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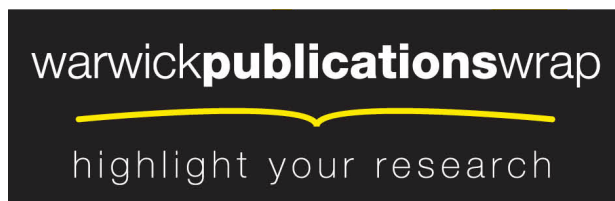
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Behavioral outcomes and psychopathology during adolescence

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Abstract

Preterm birth is associated with an increased risk of residual neurodevelopmental disability and cognitive impairment. These problems are closely associated with psychiatric disorders and thus it is unsurprising that preterm birth also confers high risk for poor long-term mental health. The risk associated with preterm birth is not a general one, but appears to be specific to symptoms and disorders associated with anxiety, inattention and social and communication problems, and manifest in a significantly higher prevalence of emotional disorders, ADHD and Autism. Adolescence is a key period for mental health and studies have shown that problems evident in childhood persist over this time and are more stable among preterm individuals than term-born peers. There is also modest evidence for an increased prevalence of psychotic symptoms in preterm adolescents. The high prevalence of psychiatric disorders, present in around 25% of preterm adolescents, requires long term screening and intervention.

Keywords: preterm; behavior; autism spectrum disorders; ADHD; anxiety; psychiatric disorders.

Abbreviations:

LBW Low birthweight

VLBW Very low birthweight

ELBW Extremely low birthweight

CBCL Child Behavior Checklist

SDQ Strengths and Difficulties Questionnaire

ASD Autism Spectrum Disorder

ADHD Attention Deficit/Hyperactivity Disorder

SGA Small for Gestational Age

In May 2012, the World Health Organization, in partnership with over thirty organisations worldwide, launched “Born Too Soon: The global action report on preterm birth.”[1] This report documented the continuing rise in global preterm birth rates and highlighted prematurity as a major cause of long term loss of human potential amongst survivors throughout the world. With concurrent improvements in survival rates for babies born at extremely low gestations[2], growing numbers of children will exert increasing demands on schools, societies and healthcare systems in coming years. An understanding of the long term sequelae of preterm birth is important for the provision of appropriate ongoing care for individuals and for service planning at the population level.

This is the case not just for neonatal services, but also for child and adolescent mental health services and education systems. Preterm birth is associated with a high risk of residual disability across multiple functional domains which affects individuals throughout their lifespan.[3] Whilst severe neurosensory disabilities were once thought to be the major adverse outcomes, population-based cohort studies have shown that cognitive deficits and behaviour, social and emotional problems are far more prevalent and account for a substantial proportion of long term impairment.[4-6] Increasingly, it is recognised that these problems are not confined to a small cluster of individuals with the most severe adverse outcomes but affect a large proportion of preterm survivors to a greater or lesser degree. In this paper we review literature pertaining to the nature and severity of behaviour, emotional and social problems and psychiatric disorders in adolescents born preterm.

Adolescence and mental health

Adolescence is typically determined using chronological age and is defined by the World Health Organisation as the period from 10 to 19 years of age. It is a time of rapid growth and development marking the transition from childhood to adulthood, during which individuals experience major physical, social and emotional changes. The biological and physical maturation associated with

puberty is accompanied by changes in social expectations and responsibility, increased societal and educational demands, and salient changes in social relationships, including increasing interest in the development of romantic relationships and a shift of support and influence from parents to peers.[7]

Adolescence is a key developmental stage in terms of mental health: a number of psychiatric disorders have their onset in adolescence and some childhood-onset disorders are associated with changes in their clinical expression during this time. This includes the onset and rise in rates of depression[8], adolescent-onset conduct disorder[9], and the emergence of psychotic symptoms.[10] Typical neurodevelopment during this sensitive period may also impact on psychiatric illness[11, 12], and the female advantage in mental health wanes with girls beginning to display more morbidity than boys, particularly for emotional disorders. Assessments earlier in childhood are thus inadequate for determining the prevalence of psychopathology throughout the adolescent years and both cross-sectional and longitudinal studies should consider this as an essential period for investigation and re-assessment.

Methodological considerations

Comparisons between population-based studies of preterm cohorts are problematic in general.[13] Differences in population denominators can result in wide variation in outcomes, and the study of birth weight-defined cohorts may confound results with the inclusion of babies born small for gestational age (SGA), which may be associated with different behavioural outcomes.[14, 15] Different assessment tools and ages at assessment can also result in varying prevalence estimates for both symptoms and disorders, especially in the case of mental health assessments. In particular, the use of self-report versus informant ratings can produce widely different outcomes.[16, 17]

The majority of studies have used behavioural screening questionnaires as these are cost and time efficient for large-scale investigations. Two have emerged as the most popular assessment tools

facilitating international and cross-cultural comparisons: the Achenbach System of Empirically Based Assessment (ASEBA)[18], comprising the Child Behavior Checklist (CBCL), Teacher's Report Form (TRF) and Youth Self-Report (YSR), and the Strengths and Difficulties Questionnaire (SDQ)[19] comprising parent, teacher and self-report scales.

These screening tools yield higher rates of individuals scoring in the clinical range than have, or would meet the criteria for, a clinical diagnosis. Thus, like other developmental screening tools, these are associated with high rates of false positive screens and relatively low positive predictive values (PPV).[20] However, the excess of identified 'cases' should not be disregarded lightly since this may be indicative of a population shift in the frequency of behavioural symptoms. For this reason, it is important to use both dimensional and diagnostic measures to capture the distribution of symptoms at a population level. Indeed, adopting both a dimensional and diagnostic approach has been proposed for studying the aetiology of childhood mental disorders as many conditions may develop on the basis of a dimensional liability with boundaries that extend more broadly than those based on diagnostic categorisations[21, 22] and may inform taxonomic classifications.[23]

Dimensional measures are also useful where the prevalence of disorders in the general population is low and large samples are therefore required for diagnostic studies. In the following sections we review literature relating to psychopathology in preterm populations focusing on studies using dimensional or clinical diagnostic measures and highlighting the practical implications of these findings.

The preterm behavioural phenotype

Although a substantial body of evidence has accumulated showing the increased risk for psychopathology in preterm populations throughout early childhood, there is a paucity of studies in adolescence. This may reflect the greater practical difficulties in maintaining long term contact with a cohort over the adolescent years and the assumption that problems identified earlier in childhood

persist later in life. In addition, reports of contemporary populations of adolescents born after the advent of modern neonatal intensive care in the 1990s are necessarily fewer and will emerge with greater frequency in coming years.

Where studies do exist these continue to show significantly increased problems over the adolescent years compared with term-born counterparts. Almost all studies using screening measures, such as those outlined above, have found significantly increased rates of behaviour problems in very preterm or VLBW adolescents. Using a cut-off for the risk of clinically significant problems, typically defined as scores >90th percentile of a standardisation sample or that of matched controls, authors have reported a 3-8 fold increased risk for behavioural problems compared with term-born peers. e.g.,[15, 16, 24-30]. Varying prevalence estimates can be attributed to differences in population denominators and sample sizes. As in all other domains of outcome, there appears to be a gestational age-related gradient in the risk for behaviour problems with a greater prevalence of positive screens associated with decreasing gestational age at birth; this has been shown in both clinical cohort studies and epidemiological investigations using population-linkage methods.[26, 31-33]

Although increasing attention has been paid to the outcomes of babies born at moderate (32-33 weeks) and late preterm (34-36 weeks) gestations in recent years, studies of behavioural outcomes remain few in number and are typically confined to assessments earlier in childhood. There is a good deal of consistency in outcomes during the preschool or early school years which have typically shown significantly increased prevalence of problems compared with term-born peers.[33]

However, the few existing studies of late preterm adolescents have inconsistent findings with some reporting increased risk for clinically significant anxiety and attention problems in 8-16 year olds[34], and others reporting no difference to term-controls from middle childhood through adolescence.[35] Although findings are currently equivocal, even sub-clinical increases in symptoms

may be important at the population level given the large proportion of children that are born at these gestations. Where differences have been identified at younger ages this is purported to be associated with medically indicated deliveries rather than preterm birth per se, and thus there may be an underlying mechanism associated with hypertensive disorders.[36]

Despite differences in prevalence estimates there is much greater consistency in the pattern of behavioural morbidities identified which has led to the proposition that there is a 'preterm behavioural phenotype' characterised by inattention, anxiety and social problems.[5] Preterm birth does not appear to confer a general risk for behavioural morbidity, but a specific risk for a triad of disorders and symptoms. This was clearly highlighted in studies using the CBCL in five different populations in which there were striking similarities in the profile of behaviour problems indicated by significantly increased scores on attention, social and thought scales in extremely preterm or ELBW children compared with term-born counterparts.[30, 37] Studies among very preterm/VLBW adolescents have also shown a consistent pattern of results[15, 17, 27, 29] which has been extended to adolescents born at late preterm gestations where studies have been conducted.[34]

Comparisons between studies are facilitated using diagnostic classifications which attenuate the effects of differing assessment tools. However, psychiatric evaluations in the adolescent years are sparse. Authors of the few studies that have been conducted have reported, with remarkable consistency, that around 1 in 4 preterm survivors have a psychiatric disorder in adolescence representing a 3- to 4-fold increased risk compared with term-born peers (Table 1). These have focused primarily on early adolescents (aged 11-15 years), but the ~25% prevalence of disorders has been associated with ELBW/extremely preterm birth[38], VLBW/very preterm birth[15, 39] and LBW.[28] A recent meta-analysis of diagnostic studies in preterm survivors reported a pooled OR of 3.7 (95% CI 2.6 to 5.2) for psychiatric disorders.[40] We are aware of only one cohort study of psychiatric disorders in late preterm adolescents in which there was no significant increase in

disorders in 19 adolescents born 31-37 weeks gestation compared with 20 term-born controls (21.1% vs. 10%; $p > 0.05$).[41] However, this study was of a small sample and a cohort born in the late 1970s. In contrast, large epidemiological investigations using population-linkage methods have shown increased risk for psychiatric disorders across the full spectrum of gestations, including early term birth (37-38 weeks gestation) in adulthood.[31, 32] Although the risk decreases stepwise with increasing gestation at birth, there is a large population-attributable risk for psychiatric disorders associated with moderate and late prematurity. More studies are needed of late and moderate preterm survivors and these are likely to emerge as current cohorts reach adolescence.

INSERT TABLE 1

The diagnostic studies shown in Table 1 lend further support for the existence of the preterm behavioural phenotype associated with a specific risk for a triad of disorders, namely Autism Spectrum Disorders (ASD), Attention deficit/Hyperactivity Disorder (ADHD) and emotional disorders; importantly, there is no concomitant increase in the prevalence of conduct disorders. Almost all have reported a significantly increased risk for ADHD and anxiety disorders and, where sample sizes are large enough to study, in ASD as well. Moreover, evidence has accumulated to show that the sequelae of preterm birth are specific to sub-types of disorders even within these diagnostic classifications further delineating the preterm phenotype. Each of these is discussed in detail in the following sections.

Autism Spectrum Disorders (ASD)

There has been a furore in recent years regarding the association of preterm birth with ASD. This was fuelled in part by reports of a markedly high prevalence of autistic features in preterm infants, with up to 25% of very preterm/VLBW[42, 43] and 41% of extremely preterm infants[44] screening positive for the risk of ASD using the Modified Checklist for Autism in Toddlers (M-CHAT). Caution

should be observed when interpreting such reports as the specificity of screening for ASD in infancy is particularly confounded in preterm populations in which there is a high prevalence of neurodevelopmental impairment and global developmental delay.[43-45] Thus, whilst the risk may remain significantly increased compared with term peers later in childhood, the prevalence of disorders would be expected to be far lower.

Indeed, this is what is found in the small number of diagnostic studies in adolescence. In studies by Indredavik and colleagues[15] and Elgen and colleagues[28], 1-2% of VLBW/LBW adolescents met diagnostic criteria for ASD, specifically Asperger's Disorder, compared with none of their controls. More recently, a 5% prevalence of ASD has been estimated in young adults born with LBW.[46] In the only study of a contemporary population of extremely preterm children born <26 weeks gestation, we have reported 8% prevalence of ASD at 11 years of age.[38] This raised concern among clinicians and the academic community given that the rate of disorders is some 65 times higher than the prevalence of narrowly defined Autistic Disorder and around 4-12 times higher than the prevalence of all ASD in the general population.[47] We are not aware of any gestationally-defined cohort studies of ASD in late preterm adolescents but expect these will emerge in coming years.

Important trends in the literature relate to the frequency of ASD symptoms and the clinical expression of disorders in preterm survivors. In studies using both a screening measure and a psychiatric evaluation, far more adolescents have clinical symptoms and screen positive for ASD than have confirmed diagnoses.[15, 46, 48] Studies using dimensional measures have also shown that preterm adolescents have significantly higher mean scores for ASD symptoms compared with term-born controls indicating an increased liability to ASD symptomatology.[24, 28, 48] Children who meet the diagnostic criteria for ASD are likely to represent the extreme end of a generally increased distribution of symptoms in preterm survivors. Crucially, this means that there are many more children with sub-threshold symptoms that may impact on daily function and forming peer

relationships but that do not meet diagnostic criteria and thus do not receive help. This has practical implications for screening and intervention in this population.

The co-morbidities and clinical expression of ASD in preterm survivors appears to be different from that of the general population. In particular, ASD has been associated with cognitive impairment, smaller head circumference, BPD, white matter abnormalities on cranial imaging studies and a weaker association with repetitive or stereotyped behaviours characteristic of classic Autism.[24, 43, 48-50] Data obtained using the Social Communication Questionnaire (SCQ) in the UK EPICure Study of extremely preterm children at 11 years has shown that the risk for ASD symptoms is greater for social and communication problems than for repetitive behaviours (Figure 1a).[48] Moreover, after adjustment for IQ, the frequency of repetitive behaviours was no longer significantly increased in the extremely preterm cohort in contrast to social and communication problems (Figure 1b). ASD features in preterm survivors may be the result of core deficits in social and communication skills that arise as a result of poor processing of social stimuli mediated by inattention and distractibility[37], and they may thus be susceptible to disorders that are qualitatively different from classic autism.

INSERT FIGURE 1a & b

Together, these findings are indicative of an environmental origin for ASD that may be associated with aberrant brain development and superimposed CNS injuries.[43] We have previously noted that this behavioural profile is similar to that of Romanian adoptees who also experience highly abnormal early environments during a critical period for development of the social brain.[48, 51] It appears that severe early deprivation and impaired social stimulation may lead to similar brain alterations and impact on social, emotional and behavioural outcomes as in preterm survivors.

Early identification of autistic features, or indeed socio-communicative difficulties, may facilitate early recognition of symptoms in order for support to be provided for families. Screening in early adolescence has been shown to have good diagnostic utility[52] and a number of studies have found that infant developmental test scores and abnormal ratings on the CBCL, particularly the withdrawn scale, are associated with ASD features in infancy and childhood.[42, 48] A recent study has also suggested that NICU graduates with ASD may display a unique behavioural profile including the persistence of abnormal neonatal neurobehaviours and a declining developmental trajectory in infancy. However, this was a heterogeneous sample of babies admitted for neonatal intensive care and the significance and predictive utility of such markers requires investigation in a purely preterm population.[53]

Attention Deficit/Hyperactivity Disorder (ADHD)

ADHD is the most well researched psychiatric outcome in relation to preterm birth. Studies using the CBCL and other DSM-based screening tools have consistently shown an increased prevalence of attention problems in preterm children and adolescents and have shown the greatest increase in symptoms in this domain.[6, 37, 54] This is mirrored in diagnostic studies of preterm adolescents in which significantly increased risk has been shown for ADHD diagnoses and the greatest prevalence associated with these disorders.[15, 28, 38, 39] Authors have reported estimates of 11.5% prevalence for extremely preterm early adolescents[38], 7%-23% for VLBW adolescents[15, 39], and 10%-16% prevalence in those born with LBW.[28] These equate to a 2-3 fold increased risk in VLBW adolescents and a 4-fold increased risk in those born extremely preterm. A meta-analysis of very preterm/VLBW children also found a similar pooled relative risk (RR) of 2.6 in 6 studies comparing these with children born at term.[54] Epidemiological studies have also shown an increased risk for ICD-defined Hyperkinetic Disorder[55], with a similar RR of 2.7 for children born <34 weeks gestation. A summary of diagnostic studies of ADHD has been published previously.[5]

As in the case of ASD, studies using both a screening tool and a diagnostic interview have consistently shown that far more children have a significant level of symptoms than meet diagnostic criteria. For example, Elgen and colleagues[28] found that 25% of LBW adolescents had clinically significant attention problems on the CBCL yet only ¼ of these had an ADHD diagnosis on psychiatric evaluation. Again, this might be expected given the preponderance of false positive on such measures, but this may also reflect the population shift in ADHD symptoms. This is demonstrated in studies using dimensional measures in which preterm children and adolescents have significantly higher mean scores than term-born peers.[6, 15, 26, 56] Using the Du Paul ADHD Rating Scale IV to assess the frequency of ADHD symptoms in the 1995-born EPICure cohort (with the presence of a symptom classified as parent-rating of often/very often), Figure 2 shows the generally increased liability for ADHD symptoms in these extremely preterm adolescents at 11 years of age compared with a matched term-reference group.[38] This has practical implications for screening and referral since many children may have symptoms that do not reach the diagnostic threshold yet may impact on their everyday function.

INSERT FIGURE 2

More recently, interest has become focused in the clinical expression of ADHD in preterm individuals. Studies using DSM-based diagnostic criteria, which permits diagnosis of sub-types of ADHD, namely ADHD-predominantly Hyperactive/Impulsive (ADHD/H), ADHD-predominantly Inattentive (ADHD/I) and ADHD-combined (ADHD/C), have shown that the risk of disorders appears to be greater, and in some cases specific to, ADHD/I.[6, 38, 39, 57] We have reported that there was no significant excess of ADHD in extremely preterm adolescents when ICD-10 criteria for Hyperkinetic Disorders were applied, indicating that hyperactivity/impulsivity may not be a specific feature of psychopathology following preterm birth.[38] The greater risk for inattention relative to hyperactivity is also borne out in dimensional studies in which significantly higher mean scores have

been found for inattention but not hyperactivity compared with term-born controls, and larger effect sizes noted for symptoms of inattention relative to hyperactivity.[6, 15, 56] The clinical expression of ADHD also differs on other dimensions. The greater risk associated with male sex in the general population is not seen in preterm children and there is a notable lack of comorbid conduct disorders in preterm survivors, at both the individual and population level, in contrast to the well-documented comorbidity of these disorders in the general population.[15, 28, 38]

These findings have lead authors to suggest that ADHD after prematurity is in fact a specific risk for inattention that is associated with a neurodevelopmental aetiology. Indeed, studies have shown significant associations between ADHD symptoms and indices of brain maturation and injury, including smaller head circumference, intraventricular haemorrhage, parenchymal lesions and/or ventricular enlargement.[15, 49, 58-60] Specifically, inattention symptoms have been associated with reduced white matter volumes and indices of aberrant white matter connectivity throughout the brain.[24, 49] These results suggest that there are different underlying mechanisms, neurological and behavioural profiles associated with inattention and lend support to the bi-factor model of ADHD.[61] In particular, preterm children may be susceptible to a childhood-onset dysexecutive syndrome in which inattention is associated with working memory difficulties, a slow processing speed and internalising difficulties, which are also characteristic of the cognitive profile of preterm adolescents.[62, 63] These findings have practical implications for assessment, management and treatment of preterm children with ADHD. In particular, inattention is an important predictor of academic achievement in both preterm and full term children and thus screening and referral for treatment may be central to improving educational outcomes and reducing long-term learning difficulties.[57]

Emotional disorders

In the general population, the most frequent childhood-onset emotional disorder is anxiety, typically separation anxiety, specific phobias and generalized anxiety disorder with around 40% of the lifetime prevalence of anxiety disorders having their onset before 10 years of age.[64, 65] In contrast, depression is rarely diagnosed before 10 years when there is a prevalence of less than 2% in both boys and girls.[65, 66] The subsequent rise in depressive disorders during adolescence is strongly related to pubertal development and associated hormonal changes.[67] Over this time a gender difference emerges that persists across the lifespan with depressive disorders being twice as common in females.[68] Anxiety and depression are often co-morbid and, in most cases, anxiety is a precursor to the onset of depression.[69] Most studies of emotional disorders in childhood thus report on anxiety problems, whilst preterm outcomes studies carried out in adolescence and adulthood focus on both anxiety and depression. Depression is one of the major contributors to the global burden of disease and its significance in conferring additional functional morbidity in preterm adolescents should not be overlooked.

The evidence for significantly increased anxiety scores in preterm survivors obtained using behavioural screening tools is surprisingly mixed in childhood.[54] In a comparison of ELBW cohorts from the USA, Canada, the Netherlands and Germany, assessed at 8-10 years, parents did not report significantly raised anxiety scores compared with cohort-specific term-born controls[37], while others have reported increased emotional problem scores in very preterm children.[70] In contrast, raised anxiety/depression scores have been consistently reported for children aged 8-11 years who were born extremely preterm using both parent and teacher reports.[30, 71] There are few studies of emotional problems in moderately or late preterm-born children which have similarly mixed results.[33]

There are even fewer studies of adolescents that have included dimensional measures of anxiety or depression. These are completely lacking for adolescents born moderately or late preterm and the only existing studies have been conducted with young adults. These are based on record-linkage studies of psychiatric diagnoses at hospital admission or discharge from Sweden and Denmark, or from records of pharmacological prescriptions such as antidepressants or sedatives.[31, 72-74] These studies, often of over 1 million individuals, indicate that the risk for a mood disorder (predominantly depression) by early adulthood is significantly increased not only in extremely and very preterm adults but also in adults born moderately or late preterm/LBW in which an excess of 10%-50% prevalence of hospitalisation, psychiatric treatment for mood disorder or antidepressant medication has been reported (Table 2). In contrast, a small New Zealand study of ex-participants in a RCT found a lower rate of probable depression in moderate to late preterm adults compared to full term controls (13% vs. 24%; OR: 0.6 95% CI 0.3-1.0). Subsequently, no significant differences between groups were found in anxiety scores at a mean follow-up age of 31 years.[75]

INSERT TABLE 2

Studies of very preterm adolescents mostly indicate a significantly increased prevalence of emotional problems as rated by parents or teachers (Table 3). However, there are notable exceptions in some studies in which no significant differences were found.[27, 76] Furthermore, where teenagers self-reported, some found higher anxious/depressed or emotional scores[17, 77] while others did not find any differences compared to full term controls.[16, 24] Thus emotional problems are more likely to be rated by parents or teachers than by the teenagers themselves. This is consistent with similarly discrepant findings for parent-reported versus self-reported quality of life.[78] It thus appears that very preterm/VLBW adolescents are more optimistic about their life than their parents or teachers, or, alternatively, that their term peers are more pessimistic at this age leading to few differences compared with preterm adolescents.

INSERT TABLE 3

Only five studies of preterm adolescents have carried out diagnostic psychiatric evaluations enabling classifications of anxiety disorders or depression; three have been from the United Kingdom[38, 39, 79] and two from Norway.[15, 28] These have reported Odds Ratios of 2.7 to 5.8 compared with term-born controls. The authors of a recent meta-analysis combining data from these five studies reported a weighted Odds Ratio of 2.92 (95% CI 1.82 to 4.67) for a diagnosis of emotional disorder in these preterm adolescents compared with term-born controls.[40] Another recent systematic review, specifically of anxiety disorders in VLBW/ELBW adolescents included three of the afore-referenced diagnostic studies and three that assigned classifications of clinically significant anxiety problems based on dimensional measures. The authors reported that preterm adolescents have a 2.3 times (95% CI 1.2 to 4.5) increased risk for anxiety problems or anxiety disorder.[80] Upon closer inspection, the review indicates that studies that included structured interviews and psychiatric diagnosis were more likely to report significantly increased anxiety disorders compared with the studies that employed dimensional measures (i.e., CBCL; YABCL) in adolescents that were free of any major impairment.

Overall, very preterm and, in particular, extremely preterm survivors are at significant but generally moderately increased risk for depression and anxiety problems and disorders in adolescence. A small excess of these emotional problems are also found in moderately and late preterm-born children according to national registry studies of psychiatric treatment. However, the vast majority of reports to date have relied on cross-sectional comparisons. In a few recent studies longitudinal analyses have indicated that emotional problems may be more stable from childhood through adolescence in preterm individuals compared with term-born peers. Hall and Wolke[81] have identified two trajectories of emotional scores in children who were repeatedly assessed from 6 to 13 years of age. While most children had consistently low scores, 23.5% had consistently high scores and this latter

group were more likely to have been born very preterm. Furthermore, mental health problems identified in adolescence by parents and clinicians have been shown to be more stable and to increase into adulthood in VLBW children compared with full term controls. Thus, apart from being more prevalent, the emotional problems of very preterm or VLBW children appear to be more stable across childhood and adolescence and may show an increase of prevalence into adulthood. Preterm children have been described as having more peer problems and to be more socially withdrawn.[82] We therefore speculate that additional environmental factors such as social rejection or bullying, previously identified as risk factors for depression [83], may contribute to the increased prevalence of emotional problems in preterm adolescents.

Psychotic disorders

Psychoses such as schizophrenia or schizophreniform disorder have their onset in late adolescence or adulthood. Recent evidence indicates that psychotic symptoms are experienced by a substantial minority of adolescents as early as 10 to 15 years of age. While most individuals with psychotic symptoms in early adolescence will not go on to develop psychotic disorder, the risk is substantially increased for developing schizophreniform disorder or schizophrenia in early adulthood.[84] This has led to the formulation of the psychosis proneness-persistence-impairment model of psychotic disorder whereby genes, early pre- and perinatal adversities and environmental trauma act together in the development of psychotic disorders.[85-87] Furthermore, prenatal and perinatal factors have been long considered as risk factors for neurodevelopmental and social problems frequently described as precursors for psychoses.[88, 89] Thus the majority of adults eventually diagnosed with schizophrenia and other psychotic illnesses show a steep increase in adjustment problems such as social withdrawal, anxiety, academic difficulties and thought problems throughout adolescence.[89]

There is a paucity of clinical studies of the impact of preterm birth on psychotic symptoms or experiences in adolescence. One recent study found no unique association between gestation and psychotic like symptoms in 12 year olds. However, maternal infection in pregnancy, maternal diabetes, the need for resuscitation and low 5-minute APGAR scores were predictors of psychotic symptoms at 12 years [90]; in turn, these factors are all associated with increased risk of preterm birth. The aforementioned registry studies from Sweden and Denmark also indicate a substantially increased risk for the development of psychosis including both non-affective psychosis, such as schizophrenia, and bipolar affective psychosis with decreasing gestation at birth (Table 2).[31, 72-74] A further recent study using data from the Danish Medical and Psychiatric Central Register modelled the effect of gestation on both schizophrenia and affective disorder. They found that premature birth per se was associated with a significantly elevated risk of developing both affective disorder and schizophrenia, an effect that remained significant after adjustment for LBW.[91] Given the high prevalence of academic difficulties, social problems and anxiety among preterm survivors throughout adolescence, further research is needed to elucidate whether these may serve as early markers for adult-onset psychoses.

Summary

Adolescence is a key period for the development and exacerbation of psychiatric symptoms and disorders and should be considered as an important phase for assessment of mental health outcomes. Findings show that 1 in 4 very preterm survivors has a psychiatric disorder in adolescence with many more exhibiting a sub-threshold level of symptoms that may nevertheless impact on daily life. There are relatively few studies of outcomes in adolescence, but where these exist the findings in childhood are mostly echoed during this period. The significant excess of symptoms and disorders associated with inattention and socio-communicative problems persists throughout adolescence while anxiety/depression symptoms show an increase in ex-preterms lending support for the notion that the psychiatric sequelae of preterm birth are specific to a triad of disorders, the development of

which are associated with neonatal complications and neurodevelopmental problems. The few longitudinal studies that have been conducted indicate that behaviour problems of preterm children are more stable over time compared with term-born controls. The findings of studies of late and moderate preterm cohorts are few as yet and have produced equivocal findings, but more studies are expected in coming years as current cohorts reach adolescence. There is some suggestion for an increased prevalence of psychotic symptoms in very preterm survivors but more research is needed, particularly to determine the significance of the high level of neurocognitive difficulties, anxiety, depression and social problems as proneness factors for adult-onset psychoses. Future advances in understanding underlying alterations in large scale brain networks may provide a powerful paradigm for investigating cognitive and affective dysfunction of psychiatric disorders in preterm adolescents. The increasing numbers of preterm survivors in coming years requires an appreciation of the prevalence of psychiatric symptoms and disorders and their clinical expression in this group for the development of appropriate mental health services and population-specific approaches to screening and treatment.

Key Guidelines

- Psychiatric symptoms and disorders confer a high level of functional morbidity in preterm survivors and planning for the future should reflect the need for long-term follow-up of this population.
- The later onset of mental health problems compared with neurodevelopmental and cognitive sequelae requires assessment and screening throughout the key period of adolescence, even among those without neurodevelopmental impairment.
- As the behavioural, social and emotional sequelae associated with preterm birth are especially important for educational achievement and integration in the labour market, identification and support during the school years may also serve to improve academic outcomes in this population.

Research directions

- Future studies should attempt to determine the nature and causes of the characteristic mental health problems of preterm adolescents. This should include investigation of underlying large scale brain networks but also of specific environmental risk factors (e.g. bullying, parenting, schooling) and their implications for population-specific approaches to assessment and intervention.
- More studies are needed of the long-term mental health outcomes of adolescents born moderately and late preterm to determine whether the psychiatric sequelae of very preterm birth extends across the spectrum of preterm, and even early term, gestations.
- The role of adolescent behavioural, emotional and social problems as early precursors of psychotic disorders in preterm-born adolescents remains to be elucidated.

Conflict of interest statement

The authors have no conflicts of interest to disclose.

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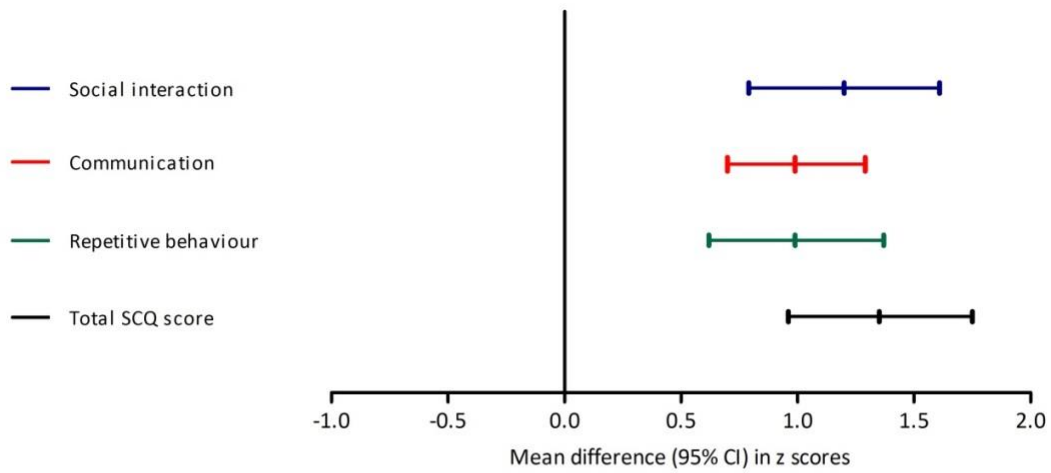


Figure 1a

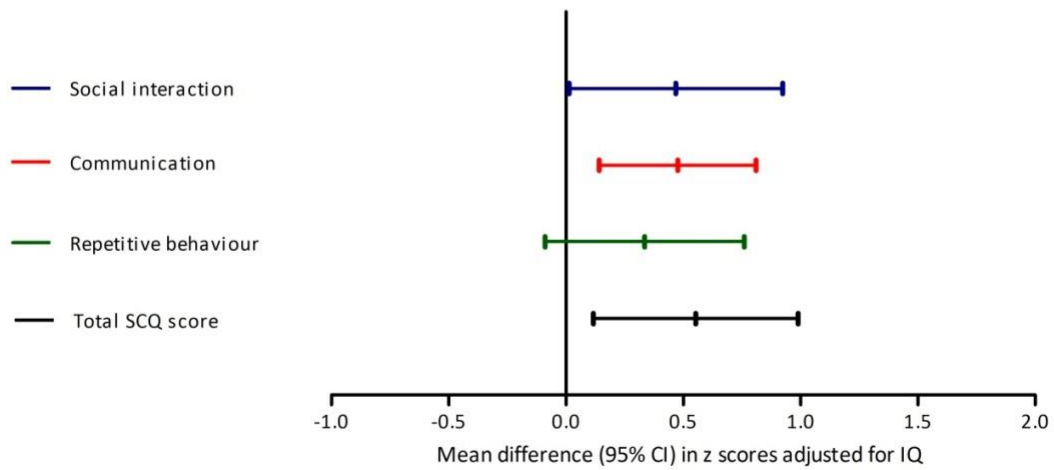


Figure 1b

Figure 1. Mean difference and 95% confidence intervals in Z-scores between 186 extremely preterm children born <26 weeks gestation and 139 term born controls on Social Communication Questionnaire sub-scale scores at 11 years of age in the EPICure Study.[48] Scores are shown for dimensions of Social Interaction, Communication and Repetitive Behaviour, both unadjusted (Figure 1a) and after adjustment for IQ (Figure 1b).

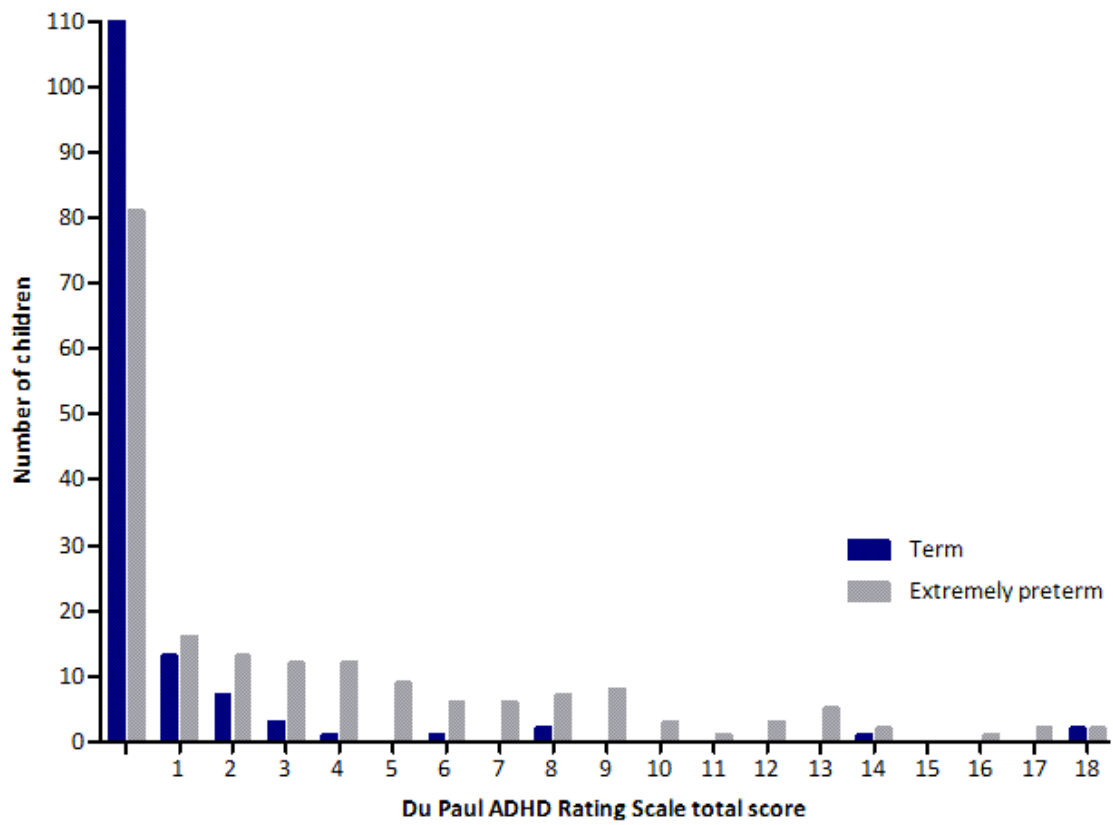


Figure 2. Frequency distribution of parent rated ADHD symptoms in extremely preterm (born <26 weeks gestation) adolescents at 11 years compared with term-born controls (The EPICure Study).[38]

Table 1: Population-based cohort studies investigating psychiatric disorders in preterm adolescents (aged 10-19 years).

Study	Year	Age	Preterm	Control	Preterm %	Control %	OR (95% CI)	Interview	Risk for specific disorders
Johnson et al. 2010[38]	1995	11	n=219 <26 weeks	n=152	23%	9%	3.2 (1.7 to 6.2)	DAWBA	ADHD, Anxiety disorders, ASD
Indredavik et al. 2005^[24]	1986-1988	14-15	n=55 <1501g	n=66	27%	6%	3.8 (1.3 to 10.5)*	KSADS	ADHD, Anxiety disorders
Indredavik et al. 2004[15]	1986-1988	14	n=56 <1501g	n=83	25%	7%	4.3 (1.5 to 12.0)	KSADS	Anxiety disorders
Elgen et al. 2002[28]	1986-1988	11	n=130 <2000g	n=131	27%	9%	3.1 (1.5 to 6.5)	CAS	ADHD
Botting et al. 1997[39]	1980-1983	12	n=136 <1501g	n=148	28%	10%	3.7 (1.9 to 7.2)*	CAPA	ADHD, Anxiety disorders
Schothorst et al. 2007[41]	1977-1978	15-17	n=24 <32 weeks	n=20	37.5%	10%	3.8 (0.9 to 15.4)	CAS	Not reported
	1977-1978	15-17	N=19 31-37 weeks	n=20	21.1%	10%	ns		

* OR calculated retrospectively from data provided. ^Indredavik et al. 2005 report data from a sub-set of the cohort reported in Indredavik 2004. Ns: not significant.

Table 2: Odds ratios or Hazard ratios for associations between gestational age at birth and hospital admissions, discharge for affective or psychotic disorder or psychotropic medication in young adulthood.

Publication	Gestational Age, week				
	24-28 OR (95% CI)	29-32 OR (95% CI)	33-36 OR (95% CI)	37-38 OR (95% CI)	39+ OR (95% CI)
Lindström et al (2009)[31]					
Mood disorder	2.7 (1.2-6.0)	1.9 (1.4-2.7)	1.3 (1.1-1.5)	1.1(1.0-1.2)	1
Psychotic disorder	1.5 (0.4-6.1)	2.4 (1.6-3.6)	1.3 (1.1-1.7)	1.2 (1.0-1.3)	1
Suicide death/suicide attempt	2.2 (0.9-5.3)	1.9 (1.4-2.7)	1.2 (1.0-1.4)	1.1 (1.0-1.2)	1

Publication	Gestational Age, week				
	23-27	28-32	33-34	35-36	37-42
Crump et al (2010)¹[72]					
Anti-Depressants	2.0 (1.4-2.9)	1.3 (1.2-1.5)	1.1 (0.9-1.2)	1.1 (1.0-1.1)	1
Hypnotics/sedatives	2.1 (1.3-3.4)	1.4 (1.2-1.6)	1.3 (1.1-1.5)	1.2 (1.1-1.3)	1
Antipsychotics	3.7 (2.0-7.1)	2.0 (1.6-2.6)	1.4 (1.1-1.8)	1.4 (1.2-1.5)	1

Publication	Gestational Age, week		
	<32 RR (95% CI)	32-36 RR (95% CI)	37-41 RR (95% CI)
Nosarti et al (2012)[74]			
Depressive disorder	2.9 (1.8-4.6)	1.3 (1.1-1.7)	1
Non-affective psychosis	2.5 (1.0-6.0)	1.6 (1.1-2.3)	1
Bipolar affective psychosis	7.4 (2.7-20.6)	2.7 (1.6-4.5)	1

Publication	Birth weight (grams)					
	500-1499 OR (95% CI)	1500-1999 OR (95% CI)	2000-2499 OR (95% CI)	2500-2999 OR (95% CI)	3000-3499 OR (95% CI)	3500-3999 OR (95% CI)
Abel et al (2010)[73]						
Affective Disorders	1.8 (1.4-2.4)	1.5 (1.3-1.8)	1.5 (1.4-1.7)	1.3 (1.2-1.4)	1.1 (1.1-1.2)	1
Schizophrenia	1.7 (1.2-2.5)	2.1 (1.6-2.6)	1.5 (1.3-1.8)	1.3 (1.2-1.4)	1.1 (1.1-1.1)	1
Neurotic, stress related and somatoform disorder	1.9 (1.5-2.3)	1.7 (1.5-2.0)	1.9 (1.7-2.0)	1.5 (1.4-1.6)	1.2 (1.2-1.2)	1

1 unadjusted. 2 Hazard Ratios ("Relative Risks") adjusted for other psychiatric conditions, sex, parity, maternal age at delivery, maternal addiction, and maternal psychiatric family history.

Table 3: Prevalence of clinically significant emotional problems in preterm adolescents assessed using dimensional measures.

Study	Sampling	Population	Measure	Mean age (y)	Informant	Emotional Problem	Mean score or % above cut off Cases/controls
Rickards et al (2001)[27]	Regional	VLBW	Adelaide Teacher Rating Scale CBCL	14	Teacher Parent	Depressed Mood Internalizing	2.9% / 6.1% NS 10.2% / 5.1% NS
Saigal et al (2003)[77]	Regional	ELBW	OCHS-R and CBCL	14	Parent Self	Depression Depression	5.7 / 4.6 <.01 6.7 / 6.6 <.01
Gardner et al (2004)[17]	Regional (3 regions)	<29 weeks	SDQ	16	Teacher Parent Self	Emotional Problem Emotional Problem Emotional Problem	10% / 1% <.01 18% / 7% <.05 8% / 2% <.05
Grunau et al (2004)[76]	Regional	ELBW	CBCL	17	Parent	Anxious/depressed Male Female Internalizing Male Female	60 / 51 NS 56 / 57 NS 58 / 43 NS 53 / 51 NS
Indredavik et al., 2005[24]	Regional	VLBW	CBCL/YSR/TRF	14	Teacher Parent ¹ Self	Anxious/depressed Anxious/depressed Anxious/depressed	4.5 / 3.5 <.05 3.2 / 1.9 <.001 3.2 / 3.5 NS
Dahl et al (2006)[16]	Regional (2 regions)	VLBW	CBCL/YSR	13-18	Parent Self	Anxious/depressed Male Female Anxious/depressed Male Female	2.8 / 1.8 <.05 3.9 / 1.8 <.001 2.4 / 4.7 <.01 ² 6.6 / 7.0 NS
Loe et al (2011)[34]	Convenience sample	24-35 weeks	CBCL	9-16	Parent	Anxious/depressed	58 / 52 <.001
Farooqi et al (2007)[30]	National	<26 weeks	CBCL/TRF	11	Teacher Parent	Anxious/depressed Anxious/depressed	19% / 9% <.01 27% / 10% <.05

¹Only mother reports included. ²VLBW male adolescents self-report less anxiety/depression.