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Comparing Autism Phenotypes in Children Born Extremely Preterm and Children Born at Term

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Abstract

Children born preterm are at increased risk for autism spectrum disorder (ASD). There is limited knowledge about whether ASD phenotypes in children born preterm differ from children born at term. The objective of this study was to compare ASD core symptoms and associated characteristics among extremely preterm (EP) and term-born children with ASD. EP participants (n=59) from the Extremely Low Gestational Age Newborn Study who met diagnostic criteria for ASD at approximately 10 years of age were matched with term-born participants from the Simons Simplex Collection on age, sex, spoken language level, and nonverbal IQ. Core ASD symptomatology was evaluated with the Autism Diagnostic Interview-Revised (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS). Developmental milestones, anthropometrics, seizure disorder, and psychiatric symptoms were also investigated. The EP group had lower parent-reported symptom scores on ADI-R verbal communication, specifically stereotyped language, and restricted, repetitive behaviors. There were no between-group differences on ADI-R nonverbal communication and ADI-R reciprocal social interaction nor with direct observation on the ADOS-2. The EP group was more likely to have delayed speech milestones and lower

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physical growth parameters. Results from female-only analyses were similar to those from whole-group analyses. In sum, behavioral presentation was similar between EP and IQ- and sex-matched term-born children assessed at age 10 years, with the exception of less severe retrospectively reported stereotyped behaviors, lower physical growth parameters, and increased delays in language milestones among EP-born children with ASD.

Lay Abstract

Children born extremely preterm (EP) are at high risk for ASD, but there is lack of information on behavioral and other characteristics in this population. We examined symptom profiles and other characteristics of EP-born compared to term-born children and found that symptoms and associated characteristics were generally similar, with some exceptions. Increased knowledge of the characteristics of EP-born children may advance earlier detection and remediation of ASD in this population.

Keywords

Autism spectrum disorder; preterm birth; phenotypes; sex; Autism Diagnostic Interview-Revised; Autism Diagnostic Observation Schedule

INTRODUCTION

Autism spectrum disorder (ASD) is defined by deficits in social communication and interaction and the presence of restricted, repetitive behaviors (American Psychiatric Association, 2013). ASD is an early onset neurodevelopmental disorder highly heterogeneous in its presentation and with a multifactor etiology, including a strong genetic component as well as environmental risk factors, including preterm birth (Lyall et al., 2017). Various associated features have been associated with ASD, including increased head circumference (Sacco et al., 2015), motor deficits (Licari et al., 2020), seizure disorder (El Achkar & Spence, 2015), and psychiatric conditions, such as attention deficit hyperactivity disorder (ADHD) (Antshel & Russo, 2019; Levy et al., 2010; Supekar et al., 2017), anxiety, and depression (Gotham et al., 2015; Rosen et al., 2018a). The male-to-female ratio within the general ASD population is approximately 3–4:1 (Loomes et al., 2017), although in cases with moderate to severe cognitive impairment, the male-to-female ratio is about 2:1 (Frazier et al., 2014; Werling & Geschwind, 2013). Prior research on term born children has demonstrated ASD phenotypic differences between males and females (Frazier et al., 2014) as well as between children who have a first degree familial relative with ASD (multiplex) and those who do not (simplex) (Taylor et al., 2015), possibly related to differences in genetic etiology between multiplex and simplex ASD (Leppa et al., 2016).

Preterm newborns are at high risk for neurological damage and developmental dysfunctions, with those born extremely preterm (less than 28 weeks' gestation) having the greatest vulnerability (O'Shea et al., 2009). Previous studies have established that preterm birth is associated with an increased risk of ASD, with a prevalence of approximately 6–7% among those born extremely preterm (Agrawal et al., 2018; Crump et al., 2021; Joseph, O'Shea et al., 2017). Prevalence of ASD in the extremely preterm population is several times greater

than the 1–2% ASD prevalence within the general population (Christensen et al., 2019; Crump et al., 2021), and ASD prevalence increases as gestational age decreases among preterm children (Crump et al., 2021; Kuzniewicz et al., 2014; Xie et al., 2017). Preterm birth is moderately heritable (Wadon et al., 2020), but like ASD is genetically complex (Strauss et al., 2018). Although ASD has a large genetic component, many perinatal risk factors have been identified, including preterm birth (Bai et al., 2019; Muhle et al., 2018). Perinatal factors, such as maternal infection and inflammation, which are associated with both preterm birth (Cappelletti et al., 2016) and increased ASD risk among term-born children (Meltzer & Van De Water, 2017), possibly contribute to the relationship between preterm birth and ASD. Placental and other prenatal abnormalities associated with preterm birth may also increase the risk of ASD (Bokobza et al., 2018; Kratimenos & Penn, 2019).

Less is known about whether ASD symptoms present differently in preterm-born children compared to term-born children. Previous studies have investigated ASD phenotypes in term-born children compared to those born preterm, but these studies have generally examined preterm individuals without distinguishing between gestational age or have focused on late preterm (34 to 36 weeks' gestation) individuals (Bowers et al., 2015; Brayette et al., 2019; Chen et al., 2019; Luu et al., 2020). Additionally, because preterm birth is associated with lower IQ (Joseph et al., 2016; Kerr-Wilson et al., 2012), and lower IQ tends to be associated with increased ASD symptom severity (Bishop et al., 2019; Bishop et al., 2006; Mayes & Calhoun, 2011), IQ differences may have confounded comparisons between preterm and term-born children in prior studies.

In this study, our primary aim was to assess the pattern and severity of core ASD symptoms between 10-year-old children born extremely preterm and at term, matched for sex, spoken language ability, and nonverbal IQ. Our secondary, more exploratory, aim was to compare the same samples on ASD associated features. In addition, we conducted sensitivity analyses to assess possible group phenotypic differences related to female sex and familial multiplicity of ASD as well as parent report biases associated with level of maternal education and the child having a prior ASD diagnosis.

METHODS

Participants

Extremely preterm ASD.—The Extremely Low Gestational Newborn (ELGAN) Study is a prospective multicenter observational study of the risk of structural and functional neurologic disorders in extremely preterm (EP) infants (O'Shea et al., 2009). From 2002–2004, a total of 1,506 infants born before 28 weeks' gestation were asked to enroll in the study at 14 sites in 11 cities in 5 states (Connecticut, Illinois, Massachusetts, Michigan, North Carolina). Of the 1,198 children who survived to age 10 years, 889 individuals participated in a 10-year follow-up assessment conducted from 2012 to 2014. Of these 889 children, 26 were excluded from an assessment of ASD, 17 because of severe motor impairment (non-ambulatory as measured by the Gross Motor Function Classification System) and severe ID (unable to comply with or to achieve basal scores on the DAS-II), 7 for functional blindness, and 2 for severe motor impairment, blindness, and ID combined.

An additional 6 children did not complete the ASD assessment, resulting in a final sample of 857 children who were assessed for ASD.

Term ASD.—The Simons Simplex Collection (SSC) is a cohort of 2418 (304 females) simplex children with ASD, recruited from community clinics across the U.S. from 2008 to 2011 (Fischbach & Lord, 2010) and who met diagnostic cutoffs for ASD on the ADI-R and ADOS. Demographic and phenotypic data on SSC probands from age 9 to 12 years were extracted from the SSC database, version 15.3 (released 8/6/2013). SSC exclusion criteria included delivery at fewer than 36 weeks' gestation (Simons Foundation Autism Research Initiative, 2014).

Procedures for this study were prospectively approved by the institutional review boards of all institutions participating in the ELGAN and SSC studies.

ASD symptom and IQ measures and procedures

Autism Diagnostic Interview-Revised (ADI-R).—The ADI-R is a semi-structured diagnostic interview, in which the primary caregiver is asked about a child's symptoms, both currently and during early development (Le Couteur et al., 2003). Diagnostic algorithms were used to calculate scores, based on "most abnormal" age 4 to 5 years or "ever", in three domains: Reciprocal Social Interaction, Verbal and/or Nonverbal Communication, and Restricted and Repetitive Behaviors (RRB). ADI-R cutoffs for both the EP and term samples were based on the slightly relaxed criteria Collaborative Programs for Excellence in Autism (CPEA) classification criteria (Lord et al., 2012; Risi et al., 2006), which were calculated as follows: meets autism cutoff for social and meets cutoff on either communication or repetitive behavior; meets cutoffs for social and communication or meets cutoff for social and within two points of communication cutoff; or meets cutoff for communication and within two points of social cutoff or within one point of both social and communication cutoffs.

Autism Diagnostic Observation Schedule (*ADOS*).—The ADOS is a well-validated semi-structured observational assessment, in which a trained clinician interacts with the child with developmentally appropriate play-based activities (Lord et al., 2009). ADOS Module 1, 2, or 3 was administered based on the child's spoken language level (no speech/single words, phrase speech, fluent speech). Over the course of the ELGAN and SCC studies, ADOS diagnostic algorithms were revised to the ADOS-2 algorithms (Gotham et al., 2008) to yield separate and more comparable sums of item-level scores across Modules 1, 2, and 3 Social Affect (reflecting the DSM-5 social communication and interaction symptom domain) and Repetitive and Restricted Behaviors (RRB). Calibrated severity scores for SA and RRB were also calculated (Gotham et al., 2009; Hus et al., 2014). For both the EP and term samples, we calculated calibrated severity scores for SA and RRB using the revised ADOS-2 algorithms. None of the ADOS ASD classifications changed as a result of using the ADOS-2 algorithms.

EP ASD Assessment: EP participants were first screened with the Social Communication Questionnaire (Rutter et al., 2003), a parent-report questionnaire that

screens for ASD symptoms. Participants who met a relaxed SCQ screening criteria score of ≥ 11 (n = 106) for individuals considered at high risk were administered the ADI-R. Children who met ADI-R criteria for ASD were administered the Autism Diagnostic Observation Schedule (ADOS). Two children (twins) who met ASD cut-offs on the ADOS-2 did not have ADI-R interview results. Nine children did not meet ADI-R criteria but were assessed with the ADOS because of a parent-reported prior clinical diagnosis of ASD or because the on-site psychologist observed ASD symptoms during the study visit. Four of these children, all of whom were within one or two points of meeting a CPEA ADI-R diagnostic classification, met ADOS-2 ASD cut-offs, and were included in the final sample of 61. Of these 61 children, four were twin pairs. To reduce potential bias from familial overrepresentation in the present study, one member from each twin pair was excluded from analyses, resulting in a final EP ASD sample of 59.

Intellectual ability.—Intellectual ability (IQ) was assessed with the Preschool or the School-Age Differential Ability Scales-II (DAS-II) Verbal (VIQ) and Nonverbal Reasoning (NVIQ) scales (Elliott, 2007). SSC term participants included in the current study who received ADOS Module 1 or 2 were tested “out of level” with the Preschool version of the DAS-II, yielding age-equivalent but not standard IQ scores. For these individuals, age-adjusted nonverbal ratio IQs were calculated by averaging the Preschool DAS-II age-equivalent Matrices and Picture Similarities subtest scores, dividing by the age of the child in months, and multiplying by 100. Verbal ratio IQ scores were similarly calculated based on the Preschool DAS-II Verbal Comprehension and Naming Vocabulary subtest scores. SSC term participants who were administered ADOS Module 3 were assessed with the School-Age version of the DAS-II, from which standard scores were derived. Seven SSC participants were missing VIQ data, 6 of 7 of whom were administered ADOS Module 1 or 2, indicating at most phrase speech at age 10. For these participants we substituted the Peabody Picture Vocabulary Test (PPVT-4) from the SSC database for DAS-II VIQ. All ELGAN participants were administered the School-Age version of the DAS-II regardless of the ADOS Module (1, 2, or 3) they received. Verbal IQ scores were not available for two EP participants.

Sample selection.—Case-control matching was conducted using SPSS version 27. ELGAN EP participants were randomly matched one-to-one to 397 SSC participants between the ages of 9 and 12 years on sex, age, ADOS Module administered (reflecting spoken language level), and nonverbal IQ. For ADOS Module matching, participants who received Modules 1 or 2 were matched as one group due to the low number of participants who had received Module 2 in the EP sample. Participants who received Module 3 (fluent speech) were matched with each other. The match tolerance for nonverbal IQ was set to the smallest value such that all ELGAN individuals were matched with an SSC individual.

Measures of associated characteristics

Gross motor delay/impairment.—For the EP sample, gross motor delay/impairment was defined as having a score greater than 0 on the Gross Motor Function Classification System (GMFCS) (Palisano et al., 2000) at age two years. A score of 0 on the GMFCS indicates no limitations in walking or other lower extremity movements. GMFCS data were

missing for three EP participants. For the term sample, gross motor delay/impairment was defined as inability to walk unaided by 24 months, based on ADI-R Item 5 “First walked unaided”.

Speech/language development.—Delays in single word speech (> 24 months) and phrase speech (> 33 months) for both EP and term samples were assessed based on ADI-R Items 9 and 10, respectively.

Anthropometrics.—Anthropometrics were similarly measured in the EP and term cohorts at age 10 years. Head circumference was taken as the widest occipital-frontal circumference, to the closest millimeter (Chaste et al., 2013; McElrath et al., 2010). BMI values were calculated as weight (in kilograms) divided by the square of height (in meters). Age- and sex-adjusted z-scores for height, weight, and BMI with respect to CDC reference norms were calculated using the CDC LMS method in Microsoft Excel (Centers for Disease Control and Prevention & National Center for Health, 2009; Flegal & Cole, 2013). Head circumference could not be converted to an age-adjusted z-score due to lack of CDC reference data on head circumference after 36 months of age. Anthropometric data were missing for one EP participant.

Seizure Disorder.—For the EP cohort, seizure disorder was identified with a validated seizure screen followed by a structured interview with a study coordinator, then an open-ended interview with a pediatric epilepsy specialist (Douglass et al., 2017). For the term cohort, seizure disorder data were obtained via parent report on the medical history interview. Parents reported whether the participant had a history of afebrile seizures: the code “2” was used to indicate likely seizure disorder, and the code “3” was used to indicate a clinical epilepsy diagnosis. Individuals with a code of “2” or “3” were considered to have seizure disorder.

Psychiatric symptoms.—The Child Symptom Inventory - 4 (CSI-4) (Gadow & Sprafkin, 2002; Sprafkin et al., 2002) was used to assess parent-reported psychiatric symptoms in the ELGAN EP cohort at age 10 years. The CSI-4 Combined ADHD T-score, including symptoms of both inattention and hyperactivity/impulsivity, was used to screen for ADHD. To assess anxiety symptoms, the average of T-scores on anxiety disorder, social phobia, and separation anxiety was used. To assess depression symptoms, the average of T-scores on major depressive disorder and dysthymic disorder was used (Moore et al., 2021). CSI-4 data were missing for three EP participants. For the SSC term cohort, parent-reported age 10 symptoms on the Child Behavior Checklist (CBCL; Achenbach, 2001) yielded CBCL T-scores on the DSM-oriented attention problems, anxiety problems, and affective problems scales, which were used to assess ADHD, anxiety, and depression symptoms, respectively. Higher scores on the CSI-4 and CBCL norm-referenced scales represent higher levels of symptomatology. Prior research has demonstrated convergent and divergent validity among the CSI-4 and CBCL ADHD, anxiety, and depression scales administered (Gadow & Sprafkin, 2002; Sprafkin et al., 2002). T-scores from the CBCL and CSI-4 were dichotomized as less than 65, indicating non-clinical or subclinical symptoms, and 65 or greater, indicating clinically significant symptoms.

Demographics and participant characteristics

Demographics.—Maternal age at birth, maternal marital status, maternal education, and race/ethnicity were obtained from parent report (Table 1). Maternal education data were missing for two EP participants and one term participant.

EP neonatal characteristics.—Among the 59 EP participants, 39 were male and 20 were female, yielding a male:female ratio of 2:1. Nine EP participants (15.3%) were born at 27 weeks gestational age, 25 (42.4%) at 25–26 weeks, and 25 participants (42.4%) at 23–24 weeks. The number of males and females in each stratum of gestational age did not differ ($X^2 = 2.1$, $p = .35$). Birthweight z-scores for gestational age were calculated as the number of standard deviations above or below the median birthweight in a reference birthweight sample (Yudkin et al., 1987). Being small for gestational age (or fetal growth restriction) is considered as a birthweight z-score < −2. Eight participants (13.6%) had a birth weight z-score < −2, six participants (10.2%) had a birth weight z-score between −2 and −1, and 45 participants (76.3%) had a birth weight z-score of −1 or higher. Detailed prenatal, perinatal, and neonatal characteristics of the EP ASD sample are reported by Joseph, Korzeniewski, et al., 2017.

Statistical analyses

Statistical analyses were conducted with SPSS version 27. T-tests and Pearson's chi-square tests were used to evaluate group differences for continuous variables and categorical variables, respectively. In secondary analyses, ELGAN EP participants (n = 7) who were multiplex (reported by parent at age 10 to have a sibling who also met diagnostic criteria for ASD) were excluded, and their SSC term matches were also removed from the sample. Analyses including only female participants (20 ELGAN cases and 20 SSC controls) were conducted because of prior evidence of phenotypic sex differences in term-born children with ASD (Frazier et al., 2014). Finally, analyses comparing ELGAN EP participants with and without a prior diagnosis and different levels of maternal education were conducted. Hypotheses were tested using an alpha of 0.05. Corrections for multiple comparisons were not made to increase sensitivity to possible group differences. Cohen's effect size (d) is reported for all t-tests.

RESULTS

Maternal, demographic, and child neonatal and age 10 characteristics

At the 10-year follow-up, mothers of children in the EP sample had received less education and were less likely to be married/partnered than mothers of children in the term sample (Table 1). There were no group differences in maternal age at birth.

As expected, age and nonverbal IQ did not differ between groups (Table 1). Notably, mean group NVIQ was approximately 2 standard deviations below the normative mean. From the EP and term samples, respectively, 25 and 24 out of 59 participants scored < 70 on nonverbal IQ. From among the 20 females in each group, seven EP and six term participants scored < 70 on nonverbal IQ. Mean verbal IQ was lower among EP relative to term participants. Finally, 21 (36%) of the EP sample did not have a prior clinical diagnosis

of ASD, whereas the term sample was recruited from community clinics based on having a prior clinical diagnosis or having been referred for an assessment of ASD.

ASD symptoms

On the ADI-R (Table 2), among participants with sufficient spoken language to be assessed for verbal communication, the EP group (n = 46) had significantly lower mean scores than the term group (n = 51), reflecting decreased symptom severity. The ADI-R verbal communication subdomain is comprised of items indicating failure to initiate or sustain conversational interchange and stereotyped, repetitive, or idiosyncratic speech. When these two subscores were analyzed separately, only stereotyped speech showed significant group differences. Because there were five fewer EP participants with ADI-R verbal communication data, we conducted follow-up analyses including only the 46 EP participants with ADI-R verbal communication ratings and their 46 term control matches. These analyses yielded similar results, with lower scores among the EP group (M = 3.0) relative to the term group (M = 4.5) in the ADI-R stereotyped speech domain, $t = 4.0$, $p < .001$, $d = .8$. The EP group also had significantly lower mean scores in the ADI-R RRB domain. In contrast, there were no group differences in the ADI-R reciprocal social interaction or nonverbal communication symptom domains. There were no group differences on ADOS-2 social affect or repetitive and restricted domain scores or calibrated severity scores. In addition, group comparisons of those scoring in the mild, moderate, and severe ranges on the ADOS CSS did not differ in social affect or RRBs scores (Supplementary Table 3).

We conducted additional analyses to address the possibility that decreased stereotyped speech among EP participants was due to lower (i.e., potentially insufficient) language ability. In an ANCOVA covarying for ADI-R onset of phrase speech, $F = 0.9$, $p = .34$, group differences in ADI-R stereotyped speech remained statistically significant, $F = 46.7$, $p < .001$. Similarly, in an ANCOVA covarying for verbal IQ, $F= 2.9$, $p = .09$, group differences in ADI-R stereotyped speech remained statistically significant, $F = 40.7$, $p < .001$. Finally, when scores for ADI-R Item 39 Verbal Rituals, potentially affected by language level, were removed from the ADI-R RRB algorithm total, the difference between the EP (M = 4.4) and term (M = 6.1) groups remained, $t = 4.1$, $p < .001$.

ASD associated features

A greater proportion of the EP group did not develop single-word speech until after 24 months and phrase speech until after 36 months, although a considerable proportion of the term cohort also had delayed speech milestones (Table 3). There were no group differences in delay of gross motor milestones at age 2 years. At age 10 years, the EP group had significantly lower mean height and weight z-scores. There were no group differences in BMI z-scores. The EP group had significantly smaller mean head circumference. There were no group differences in the frequency of seizure disorders at the age of 10 years. There were no group differences in the prevalence of ADHD symptoms. Among EP participants, 16.1% exhibited clinical levels of anxiety, compared to 47.5% of the term sample. The EP group also had a lower percentage of individuals who met the clinical threshold for depression symptoms.

Sensitivity analyses

Simplex probands only.—Secondary analyses were conducted excluding all multiplex individuals (having a first-degree relative with ASD) from the EP sample, as well as their term matches (Supplementary Tables 1 and 2). All significant group differences observed in primary analyses were maintained in secondary analyses. No additional significant group differences emerged.

Females only.—EP females had significantly lower ADI-R verbal communication scores (Table 4). As with the overall sample, this group difference was primarily driven by a lower score in the stereotyped language domain. Because there were four fewer EP participants with ADI-R verbal communication data, we repeated the analyses including only the 15 EP female participants with ADI-R verbal communication ratings and their 15 female term control matches. These analyses yielded similar results, with lower scores among EP females (M = 2.1) relative to the term group (M = 5.1) in the ADI-R stereotyped speech domain, $t(28) = 4.2$, $p < .001$, $d = 1.5$. EP females also had significantly lower ADI-R RRB domain scores. There were no significant differences between EP and term females on ADOS-2 scores. EP females had significantly smaller average head circumference and shorter height than term females (Table 5). All other comparisons between EP females and term females showed no significant group differences.

Prior clinical diagnosis.—We conducted analyses to examine whether a prior clinical diagnosis was associated with differences in ADI-R scores within the ELGAN EP group (Table 6). The EP subgroup without a prior ASD diagnosis had lower nonverbal IQ, and lower ADI-R reciprocal social interaction, verbal communication, and RRB scores. When the verbal communication subdomains were analyzed separately, only stereotyped language showed significant differences.

Maternal education and marital/partnered status.—We also conducted analyses to examine whether level of maternal education and marital/partnered status were associated with differences in ASD symptoms on the ADI-R given the differences in these variables between the EP and term ASD groups. Independent-samples t-tests conducted separately for each group with maternal education (high school vs. further formal education) as the independent variable did not show significant differences in ADI-R scores for reciprocal social interaction, nonverbal and verbal communication, including the stereotype language subdomain, or RRBs in either the EP or term groups. In addition, chi-square analyses of associations between maternal education (high school vs. further formal education) and meeting study criteria for ADHD, anxiety, or depression were not significant for either group. Parallel analyses were conducted comparing mothers who were married/partnered versus single, and all were similarly null.

DISCUSSION

We examined similarities and differences in ASD symptoms and associated characteristics between children born extremely preterm and at term who were matched on age, sex, spoken language and nonverbal IQ. The EP and term groups showed similar symptom

profiles via direct observation with the ADOS-2 at age 10 years and retrospective parent report of early childhood symptoms in total group analyses, and analyses excluding multiplex EP participants and including only females. The one exception was that parents of EP participants reported fewer restricted and repetitive behaviors, including stereotyped language, on the ADI-R. EP participants were more likely to be delayed in early speech/language milestones and had decreased physical growth parameters at age 10 years.

ASD symptoms

Whereas the EP and term groups did not differ on ADOS-2 scores, based on direct clinical observation at age 10 years, there were some differences between groups on retrospectively parent-reported symptoms on the ADI-R. These differences were in parent-report of verbal communication, specifically the use of stereotyped language, and in restricted, repetitive behaviors, for which the EP group exhibited lower scores. A possible explanation for the discrepancy in parent-report findings from the ADI-R and ADOS-2 clinical observation findings is the difference in recruitment strategies between the ELGAN EP and SSC term cohorts. SSC participants were recruited based on having a prior clinical diagnosis or suspicion of ASD (Fischbach & Lord, 2010). In contrast, among ELGAN participants, who were enrolled in the ELGAN Study at birth based on gestational age, only 64% (n=38) had received a clinical diagnosis at age 10 years. Because ADI-R diagnostic algorithm scores are based on whether the symptom was present at ages 4–5 or whether the child had ever exhibited a given symptom, particularly stereotyped language and other repetitive and restricted behaviors, parents of children with prior ASD diagnoses may have been more primed to identify symptoms. We investigated this possibility and found that parents of EP children were more likely to report these symptoms when their child had a prior clinical diagnosis. Notably, EP participants without a prior clinical ASD diagnosis scored significantly lower on NVIQ than those with a prior diagnosis. Given that lower IQ is associated with medical conditions and more severe developmental and behavioral difficulties in children with EP, these factors may have obscured the presence of restricted and repetitive behaviors from parents' and providers' point of view. Although no group differences in RRBs were found via direct ADOS-2 observation at age 10, the ADOS provides a relatively limited sampling of RRBs. Thus, whether the EP ASD symptom phenotype differs with regard to the presence of RRBs requires further investigation.

Differences in ASD symptomatology between term- and preterm-born children have previously been explored in the literature, albeit with younger children. Furthermore, previous studies have focused mainly on moderate to late preterm-born individuals. The lack of differences on ADOS-2 domain scores is consistent with previous studies conducted with children aged 2 years and 5 years (Chen et al., 2019; Luu et al., 2020). Brayette et al. (2019) did not find differences in ASD symptomatology between term and moderate-to-late preterm groups on clinician-report measures, but this study did not match groups on IQ. Chen et al. (2019) found significant differences only in ADI-R reciprocal social interaction, whereas we found differences on the ADI-R in verbal communication, specifically stereotyped language, and RRBs, but not in reciprocal social interaction.

ASD associated characteristics

Significant differences were found in developmental speech/language milestones, physical growth characteristics, as well as anxiety and depression symptoms. The EP sample had greater rates of delayed acquisition of single word speech (> 24 months) and phrase speech (> 33 months). However, the EP and term groups did not differ in rates of gross motor delay/impairment at age 2. Findings on language and motor developmental milestones are also consistent with previous literature. Among national cohorts of EP children, there are greater rates of language and motor delays (Månsson & Stjernqvist, 2014; Serenius et al., 2016). Although there were no differences in motor developmental delay prevalence, this may be due to our use of a relatively gross measure of walking unaided at age 24 months and indicates the need for more comprehensive and sensitive measures of motor function.

At age 10, the EP group had lower height z-scores, weight z-scores, and head circumference, but the two groups did not differ on BMI z-scores. These group differences are consistent with previous findings that heights and weights of EP-born children are consistently lower than those of term-born peers from early childhood to late adolescence (Ni et al., 2021; Roberts et al., 2013). Mean differences in raw HC were similar to those reported for a UK cohort of children born extremely preterm (Ni et al., 2021). The difference in raw HC corresponded to a z-score difference of 1.05 standard deviations, based on UK normative data (Ni et al., 2021). However, it should be noted that while head circumference is positively associated with neurodevelopmental outcomes within the general population (Jaekel et al., 2019), larger head circumference is associated with greater ASD symptom severity among individuals with simplex ASD (Chaste et al., 2013).

The EP and term groups did not differ on assessments of seizure disorder or ADHD symptoms. These results did not change when EP multiplex individuals and their term matches were excluded. Children and adolescents with ASD are known to be at increased risk for seizure disorder. Compared to a prevalence of 0.6–1% within the general population, between 2–26% of individuals with ASD have a co-occurring seizure disorder (El Achkar & Spence, 2015; Robertson et al., 2015). In particular, individuals with co-occurring ASD and ID are at greater risk for seizure disorder, although it should be noted that ID alone also is a risk factor for seizure disorder (El Achkar & Spence, 2015; Jokiranta et al., 2014).

Previous studies have estimated that between 40–70% of children and adolescents with ASD have co-occurring ADHD (Antshel & Russo, 2019; Levy et al., 2010; Supekar et al., 2017). Whereas the EP and term groups had similar rates of ADHD symptoms, the term group had higher rates of depression and particularly anxiety symptoms than the EP group.

One possibility is that the CBCL, which was used to assess psychiatric symptoms in the SSC term group, was more sensitive to anxiety and depression symptoms than the CSI-4, which was used to assess psychiatric symptoms in the ELGAN cohort. Prospective research using the same measures to assess co-occurring psychiatric symptoms and disorders is needed to inform diagnostic assessment and remediation of ASD in preterm as well as term born children (Rosen et al., 2018).

Results from female-only analyses were also similar to findings from the total sample. Differences in ADI-R verbal communication and repetitive and restricted behavior domains, height z-scores, head circumference, and anxiety symptoms persisted from the primary analyses. However, in contrast to primary and simplex-only analyses, there were no differences in speech developmental milestones, weight z-scores, or depression symptoms.

Study strengths and limitations

Strengths of this study include use of gold-standard ASD diagnostic assessments, the ADI-R and ADOS-2, as well as matching on multiple potential confounders, including age, sex, and nonverbal IQ. Although the sample size of this study was relatively small, it was larger or similar to previous studies (Bowers et al., 2015; Brayette et al., 2019; Chen et al., 2019; Luu et al., 2020) that investigated ASD phenotypes in children born preterm versus born at term. There is a possibility that some of the null findings in the female-only analyses resulted from decreased statistical power from reduced sample size.

A weakness of this study was that half of the EP participants with ASD had IQs in the impaired range, given their extremely low gestational age, limiting the generalizability of our findings to ASD individuals born less preterm. Additional weaknesses included the lack of matching for maternal education, married/partnered status and race and the use of different measures to assess the ELGAN EP and SSC term cohorts for ASD associated characteristics, including motor milestones, seizure diagnosis, and psychiatric symptoms. Finally, estimation of familial ASD multiplicity differed between groups.

CONCLUSIONS

EP- and term-born children showed similar ASD symptom profiles, apart from parent-reported repetitive and restricted behaviors, which were less frequent among EP participants, although there were no group differences in restricted and repetitive behavior observed directly at age 10 years. Differences in associated characteristics included relatively delayed speech/language milestones and decreased physical growth parameters at age 10 years among EP-born individuals, which are both relatively common among EP-born individuals. Our findings indicate that children born extremely preterm are at risk for standardly defined ASD that is highly similar to that found among their term-born peers and have both clinical and research implications. First, children born preterm require enhanced surveillance and remediation of ASD-related behaviors. Second, evidence indicates potential overlap in genetic and environmental risk factors for preterm birth and ASD. The confluence of these factors will only be detectable in large samples that include the entire range of children born preterm.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

Achenbach TM (2001). Manual for ASEBA school-age forms & profiles. University of Vermont, Research Center for Children, Youth & Families.

Agrawal S, Rao SC, Bulsara MK, & Patole SK (2018). Prevalence of autism spectrum disorder in preterm infants: A meta-Analysis. Pediatrics, 142(3), 20180134. 10.1542/peds.2018-0134

American Psychiatric Association. (2013). Diagnostic and Statistical Manual of Mental Disorders.

Antshel KM, & Russo N (2019). Autism Spectrum Disorders and ADHD: Overlapping Phenomenology, Diagnostic Issues, and Treatment Considerations. 10.1007/s11920-019-1020-5

Bai D, Yip BHK, Windham GC, Sourander A, Francis R, Yoffe R, Glasson E, Mahjani B, Suominen A, Leonard H, Gissler M, Buxbaum JD, Wong K, Schendel D, Kodesh A, Breshnahan M, Levine SZ, Parner ET, Hansen SN, … Sandin S (2019). Association of genetic and environmental factors with autism in a 5-country cohort. JAMA Psychiatry, 76(10), 1035–1043. 10.1001/jamapsychiatry.2019.1411 [PubMed: 31314057]

Bishop S, Farmer C, Kaat A, Georgiades S, Kanne S, & Thurm A (2019). The need for a developmentally based measure of social communication skills. Journal of the American Academy of Child and Adolescent Psychiatry, 58(6), 555–560. 10.1016/j.jaac.2018.12.010 [PubMed: 31130206]

Bishop SL, Richler J, & Lord C (2006). Association between restricted and repetitive behaviors and nonverbal IQ in children with Autism Spectrum Disorders. Child Neuropsychology, 12(4–5), 247–67. 10.1080/09297040600630288 [PubMed: 16911971]

Bokobza C, Van Steenwinckel J, Mani S, Mezger V, Fleiss B, & Gressens P (2018). Neuroinflammation in preterm babies and autism spectrum disorders. Pediatric Research, 85(2), 155–165. 10.1038/s41390-018-0208-4 [PubMed: 30446768]

Bowers K, Wink LK, Pottenger A, McDougle CJ, & Erickson C (2015). Phenotypic differences in individuals with autism spectrum disorder born preterm and at term gestation. Autism, 19(6), 758–763. 10.1177/1362361314547366 [PubMed: 25192860]

Brayette M, Saliba E, Malvy J, Blanc R, Ponson L, Tripi G, Roux S, & Bonnet-Brilhault F (2019). Incomplete gestation has an impact on cognitive abilities in autism spectrum disorder. Journal of Autism and Developmental Disorders, 49(10), 4339–4345. 10.1007/s10803-019-04105-x [PubMed: 31267284]

Cappelletti M, Della Bella S, Ferrazzi E, Mavilio D, & Divanovic S (2016). Inflammation and preterm birth. Journal of Leukocyte Biology, 99(1), 67–78. 10.1189/jlb.3mr0615-272rr [PubMed: 26538528]

Centers for Disease Control and Prevention & National Center for Health. (2009). Growth Charts - Percentile Data Files with LMS Values. https://www.cdc.gov/growthcharts/percentile_data_files.htm

Chaste P, Klei L, Sanders SJ, Murtha MT, Hus V, Lowe JK, Willsey AJ, Moreno-De-Luca D, Yu TW, Fombonne E, Geschwind D, Grice DE, Ledbetter DH, Lord C, Mane SM, Lese Martin C, Martin DM, Morrow EM, Walsh CA, … Kim SJ (2013). Adjusting head circumference for covariates in autism: clinical correlates of a highly heritable continuous trait. Biological Psychiatry, 74(8), 576–584. 10.1016/J.BIOPSYCH.2013.04.018 [PubMed: 23746936]

Chen LW, Wang ST, Wang LW, Kao YC, Chu CL, Wu CC, Hsieh YT, Chiang CH, & Huang CC (2019). Behavioral characteristics of autism spectrum disorder in very preterm birth children. Molecular Autism, 10(1), 1–9. 10.1186/s13229-019-0282-4 [PubMed: 30647876]

Christensen D, Maenner M, Bilder D, Constantino J, Daniels J, Durkin M, Fitzgerald R, Kurzius-Spencer M, Pettygrove S, Robinson C, Josephine S, White T, Zahorodny W, Pazo K, & Dietz P (2019). Prevalence and characteristics of autism spectrum disorder among children aged 4 years — Early Autism and Developmental Disabilities Monitoring Network, Seven Sites, United States, 2010, 2012, and 2014. MMWR Surveillance Summaries, 68(2), 1–19. 10.15585/mmwr.ss6802a1

Crump C, Sundquist J, & Sundquist K (2021). Preterm or early term birth and risk of autism. Pediatrics, 148(3). 10.1542/peds.2020-032300

Douglass LM, Heeren TC, Stafstrom CE, DeBassio W, Allred EN, Leviton A, O'Shea TM, Hirtz D, Rollins J, & Kuban K (2017). Cumulative Incidence of seizures and epilepsy in ten-year-old children born before 28 weeks' gestation. Pediatric Neurology, 73, 13–19. 10.1016/j.pediatrneurol.2017.05.009 [PubMed: 28619377]

El Achkar CM, & Spence SJ (2015). Clinical characteristics of children and young adults with co-occurring autism spectrum disorder and epilepsy. In Epilepsy and Behavior (Vol. 47, pp. 183–190). Academic Press Inc. 10.1016/j.yebeh.2014.12.022

Elliott CD (2007). Differential Ability Scales - Second Edition (DAS-II). San Antonio, TX: The Psychological Corporation.

Fischbach GD, & Lord C (2010). The Simons simplex collection: A resource for identification of autism genetic risk factors. Neuron, 68(2), 192–195. 10.1016/j.neuron.2010.10.006 [PubMed: 20955926]

Flegal KM, & Cole TJ (2013). Construction of LMS parameters for the Centers for Disease Control and Prevention 2000 growth charts. National Health Statistics Reports, 63.

Frazier TW, Georgiades S, Bishop SL, & Hardan AY (2014). Behavioral and cognitive characteristics of females and males with autism in the Simons Simplex Collection. Journal of the American Academy of Child and Adolescent Psychiatry, 53(3), 329–340. 10.1016/j.jaac.2013.12.004 [PubMed: 24565360]

Gadow KD, & Sprafkin J (2002). Child Symptom Inventory 4: Screening and Norms Manual. Tony Brook, NY: Checkmate Plus.

Gotham K, Brunwasser SM, & Lord C (2015). Depressive and anxiety symptom trajectories from school age through young adulthood in samples with autism spectrum disorder and developmental delay. Journal of the American Academy of Child and Adolescent Psychiatry, 54(5), 369–376. 10.1016/j.jaac.2015.02.005 [PubMed: 25901773]

Gotham K, Pickles A, & Lord C (2009). Standardizing ADOS scores for a measure of severity in autism spectrum disorders. Journal of Autism and Developmental Disorders, 39(5), 693–705. 10.1007/s10803-008-0674-3 [PubMed: 19082876]

Gotham K, Risi S, Dawson G, Tager-Flusberg H, Joseph R, Carter A, Hepburn S, McMahon W, Rodier P, & Hyman SL (2008). A replication of the Autism Diagnostic Observation Schedule (ADOS) revised algorithms. Journal of the American Academy of Child & Adolescent Psychiatry, 47(6), 642–651. [PubMed: 18434924]

Hus V, Gotham K, & Lord C (2014). Standardizing ADOS domain scores: Separating severity of social affect and restricted and repetitive behaviors. Journal of Autism and Developmental Disorders, 44(10), 2400–2412. 10.1007/s10803-012-1719-1 [PubMed: 23143131]

Jaekel J, Sorg C, Baeuml J, Bartmann P, & Wolke D (2019). Head growth and intelligence from birth to adulthood in very preterm and term born individuals. Journal of the International Neuropsychological Society, 25(1), 48–56. 10.1017/S135561771800084X [PubMed: 30426909]

Jokiranta E, Sourander A, Suominen A, Timonen-Soivio L, Brown AS, & Sillanpää M (2014). Epilepsy among children and adolescents with autism spectrum disorders: a population-based study. Journal of Autism and Developmental Disorders, 44(10), 2547–2557. 10.1007/s10803-014-2126-6 [PubMed: 24803367]

Joseph RM, Korzeniewski SJ, Allred EN, O'Shea TM, Heeren T, Frazier JA, Ware J, Hirtz D, Leviton A, Kuban K, Coster T, Henson B, Wilson R, McGhee K, Lee P, Asgarian A, Sadhwani A, Perrin E, Neger E, … Vogt K (2017). Extremely low gestational age and very low birthweight for

gestational age are risk factors for autism spectrum disorder in a large cohort study of 10-year-old children born at 23–27 weeks' gestation. American Journal of Obstetrics and Gynecology, 216(3), 304.e1–304.e16. 10.1016/j.ajog.2016.11.1009

Joseph RM, O'Shea TM, Allred EN, Heeren T, Hirtz D, Jara H, Leviton A, & Kuban KCK (2016). Neurocognitive and academic outcomes at age 10 years of extremely preterm newborns. Pediatrics, 137(4). 10.1542/peds.2015-4343

Joseph RM, O'Shea TM, Allred EN, Heeren T, Hirtz D, Paneth N, Leviton A, & Kuban KCK (2017). Prevalence and associated features of autism spectrum disorder in extremely low gestational age newborns at age 10 years. Autism Research, 10(2), 224–232. 10.1002/aur.1644 [PubMed: 27220677]

Kerr-Wilson CO, MacKay DF, Smith GCS, & Pell JP (2012). Meta-analysis of the association between preterm delivery and intelligence. Journal of Public Health, 34(2), 209–216. 10.1093/pubmed/fdr024 [PubMed: 21393308]

Kratimenos P, & Penn AA (2019). Placental programming of neuropsychiatric disease. Pediatric Research, 86(2),157–164. 10.1038/s41390-019-0405-9 [PubMed: 31003234]

Kuzniewicz MW, Wi S, Qian Y, Walsh EM, Armstrong MA, & Croen LA (2014). Prevalence and neonatal factors associated with autism spectrum disorders in preterm infants. Journal of Pediatrics, 164(1), 20–25. 10.1016/j.jpeds.2013.09.021 [PubMed: 24161222]

Le Couteur A, Lord C, & Rutter M (2003). The Autism Diagnostic Interview-Revised (ADI-R). Los Angeles, CA: Western Psychological Services.

Leppa VM, Kravitz SN, Martin CL, Andrieux J, le Caignec C, Martin-Coignard D, DyBuncio C, Sanders SJ, Lowe JK, Cantor RM, & Geschwind DH (2016). Rare inherited and de novo cnvs reveal complex contributions to ASD risk in multiplex families. American Journal of Human Genetics, 99(3), 540–554. 10.1016/j.ajhg.2016.06.036 [PubMed: 27569545]

Levy SE, Giarelli E, Lee LC, Schieve LA, Kirby RS, Cunniff C, Nicholas J, Reaven J, & Rice CE (2010). Autism spectrum disorder and co-occurring developmental, psychiatric, and medical conditions among children in multiple populations of the United States. Journal of Developmental and Behavioral Pediatrics, 31(4), 267–275. 10.1097/DBP.0b013e3181d5d03b [PubMed: 20431403]

Licari MK, Alvares GA, Varcin K, Evans KL, Cleary D, Reid SL, Glasson EJ, Bebbington K, Reynolds JE, Wray J, & Whitehouse AJO (2020). Prevalence of motor difficulties in autism spectrum disorder: analysis of a population-based cohort. Autism Research, 13(2), 298–306. 10.1002/aur.2230 [PubMed: 31625694]

Loomes R, Hull L, & Mandy WPL (2017). What is the male-to-female ratio in autism spectrum disorder? A systematic review and meta-analysis. Journal of the American Academy of Child and Adolescent Psychiatry, 56(6), 466–474. 10.1016/j.jaac.2017.03.013 [PubMed: 28545751]

Lord C, Petkova E, Hus V, Gan W, Lu F, Martin DM, Ousley O, Guy L, Bernier R, Gerdts J, Algermissen M, Whitaker A, Sutcliffe JS, Warren Z, Klin A, Saulnier C, Hanson E, Hundley R, Piggot J, … Risi S (2012). A multisite study of the clinical diagnosis of different autism spectrum disorders. Archives of General Psychiatry, 69(3), 306–313. 10.1001/archgenpsychiatry.2011.148 [PubMed: 22065253]

Lord C, Rutter M, DiLavore PC, Risi S, Gotham K, & Bishop S (2009). Autism diagnostic observation schedule. Los Angeles, CA: Western Psychological Services.

Luu J, Jellett R, Yaari M, Gilbert M, & Barbaro J (2020). A comparison of children born preterm and full-term on the autism spectrum in a prospective community sample. Frontiers in Neurology, 11, 1643. 10.3389/fneur.2020.597505

Lyall K, Croen L, Daniels J, Fallin MD, Ladd-Acosta C, Lee BK, Park BY, Snyder NW, Schendel D, Volk H, Windham GC, & Newschaffer C (2017). The changing epidemiology of autism spectrum disorders. Annual Review of Public Health, 38, 81–102. 10.1146/annurev-publhealth-031816-044318

CDC (2014). Prevalence of autism spectrum disorder among children aged 8 years - autism and developmental disabilities monitoring network, 11 sites, United States, 2010. MMWR Surveillance Summaries, 63(2), 1–21.

Månsson J, & Stjernqvist K (2014). Children born extremely preterm show significant lower cognitive, language and motor function levels compared with children born at term, as measured by the Bayley-III at 2.5 years. Acta Paediatrica, 103(5), 504–511. 10.1111/apa.12585 [PubMed: 24494838]

Mayes SD, & Calhoun SL (2011). Impact of IQ, age, SES, gender, and race on autistic symptoms. Research in Autism Spectrum Disorders, 5(2), 749–757. 10.1016/j.rasd.2010.09.002

McElrath TF, Allred EN, Kuban K, Hecht JL, Onderdonk A, O'Shea TM, Paneth N, & Leviton A (2010). Factors associated with small head circumference at birth among infants born before the 28th week. American Journal of Obstetrics and Gynecology, 203(2), 138.e1–138.e8. 10.1016/j.ajog.2010.05.006

Meltzer A, & Van De Water J (2017). Meltzer, A., & Van de Water, J. (2017). The role of the immune system in autism spectrum disorder. Neuropsychopharmacology, 42(1), 284–298. 10.1038/npp.2016.158 [PubMed: 27534269]

Moore PS, Mokrova I, Frazier JA, Joseph RM, Santos HP, Dvir Y, Hooper SR, O'Shea TM, Douglass LM, & Kuban KCK (2021). Anxiety and depression correlates at age 10 in children born extremely preterm. Journal of Pediatric Psychology, 46(4), 422–432. 10.1093/jpepsy/jsaa118 [PubMed: 33398339]

Muhle RA, Reed HE, Stratigos KA, & Veenstra-VanderWeele J (2018). The emerging clinical neuroscience of autism spectrum disorder a review. JAMA Psychiatry, 75(5), 514–523. 10.1001/jamapsychiatry.2017.4685 [PubMed: 29590280]

Ni Y, Lancaster R, Suonpera E, Bernardi M, Fahy A, Larsen J, Trickett J, Hurst JR, Wolke D, Johnson S, & Marlow N (2021). Growth in extremely preterm children born in England in 1995 and 2006: the EPICure studies. Archives of Disease in Childhood-Fetal and Neonatal Edition, 107(2), 193–200. 10.1136/archdischild-2020-321107 [PubMed: 34257100]

O'Shea TM, Allred EN, Dammann O, Hirtz D, Kuban KCK, Paneth N, & Leviton A (2009). The ELGAN study of the brain and related disorders in extremely low gestational age newborns. Early Human Development, 85(11), 719–725. 10.1016/J.EARLHUMDEV.2009.08.060 [PubMed: 19765918]

Palisano RJ, Hanna SE, Rosenbaum PL, Russell DJ, Walter SD, Wood EP, Raina PS, & Galuppi BE (2000). Validation of a model of gross motor function for children with cerebral palsy. Physical Therapy, 80(10), 974–985. [PubMed: 11002433]

Risi S, Lord C, Gotham K, Corsello C, Chrysler C, Szatmari P, Cook EH Jr, Leventhal BL, & Pickles A (2006). Combining information from multiple sources in the diagnosis of autism spectrum disorders. Journal of the American Academy of Child & Adolescent Psychiatry, 45(9), 1094–1103. [PubMed: 16926617]

Roberts G, Cheong J, Opie G, Carse E, Davis N, Duff J, Lee KJ, & Doyle L (2013). Growth of extremely preterm survivors from birth to 18 years of age compared with term controls. Pediatrics, 131(2). 10.1542/peds.2012-1135

Robertson J, Hatton C, Emerson E, & Baines S (2015). Prevalence of epilepsy among people with intellectual disabilities: A systematic review. Seizure: European Journal of Epilepsy, 29, 46–62. 10.1016/j.seizure.2015.03.016 [PubMed: 26076844]

Rosen TE, Mazefsky CA, Vasa RA, & Lerner MD (2018). Co-occurring psychiatric conditions in autism spectrum disorder. International Review of Psychiatry, 30(1), 40–61. 10.1080/09540261.2018.1450229 [PubMed: 29683351]

Rutter M, Bailey A, & Lord C (2003). Manual of the Social Communication Questionnaire. Los Angeles, CA.

Sacco R, Gabriele S, & Persico AM (2015). Head circumference and brain size in autism spectrum disorder: A systematic review and meta-analysis. Psychiatry Research: Neuroimaging, 234(2), 239–251. 10.1016/j.pscychresns.2015.08.016

Serenius F, Ewald U, Farooqi A, Fellman V, Hafström M, Hellgren K, Maršál K, Ohlin A, Olhager E, Stjernqvist K, Strömberg B, Adén U, & Källén K (2016). Neurodevelopmental outcomes among extremely preterm infants 6.5 years after active perinatal care in Sweden. JAMA Pediatrics, 170(10), 954–963. 10.1001/jamapediatrics.2016.1210 [PubMed: 27479919]

Simons Foundation Autism Research Initiative. (2014). Simons Simplex Collection. https://www.sfari.org/resource/simons-simplex-collection

Sprafkin J, Gadow KD, Salisbury H, Schneider J, & Loney J (2002). Further evidence of reliability and validity of the Child Symptom Inventory-4: parent checklist in clinically referred boys. Journal of Clinical Child and Adolescent Psychology, 31(4), 513–524. 10.1207/S15374424JCCP3104_10 [PubMed: 12402570]

Strauss JF, Romero R, Gomez-Lopez N, Haymond-Thornburg H, Modi BP, Teves ME, Pearson LN, York TP, & Schenkein HA (2018). Spontaneous preterm birth: advances toward the discovery of genetic predisposition. American Journal of Obstetrics and Gynecology, 218(3), 294–314.e2. 10.1016/J.AJOG.2017.12.009 [PubMed: 29248470]

Supekar K, Iyer T, & Menon V (2017). The influence of sex and age on prevalence rates of comorbid conditions in autism. Autism Research, 10(5), 778–789. 10.1002/AUR.1741 [PubMed: 28188687]

Taylor LJ, Maybery MT, Wray J, Ravine D, Hunt A, & Whitehouse AJO (2015). Are there differences in the behavioural phenotypes of Autism Spectrum Disorder probands from simplex and multiplex families? Research in Autism Spectrum Disorders, 11, 56–62. 10.1016/J.RASD.2014.12.003

Wadon M, Modi N, Wong HS, Thapar A, & O'Donovan MC (2020). Recent advances in the genetics of preterm birth. Annals of Human Genetics, 84(3), 205–213. 10.1111/ahg.12373 [PubMed: 31853956]

Werling DM, & Geschwind DH (2013). Sex differences in autism spectrum disorders. Current Opinion in Neurology, 26(2), 146–153. 10.1097/WCO.0b013e32835ee548 [PubMed: 23406909]

Xie S, Heuvelman H, Magnusson C, Rai D, Lyall K, Newschaffer CJ, Dalman C, Lee BK, & Abel K (2017). Prevalence of autism spectrum disorders with and without intellectual disability by gestational age at birth in the Stockholm youth cohort: a register linkage study. Paediatric and Perinatal Epidemiology, 31(6), 586–594. 10.1111/ppe.12413 [PubMed: 28898924]

Yudkin PL, Aboualfa M, Eyre JA, Redman CWG, & Wilkinson AR (1987). New birthweight and head circumference centiles for gestational ages 24 to 42 weeks. Early Human Development, 15(1), 45–52. 10.1016/0378-3782(87)90099-5 [PubMed: 3816638]

Table 1.

Maternal demographics and age 10 characteristics of EP and term born children

	EP (n = 59)	Term (n = 59)	t, X^2 p
Maternal demographics			
Maternal age, years at birth	M=30.4 (SD=5.9)	M=30.7 (SD=5.0)	t = 0.3 p = .79
Maternal education at age 10			
≤ 12 (high school)	28 (49.1%)	12 (20.7%)	X^2 = 10.7 p = .005
> 12, < 16	8 (14.0%)	16 (27.6%)	
≥ 16 (≥ college)	21 (36.8%)	30 (51.7%)	
Maternal marital status at age 10			
Single	22 (37.3%)	8 (13.6%)	X^2 = 8.8 p = .003
Married/partnered	37 (62.7%)	51 (86.4%)	
Racial identity			
White	36 (61.0%)	46 (78.0%)	X^2 = 13.8 p = .008
Black	18 (30.5%)	3 (5.1%)	
Asian	2 (3.4%)	4 (6.8%)	
Native American	0 (0%)	0 (0%)	
Mixed	2 (3.4%)	3 (5.1%)	
Not identified	1 (1.7%)	3 (5.1%)	
Hispanic			
Yes	4 (6.8%)	9 (15.3%)	X^2 = 2.3 p = .14
No	55 (93.2%)	50 (84.8%)	
Child characteristics at age 10 years			
Child age	M=10.0 (SD=0.7)	M= 10.0 (SD=0.6)	t = 0.3 p = .81
Nonverbal IQ	M=70.4 (SD=25.9)	M=72.3 (SD=23.5)	t = 0.4 p = .68
< 55	15 (25.4%)	12 (20.3%)	X^2 = .55 p = .91
55–69	10 (16.9%	12 (20.3%)	
70–84	16 (27.1%)	17 (28.8%)	
≥ 85	18(30.5%)	18(30.5%)	
Verbal IQ[1]	62.6 (28.5)	74.8 (SD=27.5)	t = 1.5 p = .13
< 55	24 (42.1%)	19 (32.2%	X^2 = 2.5 p = .52
55–69	8 (14.0%)	6 (10.2%)	
70–84	11 (19.3%)	14(23.7%)	
≥ 85	14 (24.6%)	20(33.9%)	

[1]Two EP participants were missing verbal IQ scores

Table 2.

Autism symptom scores for EP and term born children with ASD

	EP			Term			t	p	d
	n	Mean	SD	n	Mean	SD			
Social Communication									
ADI-R[1] reciprocal social interaction	57	20.2	7.2	59	21.7	5.3	1.3	.21	0.2
ADI-R nonverbal communication	57	9.1	4.1	59	10.0	3.0	1.4	.18	0.3
ADI-R verbal communication	46	6.4	2.5	51	8.1	2.0	3.9	<.001	0.8
ADI-R social initiation	46	3.3	1.2	51	3.7	0.7	2.0	.055	0.4
ADI-R stereotyped speech	46	3.0	1.8	51	4.4	1.7	4.0	<.001	0.8
ADOS-2 module 1/2 social affect	18	14.0	3.9	18	13.8	3.9	0.2	.83	0.1
ADOS-2 module 3 social affect	41	10.9	4.6	41	9.7	3.1	1.4	.16	0.3
ADOS-2 social affect calibrated severity	59	7.5	2.1	59	7.4	1.6	0.3	.77	0.1
Restricted and repetitive behaviors (RRB)									
ADI-R RRB total	57	4.8	2.9	59	6.9	2.3	4.2	<.001	0.8
ADOS-2 module 1/2 RRB total	18	5.1	2.1	18	5.1	1.9	0.1	.93	0.03
ADOS-2 module 3 RRB total	41	3.4	1.9	41	3.5	1.6	0.4	.70	0.1
ADOS-2 RRB calibrated severity	59	7.8	2.0	59	8.0	1.7	0.7	.52	0.1

[1]Two EP participants were missing ADI-R scores

Table 3.

Associated characteristics of EP and term born children with ASD

	EP (n = 59)	Term (n = 59)	t or X^2 p
Single words > 24 months			
Yes	39 (67.4%)	25 (42.4%)	$X^2 = 8.0$ p = .005
No	18 (31.6%)	34 (57.6%)	
Phrase speech > 33 months			
Yes	49 (86.0%)	40 (67.8%)	$X^2 = 5.4$ p = .021
No	8 (14.0%)	19 (32.2%)	
Gross motor delay/impairment at age 2[1]			
Yes	11 (19.6%)	6 (10.3%)	$X^2 = 1.9$ p = .16
No	45 (80.4%)	52 (89.7%)	
Anthropometrics at age 10 years[2]			
Head circumference, raw	52.4 (SD=3.0)	54.4 (SD=2.2)	t = 4.0 p <.001
Height z-score	−0.5 (SD=1.1)	0.3 (SD=1.1)	t = 3.7 p < .001
Weight z-score	−0.1 (SD=1.6)	0.5 (SD=1.2)	t = 2.4 p = .020
Body mass index z-score	0.1 (SD=1.6)	0.4 (SD=1.3)	t = 1.2 p = .23
Seizure disorder at age 10			
Yes	8 (13.6%)	4 (6.8%)	$X^2 = 1.5$ p = .22
No	51 (86.4%)	55 (93.2%)	
Psychiatric symptoms at age 10[3]			
ADHD			
T ≥ 65	20 (35.7%)	23 (39.0%)	$X^2 = 0.1$ p = .72
T < 65	36 (64.3%)	36 (61.0%)	
Anxiety			
T ≥ 65	9 (16.1%)	28 (47.5%)	$X^2 = 13.0$ p < .001
T < 65	47 (83.9%)	31 (52.5%)	
Depression			
T ≥ 65	10 (17.9%)	21 (35.6%)	$X^2 = 4.6$ p = .032
T < 65	46 (82.1%)	38 (64.4%)	

[1] Two EP participants were missing ADI-R spoken language milestone data

[2] One term participant was missing data on gross motor delay impairment

[3] One EP participant was missing anthropometric data

[4] Three EP participants were missing data on the CSI-4 screener for psychiatric symptoms

Table 4.

Autism symptom scores for EP and term born females with ASD

	EP			Term			t	p	d
	n	Mean	SD	n	Mean	SD			
Age	20	10.0	0.9	20	10.1	0.6	0.4	.70	0.1
Nonverbal IQ	20	72.1	24.7	20	74.1	21.5	0.3	.79	0.09
Verbal IQ[1]	19	65.7	31.2	19	72.2	26.2	07	.49	0.3
Social Communication									
ADI-R reciprocal social interaction	19	18.5	8.0	20	20.6	5.6	1.0	.34	0.3
ADI-R nonverbal communication	19	7.7	4.4	20	9.7	3.1	1.6	.12	0.5
ADI-R verbal communication	15	5.3	2.6	19	8.7	2.1	4.2	<.001	1.5
ADI-R B2 social initiation	15	3.2	1.3	19	3.8	0.4	1.7	.12	0.6
ADI-R B3 stereotyped speech	15	2.1	1.8	19	4.9	1.9	4.3	<.001	1.5
ADOS-2 module 1/2 social affect	4	11.5	5.5	4	11.0	4.8	0.1	.90	0.1
ADOS-2 module 3 social affect	16	10.4	4.5	16	10.6	3.6	0.2	.86	0.06
ADOS-2 social affect calibrated severity	20	7.1	2.4	20	7.4	1.8	0.5	.61	0.2
Restricted and repetitive behaviors (RRB)									
ADI-R RRB total	19	3.5	2.5	20	6.5	2.2	3.9	<.001	1.3
ADOS-2 module 1/2 RRB total	4	6.5	1.0	4	4.0	2.0	2.2	.067	1.6
ADOS-2 module 3 RRB total	16	3.1	2.1	16	3.3	1.8	0.4	.72	0.1
ADOS-2 RRB calibrated severity	20	7.5	2.7	20	7.7	1.6	0.4	.73	0.1

[1]One EP participant was missing verbal IQ score

[2]One EP participant was missing ADI-R scores

Table 5.

Associated characteristics of extremely preterm and term born females with ASD

	EP (n=20)	Term (n=20)	t or X^2 p
Single words > 24 months[1]			X^2 = 3.2 p = .075
Yes	13 (68.4%)	8 (40%)	
No	6 (31.6%)	12 (60%)	
Phrase speech > 33 months			X^2 = 1.6 p = .20
Yes	15 (79.0%)	12 (60%)	
No	4 (21.1%)	8 (40%)	
Gross motor delay/impairment at age 2[2]			X^2 = 0.3 p = .59
Yes	2 (10%)	3 (15.8%)	
No	18 (90%)	16 (84.2%)	
Anthropometrics at age 10[3]			
Head circumference, raw	51.7 (SD=2.3)	53.5 (SD=2.2)	t = 2.6 p = .013
Height, z-score	0.5 (SD=0.9)	0.4 (SD=1.3)	t = 2.6 p = .014
Weight, z-score	0.06 (SD=1.4)	0.2 (SD=1.2)	t = 0.7 p = .51
Body mass index, z-score	0.3 (SD=1.5)	0.2 (SD=1.0)	t = 0.07 p = .95
Seizure disorder at age 10			
Yes	3 (15%)	3 (15%)	X^2 = 0 p = 1.00
No	17 (85%)	17 (85%)	
Psychiatric symptoms at age 10			
ADHD			
T ≥ 65	9 (45%)	12 (60%)	X^2 = 0.9 p = .34
T < 65	11 (55%)	8 (40%)	
Anxiety			
T ≥ 65	3 (15%)	10 (50%)	X^2 = 5.6 p = .018
T < 65	17 (85%)	10 (50%)	
Depression			
T ≥ 65	5 (25%)	8 (40%)	X^2 = 1.0 p = .31
T < 65	15 (75%)	12 (60%)	

[1] One EP participant was missing ADI-R spoken language milestone data

[2] One term participant was missing data on gross motor delay/impairment

[3] One EP participant was missing anthropometric data

Table 6.

IQ and ASD symptom measures for extremely preterm children with and without prior ASD diagnosis

	Prior diagnosis			No prior diagnosis			t	p	d
	n	Mean	SD	n	Mean	SD			
Nonverbal IQ	38	75.3	26.9	21	61.5	21.7	2.0	.049	0.5
Verbal IQ[1]	36	65.9	30.6	21	56.9	23.9	1.2	.25	0.3
Social Communication									
ADI-R[2] reciprocal social interaction	36	22.1	6.5	21	16.9	7.3	2.8	.007	0.8
ADI-R nonverbal communication	36	9.6	4.1	21	8.2	4.0	1.3	.22	0.3
ADI-R verbal communication	30	7.0	2.2	16	5.1	2.5	2.7	.009	0.8
ADI-R B2 social initiation	30	3.5	1.0	16	2.9	1.3	1.7	.13	0.5
ADI-R B3 stereotyped speech	30	3.5	1.7	16	2.1	1.6	2.7	.010	0.8
ADOS-2 module 1/2 RRB total	12	13.7	3.8	6	14.8	4.4	0.6	.56	0.3
ADOS-2 module 3 RRB total	26	11.5	5.0	15	9.9	3.8	1.0	.31	0.3
ADOS-2 RRB calibrated severity	38	7.6	2.3	21	7.3	1.8	0.5	.65	0.1
Restricted and repetitive behaviors (RRB)									
ADI-R RRB total	36	5.6	2.7	21	3.5	2.8	2.7	.009	0.7
ADOS-2 module 1/2 RRB total	12	5.2	2.2	6	4.8	1.9	0.3	.76	0.2
ADOS-2 module 3 RRB total	26	3.6	1.7	15	2.9	2.1	1.1	.27	0.4
ADOS-2 RRB calibrated severity	38	8.1	1.9	21	7.3	2.2	1.3	.19	0.4

[1] Two participants were missing verbal IQ scores

[2] Two participants were missing ADI-R scores