

# Preterm babies grown up: understanding a hidden public health problem

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Even when they have grown up, the survivors of preterm birth are at increased risk of psychiatric illness. As the incidence of preterm birth is increasing, there is now a growing population of adults whose mental health needs have been neglected.

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## Introduction

Our species has an unusually long gestation period compared to other primates, possibly related to the evolution of our particularly large brain. Human gestation is normally reckoned to take between 38 and 42 weeks: we refer to babies born at 37 weeks and earlier as 'preterm'; those born at 32 weeks or less as 'very preterm'; and those born at less than 26 weeks as 'extremely preterm'. Preterm birth is a hidden public health problem in the western world, and one that has so far proved hard to prevent. Indeed, its incidence seems to be on the rise, at least in the USA, where it increased from 9.5% of births in 1981 to 12.7% in 2005 (Goldenberg *et al.* 2008). This results in a considerable economic burden; neonatal care for preterm infants costs around US\$5.8 million a year in the USA (Russell *et al.* 2007). The continuing care of preterm-born individuals is more costly still, with estimates ranging from €65 million per year in Sweden (Lindström *et al.* 2007) to US\$26.2 billion in the USA (Allen, 2008). Why so expensive? Preterm birth is associated with physical, cognitive and behavioural problems, particularly for those born at younger gestational ages ( $\leq 32$  weeks). These difficulties may impair education, and require ongoing health and social care. One major consequence of very preterm and extremely preterm birth is injury to the immature brain, which is particularly vulnerable to hypoxia and the other adverse conditions that these neonates encounter in their first weeks outside the womb. Studying the interaction between these early brain injuries and subsequent neurodevelopment is beginning to

provide new insights into the psychiatric problems suffered by this population.

## Preterm birth and adult psychiatric outcome

Disabilities including cerebral palsy, learning disability and sensory deficits are increased in children born preterm. These complications are more likely in those born at younger gestational ages (Foulder-Hughes & Cooke, 2003), but even taking the most pessimistic estimate, 80–90% of survivors of preterm birth will not suffer major disabilities (Powls *et al.* 1995). However, they may still go on to experience milder degrees of neurodevelopmental impairment later in life, and tend to do less well at school than their term-born classmates (Saigal & Doyle, 2008).

Various population and case-control studies have indicated associations between obstetric complications (which include preterm birth) and adult psychiatric illness. For example, the link between schizophrenia and obstetric complications is well established (Cannon *et al.* 2002; Walshe *et al.* 2005). Preterm birth has also been implicated as an aetiological factor in depressive disorder, attention deficit hyperactivity disorder and anorexia nervosa (Cnattingius *et al.* 1999; Thompson *et al.* 2001; Patton *et al.* 2004; Saigal & Doyle, 2008). What is less clear is the extent to which populations of preterm-born individuals are at risk of psychiatric problems as they grow up.

Two broad approaches have been used to begin to address this question. The first is made feasible by the incomparable population data available in certain Scandinavian countries, allowing the cross-linking of databases of perinatal complications and psychiatric outcome 20 or more years later. This method can call on very large numbers of subjects and is

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epidemiologically robust. Lindström *et al.* (2009) performed just such a study, using over half a million Swedish birth records. Preterm birth was associated with an increased risk of being hospitalized for a psychiatric illness in adulthood. The risk was greater for those with the severest degrees of prematurity (24–28 weeks), although, as the authors make clear, the majority of those hospitalized had ‘moderate’ preterm birth (29–32 weeks). The second approach is to take a population of children born preterm and follow them until they have grown up. As can be imagined, this is a tall order! Such approaches can tell us about the social, psychological and biological factors that influence the risk of psychiatric illness. For example, there is now some evidence to suggest that very preterm adults have altered personality styles, with reduced extraversion (Allin *et al.* 2006), reduced propensity to take risks (Hack *et al.* 2007) and increased behavioural inhibition (Pyhälä *et al.* 2009). The origin of such personality differences may include genetic predispositions, the effect of mild cognitive impairments, parenting style, and negative experiences in school or with peers, or, more likely, a combination of all these factors. There is also some evidence that very preterm adults are more likely to suffer from anxiety and depression and associated ‘common mental disorders’ (Walshe *et al.* 2008). This risk is elevated further in preterm individuals who also have a family psychiatric history, suggesting an interaction between genetic inheritance and perinatal adversity.

### The role of brain development in adolescence

Along with long gestation, another prominent feature of development in our species is our long period of adolescence, during which time our cognitive and social capabilities mature. Adolescence is also the period when many psychiatric disorders begin to manifest. Does being born preterm affect brain development during this sensitive period? Longitudinal magnetic resonance imaging (MRI) scanning studies have started to address this.

In a follow-up of individuals born at a London teaching hospital, my colleagues and I scanned two groups (one born very preterm, one born at term) at age 14 years and then again at 19 years using structural MRI. Both groups had similar overall trajectories of grey and white matter change over this time (Parker *et al.* 2008), with grey matter volume decreasing in both groups and white matter volume increasing. Such patterns are often taken to indicate synaptic pruning in grey matter and ongoing myelination in white matter, although the exact tissue correlates of MRI changes are not yet known. We also examined two brain structures that are known to be affected

by preterm birth: the cerebellum (also of interest because of its role in coordinating thought and affect) and the corpus callosum (involved in integration of information between cerebral hemispheres). Here we found interesting deviations from the expected growth trajectories. First, the cerebellum decreased in the very preterm group between adolescence and adulthood (in the term group it did not change). This cerebellar decrement was associated with worse self-rated mental health (Parker *et al.* 2008). Second, there was dramatic growth of the corpus callosum in the very preterm group. Again, this change had functional consequences in the preterm group, this time beneficial; greater corpus callosum growth was associated with higher IQ at 19 years (Allin *et al.* 2007).

A tentative explanatory model consistent with these observations is that the growth of the corpus callosum represents a plastic response to a deficit of development that includes (but may not be limited to) the cerebellum. In this model, networks that include the cerebellum fail to develop adequately to meet the cognitive and social demands of the adolescent–adult transition. This is detrimental, and is associated with poorer mental health. The corpus callosum growth then represents a plastic response, increasing brain connectivity to mitigate the functional effects of this cerebellar deficit, for example by optimizing cognitive function.

In summary, very preterm birth is a risk factor for a variety of adult psychiatric illnesses. This may in part be related to altered trajectories of brain maturation during the ‘sensitive period’ of adolescence. A lot of work remains to be done, both in identifying which other brain structures also have altered developmental trajectories and which do not, and in clarifying the effects of genes, environment and experience on adolescent development. Studying longitudinal cohorts in this way can help us to understand how neurodevelopment is involved in psychiatric illness. It should also enable us to provide appropriate support to enable preterm babies to grow up into healthy adults.

### Declaration of Interest

None.

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