

The Life Course Consequences of Very Preterm Birth

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Abstract

Around 15 million children are born preterm (<37 weeks of gestation) every year. Of these, 15% or 2.25 million are born very preterm (VP; <32 weeks of gestation). Here, the developmental outcomes of VP babies in diverse domains from motor, cognitive, and social function to mental health and well-being throughout childhood and adolescence are reviewed. Their life course adaptation in terms of romantic relationships, employment, and quality of life into adulthood is also considered. Some adverse effects reduce as individuals age, and others remain remarkably stable from childhood into adulthood. We argue that to advance understanding of developmental mechanisms and direct resources for intervention more effectively, social factors need to be assessed more comprehensively, and genetically sensitive designs should be considered with neuroimaging integrated to test alternative developmental models. As current evidence is based almost exclusively on studies from high-income countries, research from low- and middle-income countries is urgently needed.

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INTRODUCTION

To achieve the United Nations' Sustainable Development Goal 3 to ensure healthy lives and promote well-being for all at all ages, it is crucial to address the global burden of preterm birth (Chawanpaiboon et al. 2019). In 2014, 10.6% of live births or 14.84 million babies were born preterm—before 37 weeks of gestation—worldwide. Preterm birth is the leading cause of child mortality under age five (Lee et al. 2019). In the past three decades, the largest improvement in survival has been for babies born very preterm (VP), or before 32 weeks of gestation. Although VP births account for only 15% of all preterm births, they are associated with the highest costs both for initial hospitalization (Petrou et al. 2019) and for health and educational support in the long term (Petrou et al. 2013). As up to 95% of VP babies now survive in high-income countries, focus has shifted from solely reducing mortality to understanding and improving long-term outcomes and quality of life. Here we provide an overview of the life course consequences of VP birth and the developmental mechanisms leading to adverse motor, psychological, and social outcomes.

Very preterm (VP):
<32 weeks of gestation

Extremely preterm (EP): variable; ranging from gestation <28 weeks or <26 weeks

Moderate preterm (MP): 32–33 weeks of gestation

Late preterm (LP):
34–36 weeks of gestation

Low birthweight (LBW): birthweight <2,500 g

TERMINOLOGY AND EPIDEMIOLOGY

The World Health Organization defines preterm birth as all births before 37 completed weeks of gestation. The limit of viability is currently around 22 weeks, but survival at this gestational age is still rare. About 3.3–8.9% of all preterm babies are born extremely preterm (EP; <28 weeks of gestation) and about 9.8–12.8% at 28–31 weeks of gestation, with all infants born before 32 weeks classified as VP (Chawanpaiboon et al. 2019). Up to 20% of preterm babies are born moderate preterm (MP; 32–33 weeks of gestation), and 60–70% are late preterm (LP; 34–36 weeks of gestation) (Goldenberg et al. 2008).

The terms preterm and low birthweight (LBW; <2,500 g) are often used interchangeably in studies of the long-term outcomes of these infants. Approximately 7–10% of all babies are born

with LBW (Wolke 1991) and around 0.9–1.5% with very low birthweight (VLBW; <1,500 g). Extremely low birthweight (ELBW) infants are usually labeled as such if born <1,000 g (Hille et al. 2001) or sometimes <750 or <800 g (Whitfield et al. 1997).

Appropriate for gestational age and small for gestational age (SGA) infants are classified based on the relationship between gestation and birthweight using standard population or customized birthweight growth charts (Zeitlin et al. 2017). SGA children are born in the <10th or <3rd percentile or ≤ 2 standard deviations (SDs) below the mean for their gestational age (Zeitlin et al. 2017). Within the preterm population, 16–40% of babies are born SGA (<10th percentile).

In absolute numbers, most preterm babies are born in Asia (52.9% of global preterm births) and sub-Saharan Africa (28.2%). In contrast, Europe (4.7%) and the United States (3.3%) account for just a small fraction of the global burden (Chawanpaiboon et al. 2019).

Preterm labor may be spontaneous (due to spontaneous preterm labor or prelabor rupture of membranes) or clinician initiated (cesarean section or induction of labor) due to acute maternal or fetal indications such as infection, poor fetal growth, or high blood pressure (Goldenberg et al. 2008). Factors associated with preterm delivery include sociodemographic (e.g., race, poverty), nutritional (e.g., obesity), maternal genetic or microbiome, environmental (e.g., smoking), and lifestyle factors (e.g., fertility treatment, increasing maternal age), but still, in 50% of cases, the specific cause is unknown (Muglia & Katz 2010).

The number of VP births has not significantly decreased, and has even increased in many countries, while mortality rates have decreased, at least in high- and middle-income countries (Yeo et al. 2015). As such, the absolute number of survivors born VP is increasing, presenting a growing public health concern.

DEVELOPMENT AFTER VERY PRETERM BIRTH

This review focuses on motor, psychological, and social development from infancy to adulthood following VP birth. Thus, the major organ considered is the brain. Whenever possible, the focus is on high-quality studies that (a) are prospective, (b) are sufficiently powered (e.g., geographical, epidemiological, or multicenter studies), (c) have few infants lost to follow-up or good documentation of dropouts, (d) include full-term control groups for cohort-specific comparisons, (e) are long term (i.e., into school age or adulthood), (f) include differential reports of subpopulations (e.g., social class, EP versus VP), and (g) are conducted by independent researchers not involved in the care of the infants under investigation and blind to study group allocation (Johnson et al. 2008, Vohr 2007). Particular emphasis is placed on studies using contemporaneous control groups, as secular trends in cognitive and behavioral scores have been repeatedly reported (Collishaw et al. 2010, Wolke et al. 1994). Finally, we focus predominantly on reports of mean differences or differences in proportions between VP individuals and term-born controls and, where possible, refer to meta-analyses to estimate effect sizes.

Motor Development and Physical Activity

Motor difficulties following VP birth range from mild delays, such as in sitting or walking, to severe neuromotor impairment, such as cerebral palsy (CP), which remains the primary motor disorder following VP birth (Reid et al. 2016). Other deficits in coordination, balance, gross and fine motor control, and visuospatial integration are usually referred to as motor impairments without CP and may be considered developmental coordination disorder (DCD) according to DSM-V criteria (Am. Psychiatr. Assoc. 2013).

Very low birthweight (VLBW): birthweight <1,500 g

Extremely low birthweight (ELBW): birthweight <1,000 g

Appropriate for gestational age: the fetus/newborn has a weight corresponding to their gestational age (e.g., above the 10th percentile on standard weight charts)

Small for gestational age (SGA): the fetus/infant has a weight below that expected for their gestational age (e.g., below the 10th percentile on standard weight charts)

Term: ≥ 37 weeks of gestation

Findings from one of the most comprehensive CP registries in Victoria, Australia, indicate that CP rates have decreased since the mid-1990s in those born VP (28–31 weeks of gestation), from 41.5/1,000 neonatal survivors in 1983–1991 to 32.4/1,000 in 2001–2009 (Reid et al. 2016). In contrast, among EP births, CP rates increased until 2000 with a decrease thereafter (92.1, 102.5, and 70.6/1,000 neonatal survivors in 1983–1991, 1992–2000, and 2001–2009, respectively). Although VP/EP births are just 1–2% of all births, they make a large contribution to the rates of children with CP. The improvements for VP/EP births may be due to considerable change in the management of preterm infants over recent decades, but there is little evidence for the efficacy of any single intervention in reducing CP rates (Spittle & Orton 2014).

Regarding motor impairments without CP, children born VP/VLBW had scores -0.57 to -0.88 SD lower than term-born peers on standardized tests of motor performance from infancy to 15 years of age (de Kieviet et al. 2009). These differences were of a moderate to large effect size and were found in a wide range of skills, including balance, ball skills, manual dexterity, and fine and gross motor development. While motor skills improved from infancy to childhood, no significant improvement was found from childhood into adolescence. A more recent review excluding children with CP (Edwards et al. 2011) found a higher risk for DCD in VP/VLBW children, with an odds ratio (OR) of 6.29 (95% CI, 4.37 to 9.05) and an OR of 8.66 (95% CI, 3.40 to 22.07) for scoring in the <5th or 5th–15th percentile on the Movement Assessment Battery for Children (MABC), respectively. Even larger differences of 1.1–1.6 SD have been found among children born <26 weeks of gestation (Marlow et al. 2007).

A major question remains as to whether DCD has decreased with improved neonatal care. The Victorian Infant Collaborative Study (VICS) in Melbourne, Australia, recruited three consecutive cohorts of EP/ELBW babies born in 1991–1992, 1997, and 2005 from four tertiary neonatal units in the region (Spittle et al. 2018). While survival rates increased from 54% in 1991–1992 to 68% in 1997 and stabilized in 2005 at 64%, CP rates remained constant at 11%, 11%, and 12%, respectively. In contrast, non-CP motor impairment increased over time despite advances in neonatal care, with a prevalence of 13%, 15%, and 26% among EP/ELBW children, respectively (Spittle et al. 2018). Although there were consistent independent perinatal predictors of motor impairment across the three epochs, including poorer fetal growth, brain injury, surgery, and male sex, these did not explain the increased rate of motor impairment in the 2005 cohort. The authors speculated that other factors such as reduced physical activity (PA) may have adversely impacted motor outcomes in the EP/ELBW children.

Indeed, one might expect that VP/EP children participate less in sports and PA given their higher rate of motor impairments. However, according to World Health Organization recommendations, individuals born preterm are encouraged to participate in PA to improve lung function and cardiovascular fitness (Spiegler et al. 2019a). Indeed, a recent longitudinal study from birth to 14 years shows that VP children and adolescents did not engage less in PA or sports than term-born controls. Rather, PA was higher in male adolescents, those of white ethnicity, children of more highly educated parents, children taken to live sporting events at 5–7 years, or those who took part in organized PA at 5–7 years (Spiegler et al. 2019b). Thus, consistent with other studies, this study found that VP children are not less likely to be physically active, but they reduce participation in sports by adolescence just as term-born children do.

Cognitive Development

A recent meta-analysis of 71 cohort studies identified that VP/VLBW individuals had IQ scores 0.86 SD (95% CI, -0.94 to -0.78) lower than controls at age 5–20 years, equating to a 12.9-point deficit (Twilhaar et al. 2018a). Similar effect sizes have been reported in other meta-analyses, with

deficits of 10.9 (95% CI, 9.2 to 12.5) (Bhutta et al. 2002) and 11.9 (95% CI, 10.47 to 13.42) IQ points in all preterm children compared with controls. Among VP cohorts, a mean deficit of 13.9 (95% CI, 11.5 to 16.2) IQ points has been reported (Kerr-Wilson et al. 2012). Together, these studies indicate that IQ in VP individuals is, on average, 0.7 to 0.9 SD lower than term-born peers.

In two meta-analyses, the mean difference in IQ did not differ significantly over time, suggesting that cognitive outcomes have not improved significantly despite advances in neonatal care (Kerr-Wilson et al. 2012, Twilhaar et al. 2018b). The only direct comparison of IQ in consecutive cohorts from the same geographical region is from the VICS group for EP/ELBW babies born in 1991–1992, 1997, and 2005. Similar to the findings for CP outlined above, researchers found that the mean difference in IQ between EP children and controls was not significantly different for births in 2005 compared with births in the 1990s at age 8 years. Similarly, there was no significant difference in the proportion with cognitive impairment (IQ < –2 SD of controls) (Cheong et al. 2017). Thus, despite improved neonatal care and reduced prevalence of severe neurosensory disabilities (Doyle et al. 2010), there is no evidence yet of improved cognitive outcome over time.

Notably, all meta-analyses found a significant association between IQ and gestational age (Allotey et al. 2018, Bhutta et al. 2002, Kerr-Wilson et al. 2012, Twilhaar et al. 2018b), indicating a dose-response effect of gestation at birth on cognitive outcome. This association has also been shown in large, population-based studies (Poulsen et al. 2013, Wolke et al. 2015b); however, it is not yet clear whether this is a linear association among births at all preterm gestations (Bhutta et al. 2002, Kerr-Wilson et al. 2012) or an exponential relationship with increasing deficit observed in those born before 32 weeks of gestation (Jaekel et al. 2013, Wolke et al. 2015b). It is clear, however, that those born EP (<26 weeks of gestation) are at highest risk for impairments, with deficits of 1.3 to 1.6 SD in IQ in childhood (Johnson et al. 2009, Marlow et al. 2005).

A key question is whether cognitive deficits observed in early childhood persist across the life span or whether VP individuals catch up to their peers as they age. Meta-analyses have typically found that mean differences in IQ do not narrow with age (Allotey et al. 2018, Twilhaar et al. 2018b). However, these are based on successive cross-sectional comparisons rather than an analysis of developmental trajectories across time.

Studies that have tracked the development of VP/VLBW/EP individuals from birth through adulthood have failed to find evidence of developmental catch-up. The EPICure study assessed IQ in EP children at 2.5, 6, 11, and 19 years of age alongside a term-born control group assessed from 6 years of age. Deficits in IQ remained stable over time, although there was a small but statistically not significant narrowing of the gap by 0.5 IQ points per year, and an 18-point deficit remained at 19 years of age (Linsell et al. 2018). Similar results have been reported for VLBW/VP survivors, who had significantly lower IQ than term-born controls when assessed at 2, 4, 6, 8, and 26 years of age (Breeman et al. 2015).

Compared with IQ, there are fewer reports of attention and executive functions to date. Meta-analyses have found small to moderate deficits in verbal fluency (–0.57 SD), working memory (–0.36 SD), and cognitive flexibility (–0.49 SD) in VP children compared with controls (Aarnoudse-Moens et al. 2009). Standardized mean differences of –0.42 to –0.71 for working memory and –0.35 to –0.62 for processing speed have also been reported in preterm children compared with controls (Allotey et al. 2018). Similar effect sizes have been reported in VP children who had scores 0.51 SD (95% CI, –0.58 to –0.44) lower than controls on 87 measures of executive functions and 0.49 SD (95% CI, –0.60 to –0.39) lower on tests of processing speed (Brydges et al. 2018). Significant deficits have also been observed in VP cohorts in adulthood (Eryigit Madzwamuse et al. 2015); however, these are usually smaller in size than deficits in IQ. Similar to the findings for IQ, there is no evidence of improved executive functions with improved neonatal care since the 1990s (Burnett et al. 2018).

Schooling and Academic Attainment

In meta-analyses of performance on standardized achievement tests, preterm-born children have scores 0.71–0.78 SD lower than term-born controls in mathematics, 0.44–0.67 SD lower in reading, and 0.52–0.56 SD lower in spelling (Allotey et al. 2018, Twilhaar et al. 2018b). In children born VP, mathematics scores are 0.60 SD (95% CI, –0.74 to –0.46) lower than controls, reading scores 0.48 SD (95% CI, –0.60 to –0.34) lower, and spelling scores 0.76 SD (95% CI, –1.13 to –0.40) lower (Aarnoudse-Moens et al. 2009).

Population-based studies have also found a significant dose-response effect of gestation at birth on educational outcomes. Routine data linkage for 407,503 children in Scotland revealed that the risk of special educational needs increased as gestational age at birth decreased for each week of gestation below 40 weeks, with an adjusted OR of 1.16 (95% CI, 1.12 to 1.20) for children born at 37–39 weeks, OR 1.53 (95% CI, 1.43 to 1.63) for children born at 33–36 weeks, OR 2.66 (95% CI, 2.38 to 2.97) for those born at 28–32 weeks, and OR 6.92 (95% CI, 5.58 to 8.58) for children born at 24–27 weeks (MacKay et al. 2010).

A dose-response effect of birth at all gestations prior to term has also been reported in academic attainment (Pettinger et al. 2019, Wolke et al. 2015b). For example, the proportion of children who failed to reach a good level of achievement at age seven in school attainment tests increased as gestational age at birth decreased, with 43% of VP children failing to have a good level of achievement in assessment, compared with 18% of children born at full term (relative risk 1.78; 95% CI, 1.24 to 2.54) (Chan & Quigley 2014).

VP birth has a pervasive effect on learning, with children born VP having significantly poorer performance in all school subjects. However, marginally greater deficits are found in mathematics compared with other subjects (Aarnoudse-Moens et al. 2009, Allotey et al. 2018, Twilhaar et al. 2018b). This is due to VP children's general cognitive deficits, such as impairments in working memory and visuospatial skills, rather than deficits in numerical skills (Jaekel & Wolke 2014, Simms et al. 2015).

Do academic deficits observed in childhood represent a developmental delay or persistent deficits across schooling? Twilhaar and colleagues (2018a) found no significant differences in the trajectories of VP children and term-born controls in arithmetic, reading, or spelling throughout elementary school. Another investigation of results on school attainment tests found that preterm children showed gains in attainment between ages 7 and 11, closing the gap slightly with term-born peers, but not at ages 11 and 14 (Odd et al. 2019). Thus, overall, preterm children do not catch up with their peers, and substantial deficits in achievement are still evident at the end of compulsory schooling.

As with cognitive outcomes, relying on improved neonatal care for improving educational outcomes does not appear to hold the answer. In the VICS cohorts, achievement in reading, spelling, and mathematics was significantly poorer in EP children born in 2005 compared with those born in the 1990s (Cheong et al. 2017). The reasons for the deterioration in academic performance are not known, but it is clear that improvements in neonatal care need to be paralleled with improved teacher training and educational support for children born preterm (Johnson et al. 2015, Pettinger et al. 2019).

Mental Health

The assessment of mental health in cohort studies has mainly been carried out using parent, teacher, or self-completed rating scales rather than costly diagnostic evaluations. A recent meta-analysis using these measures revealed a small to moderate effect for increased internalizing symptoms [standardized mean difference (SMD) 0.42; 95% CI, 0.26 to 0.58] in EP/ELBW children

compared with controls and a small effect for externalizing problems (SMD 0.15; 95% CI, 0.02 to 0.28) (Mathewson 2017). An individual participant data meta-analysis of six cohort studies in adulthood similarly found higher scores for internalizing problems but lower scores for externalizing problems among VP/VLBW adults compared with controls (Pyhälä et al. 2017). The effects, however, were usually very small, with mean differences in z-scores ranging from 0.06 to 0.12.

In childhood, a preterm behavioral phenotype has been described, characterized by an increased risk for attention problems, emotional problems, and difficulties with social interaction, alongside no increased risk for aggressive or delinquent behavior (Johnson & Marlow 2011, Mathewson 2017). This was first evidenced by a similar pattern of findings in five cohort studies (Farooqi et al. 2007, Hille et al. 2001).

At the diagnostic level, a meta-analysis of five studies identified an OR of 3.66 (95% CI, 2.57 to 5.21) for psychiatric disorders in preterm/LBW children and adolescents relative to full-term controls, with prevalence estimates that ranged from 21% to 28% (Burnett et al. 2011). The pattern of disorders observed in preterm populations indicates an increased risk for attention-deficit/hyperactivity disorder (ADHD), depressive and anxiety disorders, and autism spectrum disorder (ASD), alongside no increased risk for disruptive, impulse-control, or conduct disorders (Johnson & Marlow 2011, Johnson & Wolke 2013).

ADHD is the most common disorder after VP birth for which fairly consistent risk estimates have been reported, with ORs of 3.3 (95% CI, 2.0 to 5.6) (Allotey et al. 2018) and 3.04 (95% CI, 2.19 to 4.21) for ADHD in VP children and adolescents (Franz et al. 2018). The odds are even higher for those born EP/ELBW (OR, 4.05; 95% CI, 2.38 to 6.87) (Franz et al. 2018). VP children with high levels of ADHD symptoms show wide-ranging cognitive deficits (James et al. 2018, Retzler et al. 2019), which might also account for the comorbidity of psychiatric disorders in this population. In particular, a highly increased risk for ASD has also been reported in VP populations, with a prevalence of 7% among children born VP (Agrawal et al. 2018) and up to 8% among those born EP (Johnson et al. 2010).

There is good evidence that internalizing symptoms assessed in rating scales in VP persist into adulthood (Mathewson 2017, Pyhälä et al. 2017, Van Lieshout et al. 2018b). In contrast, diagnoses of emotional disorders reduce by adulthood, with EP/VP survivors showing better emotional adaptation than once anticipated (Burnett et al. 2014, Jaekel et al. 2018a, Johnson et al. 2019b). Whether this is a true decline or due to reduced statistical power resulting from loss from follow-up is not yet clear. Conversely, both ADHD symptoms and diagnoses have been found to persist into adulthood (Breeman et al. 2016a, Burnett et al. 2014).

Social Development

An infant's main social relationship is with their parents. However, as children grow up, they increasingly build relationships with peers. By the end of childhood, children will have spent many more hours with peers than with their parents. Thus, parent-child and peer relationships are reviewed here.

Parent-infant relationship. Despite recent efforts of neonatal infant care unit (NICU) policies to promote parental involvement and physical proximity as early as possible, infants are often in incubator care for weeks or months, which may impact maternal attachment formation (Feldman et al. 2014). Furthermore, an unexpected preterm birth and the ensuing period of uncertainty over their infant's survival can place high levels of stress on parents (Singer et al. 1999). However, parents of preterm infants often learn to cope with the higher stress over the first years of their offspring's life (Schappin et al. 2013).

Attachment refers to the emotional bond that the infant forms with consistent caregivers who are sensitive and responsive in their social interactions (Bowlby 1969). Several reviews found no differences in secure-insecure attachment between preterm and term-born children (Field 1987, van IJzendoorn et al. 1992). In particular, maternal sensitivity has been found to be a major factor in predicting secure attachment (Miljkovitch et al. 2013, Wolke et al. 2014). A recent meta-analysis of 34 studies reported that despite the initial stress and separation, mothers of preterm children were as sensitive in their interactions with their children as mothers of term-born children (Bilgin & Wolke 2015). This suggests that similar maternal sensitivity allows mothers of preterm infants to adapt to and promote sensitive interactions (van IJzendoorn et al. 1992).

While secure and insecure attachment styles are organized patterns of dealing with reunion, disorganized attachment is manifested by contradictory, misdirected, or stereotypical behaviors (Carlson 1998) that are associated with child psychopathology (Weinfield et al. 2000). Pipp-Siegel and colleagues (1999) have suggested that neurological abnormalities can lead to behaviors similar to those that characterize disorganized attachment styles, usually associated with situations of child abuse or neglect. Indeed, there is evidence that VP/VLBW children are more likely than term-born children to have disorganized attachment. Notably, this was predicted by the infant's neurological impairment (distressing cry and developmental delay) and unrelated to parenting (maternal sensitivity) (Wolke et al. 2014).

There is some evidence that parents of VP children are more often overprotective than parents of term-born children, as indicated by being more controlling in mother-infant play interactions, even when researchers exclude children with neurosensory impairment (NSI) (Forcada-Guex et al. 2006, Wightman et al. 2007). Similar overprotection has been reported among VLBW adolescents (Indredavik et al. 2005) and VLBW young adults (Pyhälä et al. 2011). Higher parental control behavior and protection for VP children, however, may be partly explained by VP children's cognitive deficits and functional limitations and additional needs for framing and guidance (Jaekel et al. 2012). However, parents' perception of their child's vulnerability appears to depend mostly on parents' psychological factors (e.g., anxiety, parental stress) rather than the child's health (Tallandini et al. 2014). Indeed, parental anxiety has been associated with more controlling parenting and children's lower self-efficacy (Schneider et al. 2009), which may ultimately impair their resiliency (Schwarzer & Warner 2013).

Peer relationships. An important aspect of social development is the ability to relate to and form relationships with peers. A systematic review of 23 studies found that VP children and adolescents have higher levels of social withdrawal and peer problems than children born at term (Ritchie et al. 2015). Furthermore, studies that included the child's own self-report found that VP children have fewer close friends, spend less time with friends, and are less satisfied with their friendship network than their term-born peers (Heuser et al. 2018, Ritchie et al. 2018). VP children are also more than twice as likely to be socially excluded and bullied than term-born children, and this often persists from elementary to secondary school (Day et al. 2015, Ritchie et al. 2018, Wolke et al. 2015a). Poor peer relationships among VP children are important, as they are associated with emotional problems, inattention and hyperactivity, motor deficits (Day et al. 2015, Heuser et al. 2018, Ritchie et al. 2018), and the display of more autistic features (i.e., higher rates of social and communication problems) (Williamson & Jakobson 2014). Despite having fewer friends, direct observation of dyadic interactions between friends, one of whom was born preterm, found that friendship activities and behaviors are similar between children born preterm and at term, as well as their perceived relationship quality (Sullivan et al. 2012). It appears that VP children's withdrawn behavior may hinder them in forming and maintaining successful peer relationships.

ADULT LIFE

Personality

Compared with term-born controls, adults born VP are less extraverted (Eryigit-Madzwamuse et al. 2015, Pesonen et al. 2008), more agreeable and cautious (Hertz et al. 2013, Pesonen et al. 2008), more shy and withdrawn (Eryigit-Madzwamuse et al. 2015, Johnson et al. 2019b), and less prone to criminal and risk-taking behaviors, such as smoking and illicit drug and alcohol use (Eryigit-Madzwamuse et al. 2015, Hack et al. 2002, Hille et al. 2008). VP-born adults report higher levels of neuroticism and more autistic features than term-born controls (Allin et al. 2006, Eryigit-Madzwamuse et al. 2015, Hertz et al. 2013). VP adults' socially withdrawn personality or adverse peer experiences may make it more difficult for them to form and maintain social relationships.

Social Relationships

The social lives of adults born VP have typically been investigated in cohort studies and Scandinavian registry studies. In a meta-analysis of 21 such studies including 4.4 million participants, preterm/LBW adults were less likely to form romantic partnerships (OR, 0.72; 95% CI, 0.64 to 0.81), to have had sexual intercourse (OR, 0.43; 95% CI, 0.31 to 0.61), or to have become parents (OR, 0.77; 95% CI, 0.65 to 0.91) compared to adults born at term (Mendonça et al. 2019). No differences according to sex or age were found, suggesting that individuals born preterm/LBW are less likely to accomplish these milestones by their late thirties in adult life.

Social difficulties are important as they are associated with adverse outcomes (Umberson et al. 2010), such as less wealth, social isolation, and poorer physical and mental health (Jaekel et al. 2018a), and they often worry parents (Wolke et al. 2017). Prematurity is also associated with a cross-generational fertility loss: Not only are adults born preterm less likely to become parents, but their parents were also less likely to have further children after the birth of a preterm child (Alenius et al. 2018). Despite having fewer friends (Baumann et al. 2016, Darlow et al. 2013), the quality of social support from peers was perceived as being as good in adults born preterm/LBW as in those born at term. Furthermore, when preterm adults had a romantic partner, the quality of this relationship was perceived as slightly more positive than in term-born peers (Mendonça et al. 2019).

Markers of Wealth

In a meta-analysis of 23 studies including 5.9 million participants, adults born preterm/LBW were found to have lower educational qualifications (OR, 0.74; 95% CI, 0.69 to 0.80), lower employment rates (OR, 0.83; 95% CI, 0.74 to 0.92), and greater receipt of social benefits (OR, 1.25; 95% CI, 1.09 to 1.42) than adults born at term (Bilgin et al. 2018). These associations were consistent across different geographical regions and age, and a dose-response effect of gestational age was found for educational qualifications, in which adults born LMP were 18% less likely than term-born adults to have higher educational qualifications, and VP adults were 40% less likely. Although previous studies reported that preterm adults were less likely to live independently (Baumann et al. 2016, Kajantie et al. 2008), independent living was not significantly lower in this meta-analysis (Bilgin et al. 2018). This may be because Scandinavian countries have a welfare system and cultural practices that support young people's independent living (D'Onofrio et al. 2013), reducing the adverse impact of preterm birth on the transition into adult life. Investigation in other parts of the world is required.

Quality of Life

Health-related quality of life (HRQoL) refers to the subjective impact of health on an individual's overall psychological, social, and physical well-being (Horsman et al. 2003). HRQoL allows for the comparison of the effects or consequences of different exposures or treatments across all medical conditions (e.g., from cancer to preterm birth). This is helpful when difficult decisions have to be made about where to direct limited health budget resources (Wolke 2016).

A systematic review in 2008 identified 15 studies that had compared HRQoL at preschool (6 studies), at school age (1), in adolescence (4), and in early adulthood (4) between EP/VP/VLBW individuals and term-born controls (Zwicker & Harris 2008). HRQoL was lower in individuals born preterm in the preschool years, according to parent report. In adolescence, parents reported lower HRQoL for EP/VP/VLBW participants than term-born controls, but no differences were found in self-reports. Furthermore, in early adulthood (18–23 years), no significant differences were found between groups, although EP/VP/VLBW adults tended to report slightly less physical and overall functioning (Zwicker & Harris 2008).

These results need to be interpreted cautiously for a number of reasons. Firstly, different findings were found when parent versus self-reports were used, with parents reporting lower HRQoL than the participants themselves (Baumann et al. 2016, Zwicker & Harris 2008). Consistent with social comparison theory, parents may take a wider view of their offspring compared to all same-aged peers, while their offspring may compare themselves to a selection of same-aged peers they interact with. Secondly, studies that include only self-reports exclude those with severe NSI, who are less likely to be able to complete these scales. This introduces bias in favor of no group differences. Thus, studies should include both self-reports and parent reports (Baumann et al. 2016). Thirdly, whole-population studies of VP survivors have loss to follow-up, with those with NSI, those who are socially deprived, and those from ethnic minorities more likely to drop out (Hille et al. 2005; Wolke et al. 1995, 2009). These groups are more likely to have lower HRQoL (Wolke 2016). Fourthly, the various measures of HRQoL are very different in their scaling. Some just add items in subscales, while others determine utilities [i.e., multi-attribute utility scores that represent mean community preferences ranging from 0.00 (rather be dead) to 1.00 (perfect health)]. Thus, comparisons of studies are strictly only possible if the same measures are used. Finally, level of HRQoL is influenced by variations in neonatal treatment philosophy across different regions (Breeman et al. 2016b), by cultural differences, and by the general happiness of the nation (Verrips et al. 2008).

Three cohort studies of ELBW/VP/VLBW survivors in Germany (Baumann et al. 2016), the Netherlands (van Lunenburg et al. 2013), and Canada (Saigal et al. 2016) that had followed children into adulthood used an identical measure of HRQoL. A comparison of these three studies (Wolke 2016) found that, firstly, HRQoL of ELBW individuals was, on average, lower than that of VP/VLBW individuals, who in turn reported lower HRQoL than normal birthweight (NBW) adolescents and adults. Secondly, HRQoL did not improve with age in ELBW or VP/VLBW individuals. A previous comparison of the three cohorts in adolescence, at least in the German and Canadian ELBW groups, had found similar levels of HRQoL in adolescence (Verrips et al. 2008). Thirdly, NSI is a major factor that reduces HRQoL well into adulthood. Considering the stability of these differences compared to NBW individuals, it appears that whatever services ELBW or VP/VLBW individuals received from early adolescence onwards made no difference to their HRQoL in adulthood (Wolke 2016).

DEVELOPMENTAL MECHANISMS

Understanding why VP survivors have more developmental problems and why some impairments persist across time while others show plasticity is important, not just for theoretical advancement

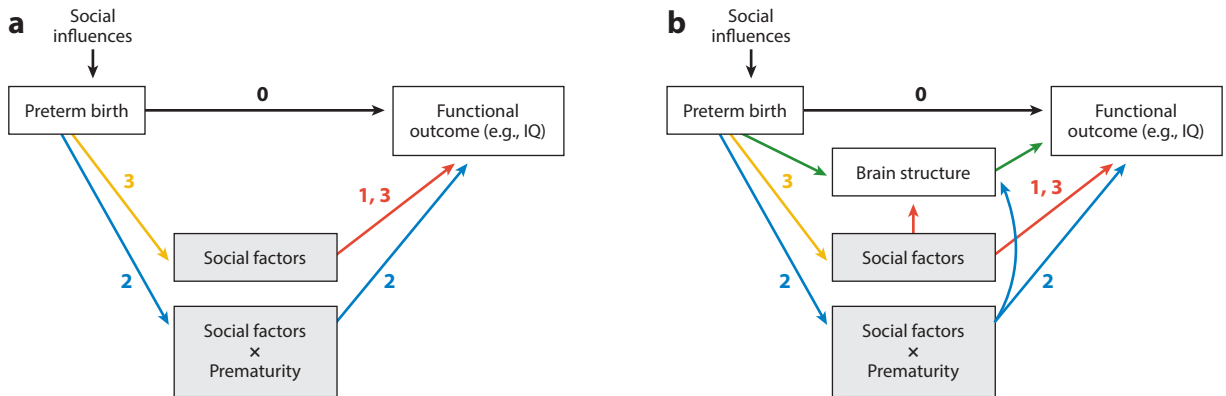


Figure 1

(a) Testing alternative models of the effect of preterm birth on functional outcome. Model 0: Preterm birth has a main effect on functional outcome ignoring other influences. Model 1: Social factors have a main effect on functional outcome in addition to preterm birth. Model 2: Social factors moderate the effects of preterm birth on functional outcome. Model 3: Social factors mediate the effect of preterm birth on functional outcome. (b) Models 0 to 3 may explore how single or joint effects impact brain development as a neural mediator. Abbreviation: IQ, intelligence quotient.

but also for informing the development of interventions. Here we explore potential developmental mechanisms to help explain the life course consequences of VP birth.

Environmental Influences

Most prospective studies have used a simple main effect model investigating the association between perinatal differences at birth and adverse developmental outcomes (see **Figure 1a**, Model 0). This approach is limited as it fails to take account of other important influences that may operate between birth and later outcomes. For illustration, we consider three such factors: socioeconomic status (SES), parenting quality, and traumatic peer influences. These factors are located in different layers in Bronfenbrenner's (1989) ecological model and may operate in different ways in conjunction with VP birth and associated complications.

Firstly, these factors may have a main effect on VP children's development (see **Figure 1a**, Model 1). For example, SES may be an additional factor predicting developmental outcome. It also means that the effects of low SES are the same for children born VP and at term, and are additive. If low SES has detrimental effects on the outcome under consideration, then low SES would be considered as a risk factor. Conversely, if high SES has beneficial effects, then it could be considered a protective factor (Luthar et al. 2000).

Alternatively, SES may be a moderator of the association between VP birth and the outcome of interest (**Figure 1a**, Model 2). This means, for example, that low SES has a significantly larger effect in VP children (i.e., they are more vulnerable to the effects of SES than children born at term), consistent with a diathesis-stress model (Ellis et al. 2011). Furthermore, if high SES provides protection against the effects of VP birth and children reach the level of functioning of those born at term, then this would be considered resilience: the ability to bounce back after exposure to risk (i.e., VP birth) (Taylor et al. 2019).

Let us consider the main effect and moderation models within the context of findings from cohort studies. Being born into a high-SES versus low-SES family has a similar effect on child (Wolke & Meyer 1999) and adult IQ (Eryigit Madzwamuse et al. 2015) in VP and term-born populations. The effect of SES on IQ is comparable to the effect of being born VP versus term in

effect size on IQ (Eryigit Madzwamuse et al. 2015). Expressed differently, having a mother whose highest educational attainment was at elementary or secondary school has the same adverse effect on IQ as having suffered severe brain damage or chronic lung disease (Benavente-Fernández et al. 2019). These findings are consistent with a main effect model with no indication of an interaction effect (**Figure 1a**, Model 1). It is thus no surprise that SES is reported as one of the major influences on cognitive outcomes in VP children (Breeman et al. 2017, Linsell et al. 2015). It is, however, disconcerting that, by 2018, only 15 of 70 studies included in a meta-analysis of VP birth and IQ considered some marker of SES (Twilhaar et al. 2018b).

SES reflects a multitude of factors, including social, family, and parenting factors (Wolke 2019), that need to be unpacked. If we wish to unlock the black box of how these factors influence development, we need to measure them in as much detail as we have perinatal complications (Wolke 2019), which will require greater collaboration across disciplines in the design of follow-up studies. Let us consider parenting, a factor strongly associated with SES (Sherman & Harris 2012) and academic achievement. Wolke and colleagues (2013) found that the effects of sensitivity of parenting assessed at 6 years of age were moderated by birth status (i.e., VP versus term): VP children were strongly and adversely affected by low sensitive parenting, while very sensitive parenting was found to lead to academic attainment nearly on par with children born at term (see **Figure 2**). Thus, the effects of VP birth on academic outcomes are moderated by sensitive parenting. This follows a diathesis-stress model and indicates potential resiliency in academic outcomes for those born VP (see **Figure 1**, Model 2).

Another interaction (see **Figure 1a**, Model 2) argues that variations in child characteristics may alter susceptibility to environmental influences (i.e., the sensitivity to both negative and positive influences). This differential susceptibility proposes that certain environmental influences such as parenting can lead to poorer outcomes under conditions of poor parenting and better outcomes

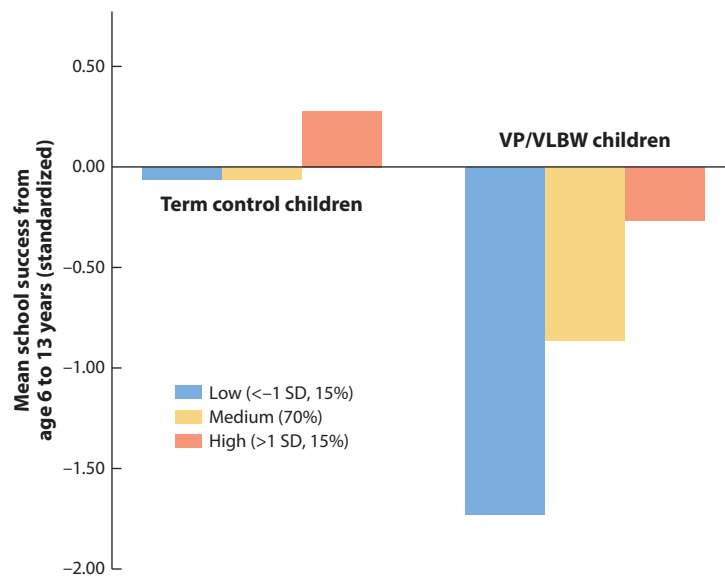


Figure 2

Effect of sensitive parenting (low, medium, or high) at 6 years of age on school success at 13 years of age. Variation by very preterm (VP)/very low birthweight (VLBW) versus term-born status. Abbreviation: SD, standard deviation. Adapted with permission from Wolke et al. (2013).

under conditions of good parenting in susceptible compared to nonsusceptible individuals (Ellis & Del Giudice 2019, Ellis et al. 2011). There is little reason to suggest that VP birth may be related to vantage sensitivity (i.e., increased sensitivity to positive experiences) (Belsky & Pluess 2013). From an evolutionary perspective, most of these infants would not have survived without modern NICU care. Indeed, when a diathesis-stress model versus differential susceptibility theory (DST) was tested in LBW children, there was little evidence for DST, but there was support for the diathesis-stress model (Jaekel et al. 2015). Thus, there is increasing evidence that VP birth makes children more vulnerable to environmental risk factors (Poehlmann et al. 2015, Van Lieshout et al. 2018a, Wolke 2018).

A third model considers environmental factors as mediators between VP birth and later outcomes (see **Figure 1**, Model 3). VP children, as reviewed here, are at higher risk for emotional problems in adolescence. Similarly, it is well documented that children who are exposed to trauma, such as being bullied by peers, are at higher risk for emotional problems (Wolke & Lereya 2015, Zwierzyńska et al. 2013). A recent investigation noted that a major part of the effect of EP/VP birth on emotional problems was explained by EP/VP children being more than twice as likely to be bullied than their term-born peers, which in turn explained the excess of emotional problems in adolescence. Thus, bullying completely mediated the effects of EP/VP birth on emotional problems (Wolke et al. 2015a).

Genetic Influences

Preterm birth is an environmental event that sets off a cascade of further environmental interventions (i.e., NICU care). In all children, genes are involved in cognitive and behavioral development. Thus, genetically sensitive designs ranging from twin studies to the use of genome-wide association studies based on polygenic risk scores may be used to determine genetic contributions to developmental outcomes. Effects of genes are dependent on whether they can be expressed or whether shared or nonshared environmental factors (e.g., neonatal complications or brain injury) reduce their expression. Indeed, in VP children, any additive genetic effects were overshadowed by shared environmental factors in twin pairs (Koeppen-Schomerus et al. 2000). More than 85% of the variance in cognitive scores at 2 years of age was explained by shared environment; thus, genetic effects may be much reduced compared to birth at term, at least in early development.

Twin designs can further help test causal links using twin pairs that are discordant for a risk factor. Groen-Blokhuis and colleagues (2011) tested three models using monozygotic and dizygotic twin pairs and unrelated individuals discordant for birthweight. Their findings showed clearly that LBW significantly predicted higher attention problems, even among children who were otherwise genetically identical. Unfortunately, while babies can be discordant for birthweight, gestation rarely varies, so effects of gestation cannot be tested within such designs. Future research including polygenic scores may serve to evaluate how VP birth as an environmental event may reduce genetic effects.

The Brain

VP birth confers an insult to normal brain development (i.e., interrupted development), and there is often the superimposed risk of acquired brain injury (e.g., hemorrhage) (Volpe 2009). At the limits of survival (22–24 weeks of gestation), the brain consists entirely of white matter. In the following 16 weeks, gray matter expands rapidly, with a dramatic increase in brain surface area through cortical folding (Hüppi et al. 1996, Kapellou et al. 2006). When babies are born

prematurely, this pattern of growth is disrupted due to alterations in growth patterns, direct injury to the white matter (Constable et al. 2008, Inder et al. 2005, Miller et al. 2005), or undetermined reasons. The earlier the birth, the greater the disruption; in addition, boys are affected more than girls (Kapellou et al. 2006, Vasileiadis et al. 2009). This leads to building a different brain than in term births, with altered gray and white matter distribution in multiple regions indicating reorganization of cortical and subcortical structures relating to brain volume, volume distribution, microstructure, and connectivity (Ball et al. 2013). These alterations are still detectable in adulthood in many areas (Bäumel et al. 2015, Meng et al. 2016).

Recent advances in neuroimaging have taken two directions. Firstly, researchers have developed MRI-compatible incubators with integrated head coils that allow for sequential scanning of the developing brain while infants are in neonatal intensive care (Hintz & O'Shea 2008). Secondly, the routine availability of MRI allows the study of anatomical differences, and, more recently, functional MRI studies are improving our understanding of differences in brain area activation and connectivity in preterm children and adults (Nosarti 2013).

A crucial research pathway will be to determine how changes in brain development due to VP birth are associated with functional outcomes such as cognitive, emotional, or social development (Montagna & Nosarti 2016) (see **Figure 1b**). Such outcomes may be related to anatomical alterations (Nosarti et al. 2008), whole network alterations (Kelly et al. 2015, Meng et al. 2016), or specific alterations such as in the cholinergic forebrain (Grothe et al. 2017) and may be potentially treatable. Early studies were promising and showed significant associations between early brain development assessed during the neonatal period and delayed development 2 years later (Kapellou et al. 2006). However, more than a decade on, comparisons of costly MRI versus the utility of cranial ultrasound are sobering. In a recent study, MRI predicted adverse motor outcomes slightly better than ultrasound, but both methods were insensitive and neither predicted cognitive problems at age 18–24 months (Edwards et al. 2018). A mild beneficial effect of MRI was found in that parents liked seeing the whole brain, which reduced their anxieties more than an ultrasound did. However, a single MRI in the United Kingdom costs approximately £300 more than a routine ultrasound. Social factors have been found to alter brain development and have to be considered in studies (Kim et al. 2018). Furthermore, simply measuring head size in the first years of life is highly correlated with brain growth and is predictive of later cognitive development (Jaekel et al. 2018b). Thus, it is important to consider what measures are required for basic science to advance knowledge of developmental mechanisms and which are sufficient for routine follow-up (Doyle et al. 2014).

In summary, to understand how VP birth leads to adverse outcomes, it is necessary to have more detailed measurement of environmental influences. Furthermore, for different outcomes and environmental factors, different mechanisms and models may apply. Understanding how VP birth alters brain development and how environmental experiences such as trauma or parenting get into the brain may help us understand the neural mechanisms underlying diverse phenotypic outcomes.

CONCLUSIONS AND FUTURE DIRECTIONS

First, VP birth has a wide range of adverse effects on motor and psychological development and well-being across the life span. **Figure 3** summarizes the effects of VP/VLBW birth on functioning across the various domains reviewed here. It shows the approximate size of the effects as reported across studies in childhood and adulthood. Effect sizes are defined as small (OR, 1.48 or inverted 0.67; Cohen's *d* between means, 0.2), moderate (OR, 3.45 or 0.29; Cohen's *d*, 0.5), or large (OR, 9 or 0.11; Cohen's *d*, 0.8) (Chen et al. 2010).

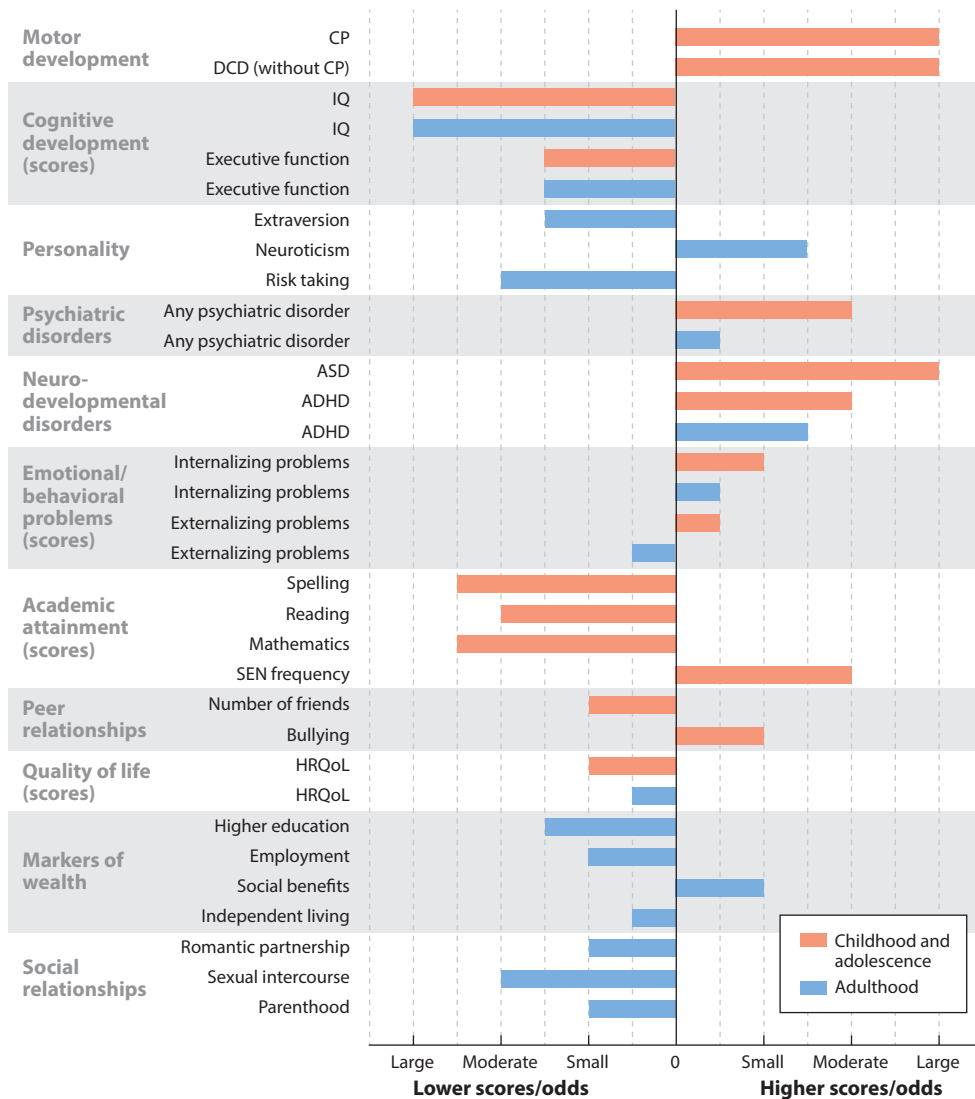


Figure 3

Approximate effect sizes for the impact of very preterm birth on long-term outcomes (compared with birth at term; zero vertical line). Outcomes assessed in childhood and adolescence are shown in red and outcomes assessed in adulthood in blue. Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; CP, cerebral palsy; DCD, developmental coordination disorder; HRQoL, health-related quality of life; IQ, intelligence quotient; SEN, special educational needs.

The largest adverse effects of VP compared to full-term birth are found for CP, DCD, IQ, and ASD. While the effect sizes are large, CP is found in less than 5% of VP/VLBW births and ASD in 7–8%, but DCD and, in particular, low IQ (<-2 SD) are found in up to 25% of VP children. Thus, DCD and IQ are the major sequelae of VP birth. VP birth has moderate effects on academic attainment—in particular, lower mathematics and spelling scores—higher special educational needs in school, and increased risk of any psychiatric disorder in childhood,

especially ADHD. Furthermore, moderate effect sizes were found for executive functions and personality, such as being less extraverted, more neurotic, and less likely to engage in risk-taking behavior. Small effect sizes were found for internalizing and externalizing problems, relationship with peers, bullying, and HRQoL in childhood. While the effect sizes are small for the latter, these usually affect a large proportion of VP individuals. Relationships with parents are little affected in regards to parental sensitivity, and the effects for overprotection are small or may be explained by VP/VLBW having higher needs for framing due to lower IQ.

Second, some adverse effects reduce across development, and others persist from childhood into adulthood. Intelligence and executive functioning show no or very little improvement with age into adulthood. Social difficulties noticed in childhood in terms of ASD symptoms and relationships with peers are still found in adulthood, manifesting in a withdrawn personality and less engagement in normative risk-taking behaviors. Overall, the risk of psychiatric disorders seems to reduce by adulthood (see **Figure 3**). Motor, cognitive, emotional, and social difficulties are likely to contribute to the difficulties some VP individuals have in the transition to adulthood, including being less likely to participate in higher education, less likely to be employed, and more likely to receive social benefits. Most notable is their decreased likelihood of forming romantic and sexual relationships and having children themselves. Thus, more VP than full-term adults may have lower social and financial support once their parents are gone, which has important implications for future public support.

Third, VP individuals who have a significant deficit in one domain (e.g., IQ) often have problems in other domains (e.g., academic achievement, social relationships). Thus, comorbidity is frequent, and, for a minority of VP children and adults, the problems are complex, requiring support from medical, psychological, and education services. However, even term-born children rarely have no problems at all (Wolke & Meyer 1999), and thus it is important to remember that, despite the often increased odds of adverse outcome, most VP children and adults develop adaptively without major problems.

Fourth, despite the significant decrease in mortality and CP for babies born VP, there is as yet no evidence that this has been matched by improved developmental outcomes across the domains reviewed here.

A multitude of challenges face future researchers, practice, and intervention. Much of the observational research on the effects of VP birth may be too simplistic, failing to go beyond medical factors associated with VP birth. Developmental science has much to contribute to help unravel what factors across life may increase risk further, provide protection or resilience, or mediate the association with life outcomes. This is unlikely to be achieved by a single profession or single longitudinal study, which is often limited in statistical power. It requires interdisciplinary collaboration and bringing together cohort and registry studies across the world. Such ongoing collaborations include the APIC initiative (<http://www.apic-preterm.org>) and a large European Union-funded project, RECAP Preterm (<http://www.recap-preterm.eu>). Neuroimaging and genetically sensitive designs should also be considered for future cohort studies.

The use of core measures across cohort studies (Doyle et al. 2014) would allow for direct comparison of whether changes in neonatal care across consecutive cohorts have led to changes in developmental outcomes. This must include measures of the social environment, such as parent and peer relations, as changes may be due as much to social changes as to advances in neonatal care.

Primary prevention of preterm birth itself is needed, but such efforts have met with little success to date. Thus, a key challenge is to minimize adverse effects of VP birth on the brain during neonatal care and to promote development after discharge. As schooling is one of the major factors affecting life course outcomes, new interventions extending beyond the first 2 years should be

trialed, including new resources to improve educational support for children born preterm (<http://www.pretermbirth.info>; Johnson et al. 2015, 2019a).

Finally, reports on developmental outcomes of VP children into adulthood come exclusively from high-income countries. However, the vast majority of preterm children are born in transitional or low-income settings (Chawanpaiboon et al. 2019), and we have no idea how they fare in life. This paucity of research in low-income countries needs to be addressed.

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