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Psychiatric Outcomes, Functioning, and Participation in Extremely Low Gestational Age Newborns at Age 15 Years

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Abstract

Objective: To evaluate the prevalence, co-occurrence, sex differences and functional correlates of DSM-5 psychiatric disorders in 15-year-old adolescents born extremely preterm.

Method: The Extremely Low Gestational Age Newborns (ELGAN) Study is a longitudinal study of children born < 28 weeks gestation. At age 15, six hundred and seventy adolescents completed the Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI-KID), the Youth Self Report, a disability scale of participation in social roles and cognitive testing. Parents completed a family psychiatric history questionnaire.

Results: The most prevalent psychiatric disorders were anxiety, attention deficit hyperactivity disorder (ADHD) and major depression. More girls met criteria for anxiety than boys. Though 66% of participants did not meet criteria for a psychiatric disorder, 15% met criteria for one, 9% for two and 8% for ≥ 3 psychiatric disorders. Those with ≥ 2 psychiatric disorders were more likely to have repeated a grade, to have an individualized educational program (IEP) and to have a lower Non-Verbal IQ than those with no psychiatric disorders. Those with any psychiatric disorder were more likely to use psychotropic medications, to have greater cognitive and functional impairment, and to have mothers who were single, on public health insurance and had less than a high school education. Finally, a positive family psychiatric history was identified more frequently among adolescents with ≥ 3 psychiatric disorders.

Conclusion: Among adolescents born extremely preterm anxiety, major depression and ADHD were the most prevalent psychiatric disorders at age 15. Adolescents with > 1 psychiatric disorder were at increased risk for multiple functional and participatory challenges.

Keywords

psychiatric disorders; preterm; adolescents; functioning; prevalence

INTRODUCTION

Improvements in perinatal care of preterm infants have resulted in increased survival rates over the past four decades.[1] Nonetheless, preterm infants continue to be at heightened risk for adverse neurodevelopmental outcomes, including increased psychiatric symptoms during adolescence.[2–4] Prior research indicates that preterm born adolescents have higher rates of autism spectrum disorder (4–13%), ADHD (7–23%), and anxiety disorders (14%) than children born at term.[4–9] Yet, few studies have assessed psychiatric outcomes using a structured diagnostic instrument in preterm born adolescents.[6,8,10,11]

Moreover, few studies have evaluated functional correlates of psychiatric disorders in preterm born adolescents. Preterm born children have higher rates of learning problems, lower IQ, increased somatic concerns and decreased social competence,[9,12–14] but the associations between these factors and psychiatric disorders during adolescence have not been well described. The ELGAN investigators found an association between demographics, health and functional variables with anxiety, depressive and positive psychiatric symptoms at age 10 years.[15,16] However, to date there has not been an in-depth evaluation of such associations in adolescents born preterm.

The ELGAN cohort has been evaluated at age 2, 10 and now at 15 years. We previously described the children as having increased inattention, dysregulation, anxiety and depressive symptoms based on psychiatric rating scales such as the Child Behavior Checklist (CBCL)

and the Child Symptom Inventory-4.[15–26] Since many psychiatric disorders including mood, psychotic and substance use disorders[27–30] manifest during adolescence, it is essential to fully explore psychiatric outcomes during adolescence and adulthood among preterm individuals. Most research on preterm born children suffers from the use of birth weight (<2500G) as an indicator of prematurity instead of gestational age (GA<37 weeks) or use a combination of low birth weight and GA. This can introduce bias associated with fetal growth restriction.[7,11,31,32] Past studies have also included relatively small sample sizes,[33–35] focused on preschool or school-age children,[19] and have not used structured diagnostic interviews to capture the prevalence of threshold psychiatric disorders. While studies using screeners and dimensional measures are helpful to understand symptom variability and to identify individuals with subclinical symptoms, we seek to first outline the prevalence of DSM-5 psychiatric disorders that achieved threshold diagnostic criteria at age 15 years. We also augment the information obtained on the most common diagnoses in the ELGAN cohort based on the Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) by including severity measures based on the CBCL (parent) and Youth Self Report (YSR).

Therefore, the primary aims of this manuscript are to describe the prevalence, sex differences in rates, co-occurrence, and the associated functional and participatory impacts of psychiatric disorders in 15-year-old adolescents born extremely preterm using a structured diagnostic interview (updated to DSM-5). We hypothesized that adolescents born extremely preterm would be at heightened risk for psychiatric disorders, particularly anxiety, mood and ADHD, when compared to rates found in epidemiologic studies involving the general U.S. adolescent population. This hypothesis is informed by the fact that preterm survivors are exposed to a variety of postnatal stressors and exposures (pain, lack of circadian cycles, disrupted regulatory functions, early inflammation, and abnormal brain development).[20,24,36] We also anticipated that we would observe sex differences, particularly in internalizing and externalizing disorders, similar to what is found in epidemiologic studies and a variety of impacts on physical, behavioral and social functioning and participation as the number of psychiatric comorbidities increased.

METHOD:

Participants

The ELGAN Study is a U.S. multi-center prospective, observational study of the risk of structural and functional neurologic disorders in extremely preterm infants.[37] During the years 2002–2004, women delivering before 28 weeks gestation in 11 cities across five states were asked to enroll in the study. A total of 1,506 infants born to 1,249 mothers were enrolled.[38] Of these, 1,200 survived to age 2 years and 1,102 participated in a 2-year assessment.[38] At age 10 years, 889 (92%) of the 966 children eligible for follow-up (due to having inflammation-related proteins from blood samples obtained during their first postnatal month) were enrolled. At age 15 years, we attempted to enroll all surviving members (N=1,198) of the ELGAN cohort. A total of 700 adolescents (58% of surviving members) were evaluated at age 15 and 670 of them (96% of those enrolled) were interviewed using the Mini International Neuropsychiatric Interview for Children and

Adolescents (MINI-KID). These 670 adolescents constitute the sample for this report. All procedures for this study were approved by the institutional review boards at all participating sites.

Procedures

All families were contacted by mail, email and/or phone to participate in the 15-year follow-up. Families lost to follow-up were searched for through publicly available resources as approved by the local institutional review boards. All families gave informed consent and the adolescents provided assent.

During the assessment visit, parents completed questionnaires which included maternal age, education, marital status, eligibility for government-provided health insurance (e.g., Medicaid) and self-reported race and ethnicity. Demographic information about the adolescent and family used in this report was collected at birth.

Adolescent measures were selected to address the ELGAN study's focus on psychiatric, cognitive, behavioral, and neurological outcomes, as well as positive health outcomes, asthma, and obesity. While the adolescent was tested, the parent or caregiver completed questionnaires regarding the child's medical, neurological status and behavioral outcomes.

Verbal and nonverbal intelligence quotient (IQ) were assessed using the Wechsler Abbreviated Scale of Intelligence (WASI)-II, a standardized test that is well validated in individuals from age 6 to 90 years.[39] In our analyses, we used z-scores for the WASI-II that are based on standardized population norms.

The Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID 7.0.2) is a structured clinical diagnostic interview designed to assess the presence of current DSM-5 and ICD-10 psychiatric disorders in youth, aged 6 to 17 years.[40] The interview is typically administered to adolescents alone but can be administered together with the parent(s) who accompany the adolescents. together with the parent(s). The MINI-KID follows the structure and format of the adult version of the interview, which has been validated against the Structured Clinical Interview for DSM-III-R and against the World Health Organization–designed Composite International Diagnostic Interview. The MINI-KID has diagnostic sections/modules, and is administered using branching tree logic (e.g., 2 to 4 screening questions per disorder, with additional questions asked only if the screen questions are endorsed). The instrument screens for 24 DSM-5 and ICD-10 psychiatric disorders and suicidality. The MINI-KID has substantial to excellent concordance with the gold standard Kiddie Schedule for Affective Disorders and Schizophrenia - Present and Lifetime Version. The MINI-KID has recently been updated (version 7.0.2) to map onto DSM-5 diagnostic criteria. For this report we only used current MINI-KID diagnoses consistent with DSM-5 durations. This includes past two weeks for major depression, past few days or one week for mania, past 3 months for eating disorder, past 6 months for Oppositional Defiant Disorder (ODD), Attention ADHD, and GAD, and past 12 months for Conduct and Substance Use Disorders.

For adolescents with a full-scale IQ (FSIQ) < 50 and/or a verbal IQ (VIQ) < 50, the MINI-KID parent-version was used. For all other adolescents, the MINI-KID adolescent-version was used. When evaluating individuals with FSIQ and/or VIQ between 50 and < 70, we used the rules of administration for children below age 13 as outlined in the introduction of MINI-KID. For these adolescents, a parent supplemented the adolescent's responses to interview questions. For adolescents interviewed with parents present, the questions were directed to the adolescent first, but the parent was encouraged to interject if he/she felt that the adolescent's response was unclear or inaccurate.

We acquired severity measures using the YSR and parent report on the CBCL.[41] If the adolescent was interviewed alone on the MINI-KID, we used the YSR, if the parent was interviewed about the adolescent, we used the CBCL parent report and if both the adolescent and parent were interviewed together we used (YSR + CBCL)/2.

The Sheehan Disability Scale (SDS) was originally developed to measure impairment across family, school/work and community environments in treatment studies.[42] The SDS is an unweighted composite of three self-rated subscales including family life/home responsibilities, work/studies, and social life. Each item subscale is rated from 0–10 in terms of impact on functioning: 0 meaning not at all, 1–3 mildly, 4–6 moderately, 7–9 markedly, and 10 extremely. Total scores from 0 to 30 are calculated for patients who rate all three items (mildly 1–9, moderately 10–18, markedly 19–27, extremely 28–30).

The DSM-5 Family Mental Health and Neurobehavior Form is a structured interview with parents assessing psychiatric history of the adolescent's first-degree relatives and takes about 20 minutes to administer. This measure was designed specifically for ELGAN and is adapted from The Family History Screen[43] and the NIH Autism Centers of Excellence (ACE) Family History Form.[44]

Data Analyses

The maternal and newborn characteristics at birth were compared for those within the MINI-KID sample versus those not in the sample using chi-square tests. We evaluated the prevalence rates of psychiatric disorders based on the MINI-KID and compared the prevalence rates by sex using chi-square tests. To quantify psychiatric comorbidity, the prevalence of ELGAN adolescents who had no psychiatric disorder, one psychiatric disorder, two disorders and three or greater psychiatric disorders (total, girls, and boys), excluding suicidality were tabulated. We evaluated the association between number of co-occurring psychiatric disorders and maternal and child characteristics at birth as well as the family psychiatric history and child's functional outcomes at age 15, using chi-square tests. We used chi-square tests to evaluate the association between postnatal characteristics and neurologic burden relative to number of co-occurring psychiatric disorders based on the MINI-KID. A Bonferroni correction was applied to correct for multiple comparisons. To explore if the findings from the present study are consistent with the preterm behavioral phenotype as described by Burnett and colleagues,[32] we also performed a sub-analysis of psychiatric comorbidities in the adolescents who were seen at both age 10 and 15 and compared those who were diagnosed at age 10 with ASD using the ADOS (n=39) versus those who did not have ASD (n=597). Finally, due to the attrition in our sample, all

significant results were evaluated for whether the results remained significant when inverse probability weighting or multiple imputation were applied. All data analyses were carried out using SAS 9.4.[45]

RESULTS

Sample Characteristics

Demographic characteristics of the sample were collected at birth and are presented in Table 1, which contrasts participants and non-participants. Of the 1,198 surviving members of the ELGAN cohort, 700 were assessed at age 15 years (mean age 15.45 ± 0.49 years, range 14.42–17.71) and 670 completed a MINI-KID assessment. Of the 670 completed MINI-KID assessments, 604 (90%) were adolescent interviews, 28 (4%) were adolescent interviews supplemented by parents, and 38 (6%) were parent interviews.

The majority of participating adolescents were born to mothers between the ages of 21 and 35 years (78%). Thirty-seven percent of mothers had no formal education beyond high school, while 40% of mothers had a college degree or higher. With the exception of a higher prevalence of bronchopulmonary dysplasia (BPD) among participants, as compared to all surviving cohort members, we found no difference in newborn characteristics at birth (sex, gestational age, birth weight and birth weight z-score) or in postnatal medical complications (echolucent lesion, ventriculomegaly, necrotizing enterocolitis, retinopathy of prematurity). Participating adolescents were born to mothers who were somewhat older, more likely to have completed high school education, more likely to be married, less likely to receive both public health insurance and public nutritional assistance, more likely to be White and less likely to be Hispanic than non-participants. These characteristics are presented in Table 1.

Prevalence of DSM-5 Psychiatric Disorders in ELGANs at Age 15 Years

At age 15 years, among the most prevalent psychiatric disorders in the ELGAN participants were anxiety disorders (Any Anxiety Disorder 16.5%, GAD 8%, Panic Disorder 2%, Agoraphobia 4%, Separation Anxiety Disorder 4%, and both Social Anxiety and Specific Phobia 5%), ADHD (Any ADHD 18%, ADHD-inattentive type 9%, ADHD-combined 6% and ADHD-hyperactive type 2%) and mood disorders (Major Depression 4% and Bipolar 1 Disorder 1%) (see Table 2). When inverse probability weighting (IPW) was applied, associations found in the original analyses were confirmed and a few additional associations were found. When IPW or multiple imputation (MI) was used to estimate the prevalences of the three most frequent disorders identified in our study (ADHD, anxiety, and depression), estimated prevalences were higher than were observed within the 670 study participants who returned for evaluation at age 15. For example, ADHD was found in 18% of the study sample, while IPW gave an estimated prevalence of 17% and MI gave an estimated prevalence of 18% (see Tables S1 and S2).

Severity Measures of most prevalent psychiatric disorders based on T-scores of DSM-Oriented scales on the YSR/CBCL:

The mean T-score on the DSM Oriented ADHD problems scale for ELGAN youth who met criteria for any ADHD disorder on the MINI-KID was 61.9 ± 8.1 compared to 54.1 ± 5.4

for those who did not meet criteria for any ADHD. For the overall sample the T-score on the DSM Oriented ADHD problems scale was 55.3 ± 6.5. ELGAN youth who met criteria for any anxiety disorder on the MINI-KID had a T-score on the DSM oriented anxiety problem scale of 60.3 ± 9.8 compared to 53.5 ± 5.8 for those who did not meet criteria for any anxiety disorder on the MINI-KID. For the overall sample the T-score for any anxiety disorder was 54.4 ± 6.4. Finally, those youth with current MDD based on the MINI KID had a T-score on the DSM-oriented affective problems scale of 65.1 ± 8.7 compared to 54.3 ± 6.2 for those youth who did not meet criteria for MDD on the MINI-KID. For the overall sample the T-score for affective problems was 54.7 ± 6.7.

Sex Differences in the Prevalence Rates of Psychiatric Disorders in ELGANs at Age 15 Years

Sex differences in the prevalence of various psychiatric disorders included a higher rate of major depression among girls compared to boys (6% vs 2%), a higher prevalence of several anxiety disorders among girls: GAD (11% vs 5%); Agoraphobia (7% vs 1%); Separation Anxiety Disorder (6% vs 2%); and Social Anxiety Disorder (8% vs 3 %), and a higher prevalence of ADHD-hyperactive type among boys (4% vs 1%). After correcting for multiple comparisons, the only significant sex difference was in the rate of Agoraphobia. When multiple imputation was applied, none of the sex differences described persisted (see Table S1). However when IPW was applied more significant sex differences emerged (see Table S2)

Sub-Analysis of ELGAN Cohort with ASD vs Those without ASD at age 10 who were also seen at age 15.

Individuals in the ELGAN cohort with ASD were more likely to have ADHD (inattentive+hyperactive+combined) and anxiety of any type (GAD+Panic+Agoraphobia+Social Anxiety+Specific Phobia+Separation Anxiety) compared to those without ASD (46.2 vs 27%; OR 0.4 (0.1 – 1.6)). Interestingly, the increased prevalence in anxiety and ADHD in girls with ASD compared to girls without ASD (61.5% vs 26.7%) was greater than the corresponding increase in prevalence in boys with ASD compared to boys without ASD (38.5% vs 27.2%).

Burden of Psychiatric Disorders Based on Number of Psychiatric Co-Morbidities.

A significant majority of the ELGAN cohort (66%) did not meet criteria for any psychiatric disorder at age 15 (Table 3). Fifteen percent of the adolescents met criteria for one psychiatric disorder, 9% had two co-occurring psychiatric disorders and 8% had 3 or more co-occurring psychiatric disorders. There was no sex difference seen in those with no or one psychiatric disorders. Similarly, 11% of boys had 2 comorbid psychiatric conditions compared with 8% of girls and 10% of girls had 3 or greater co-morbid psychiatric disorders compared to only 6% of boys, these differences were not significantly different.

Associations Between Number of Psychiatric Disorders, Functional Impairment, Family Psychiatric History and Maternal and Infant Characteristics at Birth

Number of DSM-5 Psychiatric Disorders and School/Cognitive Functioning— School functioning was more likely to be impaired when an adolescent had a higher number of psychiatric disorders. When compared to adolescents with no psychiatric disorders, adolescents with 2 or more psychiatric disorders had higher impairments 27% vs 16% repeated a grade, 71% vs 46% had an IEP, 23% vs 16% had WASI VIQ z-score < −1, and 38% vs 20% had a WASI nonverbal IQ z-score < −1.

Number of DSM-5 Psychiatric Disorders and Exposure to Psychotropic Medications.—In general, exposure to current psychotropic medications was more likely in adolescents with any psychiatric disorder compared to those with no psychiatric disorder. Among adolescents born extremely preterm in the ELGAN cohort, only 11% of those who did not meet criteria for any psychiatric disorder had exposure to medication for ADHD, mood disorder, anxiety, or tic disorder, contrasted with 44% who met criteria for one or more psychiatric disorders.

Number of DSM-5 Psychiatric Disorders and Functional Impairment.— Adolescents who did not meet criteria for any psychiatric disorders were functioning better in social roles based on the SDS compared to those who met criteria for any psychiatric disorder. For example, 77% of those with no psychiatric disorders had no functional impairment, whereas only 27% of those with 1 or more psychiatric disorders had no impairment. Conversely, those who met criteria for one or more psychiatric disorders were more likely to have moderate or severe impairment compared to those without a psychiatric disorder (35% vs. 5%) (see Table 4).

Number of DSM-5 Psychiatric Disorders and Family History of Psychiatric Illness.—Of the 670 youth in the MINI-KID sample, 53% had at least one first-degree relative with a psychiatric history. Seventy-one percent of youth with > 3 psychiatric disorders had a family history of psychiatric disorders. However, after Bonferroni correction, having a first-degree relative with a psychiatric history was not associated with the number of psychiatric disorders identified in study participants.

Number of DSM-5 Psychiatric Disorders and Social and Demographic Characteristics of the Mother and Infant at Birth.—Adolescents who met criteria for one or more psychiatric disorders, compared to those without a psychiatric disorder, tended to have mothers with less than a high school education (47% vs. 31%), single marital status (44% vs. 30%) and public health insurance (45% vs. 27%).

Associations Between Number of Psychiatric Co-Morbidities, Postnatal Characteristics and Neurologic Burden

Adolescents in our cohort who met criteria for two or more psychiatric disorders were more likely to have cognitive impairment than those with one or no psychiatric disorders (36% vs 18%) but other disorders that Hirschberger and colleagues[46] considered to comprise “neurological burden” (cerebral palsy, autism spectrum disorder and epilepsy) were not

more likely among those with two or more psychiatric disorders (8% vs 8%).[46] We found no association of echolucent lesions or ventriculomegaly on cranial ultrasound studies, necrotizing enterocolitis, retinopathy of prematurity and BPD with number of psychiatric disorders (see Table 5).

DISCUSSION

This study is novel in examining psychiatric comorbidities using a structured diagnostic interview and their associated functional correlates in the ELGAN cohort at age 15 years. As hypothesized adolescents born extremely preterm had higher rates of several psychiatric disorders that have been observed in samples representative of adolescents. The most prevalent psychiatric disorders in the ELGAN cohort included ADHD (18%), Anxiety Disorders (16.5%), and Major Depression (4%). The rates of major depression (4%) and GAD (8%) in the ELGAN cohort are higher than the 2.6 and 0.4% found in the National Comorbidity Survey (NCS) for youth aged 13–17 years, respectively.[47] As compared to findings from the NCS Study, we found a slightly higher prevalence of ADHD-combined type (6% vs. 4.5%), and slightly lower prevalence of Conduct Disorder (1% vs. 1.5%), ODD (2% vs. 2.9%), alcohol use disorder (<1% vs. 1.3%) and substance use disorder (1% vs. 2.6%). The lower rates of Conduct Disorder, ODD, alcohol use and substance use disorders are consistent with previous reports that adolescents born preterm are less likely to engage in risky behaviors.[48,49] A more contemporaneous study is the National Survey of Children's Health (NSCH), which surveyed parents of children and adolescents from July 2016 to February 2017 as to whether their offspring had a current psychiatric diagnosis. Compared to the adolescents who were ages 12–17 in that study, the ELGAN cohort has higher rates of ADHD+ODD+Conduct (21%- predominantly due to elevated rates of ADHD vs 7.5% - labeled as behavioral or conduct problems in the NSCH) and of anxiety (16.5 vs 10.1%). However, the NSCH had a slightly higher rate of MDD (6.1% vs 4%).[50]

The majority of studies of psychiatric outcomes in individuals born preterm have focused on early childhood or school age assessments.[19] Among studies of adolescent psychiatric outcomes, only four used a structured or semi-structured interview, while the majority used psychiatric symptom screeners. The four studies that used semi- or structured interviews had relatively small sample sizes and enrolled samples based on low birth weight alone or in combination with gestational age rather than based on gestational age alone.[10,11,51] Similar to the findings in the present study, these prior studies found that ADHD and anxiety disorders were quite common. Only one of these studies used the ADHD and anxiety modules of the MINI-KID to assess 61 adolescents born preterm in Taiwan (mean age 13.4 years) and found 21% had ADHD and 20% had anxiety,[10] similar to but slightly higher than our rates of 18% and 16.5%, respectively. The EPICURE investigators evaluated an extremely preterm cohort, using a structured diagnostic interview completed by parents, at 11 and 19 years. Compared to a control group born at term, the EPICURE cohort had elevated rates of ADHD, emotional disorders, anxiety disorders and ASD, similar to our findings at age 15.[3,52,53]

We found a greater percentage of adolescent ELGAN girls had internalizing disorders than boys, and a greater percentage of boys had ADHD-hyperactive type than girls. These

observed sex differences are consistent with sex differences in the prevalence of psychiatric disorders reported in adolescents in epidemiologic studies in the general population.[47,54] However, we found that the frequencies of psychiatric disorders in our sample for both males and females were higher than those reported in population-based studies. For example, 11% of girls and 5% of boys in our sample had GAD compared to 1.5 % and 0.5% reported in girls and boys aged 15–16 years in the Great Smoky Mountains Study.[54] We also found elevated rates of Panic Disorder, Agoraphobia, Separation Anxiety Disorder, Social Anxiety Disorder and Specific Phobia for both boys and girls when compared to the GSMS study.

One third of our sample had ≥ 1 psychiatric disorders, a slightly higher rate than was found in a recent sample of preterm born adolescents evaluated by structured interview,[11] and almost 50% higher than the rate in a population-based sample.[47] The co-occurrence rate of psychiatric disorders reported in the present study is higher than described in epidemiologic studies that used structured diagnostic instruments in the general adolescent population or in preterm born adolescents and term born controls.[11,47] For example, 15% of the ELGAN cohort met criteria for one psychiatric disorder, 9% had two, and 8% had ≥ 3 psychiatric disorders. In sharp contrast, Yates and colleagues (2020) found that only 4% of their ELBW and low GA sample and 2% of their term born controls had 2 comorbid diagnoses and 4% of the preterm group and 2% of the controls had ≥ 3 comorbid diagnoses.[11] In the NCS Study of a general adolescent population, only 4.8% of their cohort had two disorders and only 2.2% of their sample had ≥ 3 psychiatric disorders.[47] In general, no particular set of psychiatric disorders clustered together more often than others. However, individuals with ASD in our sub-analysis were more likely to have ADHD and anxiety.

ELGAN participants with ≥ 2 psychiatric disorders were more likely to have repeated a grade, have an IEP and have a lower nonverbal IQ than those with no psychiatric disorders. This is similar to our finding from age 10 years demonstrating that ELGAN participants who screened positive for a higher number of psychiatric disorders were more likely to have impaired school functioning.[15] Our finding that participants who met criteria for ≥ 2 psychiatric disorders were much more likely to exhibit diminished nonverbal/fluid intelligence, relative to those without psychiatric disorder, also raised an interesting observation about psychiatric burden. These findings were consistent with recent findings from a large population-based study of adolescents,[55] suggesting that increased psychiatric burden interferes with efficient and adaptive novel problems skills and they were consistent with findings showing lower nonverbal IQ to be associated with higher rates of anxiety disorders[56] and suicidal ideation in individuals with bipolar disorder.[57] The association with psychiatric burden and nonverbal/fluid intelligence also begs the question of the importance of executive functions with respect to affective and behavioral regulation, and ongoing investigation of the relationship of nonverbal/fluid abilities and related cognitive abilities (e.g., executive functions) with adolescent psychopathology remains an important avenue for research as well as a potential avenue for clinical interventions (e.g., improvement of self-regulation, novel problem solving, etc.). We also found that as psychiatric comorbidities increased so too did neurodevelopmental co-morbidities, a finding not previously described in preterm born adolescents. Those who met criteria for ≥2 psychiatric disorders had greater neurodevelopmental impairments in cognition when compared to those with ≤

1 psychiatric disorder (32% vs 26%). This increase in neurodevelopmental disorder was not due to increased rates of the other neurological impairments that we studied (epilepsy, cerebral palsy, ASD).[46] This finding suggests the need for examining even more subtle neurodevelopmental contributions to psychiatric manifestations in adolescents born extremely preterm. In addition, this is one of the first studies that has reported on functional impairment, measured on the SDS,[42] in relationship to psychiatric impact on social participation. Not surprisingly, functional impairment and restricted social participation increased as the number of psychiatric co-occurrences increased.

Fifty-three percent of the ELGAN cohort that was assessed at age 15 had a positive family history of at least one first-degree relative with a psychiatric disorder (mother, father and/or sibling). Unfortunately, we currently do not have a breakdown as to which first-degree relative of each adolescent was affected by psychiatric illness. Study participants with > 3 psychiatric disorders were the most likely to have a positive family psychiatric history versus those with no psychiatric disorders (71% compared to 51%), 52% in those with one psychiatric disorder, and 59% in those with 2 psychiatric disorders). Although not statistically significant, this finding suggests the need for more study of the relationship of familial genetic loading and psychiatric illness. Others have reported that mothers with any psychiatric disorder are at heightened risk of having a preterm born infant.[58] Therefore, future work should focus on determining which first-degree relative had a psychiatric disorder and examining the association with psychiatric outcomes in preterm born individuals while accounting for other confounds associated with psychiatric disorders in mothers and with preterm births in offspring. These confounders include low socioeconomic status, single marital status, and < high school education.[59] Additionally, it would be important to assess the association between the degree of genetic vulnerability and the likelihood of a preterm individual having any psychiatric disorder and/or a specific psychiatric disorder.

Interestingly, of the 11% of adolescents who had no current psychiatric disorder, 37 were on medications to treat ADHD, 16 were on medications for anxiety and 18 were on medications to treat depression/ mood disorder. In these cases, the most likely reason they did not meet threshold for any current diagnosis on the MINI-KID is that they were adequately treated or if symptoms remained, they were subclinical in nature.

The strengths of this study include the large multi-center sample and the selection of patients based on GA rather than on birth weight (BW) alone or in combination with GA, which lessens bias based on fetal growth restriction.[31] Recall bias was minimized due to the prospective nature of our study and the use of only current MINI-KID psychiatric disorders. Finally, our study is one of the first to report on the prevalence of psychiatric disorders in adolescents who were born extremely preterm based on the administration of a structured diagnostic instrument that had been updated to DSM-5, rather than on a screening instrument. Additional strengths include collection of data on functional and social participatory challenges and information about first-degree relatives with psychiatric disorders.

A limitation of our study is the lack of a control group of adolescents born at term, which would have allowed more robust conclusions than can be drawn from comparing prevalence rates reported here to those reported from population-based studies of U.S. adolescents. Nonetheless, within our sample of adolescents born preterm we were able to compare those with and without psychiatric illness, and to compare prevalence between girls and boys. While we feel the use of a structured psychiatric interview is a strength of our study, those who do not meet criteria for these disorders on the MINI-KID had relatively elevated T-scores on severity scales, suggesting that they may have subclinical symptoms which were not adequately captured using the structured interview alone. Another limitation of our study is the relatively high attrition rate.

Based on their heightened risk of psychiatric disorders, adolescents born extremely preterm should be screened and monitored for these disorders in the context of primary care. Early identification of single and/or co-occurring psychiatric disorders in preterm born youth will lead to interventions that have the promise of improving associated functional impairments and participatory roles. In addition, using measures of psychiatric symptom severity to augment the MINI-KID are important in order to identify youth with subclinical symptoms so that they too can be monitored and assessed longitudinally to identify and track the trajectory of psychiatric disorders and symptoms. The data from this study will inform future research focused on the genetics of psychiatric disorders in preterm born individuals, studies focused on prevention, identification and intervention efforts and studies addressing health disparities for vulnerable pediatric populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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The ELGAN (Extremely Low Gestational Age Newborns) Research Study website: http://www.elganstudy.org/.

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Table 1.

Extremely Low Gestational Age Newborns (ELGAN) Age 15 Assessment: Maternal and Perinatal Characteristics of Those in the Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) Sample and not in the MINI-KID Sample

		In Sample	Not in Sample	
		n (%) 670	n (%) 528	X^2
Maternal characteristics at birth		Column Percent		
Age, years	<21	81 (12)	89 (17)	$X^2(2)=11.05^{**}$
	21–35	444 (66)	358 (68)	
	>35	145 (22)	81 (15)	
Education, years	≤ 12 (high school)	241 (37)	265 (53)	$X^2(2)=39.70^{***}$
	< 12–16>	151 (23)	119(24)	
	≥ 16 (≥ college)	259 (40)	117 (23)	
Single marital status	Yes	235 (35)	278 (53)	$X^2(1)=37.26^{***}$
Public insurance	Yes	217 (33)	247(48)	$X^2(1)=27.63^{***}$
Supplemental different social support- public nutritional assistance	Yes	72 (11)	94 (18)	$X^2(1)=13.09^{***}$
Racial identity	White	445 (67)	269 (52)	$X^2(2)=26.57^{***}$
	Black	157 (24)	165 (32)	
	Other	66 (10)	85 (16)	
Hispanic	Yes	62 (9)	85 (16)	$X^2(1)=12.92^{***}$
Newborn characteristics at time of birth				
Sex	Male	344 (51)	277 (52)	$X^2(1)=0.15$ *n.s.*
Gestational age, weeks	23–24	141 (21)	104 (20)	$X^2(2)=0.40$ *n.s.*
	25–26	309 (46)	244 (46)	
	27	220 (33)	180 (34)	
Birth weight, grams	≤ 750	248 (37)	188 (36)	$X^2(2)=0.35$ *n.s.*
	751–1000	290 (43)	230 (44)	
	> 1000	132 (20)	110 (21)	
Birth weight Z-score	< −2	42 (6)	20 (4)	X^2 (2) = 3.7 *n.s.*
	< −1	85 (13)	68 (13)	
	≥ −1	543 (81)	440 (83)	
Postnatal characteristics				
Echolucent lesion on cranial ultrasound studies	Yes	44 (7)	36 (7)	$X^2(1)=0.04$ *n.s.*
	No	626 (93)	490 (93)	
Ventriculomegaly on cranial ultrasound studies	Yes	68 (10)	47 (9)	$X^2(1)=0.50$ *n.s.*
	No	602 (90)	479 (91)	
Necrotizing enterocolitis (Bell stage 3b)	Yes	76 (11)	59 (11)	$X^2(1)=0.01$ *n.s.*
	No	594 (89)	469 (89)	
Retinopathy of prematurity (prethreshold)	Yes	92 (14)	64 (12)	$X^2(1)=0.61$ *n.s.*

		In Sample	Not in Sample	
		n (%) 670	**n (%) 528**	X^2
Maternal characteristics at birth		**Column Percent**		
	No	568 (86)	453 (88)	
Bronchopulmonary dysplasia (oxygen at 36 wks)	Yes	355 (53)	243 (47)	$X^2(1)=5.34^*$
	No	311 (47)	279(53)	

Note:

* p < .05

** p < .01

*** p < .001; n.s.p ≥ .05.

Table 2.

Sex Differences in Current Psychiatric Disorder Prevalence Rates at Age 15 in the Extremely Low Gestational Age Newborns (ELGAN) Study

	Girls	Boys			Total
MINI-KID MODULES (DSM 5;Current)	**n=326**	**n=344**	**Odds Ratio (95% Confidence interval)**	**Significance of Differences Between Girls and Boys**	**N=670**
Major Depressive Disorder	19 (6%)	7 (2%)	0.3 (0.1 – 0.8)	*	26 (4%)
Suicidality	17 (5%)	10 (3%)	0.6 (0.3 – 1.2)	n.s.	27 (4%)
Suicide Behavior Disorder	8 (3%)	7(2%)	0.8 (0.3 – 2.3)	n.s.	15 (2%)
Manic Episode	11 (3.%)	11 (3%)	1.0 (0.4 – 2.2)	n.s.	22 (3%)
Hypomanic Episode	2 (1%)	0 (0%)	0 (0 – Inf)	n.s.	2 (<1%)
Bipolar I Disorder	5 (2%)	2 (1%)	0.4 (0.1 – 2.0)	n.s.	7 (1%)
Bipolar II Disorder	1 (<1%)	0 (0%)	0 (0 – Inf)	n.s.	1 (<1%)
Other Specified Bipolar and Related Disorder	1 (<1%)	0 (0%)	0 (0 – Inf)	n.s.	1 (<1%)
Generalized Anxiety Disorder	37 (11%)	18 (5%)	0.4 (0.2 – 0.8)	**	55 (8%)
Panic Disorder	10 (3%)	5 (1%)	0.5 (0.2 – 1.4)	n.s.	15 (2%)
Agoraphobia	22 (7%)	4 (1%)	0.2 (0.1 – 0.5)	***	26 (4%)
Separation Anxiety Disorder	19 (6%)	6 (2%)	0.3 (0.1 – 0.7)	**	25 (4%)
Social Anxiety Disorder	26 (8%)	9 (3%)	0.3 (0.1 – 0.7)	**	35 (5%)
Specific Phobia	23 (7%)	13 (4%)	0.5 (0.3 – 1.0)	n.s.	36 (5%)
Obsessive-Compulsive Disorder	19 (6%)	10 (3%)	0.5 (0.2 – 1.1)	n.s.	29 (4%)
Posttraumatic Stress Disorder	4 (1%)	3 (1%)	0.7 (0.2 – 3.2)	n.s.	7 (1%)
Alcohol Use Disorder	1 (<1%)	0 (0%)	0 (0 – Inf)	n.s.	1 (<1%)
Substance Use Disorder	1 (<1%)	3 (1%)	2.9 (0.3 – 27.6)	n.s.	4 (1%)
Tourette's Disorder	1 (<1%)	3 (1%)	2.9 (0.3 – 27.6)	n.s.	4 (1%)
Persistent Chronic Motor Tic Disorder	8 (3%)	12 (4%)	1.4 (0.6 – 3.6)	n.s.	20 (3%)
Persistent Chronic Vocal Tic Disorder	3 (1%)	1 (<1%)	0.3 (0.0 – 3.0)	n.s.	4 (1%)
Provisional Tic Disorder	4 (1%)	5 (2%)	1.2 (0.3 – 4.5)	n.s.	9 (1%)
ADHD Combined	16 (5%)	27 (8%)	1.7 (0.9 – 3.1)	n.s.	43 (6%)
ADHD Inattentive	25 (8%)	37 (11%)	1.5 (0.9 – 2.5)	n.s.	62 (9%)
ADHD hyperactive	3 (1%)	13 (4%)	4.2 (1.2 – 15.0)	*	16 (2%)
Conduct Disorder	1 (<1%)	6 (2%)	5.8 (0.7 – 48.3)	n.s.	7 (1%)
Oppositional Defiant Disorder	6 (2%)	8 (2%)	1.3 (0.4 – 3.7)	n.s.	14 (2%)
Any Psychotic Disorder	4 (1%)	1 (<1%)	0.2 (0.0 – 2.1)	n.s.	5 (1%)
Major Depressive Disorder with Psychotic Features	2 (1%)	1 (<1%)	0.5 (0.0 – 5.3)	n.s.	3 (<1%)
Bipolar Disorder with Psychotic Features	5 (2%)	1 (<1%)	0.2 (0.0 – 1.6)	n.s.	6 (1%)
Anorexia Nervosa	2 (1%)	2 (1%)	1.0 (0.1 – 6.8)	n.s.	4 (1%)

	Girls	Boys			Total
MINI-KID MODULES (DSM 5;Current)	**n=326**	**n=344**	**Odds Ratio (95% Confidence interval)**	**Significance of Differences Between Girls and Boys**	**N=670**
Bulimia Nervosa	0 (0%)	0 (0%)	1 (0 – Inf)	n.s.	0 (0%)
Binge Eating Disorder	1 (<1%)	1 (<1%)	1.0 (0.1 – 15.2)	n.s.	2 (<1%)
Adjustment Disorders	1 (<1%)	0 (0%)	0 (0 – Inf)	n.s.	1 (<1%)

Note: ADHD = attention-deficit/hyperactivity disorder; MINI-KID = Mini International Neuropsychiatrie Interview for Children and Adolescents.

* $p < .05$

** $p < .01$

*** $p < .001$ (significant after Bonferroni correction); n.s.$p \geq .05$.

Table 3:

The Co-Occurrence of Psychiatric Disorders in Girls and Boys in the ELGAN Study based on the Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI-KID)

Number of MINIKID current psychiatric disorders	Girl n (%)	Boy n (%)	Total N (%)
0	217 (67)	229 (67)	446 (66)
1	48 (15)	56 (16)	105 (15)
2	27 (8)	37 (11)	64 (9)
≥3	34 (10)	21 (6)	55 (8)
Total	326	343[a]	669

Note: MINI-KID = Mini International Neuropsychiatric Interview for Children and Adolescents.

[a]missing data on one boy

Table 4.

Differences in child function and characteristics by number of current psychiatric disorders.

Child Function and Characteristics		Number of psychiatric disorders				*p* of chi-square test
		0 n=446	1 n=104	2 n=64	≥ 3 n=55	
		Column Percents n (%)				
Repeated a grade	Yes	70 (16)	17 (17)	20 (32)	13 (25)	0.02
	No	362 (84)	84 (83)	43 (68)	40 (75)	
Has had an IEP	Yes	197 (46)	63 (62)	49 (78)	35 (66)	< 0.001 *
	No	233 (54)	38 (38)	14 (22)	18 (34)	
WASI Vocabulary IQ z score at age 15	< −2	24 (6)	7 (7)	6 (10)	3 (6)	0.540
	−2 to −1	46 (11)	15 (15)	10 (16)	8 (17)	
	−1 to 1	256 (60)	53 (54)	36 (59)	24 (50)	
	1+	98 (23)	23 (24)	9 (15)	13 (27)	
WASI Matrix Reasoning: Nonverbal IQ z score	< −2	30 (7)	7 (7)	11 (18)	11 (22)	0.001 *
	−2 to −1	59 (14)	13 (13)	14 (23)	9 (18)	
	−1 to 1	268 (63)	68 (69)	31 (52)	26 (51)	
	1+	66 (16)	11 (11)	4 (7)	5 (10)	
Sheehan Disability Scale (SDS)	19–27 Severe	2 (<1)	6 (6)	2 (3)	9 (17)	<0.001 *
	10–18 Moderate	21 (5)	26 (26)	17 (27)	19 (36)	
	3–9 Mild	77 (18)	26 (26)	29 (47)	19 (36)	
	None (0–2)	331 (77)	41 (41)	14 (23)	6 (11)	
Number of psychotropic medications	0	397 (89)	66 (63)	32 (50)	26 (47)	<0.001 *
	1	34 (8)	28 (27)	23 (36)	12 (22)	
	≥ 2	15 (3)	10 (10)	9 (14)	17 (31)	
Family History of mental health disorders in first degree relatives	Yes	227 (51)	54 (52)	37 (59)	39 (71)	< 0.01
	No	221 (49)	49 (48)	27 (42)	16 (29)	
Maternal Characteristics at Birth						
Age, years	<21	44 (10)	19 (18)	8 (13)	9 (16)	0.203
	21–35	301 (67)	62 (60)	46 (72)	35 (64)	
	>35	101 (23)	23 (22)	10 (16)	11 (20)	
Education, years	≤12	135 (31)	50 (50)	27 (44)	28 (51)	<0.001 *
	13–15	102 (24)	19 (19)	19 (29)	12 (22)	
	16+	197 (45)	30 (30)	17 (27)	15 (27)	
Single marital status	Yes	136 (30)	48 (46)	26 (41)	24 (44)	0.006
	No	310 (70)	56 (54)	38 (59)	31 (56)	
Public insurance	Yes	120 (27)	44 (44)	27 (42)	29 (53)	<0.001 *
	No	318 (73)	57 (56)	37 (58)	26 (47)	

Child Function and Characteristics		Number of psychiatric disorders				*p* of chi-square test
		0 n=446	1 n=104	2 n=64	≥ 3 n=55	
		Column Percents n (%)				
Race	White	309 (70)	63 (61)	36 (56)	37 (67)	0.22
	Black	93 (21)	28 (27)	20 (31)	15 (27)	
	Other	42 (9)	13 (13)	8 (13)	3 (6)	
Hispanic	Yes	41 (9)	7 (7)	10 (16)	4 (7)	0.249
	No	403 (91)	97 (93)	54 (84)	51 (93)	
Newborn Characteristics at Birth						
Sex	Female	217 (49)	48 (46)	27 (42)	34 (62)	0.161
	Male	229 (51)	56 (54)	37 (58)	21 (38)	
Gestational Age, weeks	23–24	94 (21)	16 (15)	16 (25)	15 (27)	0.200
	25–26	209 (47)	46 (44)	33 (52)	20 (36)	
	27	143 (32)	42 (40)	15 (23)	20 (36)	
Birth Weight Z-Scores	<−2	22 (5)	6 (6)	7 (11)	7 (13)	0.210
	< −1	58 (13)	15 (14)	6 (9)	6 (11)	
	≥−1	366 (82)	83 (80)	51 (80)	42 (76)	

Note: IEP= Individualized Education Program; IQ= Intelligence Quotient; WASI= Wechsler Abbreviated Scale of Intelligence

*Significant after Bonferroni correction

Table 5.

Postnatal Characteristics and Neurologic Burden Relative to Psychiatric Burden

		Number of Psychiatric Disorder				*p*
		0 n=446	**1 n=104**	**2 n=64**	**≥3 n=55**	
Postnatal characteristics		**Column Percents n (%)**				
Echolucent lesion on cranial ultrasound studies	Yes	31 (7)	5 (5)	7 (11)	1 (2)	0.2
	No	415 (93)	99 (95)	57 (89)	54 (98)	
Ventriculomegaly on cranial ultrasound studies	Yes	49 (11)	8 (8)	6 (9)	4 (7)	0.664
	No	397 (89)	96 (92)	58 (91)	51 (93)	
Necrotizing enterocolitis (Bell stage 3b)	Yes	36 (8)	7 (7)	4 (6)	4 (7)	0.935
	No	410 (92)	97 (93)	60 (94)	51 (93)	
Retinopathy of prematurity (prethreshold)	Yes	67 (15)	8 (8)	11 (17)	6 (11)	0.196
	No	374 (84)	94 (90)	52 (81)	47 (85)	
Bronchopulmonary dysplasia	Yes	222 (50)	62 (60)	38 (59)	32 (58)	0.158
	No	221 (50)	42 (40)	26 (40)	22 (40)	
Neurologic Burden[46]						
Normal or mildly impaired cognition and no CP, ASD, epilepsy		304 (68)	65 (63)	32 (50)	29 (53)	0.004[a]
Normal or mildly impaired cognition with at least one of following: CP, ASD, epilepsy		32 (7)	13 (10)	7 (11)	3 (5)	
Moderate or severe cognitive impairment J		80 (18)	19 (18)	20 (31)	19 (35)	

Note: CP=Cerebral Palsy; ASD=Autism Spectrum Disorders

[a]Significant after Bonferroni correction