

## Review

# Growing up after extremely preterm birth: Lifespan mental health outcomes

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## S U M M A R Y

**Keywords:**

Attention deficit hyperactivity disorder  
 Autism spectrum disorders  
 Comorbidity  
 Mental health  
 Outcomes  
 Preterm birth

There is growing interest in the long-term mental health sequelae of extremely preterm birth. In this paper we review literature relating to mental health outcomes across the lifespan. Studies conducted in the preschool years, school age and adolescence, and adulthood show continuity in outcomes and point to an increased risk for inattention, socio-communicative problems and emotional difficulties in individuals born extremely preterm. Both behavioural and neuroimaging studies also provide evidence of a neurodevelopmental origin for mental health disorders in this population. Here we summarise contemporary evidence and highlight key methodological considerations for carrying out and interpreting studies in this field.

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## 1. Introduction

Extremely preterm (EP) births, before 28 weeks of gestation, continue to pose the greatest challenge for neonatal medicine. Providing life-sustaining treatment, minimising environmental stressors and supporting the family through a traumatic life event are key challenges for neonatologists and other professionals involved in perinatal care. For these babies and their families, however, the care does not end there. The biological vulnerability conferred by EP birth, which may be amplified through socio-economic disadvantage, can have a profound impact on development with consequences that extend across the lifespan. Although EP births comprise just 0.6% of all births, morbidity is highest among these survivors [1,2]. Cognitive impairments are the most frequent adverse outcomes [3,4], but there is growing interest in the impact of preterm birth on mental health and wellbeing. Here we review literature relating to mental health outcomes following EP birth. Although we focus on reports from the most contemporary cohorts, much may be gained through understanding outcomes for older cohorts now in adult life.

## 2. Studying mental health following extremely preterm birth

Mental health outcomes are generally evaluated as part of longitudinal studies which have, for the most part, sought to identify

the prevalence of disorders at various ages. Like all outcome studies, these suffer the inherent problems of selective drop-out. Some of the issues relating to the maintenance of cohorts have recently been discussed [5]. Key aspects of cohort evaluations are:

- Having a clear denominator in order to evaluate how the findings may be extrapolated to other studies and how representative they are of the population from which they are drawn.
- Evaluating the effect of drop-outs and, where necessary, supplementing the findings with sensitivity analyses or imputation techniques.
- Having due regard to these in drawing conclusions.

Single centre studies are more practical to manage, but groups of babies born in individual hospitals may not be representative of the wider population. Further challenges occur by the simple fact that populations change over time, such that more contemporary cohorts comprise a higher proportion of EP children making comparison with historical reports challenging. When studying outcomes it is important that there is a strong underlying hypothesis and that pre-study power calculations using realistic estimates of group differences are computed.

It is widely considered preferable to use diagnostic criteria for studying mental health disorders and to facilitate comparison between studies, yet variation may still exist depending on the measure used [6]. However, the often insurmountable economic and practical challenges of implementing diagnostic interviews mean that most studies have relied solely on behavioural questionnaires (see Johnson [7] and Arpi and Ferrari [8] for reviews). These typically generate higher rates of individuals that score above

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the cut-off for clinically significant problems than meet the criteria for disorders. This is illustrated using data from the UK EPICure Study (Fig. 1) [9]. As part of a follow-up at 11 years of age, emotional, conduct, hyperactivity/inattention and peer relationship problems in a cohort of children born EP (<26 weeks) were assessed using parent and teacher questionnaires; diagnoses of corresponding disorders were obtained concurrently [10]. For all domains, parents reported significantly more problems than disorders and teachers reported more attention and peer problems (Fig. 1). This begs the question of who is the most appropriate respondent for assessing childhood psychopathology. It is well-documented that parent and teacher reports are only modestly correlated and that parents report higher rates of problems than teachers or adolescents themselves, particularly for emotional disorders [11–17]. Obtaining multi-informant data is therefore advocated for mental health assessment [18,19].

The use of dimensional measures is also advocated for studying childhood psychopathology in order to quantify the degree to which symptoms are manifest in individuals and populations [20–23]. These considerations are particularly important for studying mental health following EP birth in which there appears to be a general population shift in psychopathology and a cluster of symptoms that extends across diagnostic boundaries (see Section 4) [24–26]. As the expression of childhood psychopathology alters with development, the nature, severity and frequency of behaviours that are considered typical at one age may be rated as pathological at another [20]. It is therefore important to use age- and gender-specific norms and to obtain contemporaneous reference data from term-born controls. Where possible, control groups should be matched, or analyses adjusted, for confounding factors such as age, sex and socio-economic status. There is controversy over adjusting for IQ given statistical and theoretical limitations [27,28] and the comorbidity of neurocognitive sequelae in EP children (see Section 4.5). Parental mental health may also be a confounder in light of the higher risk for psychopathology in the offspring of those with disorders [29]. However, although parents of preterm children are at risk for parenting stress and poor mental health [30–32] medical, biological and neurodevelopmental variables are stronger predictors of childhood psychopathology in preterm samples [33–36], and there is inconsistency in studies of

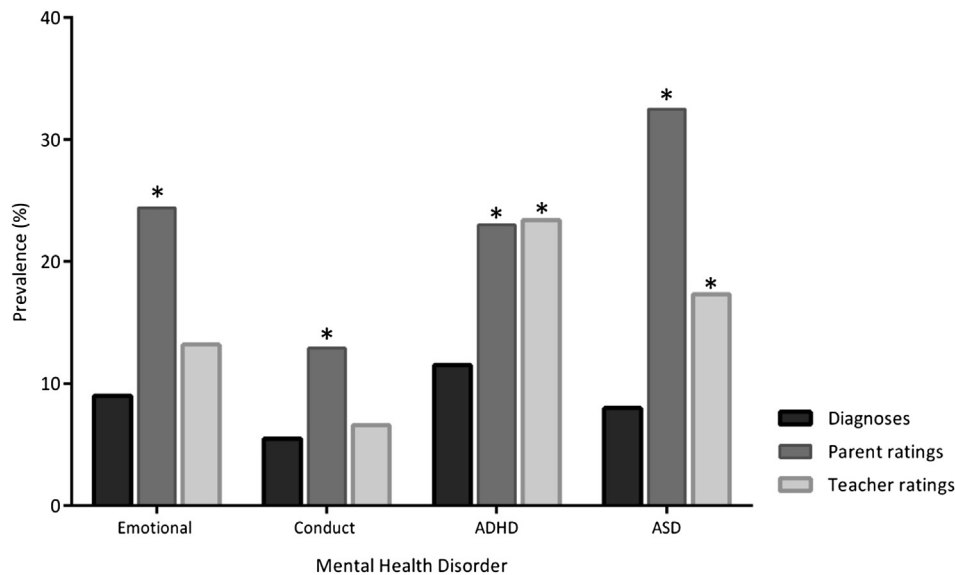
the relationship between parental mental health and preterm children's socio-emotional development [15,30,37,38]. These associations are likely to be bidirectional, potentially mediated by the quality of parent–infant interaction [30,39–41]. The importance of parental mental health as a causal factor in EP children's psychopathology requires elucidation in longitudinal studies. Parental mental health is discussed further in this issue by Karli Treyvaud (Chapter 10).

### 3. The preschool years

#### 3.1. Behaviour and emotional problems in the preschool years

There is a surprising lack of research regarding behavioural outcomes during the preschool years. Studies in infancy have focused on the development of attachment relationships, temperament and parent–infant interaction (see Korja et al. [42] and Vanderbilt [43] for reviews). The assessment of early psychopathology becomes more refined from the age of 2–3 years when well-standardised tools are available to identify clinically significant difficulties, such as the Child Behavior Checklist (CBCL) [44] and the Strengths and Difficulties Questionnaire (SDQ) [45].

Only a few recent studies have investigated outcomes in EP or extremely low birthweight (ELBW) preschoolers (Table 1). In two studies, children had more problems on all SDQ scales, suggesting a generic risk for mental health problems following EP birth [46,47]. Interestingly, Elgen et al. [47] reported that 38% of EP children had clinically significant scores yet only 8% had been referred for psychiatric follow-up, highlighting the preponderance of subclinical symptoms. In a longitudinal study, EP children had significantly poorer emotional and behavioural regulation than term-born children at both 2 and 4 years of age (Table 1); moreover, they showed less developmental gain than full-term and VP children, which is suggestive of a specific vulnerability in the development of early regulatory competence in EP children [48]. More recently, Scott et al. [49] obtained multi-informant data on EP/ELBW children at 5 years of age. Using both a dimensional and diagnostic approach, the authors reported greater specificity in outcomes compared with earlier studies; only attention deficit/hyperactivity disorder (ADHD) symptoms were significantly and consistently



**Fig. 1.** Prevalence of parent- and teacher-reported emotional, conduct, attention and peer problems and diagnoses of corresponding psychiatric disorders at 11 years of age among 219 children born extremely preterm (<26 weeks of gestation; EPICure Study) [10]. Asterisks denote significant between-group differences between informant-rated Strengths and Difficulties Questionnaires and psychiatric diagnoses ( $P < 0.05$ ). ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorders.

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