risk for autism. Child Dev. 2014;85:2218-2231.
11. Trevarthen C, Delafield-Butt JT. Autism as a developmental disorder in intentional movement and affective engagement. Front Integ Neurosci. 2013;17:49.
12. Yirmiya N, Charman T. The prodrome of autism: early behavioral and biological signs, regression, peri- and post-natal development and genetics. J Child Psychol Psychiatry. 2010;51:432-458.
13. Zwaigenbaum L, Bryson S, Garon N. Early identification of autism spectrum disorders. Behav Brain Res. 2013;251:133-146.
14. Chawarska K, Paul R, Klin A, Hannigeb S, Dichtel LE, Volkmar F. Parental recognition of developmental problems in toddlers with autism spectrum disorders. J Autism Dev Disord. 2007;37:62-72.
15. Glascoe FP. Parents' evaluation of developmental status: how well do parents' concerns identify children with behavioral and emotional problems? Clin Pediatr. 2003;42:133-138.
16. Zwaigenbaum L, Thurm A, Stone W, *et al*. Studying the emergence of autism spectrum disorders in high-risk infants: methodological and practical issues. J Autism Dev Dis. 2007;37:466-480.
17. Wetherby AM, Woods J, Allen L, Cleary J, Dickinson H, Lord C. Early indicators of autism spectrum disorders in the second year of life. J Autism Dev Dis. 2004;34:473-493.
18. Hess CR, Landa RJ. Predictive and concurrent validity of parent concern about young children at risk for autism. J Autism Dev Dis. 2012;42:575-584.
19. Ozonoff S, Young GS, Steinfeld MB, *et al*. How early do parent concerns predict later autism diagnosis? J Dev Behav Pediatrics. 2009;30:367-375.
20. Zwaigenbaum L, Bryson S, Rogers T, Roberts W, Brian J, Szatmari P. Behavioral manifestations of autism in the first year of life. Int J Dev Neurosci. 2005;23:143-152.
21. Lord C, Risi S, Lambrecht L, *et al*. The Autism Diagnostic Observation Schedule–Generic: a standard measure of social and communication deficits associated with the spectrum of autism. J Autism Dev Dis. 2000;30:205-223.
22. Mullen E. Mullen Scales of Early Learning: American Guidance Services. Circle Pines, MN: American Guidance Service; 1995.
23. Sparrow SS, Balla D, Cicchetti D. Vineland Adaptive Behavior Scales (Survey Form). Circle Pines, MN: American Guidance Service; 1984.
24. Zwaigenbaum L, Bryson SE, Szatmari P, *et al*. Sex differences in children with autism spectrum disorder identified within a high-risk infant cohort. J Autism Dev Dis. 2012;43:2585-2596.
25. Lord C, Rutter M, Le Couteur AJ. Autism Diagnostic Interview—Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. J Autism Dev Disabil. 1994;24:659-685.
26. Gotham K, Pickles A, Lord C. Standardizing ADOS severity scores for a measure of severity in autism spectrum disorders. J Autism Dev Dis. 2009;39:693-705.
27. Fleiss JL. Statistical Methods for Rates and Proportions. 2nd ed. New York: John Wiley; 1981.
28. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J Roy Stat Soc Series B. 1995;57:289-300.
29. Cohen J. Statistical Power Analyses for the Behavioral Sciences. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988.
30. Ozonoff S, Young GS, Belding A, *et al*. The broader autism phenotype in infancy: when does it emerge? J Am Acad Child Adolesc Psychiatry. 2014;53:398-407.e2.

31. Messinger D, Young GS, Ozonoff S, *et al*. Beyond autism: a Baby Siblings Research Consortium study of high-risk children at three years of age. J Am Acad Child Adolesc Psychiatry. 2013;52:300-308.e1.
32. Robins DL, Fein D, Barton ML, Green JA. The Modified Checklist for Autism in Toddlers: an initial study investigating the early detection of autism and pervasive developmental disorders. J Autism Dev Disabil. 2001;31:131-144.
33. Elison JT, Paterson SJ, Wolff JJ, *et al*. White matter microstructure and atypical visual orienting in 7-month-olds at risk for autism. Am J Psychiatry. 2013;170:899-908.
34. Elsabbagh M, Mercure E, Hudry K, *et al*. Infant neural sensitivity to dynamic eye gaze is associated with later emerging autism. Curr Biol. 2012;22:338-342.
35. Chawarska K, Macari S, Shic F. Decreased spontaneous attention to social scenes in 6-month-old infants later diagnosed with autism spectrum disorders. Biol Psychiatry. 2013;74:195-203.
36. Cohen IL, Gardner JM, Karmel BZ, *et al*. Neonatal function and 4-month arousal-modulated attention are jointly associated with autism. Autism Res. 2013;6:11-22.
37. Jones W, Klin A. Attention to eyes is present but in decline in 2-6-month-old infants later diagnosed with autism. Nature. 2013;504:427-431.
38. Johnson CP, Myers SM. American Academy of Pediatrics Council on Children with Disabilities. Identification and evaluation of children with autism spectrum disorders. Pediatrics. 2007;120:1183-1215.
39. Chawarska K, Shic F, Macari S, *et al*. 18-Month predictors of later outcomes in younger siblings of children with autism spectrum disorder: a Baby Siblings Research Consortium study. J Am Acad Child Adolesc Psychiatry. 2014;53:1317-1327.
40. Jones EJ, Gliga T, Bedford R, Charman T, Johnson MH. Developmental pathways to autism: a review of prospective studies of infants at risk. Neurosci Biobehav Rev. 2014;39:1-33.
41. Robins DL. Screening for autism spectrum disorders in primary care settings. Autism. 2008;12:537-556.