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BRIEF REPORT

Sex Differences in Autistic Youth Born Extremely Preterm

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Abstract

Purpose To evaluate sex differences in autistic traits in youth born extremely preterm (EP; 23–27 weeks) who were later diagnosed with autism spectrum disorder (ASD) at 10-years.

Method A longitudinal cohort design from the Extremely Low Gestational Age Newborn Study (ELGAN) followed $N = 857$ EP infants from birth through 10-years. EP infants later diagnosed with ASD ($N = 61$, 20 females) participated in the study. Group differences were evaluated via inferential and Bayesian statistics (values > 1 suggest evidence for alternate hypothesis) on ASD screeners (M-CHAT at 2-years, SCQ and SRS-2 at 10-years), and gold-standard diagnostic measures (ADOS-2, ADI-R) at 10-years.

Results Males scored significantly higher than females on measures of Social Affect from the ADOS-2, $t(34.27) = -2.20$, $BF_{10} = 2.33$, and measures of Repetitive and Restricted Behaviors from the ADI-R, $t(40.52) = -2.85$, $BF_{10} = 5.26$. Bayesian estimates suggested marginal evidence for sex differences in Nonverbal Communication, $t(30.66) = -1.81$, $BF_{10} = 1.25$, and Verbal Communication, $t(24.64) = -1.89$, $BF_{10} = 1.39$, from the ADI-R, wherein males scored higher than females. No statistically significant sex differences were identified on any of the ASD screeners at 2 (M-CHAT) or 10 years (SCQ). No significant sex differences were observed on any subscales of the SRS at 10 years.

Conclusions EP autistic males present with more autistic traits than EP autistic females on gold-standard diagnostic measures of autism at 10-years of age, despite not presenting with higher autistic traits on screeners at either age. These results align with sex differences observed in full-term, autistic youth. These results suggest ASD screeners may under identify autism in EP youth, particularly females.

Keywords Autism · Preterm · Sex differences · Low birthweight

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Autism spectrum disorder (ASD) is a pervasive neurodevelopmental condition currently diagnosed in one out of every 36 children (Maenner et al., 2023). Historic prevalence rates suggest a male to female ratio of 3.8:1 in autism (Loomes et al., 2017; Maenner et al., 2023), with recent works suggesting the true sex ratio may be closer to 1:1 (Burrows et al., 2022). Reasons for sex differences in prevalence of ASD range from biases in diagnostic instruments (Beggiato et al., 2017) to a distinct female phenotype (Lai et al., 2015), or importantly for the current study, the samples being studied (Burrows et al., 2022). One such group that has not been systematically evaluated for sex differences is individuals born preterm, despite their increased likelihood of receiving an autism diagnosis (Atladóttir et al., 2016). The current paper evaluates sex differences in core autism traits and associated characteristics in extremely preterm (EP) infants later diagnosed with autism from the Extremely Low Gestational Age Newborn (ELGAN) Study.

Infants born preterm have a greater likelihood of developing neurodevelopmental and medical conditions (Fitzgerald et al., 2018). Specific to autism, the likelihood of receiving an autism diagnosis increases as gestational age decreases (Atladóttir et al., 2016), ranging from a ten-fold increase (gestational weeks 23–27) to a two-fold increase (32 weeks+) in likelihood compared to infants born full-term (Atladóttir et al., 2016). Prevalence estimates of autism in preterm infants range from 6 to 8% for EP newborns (Agrawal et al., 2018; Johnson et al., 2010; Joseph et al., 2017), with a recent meta-analysis indicating 7% (Agrawal et al., 2018). These prevalence rates are significantly higher than the national average for full-term infants (~2.7%) (Maenner et al., 2023), and indicate that EP infants may represent a distinct sample in which to evaluate sex differences.

Although EP males are more likely than EP females to be diagnosed with autism (Crump et al., 2021), the sex ratio for autism prevalence in EP infants is *significantly lower* than the sex ratio observed in full-term infants. Estimates suggest a sex ratio of 2:1 (male:female) in EP infants (Johnson et al., 2010; Joseph et al., 2017), which is significantly lower than the 3.8:1 ratio estimated in full-term infants (Maenner et al., 2023). Underlying causes for these sex differences have been well-studied in full-term autistic youth, with limited research in EP samples. Recent reviews suggest restricted and repetitive behaviors (RRBs) are more predictive of a diagnosis in full-term males, whereas subtle differences in social communication, such as greater difficulties with friendships in adolescence, may be more indicative of a diagnosis in full-term females (McFayden et al., 2023). Despite these well-characterized sex differences in full-term youth, only a few studies have investigated sex differences in EP youth. The main findings from these studies include (a) no sex differences in passing/failing autism screening at two years of age (Wong et al., 2014), (b) autistic EP males have greater social withdrawal and peer difficulties than autistic EP females during childhood and adolescence (Ritchie et al., 2015; Spittle et al., 2009), and (c) autistic EP youth are significantly more likely to be nonverbal than full-term autistic youth, although this pattern was only observed in females, not in males (Bowers et al., 2015). These disparate findings based on varied approaches suggest the need for further investigation of sex differences in autism traits in EP youth.

In the present study, we assessed sex differences between autistic males and females born EP from the ELGAN Study at ages 2- and 10-years. Importantly, the current study evaluated sex differences on gold-standard measures of ASD diagnostic criteria and characteristics, which have yet to be investigated in EP youth. Based on findings among individuals born full-term (McFayden et al., 2023), we predict EP autistic females will show strengths in social communication relative to males, and EP autistic males will show higher reports of RRBs compared to females.

Method

Data Source

The ELGAN Study is an observational study of the risk of structural and functional neurologic disorders in EP infants. During the years 2002–2004, women delivering before 28 weeks' gestation in 11 cities in five U.S. states were invited to enroll in the study. A total of $N = 1506$ infants, born to 1249 mothers, were enrolled and 1198 survived to age 10 years. Among survivors, $n = 1{,}102$ participated in a 2-year assessment (Helderman et al., 2012), and $n = 889$ were evaluated at 10-years. Of these 889 children, 26 were excluded from an autism evaluation ($n = 17$ non-ambulatory, $n = 7$ blind, $n = 2$ severe motor impairment) and an additional six did not complete the autism assessment, resulting in a total sample of 857 children who were assessed for ASD. For detailed autism evaluation procedure, see the Supplementary Material 1. All procedures for this study were approved by the institutional review boards of all participating institutions.

Participants

Of the 857 ELGAN infants who participated in the 10-year ASD assessment, $N = 61$ (20 females) were diagnosed with ASD and comprise the current sample. Infants were born at an average of 25.3 weeks gestation ($SD = 1.24$). Parents identified their child as white (62.3%), Black (29.5%), or another race (8.2%). Mothers were an average of 30.4 years old ($SD = 5.78$), with 32.8% on Medicaid, 63.9% married,

and 37.7% college graduates. Descriptive statistics are presented in Table 1.

Measures

Maternal and Newborn Characteristics

Maternal age, education, marital status, eligibility for government-provided medical care insurance, and racial identity were self-reported at birth. Gestational age and birth weight were defined according to standard procedures described in detail in prior ELGAN publications (Joseph et al., 2017).

2-Year Assessment

Bayley Scales of Infant Development – Second Edition The BSID-2 (Bayley, 1993) is a developmental assessment of mental and motor abilities designed for infants and toddlers. The Mental Development Index (MDI) standardized score was used in the current study as a metric of cognitive developmental level.

Modified Checklist for Autism in Toddlers The M-CHAT (Robins et al., 1999) is a parent-reported screener for ASD for toddlers ages 16–30 months that comprises 23 yes/no questions. Children screen positive for autism if they fail three or more items in total or if they fail two or more out of six critical items (Robins et al., 2001).

10-Year Assessment

Autism Diagnostic Interview–Revised The ADI-R (Lord et al., 1994) is a parent interview that assesses the core domains of verbal and nonverbal communication, reciprocal social interaction, and restricted and repetitive behavior, and classifies ASD based on 30 to 36 ratings, depending on the child's language level. Diagnostic algorithms were used to calculate scores in four domains: Reciprocal Social Interaction, Verbal Communication, Nonverbal Communication, and Restricted and Repetitive Behaviors.

Autism Diagnostic Observation Schedule, Second Version The ADOS-2 (Lord et al., 2000) is a semi-structured, observation protocol in which the examiner interacts with the child to assess social-communication and repetitive behaviors. Module 1, 2, or 3 was administered based on the child's spoken language level at age 10 years. The ADOS-2 generates a Social Affect score, Repetitive and Restricted

Table 1 Demographics

Demographic Variable	Total Sample	Males	Females	*p*-value
	N = 61	*n* = 41	*n* = 20	
Gestational Age (*M, SD*)	25.3 (1.24)	25.3 (1.28)	25.4 (1.17)	0.832
Birth Weight Z-score (*M, SD*)	-0.39 (1.14)	-0.01 (0.89)	-1.18 (1.21)	0.001***
Child Race (*n, %*)				
White	38 (62.3%)	25 (61.0%)	13 (65.0%)	0.839
Black	18 (29.5%)	13 (31.7%)	5 (25.0%)	
Other	5 (8.20%)	3 (7.32%)	2 (10.0%)	
Maternal Age (*M, SD*)	30.4 (5.78)	30.4 (5.24)	30.3 (6.90)	0.939
Maternal Education (*n, %*)				0.718
Less Than High School	8 (13.1%)	4 (9.76%)	4 (20.0%)	
High School Graduate	20 (32.8%)	13 (31.7%)	7 (35.0%)	
Some College	8 (13.1%)	5 (12.2%)	3 (15.0%)	
College Graduate or Above	23 (37.7%)	17 (41.5%)	6 (30.0%)	
Missing	2 (3.28%)	2 (4.88%)	0 (0.00%)	
Medicaid (*n, %*)				1.000
No	40 (65.6%)	27 (65.9%)	13 (65.0%)	
Yes	20 (32.8%)	13 (31.7%)	7 (35.0%)	
Missing	1 (1.64%)	1 (2.44%)	0 (0.00%)	
Maternal Marital Status (*n, %*)				0.590
Married	39 (63.9%)	24 (58.5%)	15 (75.0%)	
Separated or Divorced	3 (4.92%)	3 (7.32%)	0 (0.00%)	
Living together	13 (21.3%)	9 (22.0%)	4 (20.0%)	
Single	6 (9.84%)	5 (12.2%)	1 (5.00%)	

Note. M = Mean, SD = Standard Deviation, *n* = sample size. Birth Weight Z-score reflects birthweight for gestational age. "Other" race comprised Asian, Native American, Mixed Race, or Other Race not represented by the aforementioned categories. ***$p < .001$

Behaviors (RRB) score, and a Calibrated Severity Score (CSS, range = 1–10).

Differential Ability Scales–II (DAS-II) General cognitive ability was assessed with the Differential Ability Scales–II (Elliot, 2008) at age 10 years. Verbal and Nonverbal Reasoning scales ($M = 100$, $SD = 15$) were used in the current study.

IEP Status At the 10-year visit, caregivers were asked to report on whether their child had an individualized education plan (IEP). Their responses were coded as *0 = no IEP* and *1 = currently or previously used an IEP*.

Social Communication Questionnaire- Lifetime The SCQ (Rutter et al., 2003) is a parent-report screener that assesses autism behaviors observed at any time in the child's life. The total raw score (range = 0–39) was used for the current study.

Social Responsiveness Scale The SRS (Constantino & Gruber, 2005) is a parent-report measure that assesses autism-related characteristics in social communication and restricted/repetitive interests and behaviors (termed Autistic Mannerisms) and provides a continuous measure of overall severity. Three summary scores were evaluated: the social communication subscale raw score, the autistic mannerisms subscale raw score, and the SRS total raw score. Raw scores were used as to not pre-adjust for sex differences (Kaat et al., 2021).

Analytic Plan

Descriptive statistics were evaluated to investigate sex differences in demographic variables. Shapiro-Wilks tests for normality were conducted for each sex (M, F) on each variable of interest to evaluate violations of assumptions of normality. Cross-sectional group differences were assessed in the core variables of interest related to autism traits, including broadband/screening measures (SCQ, SRS, M-CHAT), and diagnostic measures (ADOS-2, ADI-R) by either Welch's *t*-tests (continuous, normal), Wilcoxon Signed Rank Tests (continuous, non-normal) or Fisher's Exact tests (categorical). Due to small sample sizes, non-significant *p*-values did not sufficiently distinguish between two interpretation alternatives (e.g., the groups do not differ, or the data are inconclusive; (Dienes, 2016). Therefore, Bayes Factors ($BF_{10;}$ BayesFactor in R (Morey et al., 2022) were calculated to evaluate how well data are predicted by the alternate hypothesis versus the null hypothesis. An additional strength of Bayesian analyses is the conservative nature of the analytic approach that does not require correction for multiple comparisons, which is appropriate for the current investigation (Gelman & Tuerlinckx, 2000). The current Bayesian model assumed the true standardized difference of zero under the null hypothesis and a Cauchy distribution width of 0.707 under the alternative (Rouder et al., 2009). BF_{10} values close to 1 suggest both the null and alternative hypotheses fit the data equally well; values from 1 to 10 suggest some evidence for the alternate hypothesis, 10–30 strong evidence, 30–100 very strong, and 100 + extremely strong evidence for the alternate hypothesis (Dienes, 2016). Analyses were conducted in R v4.1.2.

Results

Descriptive Statistics

Males and females did not differ significantly on maternal demographic variables, including maternal age, education, marital status, insurance, and race as evidenced by *t*-tests and Chi-square ($ps > 0.31$; see Table 1). A significant sex difference was observed in births small for gestational age, wherein females were born at a significantly smaller birthweight (Z=-1.18, $SD = 1.21$) compared to males (Z=-0.01, $SD = 0.89$), t=-3.84, $p = .001$, $BF_{10} = 280.32$. Males and females did not significantly differ at the 2-year assessment on the BSID-2 MDI (M_{males}=66.4, SD_{males}=18.9; $M_{females}$=67.9, $SD_{females}$=24.6), $t(30.07) = 0.23$, $p = .82$, $BF_{10} = 0.29$. Similarly, males and females did not significantly differ on DAS-II verbal (M_{males}=60.9, SD_{males}=27.3; $M_{females}$=65.7, $SD_{females}$=31.2), $t(31.51) = 0.58$, $p = .57$, $BF_{10} = 0.33$, or nonverbal (M_{males}=69.1, SD_{males}=26.1; $M_{females}$=70.2, $SD_{females}$=23.8), $t(38.38) = 0.16$, $p = .87$, $BF_{10} = 0.28$, standard scores at age 10. Despite equivalent cognitive performances between males and females at 2- and 10-years, males were significantly more likely to have an IEP than females, $p = .009$, $BF_{10} = 13.05$, with 100% of males having an IEP compared to 80% of females.

Sex Differences in Autism Characteristics

Means and standard deviations of outcome variables are shown in Table 2. There were no significant sex differences on M-CHAT pass/fail classification at 2-years, $p = .54$, $BF_{10} = 0.76$, or the total number of failed items, $W = 329$, $p = .40$, $BF_{10} = 0.31$. Similarly, at age 10 years, there were no significant sex differences on the SCQ total

Table 2 Sex differences in autistic traits

Dependent Measure	Total Sample (M, SD)	Males (M, SD)	Females (M, SD)	T-test (t) or Wilcoxon (W)	*p*-value	Bayes Factor
	N = 61	*n* = 41	*n* = 20			
MCHAT Number of Failed Items	4.60 (4.16)	4.82 (4.12)	4.20 (4.31)	329.0	0.404	0.312
SCQ Total Score	19.6 (7.51)	20.0 (7.56)	18.9 (7.55)	-0.5171	0.608	0.309
SRS Total Raw Score	90.9 (23.9)	91.1 (26.2)	90.7 (19.4)	370.5	0.882	0.278
SRS Social Communication	17.8 (5.54)	17.6 (5.98)	18.2 (4.70)	0.3974	0.693	0.293
SRS Autistic Mannerisms	17.7 (6.81)	18.1 (7.08)	17.1 (6.39)	-0.4923	0.625	0.305
ADOS-2 Social Affect	11.4 (4.86)	12.4 (4.49)	9.45 (5.07)	0.034	0.034*	2.331^
ADOS-2 RRBs	4.12 (2.04)	4.25 (1.97)	3.85 (2.21)	0.498	0.498	0.340
ADOS-2 CSS	15.9 (5.54)	16.6 (5.53)	14.3 (5.37)	310.0	0.160	0.722
ADI-R Reciprocal Social	20.3 (7.16)	21.2 (6.67)	18.5 (7.96)	300.0	0.160	0.616
ADI-R Nonverbal Communication	9.17 (4.04)	9.85 (3.72)	7.74 (4.41)	273.0	0.081	1.245^
ADI-R Verbal Communication	6.33 (2.44)	6.79 (2.29)	5.33 (2.55)	162.5	0.057	1.392^
ADI-R RRB	4.88 (2.90)	5.55 (2.86)	3.47 (2.48)	-2.8551	0.007**	5.260^^

Note. Shapiro-Wilks tests of normality were conducted for each sex (M,F) on each variable of interest to probe for normality. If normality assumptions were violated, non-parametric Wilcoxon tests (W) are presented. If assumptions of normality were met, t-tests (t) are presented. M = Mean, SD = Standard Deviation, MCHAT = Modified Checklist for Autism in Toddlers, SCQ = Social Communication Questionnaire, SRS = Social Responsiveness Scale, ADOS-2 = Autism Diagnostic Observation Schedule 2nd Edition, ADI-R = Autism Diagnostic Interview, Revised, RRBs = Repetitive/Restricted Behaviors, CSS = Calibrated Severity Score. Repetitive behaviors and restricted interests on the first edition of the SRS were termed "Autistic Mannerisms", explained further in the Method. Bayes Factors can be interpreted as follows: 0.10-0.33 = moderate evidence for the null hypothesis, 0.33 – 1.0 = mild evidence for the null hypothesis, 1.0 = equal evidence for the null and alternate hypotheses, 1.0–3.0 = mild evidence for the alternate hypothesis. * $p < .05$, ** $p < .01$; ^ = $BF_{10} > 1$, ^^ = $BF_{10} > 3$

score, $t(38.46) = -0.52$, $p = .61$, $BF_{10} = 0.31$, SRS total score, $W = 370.5$, $p = .88$, $BF_{10} = 0.28$, SRS social communication, $t(47.52) = 0.40$, $p = .69$, $BF_{10} = 0.29$, or SRS autistic mannerisms, $t(42.37) = -0.49$, $p = .63$, $BF_{10} = 0.31$.

On the diagnostic assessment at 10-years, there was an equal sex distribution across the three ADOS-2 modules, $p = .57$, with the majority receiving a module 3 (70.5%). Scores on the Social Affect domain differed significantly by sex, $t(34.27) = -2.20$, $p = .034$, $BF_{10} = 2.33$, wherein males received a higher score compared to females, indicating greater social affective autism characteristics. There were no significant sex differences on the ADOS-2 RRB domain, $t(34.50) = -0.69$, $p = .50$, $BF_{10} = 0.34$, or the ADOS-2 CSS, $W = 310$, $p = .16$, $BF_{10} = 0.72$. A significant sex difference emerged on ADI-R RRBs, $t(40.52) = -2.86$, $p = .007$, $BF_{10} = 5.26$, wherein males scored significantly higher than females. There was no significant sex difference on ADI-R Reciprocal Social Communication, $W = 300$, $p = .20$, $BF_{10} = 0.62$. Inferential statistics did not reach a-priori alpha levels for the other two ADI-R domains, but Bayesian analyses suggested anecdotal evidence for group differences in Nonverbal Communication, $W = 273$, $p = .08$, $BF_{10} = 1.25$, and Verbal Communication, $W = 162.5$, $p = .06$, $BF_{10} = 1.39$, with males scoring higher than females in both domains.

Discussion

The current study evaluated sex differences in autistic traits in EP autistic youth. Importantly, sex differences were assessed using gold-standard assessment measures, which has not yet been evaluated in EP autistic youth. Sex differences were apparent for ASD assessments conducted at age 10, including ADOS-2 Social Affect (males > females), ADI-R RRB (males > females), and ADI-R Verbal and Nonverbal scores, supported by Bayesian estimates (males > females). In contrast, no significant differences emerged on measures of cognition or autism characteristics at 2- (BSID-2, MCHAT) or 10-years (DAS, SCQ, SRS). The resulting group differences between males and females were not consistent across measures, and thus may point to measurement variance or test performance differences in this specific population of extremely low gestational age newborns later diagnosed with autism.

These results are consistent with previous sex differences observed in full-term autistic youth. Research with full-term samples (McFayden et al., 2023) has demonstrated more pronounced autistic characteristics in males, especially RRBs (Kaat et al., 2021; Knutsen et al., 2019; McFayden et al., 2019; Ratto et al., 2018), argued to be more representative of an ASD diagnosis in males compared to females (Hiller et al., 2014). The current study replicated full-term research and evidenced that EP males present with more RRBs than females; a finding that has not been previously reported in the EP literature. In the present study, males also showed more childhood social difficulties than females.

This finding, captured from gold-standard assessments, extends previous research suggesting EP males demonstrate more friendship difficulties compared to females (Spittle et al., 2009). These findings echo full-term studies involving both naturalistic (Dean et al., 2017; Hiller et al., 2014) and standardized measures of social abilities (Dillon et al., 2021) suggesting a female advantage. Importantly, females appear to demonstrate greater social difficulty in later childhood or early adolescence, as social pressures increase in later development (Bargiela et al., 2016). Thus, our findings, suggesting stronger social skills in females, may not persist throughout adolescence, warranting further research beyond the 10-year mark.

The lack of observed sex differences in the ASD screener and quantitative trait measures also supports and extends previous literature with both EP and full-term samples. Previous research with EP autistic youth reported an equal proportion of males and females score above threshold on autism screeners at 2-years (Wong et al., 2014), which has been attributed to an overall high number of EP infants screening positive for ASD due to developmental differences such as delayed motor skills (Guy et al., 2015; Limperopoulos et al., 2008; Moore et al., 2012). However, in the current sample, only half of autistic individuals failed the M-CHAT at 2-years (45% females, 51% males), suggesting the M-CHAT was not sensitive enough to detect nearly half the sample that was later diagnosed with ASD. Furthermore, the SCQ and SRS conducted at 10-years also revealed no significant sex differences, which should be more robust to developmental differences observed earlier in life. Importantly, the group averages for autistic males and females on the SCQ and SRS did exceed clinical thresholds and cut points, suggesting these measures are detecting atypicalities in social responsiveness, but are not elucidating sex differences akin to other measures in this population.

Of note, the only demographic sex difference in the current sample was small for gestational age (SGA), wherein autistic EP females were significantly smaller than males. This finding warrants discussion, as SGA has been linked to elevated likelihood of ASD with and without intellectual disability (Abel et al., 2013; Joseph et al., 2017). Interestingly, despite females in the current sample being smaller than males, females still scored lower on measures of ASD characteristics, suggesting lower prevalence and interference of autistic characteristics, and equivalently on cognitive measures, suggesting no deleterious effect of SGA on intellectual abilities. These results suggest that although SGA is a risk factor for ASD, especially in the case of intellectual disability (Abel et al., 2013), 10-year-old females may show a protective effect against this previously-established relationship.

With all studies, the current results should be interpreted considering limitations. The current sample size is small, with unbalanced cell sizes. Bayesian estimates were used mitigate these limitations, to avoid Type II errors due to multiple comparisons, and to enhance detection of possible sex differences for future research. Future studies with larger groups spanning multiple developmental periods may reveal smaller, undetected sex differences.

Conclusion

The current study evaluated a well-characterized sample of autistic youth born EP followed from birth through age 10, using gold-standard screening and diagnostic measures. To our knowledge, this is the first study to evaluate sex differences in autistic traits using these well-validated measures in EP youth, with implications for ASD screening and identification, especially in females. Sex differences were apparent for some measures, but not all. Males showed higher parent-reported and clinician-observed autistic characteristics across social affective (ADOS-2) and RRB domains (ADI-R) than females; however, no differences were observed on measures of cognition or autistic traits at 2- (BSID-2, MCHAT) or 10-years (DAS, SCQ, SRS). The sex differences we observed were consistent with/replicated those found among full-term youth.

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Data Availability Data is available upon request from the authorship team.

Declarations

Competing interests The authors have no relevant financial or non-financial interests to disclose.

Ethics Approval and Consent to Participate Informed consent was obtained from all research participants. The current manuscript's procedures were approved by multiple IRB sites from participating institutions.

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