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Psychiatric outcomes at age seven for very preterm children: rates and predictors

Karli Treyvaud^{1,2}, Alexandra Ure^{1,3}, Lex W. Doyle^{1,4,5}, Katherine J. Lee^{1,2}, Cynthia E. Rogers⁶, Hiroyuki Kidokoro⁶, Terrie E. Inder^{1,6}, and Peter J. Anderson^{1,2}

¹Murdoch Childrens Research Institute, Vic., Australia

²Department of Paediatrics, University of Melbourne, Vic., Australia

³School of Psychological Sciences, University of Melbourne, Vic., Australia

⁴Department of Obstetrics and Gynaecology, University of Melbourne, Vic., Australia

⁵Clinical Research Development, Royal Women's Hospital, Vic., Australia

⁶Department of Pediatrics, Washington University, St Louis, USA

Abstract

Background—Uncertainty remains about the rate of specific psychiatric disorders and associated predictive factors for very preterm (VPT) children. The aims of this study were to document rates of psychiatric disorders in VPT children aged 7 years compared with term born children, and to examine potential predictive factors for psychiatric diagnoses in VPT children.

Methods—Participants were 177 VPT and 65 term born children. Perinatal medical data were collected, which included brain abnormalities detected using magnetic resonance imaging. The Infant-Toddler Social-Emotional Assessment (ITSEA) and Strengths and Difficulties Questionnaire (SDQ) were administered at 2 and 5 years respectively. At 7 years of age, the Developmental and Well-being Assessment (DAWBA) was used to indicate psychiatric diagnoses.

Results—Compared with term born children, VPT children had three times the odds of meeting criteria for any psychiatric diagnosis at age 7 years (odds ratio 3.03; 95% confidence interval 1.23, 7.47, $p = .02$). The most common diagnoses were anxiety disorders (11% VPT, 8% term), attention-deficit/hyperactivity disorder (10% VPT, 3% term) and autism spectrum disorder (4.5% VPT, 0% term). For VPT children, those with severe global brain abnormalities ($p = .02$), those who displayed social-emotional problems at age 5 ($p = .000$) and those with higher social risk at age 7 ($p = .001$) were more likely to meet criteria for a psychiatric illness at age 7.

Conclusions—Compared with term born children, VPT children have higher rates of psychiatric diagnoses at early school age, predicted by neonatal brain abnormalities, prior social-emotional problems and social factors.

Keywords

Preterm; psychiatric disorder; brain abnormality; predictor; mental health

Introduction

Survival rates for very preterm (VPT; born <32 weeks' gestation) children have greatly improved in recent decades (Doyle & VICS, 2004); however, over 55% of these children face significant developmental challenges by school age. These challenges include cognitive deficits, learning disabilities, emotional problems and behavioural dysregulation (Anderson & Doyle, 2003; Clark, Woodward, Horwood, & Moor, 2008; Nomura, Wickramaratne, Warner, Mufson, & Weissman, 2002; Spittle et al., 2009). The rates, nature and origin of mental health problems in these children, however, remain to be established.

Many studies examining social-emotional and mental health outcomes for VPT children have utilised screening measures for mental health problems, such as the Child Behavior Checklist (CBCL), Behavior Assessment System for Children (BASC) or the Strength and Difficulties Questionnaire (SDQ). Using such measures, VPT children have been found to have elevated rates of behavioural difficulties (Anderson & Doyle, 2003; McCormick, Workman-Daniels, & Brooks-Gunn, 1996) and internalising problems (Anderson & Doyle, 2003; Johnson & Marlow, 2011). While some studies have incorporated a clinical diagnostic measure in their methodology to show elevated rates of mental health problems in VPT children, they often focussed on selective mental health diagnoses such as mood disorders. For example, Patton, Coffey, Carlin, Olsson, and Morely (2004) reported a sixfold increase in rates of major depressive disorders in adolescents born preterm compared with those born at term.

Indredavik et al. (2005) reported higher rates of any psychiatric disorder, ADHD and anxiety disorders in very low birth weight (VLBW; birth weight <1250 g) adolescents (most of whom were VPT) compared with term born adolescents. More recently, Johnson et al. (2010) found that compared with term born children, extremely preterm (<26 weeks' gestational age) children were three times more likely to be diagnosed with any psychiatric disorder, and four times more likely to be diagnosed with ADHD or an anxiety or depressive disorder. They also reported that the rate of autism spectrum disorders (ASDs) in their sample of extremely preterm children was 8%, compared with current estimates of the population prevalence of between 0.2% (Fombonne, 2009; Williams, Brayne, & Higgins, 2006) and 2.64% (Kim et al., 2011). Another study with 6-year-old VPT children reported approximately double the rates of ADHD in VPT children compared with term born children (Botting, Powls, Cooke, & Marlow, 1997). Overall, the results from previous studies suggest an approximately 2–6 times increased rate of certain mental health disorders in preterm compared with term born children. The variability in the estimated rate may be a consequence of the large range of gestational ages (and likely vulnerability) of the preterm children in these studies (between <26 weeks and <37 weeks). Age at assessment is also likely to influence rates of psychiatric diagnoses due to changes in prevalence rates for certain diagnoses over development (e.g., depressive disorders become more prevalent during adolescence; American Psychiatric Association, 2000).

Poorer social-emotional outcomes for preterm children have been linked with factors such as cognitive impairment (Botting et al., 1997; Hack et al., 2005; Johnson et al., 2010; Samara, Marlow, & Wolke, 2008) serious functional disability (Johnson et al., 2010), male gender (Johnson et al., 2010; Samara et al., 2008), and increased social risk (Delobel-Ayoub et al., 2009). There is also evidence that a previous history of social-emotional or mental health problems is a strong predictor of current symptoms (Delobel-Ayoub et al., 2009; Johnson et al., 2010; Treyvaud et al., 2012). In terms of neonatal predictors, Johnson et al. found some evidence for a relationship between necrotizing enterocolitis (NEC) and poorer psychiatric outcome for extremely preterm children. Others have reported an association between lower

birth weight and increased risk for psychiatric diagnosis in VLBW adolescents (Indredavik et al., 2010).

Another potential risk factor for social-emotional and psychiatric disorders is neonatal brain injury. Focal and diffuse cerebral white matter injury is commonly associated with preterm birth (Volpe, 2009), with approximately 71% of VPT infants displaying white matter abnormalities (WMA) at term equivalent age using magnetic resonance imaging (MRI; Inder, Wells, Mogridge, Spencer, & Volpe, 2003). MRI-defined WMA at term corrected age in VPT children has been associated with social-emotional difficulties (Spittle et al., 2009), and reduced emotional and behavioural regulation at preschool age (Clark et al., 2008). Using the same cohort of VPT children as the current study, we recently reported associations between regional brain development at term corrected age and behavioural problems at age 5 (Rogers et al., 2012). Cerebral WMA detected using MRI during adolescence has also been linked with psychiatric symptoms for a cohort of adolescents born with VLBW (Indredavik et al., 2005; Skranes et al., 2007), and a recent review reported an association between cerebral WMA and symptoms of ADHD and ASD in preterm children (Johnson & Marlow, 2011). Others have also reported a relationship between neonatal cerebral ultrasound abnormalities and adolescent psychiatric outcomes in low birth weight (LBW) children (Whitaker et al., 2011). Additional research using well-validated psychiatric diagnostic measures is needed to build upon these preliminary findings.

The first aim of the current study was to provide a summary of the rates of different psychiatric diagnoses in a large representative cohort of VPT children compared with term born children. This will be one of the few studies to comprehensively assess mental health in VPT children using a clinical diagnostic measure at age 7 years. The second aim was to examine factors that are predictive of having a psychiatric disorder for VPT children, including MRI-defined neonatal brain abnormalities, another novel aspect of this study.

Method

Participants and procedure

Participants were families from the Victorian Infant Brain Studies (ViBeS) cohort, which included 227 infants born at <30 weeks' gestation or with a birth weight <1250 g at the Royal Women's Hospital, Melbourne Australia, between 2001 and 2003 (VPT group). A comparison group including 77 full term children (>36 weeks' gestation) were recruited at birth from the Royal Women's Hospital maternity wards between 2001 and 2003 ($n = 46$) or at 2 years from maternal-child health centres in 2004 ($n = 31$), both in Melbourne Australia. At term corrected age brain, MRI was performed on VPT children and the 46 controls recruited in the newborn period. Follow-up assessments were performed at age 2, 5 and 7 years (all corrected age). For the VPT group, psychiatric diagnosis information was available for 177 (78% of original sample) children at age 7. Of the 50 VPT children without psychiatric outcomes at 7 years, two had died, 27 declined, withdrew, or were lost to follow-up and 21 parents did not complete the primary outcome measure [Developmental and Well-being Assessment (DAWBA)]. For the term group, psychiatric diagnostic information was available for 65 (85% of original sample) children at age 7. Of the 12 controls without psychiatric outcomes at 7 years, six declined, one family was uncontactable and five parents did not complete the primary outcome measure. During each of the follow-up assessments, age appropriate psychological measures were completed with the children while parents completed questionnaires and interviews. The study was approved by the Human Research Ethics Committees of the Royal Women's Hospital and the Royal Children's Hospital, and informed written consent was obtained from parents for all children.

Measures

The primary outcome measure for the current study was any psychiatric diagnosis (i.e., the overall variable indicating the presence or absence of any diagnosis) obtained via the DAWBA (Goodman, Ford, Richards, Gatward, & Meltzer, 2000) at age 7 years. Individual diagnoses were examined as secondary outcomes. The DAWBA is a structured psychiatric evaluation used to assign DSM-IV-TR (American Psychiatric Association, 2000) diagnoses, and was completed online by parents with regards to their child during the 7-year follow-up visit. The DAWBA demonstrates good validity when compared with psychiatric diagnoses assigned by clinicians (Goodman et al., 2000). The DAWBA computer program identifies potential cases using scoring algorithms (see <http://www.dawba.com> for more information), which were used as the starting point for raters to assign psychiatric diagnoses. Raters were two clinical psychologists with diagnostic experience who completed the online DAWBA rater training. Both raters reviewed the DAWBA for each participant separately blinded to group membership (VPT or term) and other clinical details of the participants. Follow-up phone interviews with parents were used when the information provided on the DAWBA remained unclear or contradictory ($n = 65$). Final diagnoses were based on the clinical judgement of each rater. Using this process, interrater agreement was 86%, with 35 participants flagged as uncertain by one or both raters. After discussion of these 35 participants, 14 were assigned a diagnosis, four changed subcategory within a diagnosis (e.g., ADHD inattentive changed to ADHD combined type) and 17 were not assigned a diagnosis. Agreement was reached for all cases following discussion.

Predictors

The following measures were explored as predictors of psychiatric diagnoses: perinatal medical data including brain abnormality defined by MRI, social-emotional difficulties at 2 and 5 years, and familial social risk and neurodevelopmental disability at 7 years. Perinatal medical data were collected during the primary hospitalisation (see Table 1). MRI was performed at term equivalent age as previously described (Woodward, Anderson, Austin, Howard, & Inder, 2006). Presence and severity of brain abnormalities were assessed using a qualitative scoring system that extends an approach we have used previously (Kidokoro, Neil, & Inder, under review). The global brain abnormalities score used in the current study reflects the summed scores from four separately evaluated factors: white matter abnormalities, cortical and deep grey matter abnormalities and cerebellar abnormalities. The global score was then classified into categories: none 0–3, mild 4–7, moderate 8–11, severe 12.

Children were classified as displaying clinically significant social-emotional difficulties at age 2 (corrected) if they met the clinical cut point for one or more of the four domains (internalising problems, externalising problems, dysregulation, social-emotional competence) of the Infant-Toddler Social and Emotional Assessment (ITSEA, prepublication version; Briggs-Gowan & Carter, 2000). The ITSEA is a parent-rated measure, which demonstrates acceptable test–retest reliability and external validity (Carter, Briggs-Gowan, Jones, & Little, 2003). Clinical cut points were mean scores at or below the 10th percentile for competence, and at or above the 90th percentile for externalising, internalising and dysregulation. Children were classified as displaying clinically significant social-emotional difficulties at age 5 (corrected) if they met the clinical cut point for one or more of the four problem domains (emotional symptoms, conduct problems, hyperactivity, peer problems) of the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997), which is a reliable and well-validated parent-rated questionnaire (Goodman, 2001).

Familial social risk at 7 years was calculated based on a composite measure assessing six social risk factors (family structure, education of primary caregiver, occupation and

employment status of primary income earner, language spoken at home and maternal age when the child was born) as used previously (Roberts et al., 2008). Each domain was scored on a 3-point scale, where zero represented lowest risk and two represented highest risk, summed to give a total score 0–12. Neurodevelopmental disability at age 7 was defined as having a score <70 on the Full Scale Intelligence Quotient (FSIQ) on the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999), severe cerebral palsy (i.e., not walking), blindness (visual acuity worse than 20/200 in the better eye) or significant hearing loss (requiring hearing aids or worse).

Statistical Analysis

Data were analysed using Stata 11.2 (StataCorp, 2007). First, chi-squared, Wilcoxon rank-sum tests and *t*-tests were used as appropriate to compare sociodemographic variables between participating and nonparticipating families, and between VPT and term groups. Differences in the proportion of VPT and term children with psychiatric diagnoses were examined using separate logistic regression models for each outcome domain, fitted using Generalised Estimating Equations (GEEs) with an exchangeable correlation structure and robust standard errors to allow for correlations between twins/triplets in the study (Carlin, Gurrin, Sterne, Morley, & Dwyer, 2005; Hanley, Negassa, deB Edwardes, & Forrester, 2003). Where regression models could not be fitted (i.e., where there were no cases in one of the groups), chi-squared tests were used to compare VPT and term children. Where evidence of group differences existed, regression equations were re-run with the inclusion of neurodevelopmental disability and social risk as covariates to adjust for any differences between the groups explained by these variables. To examine which factors were predictive of having any psychiatric diagnosis for VPT children, the predictor variables described above were each entered into separate univariable logistic regression models (fitted using GEEs) for the binary outcome of having any psychiatric diagnosis. Factors showing an association ($p < .15$) with psychiatric outcome in univariable models were entered into a final multivariable regression model to assess independent predictors.

Results

There was little evidence of differences between families who completed the DAWBA at 7 years and those who did not, although there was a trend for completers to have a lower social risk score than noncompleters (median score = 2 (interquartile range [IQR] = 1, 3) versus median = 3 (IQR = 1, 5), rank sum $p = .06$). Within the study population, VPT children were more likely to be a multiple ($p < .001$) and have a higher social risk score ($p = .002$) compared with children born at term (Table 1).

Psychiatric outcomes

Compared with term children, VPT children had three times higher odds of meeting criteria for any psychiatric disorder ($p = .01$, see Table 2). The evidence for this difference remained after adjustment for social risk [odds ratio (OR) = 2.55, 95% confidence interval (CI) = 1.01, 6.43, $p = .047$], but was weakened slightly after adjustment for social risk and neurodevelopmental disability (OR = 2.35, 95% CI = 0.92, 5.98, $p = .07$). While this trend for increased odds for a psychiatric diagnosis in VPT children persisted across the majority of diagnostic categories (see Table 2), the differences were smaller and did not reach statistical significance (significance defined as $p < .05$). Within diagnoses, the largest group differences were evident in ASD (4.5% VPT, 0% term), ADHD (10% VPT, 3% term), any anxiety disorder (11% VPT, 8% term) and other DSM-IV diagnosis (3% VPT, 0% term). Of note, there was little evidence for group differences in the likelihood of having comorbid psychiatric diagnoses (6% of VPT children and 5% of term children, OR = 1.37, 95% CI = 0.37, 5.04, $p = .63$).

Predictors of psychiatric diagnoses for VPT children

The univariable results found some evidence that global brain injury, social risk and social-emotional problems at age 5 years were all associated with any psychiatric diagnosis at age 7 (Table 3). Gender was included in the final adjusted model due to a weak association with psychiatric diagnosis ($p = .13$). The final adjusted model (Table 3) suggested that VPT children who had higher social risk at aged 7 years, brain abnormality at term, or who displayed a clinically significant level of social-emotional problems at age 5 years were more likely to be diagnosed with a psychiatric disorder at age 7 years ($R^2 = .17$). There was also weak evidence in the adjusted model that female VPT children were more likely to be diagnosed ($p = .08$). Further analysis indicated that only the severe category of brain abnormality was predictive of psychiatric disorder (compared with the no abnormality category; adjusted OR = 5.63 (95% CI = 1.18, 26.81), $p = .03$).

Discussion

The current study found that, compared with term children, VPT children had three times higher odds of meeting criteria for any psychiatric disorder at age 7. In this study, almost one quarter (24%) of the VPT children met criteria for any psychiatric diagnosis at age 7, which is consistent with the reported rates of psychiatric diagnosis of 22–27% in LBW/VLBW children born in the 1980s (Johnson & Marlow, 2011). In the current study, the most common psychiatric diagnoses for VPT children were anxiety disorders (11%), ADHD (10%) and ASD (4.5%), consistent with previous research (Bhutta, Cleves, Casey, Craddock, & Anand, 2002; Indredavik et al., 2005; Patton et al., 2004). The most common anxiety disorders for VPT children were specific phobia and separation anxiety. Similar to Johnson et al. (2010), there was little evidence of group differences in the likelihood of having a comorbid psychiatric diagnosis. Although the trend for increased odds of meeting criteria was evident across many diagnostic categories, the low numbers of cases and resulting lack of power meant that no other group comparisons reached statistical significance. Nevertheless, the trends from the current study are consistent with those reported by Johnson et al. (2010), suggesting that increased psychiatric morbidity is seen not only in those children born <26 weeks' gestation, but also those born <30 weeks' gestation. The rate of 4.5% of VPT children in the current study meeting criteria for ASD is also particularly noteworthy, as this is higher than reported in the general population (e.g., 0.2–2.64%; Fombonne, 2009; Kim et al., 2011; Williams et al., 2006). This finding is consistent with that reported by Johnson et al., although is lower in magnitude, likely reflecting the different gestational ages of the cohorts. The rates of ADHD, ASD, and anxiety in VPT compared with term born children in the current study are consistent with the “preterm behavioural phenotype” (characterised by inattention/hyperactivity, social and emotional difficulties) suggested by Johnson and Marlow (2011) as one way to view the social-emotional and behavioural difficulties experienced by VPT children.

The relationships between psychiatric illness and neurosensory or cognitive disability in VPT children are complex. Johnson et al. (2010) found that adjustment for cognitive and neurosensory impairment reduced the evidence for differences between extremely preterm and term born children on all psychiatric diagnoses except ASD. The current study found similar results for the effect of group on any psychiatric diagnosis after adjustment for neurosensory disability. However, Johnson et al. also found that extremely preterm children with a neurosensory or cognitive impairment were more likely to meet criteria for a psychiatric outcome compared with extremely preterm children without these impairments. Similarly, the current study reported that neurosensory disability was not strongly predictive of psychiatric disorder for VPT children; however, the rate of neurosensory disability in VPT children with a psychiatric disorder was twice the rate for VPT children without a psychiatric disorder (10% vs. 4% respectively). It is likely that cognitive and neurosensory

impairment is associated with the development of certain psychiatric disorders, such as autistic disorder (for which language delay is one of the primary criteria), and further detailed research into how aspects of cognitive development, such as language, memory or emotional processing and neurosensory impairments may contribute to psychiatric outcomes, is needed to better understand these relationships.

Although some previous research within preterm populations identified that males had a higher risk of poorer social-emotional outcomes by school age (Johnson et al., 2010; Samara et al., 2008), a recent review (Johnson & Marlow, 2011) indicated that the literature regarding gender differences in psychiatric outcomes among preterm children is mixed. The results from the current study suggested that female VPT children were more likely to meet criteria for a psychiatric diagnosis than VPT males. However, the relationship was weak, and while the results from the current study are interesting, additional research is needed to confirm whether strong gender differences do exist. Consistent with the results from the current study, evidence suggests that preterm children with early indicators of social-emotional difficulties are more likely to experience later mental health problems (Johnson et al., 2010; Treyvaud et al., 2012), with evidence of moderate stability over time (Delobel-Ayoub et al., 2009; Gray, Indurkha, & McCormick, 2004; Hall & Wolke, 2012), a finding that has clinical implications for VPT children and their families. Also, consistent with the literature is the finding that increased social risk was associated with higher odds of meeting criteria for any psychiatric diagnosis (Delobel-Ayoub, Kaminski, Marret, Burguet, Marchand, Guyen, and ... for the EPIPAGE Study Group., 2006; Spittle et al., 2009).

Johnson et al. (2010) suggested that global changes to brain structure (and possibly function) following preterm birth may influence multiple areas of development, including mental health. The results from the current study support the notion that alterations to brain structure evident in the neonatal period are associated with later psychiatric morbidity, specifically that VPT children with severe global brain abnormalities are at higher risk of psychiatric problems. This finding is consistent with previous research with this cohort at age 5 (Rogers et al., 2012), which reported associations between reduced hippocampal volume and higher symptoms of inattention and hyperactivity, peer problems and total social-emotional difficulties in females. In addition, WMA has been associated with social-emotional, behavioural and psychiatric outcomes in preterm children (Clark et al., 2008; Indredavik et al., 2005; Johnson & Marlow, 2011; Rogers et al., 2012; Spittle et al., 2009), but not using both a structured psychiatric interview and MRI-defined brain abnormalities at this age before. Although more detailed investigation using specific areas of the brain theorised to be involved with psychiatric outcomes is needed, the results presented here raise the possibility that close monitoring and early intervention with infants with severe brain abnormalities identified using MRI in the neonatal period may help reduce later psychiatric morbidity. Although social-emotional problems at age 5 were a stronger predictor of later psychiatric outcomes than global brain abnormalities, waiting until VPT children are 5 years-old to identify those who might benefit from intervention to treat social-emotional difficulties is too long and misses an opportunity for prevention and/or earlier intervention.

Strengths of the current study include the use of a structured and well-validated psychiatric interview to measure mental health at age 7 years and high retention rates for children in the cohort. In addition, the unique aspect of the current study is that neonatal global brain abnormality was measured and examined in relation to outcomes using a structured psychiatric interview. One of the limitations is the lack of self-report from VPT children about their mental health, as it is possible that children may have been more accurate reporters of some symptoms such as anxiety. Although the measure of mental health used in the current study, the DAWBA, has a self-report version of the interview for children aged 11–17, this was not appropriate for our cohort of 7-year-old children. The small sample size

for the term born group which limited the power to detect group differences in specific psychiatric disorders (some of which have low general population rates for young children) was another limitation of the current study and was due to timing and funding restrictions. Larger studies are needed to replicate and confirm the trends identified here.

The results from the current study have important clinical implications. Not only are VPT children at higher risk for psychiatric morbidity compared with term born children, but this study has identified several factors that predict the likelihood that a VPT child will meet criteria for a psychiatric diagnosis at age 7 years. Importantly, the risk factors can be identified early in a child's life, increasing the opportunities for monitoring and early intervention. With the growing literature highlighting the increased risk for psychiatric morbidity in VPT children and identifying the specific biological and environmental factors contributing to this risk, effort is needed to provide appropriate monitoring, screening and intervention for VPT children and their families. Evidence-based interventions for the treatment of mental health problems, such as ADHD and anxiety disorders in children exist (e.g., Pelham & Fabiano, 2008; Silverman, Pina, & Viswesvaran, 2008), and are likely to be effective for VPT children. Furthermore, results from a randomised controlled trial of a preventative home visiting programme developed by our group for VPT children and their parents indicated that at age 2, children in the intervention group had fewer difficulties regulating their physical and emotional states, and parents in the intervention group reported fewer symptoms of depression and anxiety (Spittle et al., 2010). It is important that these preventative and treatment programmes continue to be developed and evaluated within the VPT population, and in particular for children with risk factors, such as severe perinatal brain injury, early social-emotional problems and higher social risk.

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References

- American Psychiatric Association. Diagnostic and statistical manual of mental disorders, fourth edition, text revision. 4. Washington, DC: American Psychiatric Association; 2000.
- Anderson P, Doyle LW. Neurobehavioral outcomes of school-age children born extremely low birth weight or very preterm in the 1990s. *JAMA*. 2003; 289:3264–3272. [PubMed: 12824207]
- Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand JS. Cognitive and behavioral outcomes of school-aged children who were born preterm: A meta-analysis. *JAMA*. 2002; 288:728–737. [PubMed: 12169077]
- Botting N, Powls A, Cooke RW, Marlow N. Attention deficit hyperactivity disorders and other psychiatric outcomes in very low birthweight children at 12 years. *Journal of Child Psychology and Psychiatry*. 1997; 38:931–941. [PubMed: 9413793]
- Briggs-Gowan, MJ.; Carter, AS. The infant toddler social and emotional assessment (ITSEA). Pre-publication version. New Haven: Yale University, Boston: University of Massachusetts; 2000.
- Carlin JB, Gurrin LC, Sterne JAC, Morley R, Dwyer T. Regression models for twin studies: A critical review. *International Journal of Epidemiology*. 2005; 34:1089–1099. [PubMed: 16087687]
- Carter A, Briggs-Gowan MJ, Jones MJ, Little TD. The Infant–Toddler Social and Emotional Assessment (ITSEA): Factor structure, reliability, and validity. *Journal of Abnormal Child Psychology*. 2003; 31:495–514. [PubMed: 14561058]

- Clark CAC, Woodward LJ, Horwood LJ, Moor S. Development of emotional and behavioural regulation in children born extremely and very preterm: Biological and social influences. *Child Development*. 2008; 79:1444–1462. [PubMed: 18826535]
- Delobel-Ayoub M, Arnaud C, White-Koning M, Casper C, Pierrat V, Garel M. for the EPIPAGE Study group. Behavioural problems and cognitive performance at 5 years of age after very preterm birth: The EPIPAGE study. *Pediatrics*. 2009; 123:1485–1492. [PubMed: 19482758]
- Delobel-Ayoub M, Kaminski M, Marret S, Burguet A, Marchand L, Guyen SN. for the EPIPAGE Study Group. Behavioural outcome at 3 years of age in very preterm infants: The EPIPAGE study. *Pediatrics*. 2006; 117:996–2005.
- Doyle LW. Victorian Infant Collaborative Study Group. Neonatal intensive care at borderline viability: Is it worth it? *Early Human Development*. 2004; 80:103–113. [PubMed: 15500991]
- Fombonne E. Epidemiology of pervasive developmental disorders. *Pediatric Research*. 2009; 65:591–598. [PubMed: 19218885]
- Goodman R. The Strengths and Difficulties Questionnaire: A research note. *Journal of Child Psychology and Psychiatry*. 1997; 38:581–586. [PubMed: 9255702]
- Goodman R. Psychometric properties of the Strengths and Difficulties Questionnaire. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2001; 40:1337–1345. [PubMed: 11699809]
- Goodman R, Ford T, Richards H, Gatward R, Meltzer H. The Development and Well-Being Assessment: Description and initial validation of an integrated assessment of child and adolescent psychopathology. *Journal of Child Psychology, Psychiatry and Allied Disciplines*. 2000; 41:645–655.
- Gray RF, Indurkha A, McCormick MC. Prevalence, stability, and predictors of clinically significant behavior problems in low birth weight children at 3, 5, and 8 years of age. *Pediatrics*. 2004; 114:736–743. [PubMed: 15342847]
- Hack M, Youngstrom EA, Cartar L, Schluchter M, Taylor GH, Flannery DJ, Borawski W. Predictors of internalising symptoms among very low birth weight young women. *Journal of Developmental and Behavioral Pediatrics*. 2005; 26:93–104. [PubMed: 15827460]
- Hall J, Wolke D. A comparison of prematurity and small for gestational age as risk factors for age 6–13 year emotional problems. *Early Human Development*. 2012; 88:797–804. [PubMed: 22698435]
- Hanley JA, Negassa A, deB Edwardes MD, Forrester JE. Statistical analysis of correlated data using generalised estimating equations: An orientation. *American Journal of Epidemiology*. 2003; 157:364–375. [PubMed: 12578807]
- Inder TE, Wells SJ, Mogridge NB, Spencer C, Volpe JJ. Defining the nature of the cerebral abnormalities in the premature infant: A qualitative magnetic resonance imaging study. *Journal of Pediatrics*. 2003; 143:171–179. [PubMed: 12970628]
- Indredavik MS, Skranes JS, Vok T, Heyerdahl S, Romundstad P, Myhr GE, Brubakk AM. Low-birth-weight adolescents: Psychiatric symptoms and cerebral MRI abnormalities. *Pediatric Neurology*. 2005; 33:259–266. [PubMed: 16194724]
- Indredavik MS, Vik T, Evensen KAI, Skranes J, Taraldsen G, Brubakk AM. Perinatal risk and psychiatric outcome in adolescents born preterm with very low birth weight or term small for gestational age. *Journal of Developmental Behavioural Pediatrics*. 2010; 31:286–294.
- Johnson S, Hollis C, Kochhar P, Hennessy E, Wolke D, Marlow N. Psychiatric disorders in extremely preterm children: Longitudinal finding at age 11 years in the epicure study. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2010; 49:453–463. [PubMed: 20431465]
- Johnson S, Marlow N. Preterm birth and childhood psychiatric disorders. *Pediatric Research*. 2011; 69:11R–18R.
- Kidokoro, H.; Neil, J.; Inder, TE. A new assessment tool for brain abnormalities in very preterm infants on term MRI. (under review)
- Kim YS, Leventhal BL, Koh YJ, Fombonne E, Laska E, Lim EC, Grinker RR. Prevalence of autism spectrum disorders in a total population sample. *American Journal of Psychiatry*. 2011; 168:904–912. [PubMed: 21558103]
- McCormick MC, Workman-Daniels K, Brooks-Gunn J. The behavioural and emotional well-being of school-age children with different birth weights. *Pediatrics*. 1996; 97:18–25. [PubMed: 8545219]

- Nomura Y, Wickramaratne PJ, Warner V, Mufson L, Weissman MM. Family discord, parental depression, and psychopathology in offspring: Ten-year follow-up. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2002; 41:402–409. [PubMed: 11931596]
- Patton GC, Coffey C, Carlin JB, Olsson CA, Morely R. Prematurity at birth and adolescent depressive disorder. *British Journal of Psychiatry*. 2004; 184:446–447. [PubMed: 15123510]
- Pelham WE, Fabiano GA. Evidence-based psychosocial treatments for attention-deficit/hyperactivity disorder. *Journal of Clinical Child & Adolescent Psychology*. 2008; 37:184–214. [PubMed: 18444058]
- Roberts G, Howard K, Spittle AJ, Brown NC, Anderson PJ, Doyle LW. Rates of early intervention services in very preterm children with developmental disabilities at age 2 years. *Journal of Paediatric Child Health*. 2008; 44:276–280.
- Rogers C, Anderson P, Thompson D, Kidokoro H, Wallendorf M, Treyvaud K, Inder TE. Regional cerebral development at term relates to school-age social-emotional development in very preterm children. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2012; 51:181–191. [PubMed: 22265364]
- Samara M, Marlow N, Wolke D. Pervasive behaviour problems at 6 years of age in a total-population sample of children born at <25 weeks of gestation. *Pediatrics*. 2008; 122:562–573. [PubMed: 18762527]
- Silverman WK, Pina AA, Viswesvaran C. Evidence-based psychosocial treatments for phobic and anxiety disorders in children and adolescents. *Journal of Clinical Child & Adolescent Psychology*. 2008; 37:105–130. [PubMed: 18444055]
- Skranes J, Vangberg TR, Kulseng S, Indredavik MS, Evensen KAI, Martinussen M, Brubakk AM. Clinical findings and white matter abnormalities seen on diffusion tensor imaging in adolescents with very low birth weight. *Brain*. 2007; 130:654–666. [PubMed: 17347255]
- Spittle AJ, Treyvaud K, Doyle LW, Roberts G, Lee KJ, Inder TE, Anderson PJ. Early emergence of behaviour and social-emotional problems in very preterm infants. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2009; 48:909–18. [PubMed: 19633579]
- Spittle AJ, Anderson PJ, Lee KJ, Ferretti C, Eeles A, Orton J, Doyle LW. Home based preventative care program for very preterm infants improves infant and caregiver outcomes at two years: Results of a randomized controlled trial. *Pediatrics*. 2010; 126:171–178.
- StataCorp. Statistical software: Release 10.0. College Station, TX: Stata Corporation; 2007.
- Treyvaud K, Doyle LW, Lee KJ, Roberts G, Lim J, Inder TE, Anderson PJ. Social-emotional difficulties in very preterm and term two-year olds predict specific social-emotional problems at five years. *Journal of Pediatric Psychology*. 2012; 37:779–785. [PubMed: 22408055]
- Volpe JJ. Brain injury in premature infants: A complex amalgam of destructive and developmental disturbances. *Lancet Neurology*. 2009; 8:110–124. [PubMed: 19081519]
- Wechsler, D. Wechsler Abbreviated Scale of Intelligence (WASI). San Antonio, TX: Harcourt Assessment; 1999.
- Whitaker AH, Feldman JF, Lorenz JM, McNicholas F, Fisher PW, Shen S, Paneth N. Neonatal head ultrasound abnormalities in preterm infants and adolescent psychiatric disorders. *Archives of General Psychiatry*. 2011; 68:742–752. [PubMed: 21727256]
- Williams JG, Brayne CEG, Higgins JPT. Systematic review of prevalence studies of autism spectrum disorders. *Archives of Disease in Childhood*. 2006; 91:8–15. [PubMed: 15863467]
- Woodward LJ, Anderson PJ, Austin N, Howard K, Inder TE. Neonatal MRI to predict neurodevelopmental outcomes in preterm infants. *New England Journal of Medicine*. 2006; 355:685–694. [PubMed: 16914704]

Key points

- Very preterm children have increased rates of certain psychiatric disorders, but uncertainty remains about rates across all disorders and for recently born cohorts.
- Using a diagnostic interview, the current study showed that very preterm children had elevated rates of psychiatric disorder at age 7 compared with term born peers, particularly for ADHD and ASD.
- Factors associated with psychiatric disorder for very preterm children included global neonatal brain abnormalities, history of social-emotional problems and social risk.
- Risk factors for psychiatric disorder in very preterm children can be identified early in life, increasing opportunities for monitoring, prevention and intervention programmes.

Table 1

Characteristics of the study population

	VPT (<i>n</i> = 177)	Term (<i>n</i> = 65)
Birth weight (g), <i>M</i> (<i>SD</i>)	975 (223)	3320 (499)
BWSDS, <i>M</i> (<i>SD</i>)	−0.54 (0.95)	0.15 (0.90) ^a
Gestational age (weeks), <i>M</i> (<i>SD</i>)	27.5 (1.94)	39.1 (1.3)
Female, <i>n</i> (%)	83 (47)	31 (48)
Singleton, <i>n</i> (%)	100 (56)	61 (94)
Maternal age (years), <i>M</i> (<i>SD</i>)	32.4 (5.7)	33.7 (4.5)
Social risk, median (IQR)	2 (1, 3)	1 (0, 2)
SGA, <i>n</i> (%)	16 (9)	1 (1)
Oxygen at 36 weeks, <i>n</i> (%)	57 (32)	–

M, mean; *SD*, standard deviation; IQR, interquartile range; BWSDS, birth weight SD score (a measure of growth restriction in utero); SGA, small for gestational age.

^a
n = 40 for term participants.

Table 2

DSM-IV diagnoses at 7 years

	VPT (<i>n</i> = 177)		Term (<i>n</i> = 65)		Unadjusted OR (95% CI)	<i>p</i>
	<i>n</i>	%	<i>n</i>	%		
ASD	8	4.5	0	—	—	.08 ^a
Separation anxiety	6	3	2	3	1.11 (0.22, 5.68)	.90
Specific phobia	7	4	2	3	1.30 (0.26, 6.44)	.75
Social phobia	2	1	0	—	—	.39 ^a
PTSD	1	<1	0	—	—	.54 ^a
Panic	0	—	0	—	—	—
OCD	0	—	1	2	—	.10 ^a
General anxiety	4	2	1	2	1.44 (0.16, 12.83)	.75
Anxiety (any)	19	11	5	8	1.41 (0.51, 3.92)	.50
Depression	1	<1	2	3	0.18 (0.02, 2.04)	.17
ADHD (any)	18	10	2	3	4.09 (0.93, 18.00)	.06
ADHD combined	11	6	2	3	2.09 (0.46, 9.59)	.34
ADHD inattentive	4	2	0	—	—	.22 ^a
ADHD hyp-impuls	2	1	0	—	—	.39 ^a
ADHD NOS	1	<1	0	—	—	.54 ^a
ODD	3	2	0	—	—	.29 ^a
Conduct disorder	0	—	0	—	—	—
Eating disorder	0	—	0	—	—	—
Tic disorder	2	1	0	—	—	.39 ^a
Other DSM-IV disorder	6	3	0	—	—	.13 ^a
Any DSM-IV disorder	42	24	6	9	3.13 (1.27, 7.71)	.01

ADHD hyp-impuls, ADHD hyperactive-impulsive; ASD, autism spectrum disorder; OCD, obsessive-compulsive disorder; ODD, oppositional defiant disorder; PTSD, posttraumatic stress disorder; other DSM-IV diagnoses, two anxiety disorder NOS, two disruptive behaviour disorder, one mixed anxiety-depressive disorder, one adjustment disorder; OR, odds ratio.

^aChi-squared *p* value.

Table 3

Predictors of psychiatric disorder at age 7 years for VPT children

	Psychiatric disorder (<i>n</i> = 42)	No psychiatric disorder (<i>n</i> = 135)	Unadjusted OR (95% CI), <i>p</i>	Final adjusted OR ^b (95% CI), <i>p</i> (<i>n</i> = 161)
Gender, <i>n</i> female (%)	24 (57)	59 (44)	1.38 (0.86, 3.29), .13	2.05 (0.93, 4.55), .08
Multiple (twin or triplet), <i>n</i> (%)	17 (40)	60 (44)	0.76 (0.42, 1.38), .36	–
BWSDS, <i>M</i> (<i>SD</i>)	−0.73 (0.96)	−0.49 (0.95)	0.77 (0.54, 1.11), .16 ^a	–
Gestational age (weeks), <i>M</i> (<i>SD</i>)	27 (2.12)	28 (1.88)	0.98 (0.81, 1.18), .81 ^a	–
Received antenatal corticosteroids, <i>n</i> (%)	34 (81)	119 (88)	0.55 (0.23, 1.33), .18	–
Oxygen at 36 weeks, <i>n</i> (%)	12 (29)	45 (33)	1.24 (0.90, 1.72), .19	–
Global brain abnormality	–	–	1.50 (1.03, 2.21), .04	1.67 (1.09, 2.56), .02
<i>n</i> mild (%)	18 (43)	55 (41)	–	–
<i>n</i> moderate (%)	9 (21)	25 (19)	–	–
<i>n</i> severe (%)	5 (12)	5 (4)	–	–
Neurodevelopmental disability, <i>n</i> (%)	4 (10)	5 (4)	2.61 (0.63, 10.85), .19	–
Social risk at 7 years, <i>M</i> (<i>SD</i>)	2.8 (1.8)	1.9 (1.7)	1.31 (1.09, 1.60), .005 ^a	1.45 (1.17, 1.81), .001 ^a
Social-emotional difficulty 2 years, <i>n</i> (%)	16 (38)	39 (29)	1.51 (0.72, 3.14), .27 ^a	–
Social-emotional problem 5 years, <i>n</i> (%)	14 (33)	9 (7)	4.09 (1.90, 8.81), .000 ^a	4.75 (2.07, 10.89), .000 ^a

BWSDS = birth weight SD score; social-emotional difficulty 2 years = clinically significant score on at least one domain of ITSEA; social-emotional problem 5 years = clinically significant total score on SDQ; neurodevelopmental disability = FSIQ score <70, severe cerebral palsy, blindness, visual acuity worse than 20/200 in the better eye or significant hearing loss.

^aRepresents change in odds of meeting criteria for psychiatric diagnosis per 1 unit change in predictor variable, for example, for BWSDS, OR per SD change; percentages in psychiatric and no psychiatric disorder columns reflect those in each group for the indicated category, that is, 57% of those with psychiatric disorder were girls, meaning 43% (*n* = 18) with psychiatric disorder were boys.

^bResults from the final multivariable regression model including gender, global brain abnormality, social risk and social-emotional problem 5 years as predictor variables in a single regression model.