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Behavioural and educational outcomes following extremely preterm birth:

Current controversies and future directions

For Hot Topics and Controversies in Neonatology;

Part 4 Long Term Effects Following Extreme Prematurity

by

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Abstract

As a consequence of improved survival rates for extremely preterm (EP; <28 weeks of gestation) births, there is a growing body of evidence detailing the impact of extreme prematurity on outcomes throughout childhood and adolescence. Historically, attention first focused on documenting rates of sensory impairments and severe neurodevelopmental disabilities. However, over recent years, there has been growing interest in the impact of EP birth on long term mental health and educational outcomes. In this chapter we review literature relating to the impact of EP birth on attention, social and emotional problems, psychiatric disorders and educational outcomes. We also outline current controversies in the field. In particular, we present emergent research exploring developmental trajectories to determine whether the sequelae associated with EP birth represent a developmental delay or persistent deficit, and we consider what approaches to intervention may be most fruitful in improving behavioural and educational outcomes in this population.

Introduction

Extremely preterm (EP) births, before 28 weeks of gestation, continue to pose one of the greatest challenges to neonatal medicine, not just in terms of reducing mortality and short term morbidity, but in minimising the impact of immaturity at birth on lifelong health and development. Since the advent of contemporary neonatal care in the 1980s, and the continued improvement in survival rates, the long term consequences of EP birth have garnered increasing public, parent and professional concern. This has resulted in a growing body of research in which outcomes throughout childhood and adolescence have been well documented, particularly relating to the risk for neurodevelopmental impairments (see Chapter 20). As rates of severe sensory disabilities have fallen, and follow up has become increasingly interdisciplinary, greater attention has been paid to the impact of EP birth on behavioural and educational outcomes and quality of life. Here we present an overview of what is known about behavioural and educational outcomes following EP birth and outline current controversies in the field.

Where possible, we present data from EP birth cohort studies that have utilised gestational age defined inclusion criteria. However, given the continuity in outcomes across the full spectrum of preterm gestations, evidence from extremely low birthweight (ELBW; <1000g) cohorts, very preterm/very low birthweight (VP/VLBW; <32 weeks/<1500g) cohorts or whole population studies are included where these illustrate pertinent findings or where data from EP cohorts are lacking.

Attention, social and emotional problems

Herein we adopt a broad definition of behavioural outcomes, encompassing research relating to behaviour, attention, social and emotional problems and mental disorders. The majority of extant data stem from VP/VLBW cohort studies, and from the use of parent, teacher or self completed rating scales given their utility on a large scale. The results of such studies are largely convergent, and have identified a greater risk for internalising than externalising problems among children born

EP. For example, a recent meta-analysis of parent reported outcomes in EP/ELBW children compared with term born controls identified a moderate effect size for internalising problems (Standardised Mean Difference (SMD) 0.42; 95% CI 0.26, 0.58; 11 studies) and a small effect size for externalising problems (SMD 0.15; 95% CI 0.02, 0.28; 5 studies) (Figure 1a).(1)

FIGURE 1

Results on such summary scales can mask differences in outcomes across functional domains. When the same authors analysed data for specific disorders, they found a large effect size for symptoms of combined Attention-Deficit/Hyperactivity Disorder (ADHD) and moderate effect sizes for inattention, hyperactivity, social problems and autistic symptoms. In contrast, there was a small effect size for conduct problems and no significant difference in oppositional defiant disorder (ODD) problems between EP/ELBW children and controls (Figure 1a).(1) Although there are fewer studies in adolescence, their meta-analyses revealed similar findings. As shown in Figure 1b, there were no significant differences between EP/ELBW adolescents and controls in parent reported externalising, conduct disorder or ODD problems, a small effect size for hyperactivity, but moderate effect sizes for social problems, combined ADHD symptoms, inattention and internalising problems (Figure 1b).(1) Indeed EP children identify poor peer relationships and mental wellbeing as salient characteristics.(2)

These findings are reflective of the broader literature, including studies of VP/VLBW cohorts, which have led to the putative 'preterm behavioural phenotype'. This is a universal pattern of outcomes characterised by an excess of problems and disorders associated with inattention, emotional symptoms, and social problems(3); these are typically paralleled by a smaller or, in some , no increased risk for conduct disorder or ODD problems.(3, 4) This phenotype was evidenced in early reports by a strikingly similar pattern of outcomes in five European and North American ELBW/EP cohorts born in the 1970s-1990s.(5, 6) In each cohort, parents rated ELBW/EP children with a significant excess of attention, social and thought problems on the Child Behavior Checklist (CBCL)

compared with term born controls; this was alongside no increased risk for aggressive or delinquent behaviour problems. These studies highlighted the cross-cultural and temporal consistency in outcomes despite improved neonatal care and the consequent increase in survival of EP babies over this period.

Whilst the majority of research has focused on middle childhood, problems are already evident in the early years.(7-9) Among children born at <29 weeks of gestation in the French EPIPAGE Study, 24% had clinically significant problems compared with 9% of full term controls at three years of age.(10) At five years of age, 38% of Norwegian children born <28 weeks of gestation had clinically significant problems compared with 11% of controls (OR 5.1; 95% CI 3.7, 7.1).(11) An increased risk for regulatory problems, poor socio-emotional competence and withdrawn behaviour has also been observed in EP born infants (12-15) which has been associated with an increased risk for later psychiatric disorders.(16, 17)

A number of studies have also identified an increased risk of conduct problems among children born EP (8, 10, 11, 18), which may be inconsistent with the behavioural phenotype described above. However, externalising problems in early childhood may manifest as inattention, autistic traits or psychiatric disorders later in life.(16, 17) In addition, the phenotype was observed from the co-occurrence of problems at a population level. Although there is greater comorbidity of psychological problems in EP children than controls (19), the extent to which ADHD, ASD and emotional disorders cluster within individuals is less well defined, particularly as not all EP survivors will go on to have long term morbidity. Using latent profile analysis, it was recently reported that 20% of EP survivors exhibit an outcome profile consistent with the preterm behavioural phenotype, with the remaining having only minimal difficulties (55%) or having elevated scores in multiple behavioural domains (25%).(20)

Psychiatric disorders

In a meta-analysis of five cohort studies of children born preterm (<37 weeks of gestation) or with low birthweight (LBW; <2500g), prevalence estimates for psychiatric disorders ranged from 21% to 28%, with a pooled Odds Ratio (OR) of 3.66 (95% CI 2.57, 5.21) relative to term born controls.(21) The authors also identified an increased risk for emotional disorders (anxiety or depression) in preterm/LBW survivors (OR 2.86; 95% CI 1.73, 4.73; 5 studies).(21) Another recent meta-analysis reported a pooled OR of 4.05 (95% CI 2.38, 6.87; 4 studies) for ADHD in EP/ELBW children.(22)

There is growing concern regarding the high risk for ASD in children born preterm, fuelled by reports that 13%-41% of EP children screen positive for autism in the first two years of life.(23-26) However, screening for ASD in EP populations is confounded by the high risk for other neurodevelopmental sequelae.(25, 27) Thus, the predictive validity of early screens is poor, with sensitivity and positive predictive values estimated to be 52% and 20%, respectively, for later ASD diagnoses.(28) A recent meta-analysis identified an ASD prevalence of 7% among children born VP(29), which is markedly increased relative to 62/10,000 reported in the general population.(30)

Behavioural outcomes: current controversies and research directions

One of the key current questions relates to the extent to which behavioural problems observed in childhood persist into adulthood; in particular, whether early sequelae represent a developmental delay, or whether EP birth limits developmental plasticity thus conferring deficits that persist across the lifespan. Data for EP adults remain sparse, but as the VP/VLBW/ELBW cohorts from the 1970s and 1980s transition to adulthood these questions are beginning to be answered.

In a recent narrative review of six studies, the authors reported that ELBW adults are at increased risk for internalising behaviours, anxiety problems, shyness, poor mental health and reduced social functioning. However, they found no excess of ADHD and externalising behaviour problems, and a decreased risk for substance use disorders.(1) This is similar to the results of a recent meta-analysis, which identified that VP/VLBW adults are more likely to have internalising problems and avoidant personality than term born adults, but are less likely to have externalising problems and anti-social

behaviour.(31) These studies are also consistent with other reports in which VP/VLBW adults have been found to be more agreeable, socially withdrawn and introverted, and less likely to engage in substance use and risk taking behaviours.(32, 33)

The most recent data available for EP survivors are from the UK and Irish EPICure Study in which trajectories of parent reported behaviour, attention, social and emotional problems have been explored (Figure 2). Using the Strengths and Difficulties Questionnaire (SDQ) at 6, 11, 16 and 19 years of age, mean scores for ADHD and emotional problems were persistently higher in EP than term born individuals, but the risk for clinically significant problems declined from childhood to adulthood, with the group difference at 19 years no longer being significant. In contrast, the risk for clinically significant peer relationship problems was increased at all ages in EP survivors, peaking in adolescence. Notably, the risk for conduct problems was only increased at 6 years of age and progressively declined with age relative to controls.(34)

FIGURE 2

However, these results were based on parent report. Most recently, the results of self-completed evaluations among this cohort at 19 years of age revealed higher scores for symptoms of anxiety, depression, withdrawn behaviour and avoidant personality. However, there was no increased risk for clinically significant problems in these areas, or for mood and anxiety disorders at 19 years of age(35), similar to reports of mood and anxiety disorders in VP/VLBW samples.(36) This is reassuring and suggests that, whilst sub-clinical problems may persist to adulthood, mental health outcomes for EP survivors may be better than once anticipated. The decreasing risk may be a result of reduced statistical power due to participant attrition, therefore these findings require confirmation in larger studies.

Another focus of current interest is the need to identify interventions to improve outcomes in this population, with a key question being whether these need to be population-specific, reflecting different mechanisms for psychiatric sequelae in preterm populations, or whether existing therapies

are likely to be effective. Forging an understanding of the underlying risk pathways for mental health disorders is therefore a focus of current research, and is particularly evident in relation to ADHD.

In a recent meta-analysis of VP/VLBW cohort studies, the risk for symptoms of inattention (SMD 1.31; 95% CI 0.66, 1.96) was larger than for hyperactivity (SMD 0.74; 95% CI 0.35, 1.13), a finding that has been observed in other population based cohorts.(37-40) These findings are indicative of a different clinical presentation and, potentially, a different aetiology for ADHD in preterm born children. Recent studies have thus focused on elucidating the cognitive processes underlying ADHD in preterm populations and have suggested that, whilst some cognitive impairments are overlapping between VP children and term born children with ADHD, VP children show additional impairments reflecting more wide-ranging cognitive deficits.(41-43) Interruption to fetal brain development in the third trimester may result in trauma to the brain networks associated with ADHD(44), in addition to networks associated with other impairments, resulting not just in ADHD symptoms but in increased comorbidity in neurodevelopmental disorders observed in this population.(41) Similarly, there is growing evidence for an association between deficits in general cognitive functions, such as in executive function and/or working memory, and attention and social problems in children born preterm.(45-49) Improving these cognitive abilities may therefore be a potential target for intervention, the efficacy of which is discussed in the following sections.

Academic attainment and special educational needs

It is well documented that children born EP are at increased risk for intellectual impairments (see Chapter 20). Deficits in a range of general cognitive abilities are frequently reported, including poorer executive function, processing speed, working memory and visuospatial skills relative to term born controls.(50-52) It is therefore unsurprising that preterm birth has a marked impact on children's academic attainment and the need for special educational provision.

Deficits in the acquisition of early learning skills between EP children and their term born peers are already evident before the start of schooling. For example, significant deficits in school readiness

have been observed in children born ELBW/VP(53-55), and these have been shown to predict later achievement in reading, spelling and mathematics.(56) Already at age five, VP children in the UK have poorer attainment at the end of the reception year, with 66% failing to have a good level of achievement compared with 51% of children born at term (RR 1.19; 95% CI 1.00, 1.42).(57) By age seven, in the same cohort, 43% of VP children failed to have a good level of achievement in reading, writing and mathematics, compared with 18% of children born at full term (RR 1.78, 95% CI 1.24, 2.54).(58)

Outcomes for EP children are likely to be even poorer given the gestational age related gradient in outcomes. Indeed poorer mathematical and reading skills have been observed among EP/ELBW children compared with controls at age five in a representative sample of children in the US.(59) In middle childhood, by eight years of age, EP/ELBW children continue to have significantly poorer attainment in reading, spelling and arithmetic compared to children born at term(60), and by 10-11 years of age, substantial deficits in mathematics and reading and poorer performance in national tests have been observed among EP/ELBW children.(61, 62) By the end of primary school, half of all EP children in the EPICure Study of births before 26 weeks of gestation had attainment below the national average compared with just 5% of their term born peers (OR 18.2, 95% CI 8.0, 41.4).(63) Underachievement compared to term born peers continues to be evidenced at the end of formal schooling. At age 16, poorer scores on school leaving qualifications in mathematics, literacy and foreign language learning have been observed among adolescents born at <29 weeks of gestation, and poorer reading, spelling and mathematics skills have been reported at age 18 years in EP/ELBW young adults.(64, 65) Children born EP are also less likely to complete basic school than their term born peers, a risk that increases with decreasing gestational age at birth, particularly below 31 weeks of gestation.(66)

Poor academic attainment has broader economic consequences, which are evidenced in the increased receipt of special educational needs (SEN) support among children born EP. School census

data from Scotland show a clear gestational age related gradient in SEN, with the proportion of children requiring support increasing exponentially with decreasing gestational age at birth (Figure 3). Among those born EP in this study, 29% had SEN compared with just 4% of children born at 40 weeks of gestation (adjusted OR 6.92, 95% CI 5.58, 8.58).(67) The proportion with SEN is even greater amongst the most immaturity born children, with 62% of children born below 26 weeks of gestation in the EPICure Study having SEN or attending special school compared with just 11% of term born controls (OR 13.1, 95% CI 7.4, 23.3).(62)

FIGURE 3

Ultimately, poorer educational outcomes result in poorer occupational status and wealth in adulthood.(68) A recent meta-analysis of 23 studies identified that VP/VLBW adults are less likely to complete education beyond high school and be employed, and are more likely to be in receipt of benefits than adults born at term; however there was no significant difference in the proportion living independently (Figure 4).(69)

FIGURE 4

Developmental delay or developmental deficit?

Just as is the case for behavioural outcomes, a key controversy relates to whether poorer educational outcomes in childhood represent developmental deficits that persist across the lifespan, or whether, as EP children mature, they catch up with their peers. Similar to studies tracking IQ in EP/VP/VLBW cohorts(70, 71), recent longitudinal studies have failed to provide robust evidence of catch-up in academic outcomes. In a study of VP children and term born controls assessed through Grades 1-6 in the Netherlands, there was no significant difference in the trajectories of VP children and controls in either arithmetic, reading comprehension or spelling. This indicates that between-group differences remained stable over time and that VP children did not catch up with their peers by the end of primary school.(72) Most recently, an investigation of trajectories in results on national

school attainment tests at ages 7, 11, 14 and 16 years in the UK found that children born preterm displayed some catch-up between 7 and 11 years, after which they had similar trajectories to their term born peers. As such, term born adolescents continued to out-perform their preterm counterparts at the end of compulsory schooling.(73) It may be that EP birth places even greater limits on developmental plasticity and that trajectories may be more immutable in this population. To investigate this, the authors examined trajectories for those born VP and, whilst the overall trajectory was similar to the total preterm group, some of the catch-up observed between age 7 and 11 years was lost again at secondary school.(73) The trajectory of attainment in EP children remains to be determined.

Current evidence is consistent with a developmental deficit rather than delay. However, the authors of the above studies argue that, despite the persistent deficits in academic attainment, the similarity in trajectories between preterm and term born children suggests that preterm children have intact learning abilities, thus affording opportunities for intervention.(72, 73) It is therefore important to elucidate the cognitive mechanisms underlying poor academic attainment in preterm populations in order to inform the development of intervention strategies, as discussed in the following sections.

Supporting the learning of children born preterm

Supporting the learning and academic attainment of EP children has never been more crucial since recent reports suggest that motor, cognitive and academic outcomes may be deteriorating despite ongoing advances in neonatal care.(74-76) Interest initially focused on preventive interventions delivered during the neonatal period or during the first few years of life. Whilst there was initial enthusiasm following reports that these might improve outcomes in the short term, meta-analyses have shown that the long term benefit of such programmes is limited; beneficial effects are rarely sustained beyond the period of intervention delivery and any impact on cognitive function is washed

out by school age.(77, 78) Thus, if the aim is to improve academic outcomes, then intervention at school age may be most effective.

The aetiology of academic underachievement following EP birth is a focus of current research, especially in mathematics as EP children have greatest difficulties in this subject.(62, 79, 80) Such studies indicate that EP children's poor achievement in mathematics is not related to a specific deficit in numerical magnitude processing, but rather to deficits in general cognitive abilities such as working memory, executive function, visuospatial skills and processing speed.(48, 52, 81-83) Thus, converging evidence suggests that poor general cognitive abilities may underlie both behavioural and educational problems in EP children and that improving these abilities may improve a range of outcomes. The notion that a single intervention may improve outcomes across multiple developmental domains is certainly enticing; however attempts so far have met with little success. For example, attention has focused on the use of computerised adaptive working memory training for improving cognitive and academic outcomes. Whilst some studies have reported short term positive effects in VP/VLBW samples, these have lacked an active control or have been underpowered.(84, 85) There remains no robust evidence of long term benefits of working memory training, particularly for enhancing academic attainment.(86-88) Given the evidence to date, it is perhaps time to focus efforts on identifying other strategies for improving outcomes in this population.

One approach gaining ground lies in improving educational support in the classroom. Knowledge and preparation about health conditions is crucial for the provision of appropriate educational management(89, 90), yet research has shown that teachers lack training about preterm birth and have poor knowledge of the impact it may have on children's learning.(91) As education professionals have a key role to play in supporting preterm children in the long term this represents a significant public health concern. This was recognised in the recent European Standards of Care for Newborn Health in which it was recommended that education professionals receive training about

preterm birth.(92) Improved communication of clinical research to teachers and better information sharing between healthcare and education services may serve to improve educational support for children born preterm. An evidence-based e-learning resource that has been shown to significantly improve teachers' knowledge of the consequences of preterm birth and their confidence in supporting children in the classroom(93) was released in 2019 (see: www.pretermbirth.info). The impact of this on improving outcomes for children born preterm remains to be seen.

Delayed school entry

Perhaps one of the most controversial potential approaches to supporting the development of children born preterm is that of delayed school entry. The implicit underlying theoretical model for delayed school entry is that, given time, EP children will continue to develop and will reach the same level of cognitive and social maturity as term born children who enter compulsory education at the appropriate age. This is in stark contrast to the studies presented above, which consistently show that deficits in cognitive, attention and emotional function persist into adulthood.(34, 70, 71)

The evidence for or against delayed school entry has been recently reviewed and existing studies are inconclusive.(94, 95) Using a natural experiment we recently investigated the effects of delayed versus age-appropriate school entry on academic attainment and attention using data from the Bavarian Longitudinal Study. The results indicated that delayed school entry had no beneficial effect on teacher ratings of academic performance at the end of the first year of schooling, but was associated with poorer performance in standardised tests of reading, writing, mathematics and attention at 8 years of age.(95, 96) Thus keeping children back for a whole year did not have a noticeable "maturation effect", but deprived these children from learning opportunities so that they did worse in achievement tests at the same age as those who had entered school at the compulsory entry age. Considering the adverse effects that low socio-economic status (SES) or poor parenting

can have on the development of EP children, delaying school entry for EP infants from disadvantaged families may increase social disadvantage further.

Nonetheless, parents of preterm children often believe that delayed school entry may be helpful. Indeed, preterm children should not be disadvantaged compared to term born children due to their preterm birth. For example, in the UK, children enter school in the September after their 4th birthday. However, EP born children who would have had their expected date of delivery in October may be born in July but are expected to enter school, considering post-conceptual age, younger than their term born peers. In these circumstances, delayed entry may be indicated to allow an EP child to enter school at the same time as children of the same post-conceptual age. However, delaying entry for all EP children due to the increased risk for developmental problems may not be beneficial according to the evidence to date.

To test whether delayed school entry may be a simple intervention that works, a randomised controlled trial is needed. Our recent feasibility study indicated that such a trial would not be feasible as parents expressed that the decision about whether or not to delay entry for their child was too important to be determined by randomisation.(94) Despite the controversial evidence, a report published in the UK in 2018 highlighted that the number of parents of summer born children that requested delayed entry doubled in 2016-2017 after legislation allowing this came into force.(97) The report also provided no evidence that delayed school entry improved children's scores in a phonics screening test in Year 1. Thus, evidence will have to rely on future observational studies tracking the impact of delayed school entry on academic achievement controlling carefully for social selection factors.

The need for theory driven research

Moving forwards, the elucidation of effective interventions requires a greater focus on theory driven research. Most EP cohort studies have used a simple main factor model investigating perinatal differences at birth, such as in gestational age or neonatal complications, and documenting whether

these are associated with adverse developmental outcomes. This approach ignores that many other influences may operate between birth and outcomes in childhood and adulthood. One simple environmental factor to assess is the socioeconomic status (SES) of the family. For example, studies have shown that being born into a high versus low SES family has as much of an effect on long term outcomes as being born VP versus at term.(98) Similarly, having a mother whose highest educational attainment was at primary or secondary school compared to one who has received postgraduate education has the same adverse effect on the IQ of EP children as having suffered severe IVH or chronic lung disease.(99) It is thus no surprise that SES has been reported as one of the major influences on cognitive outcomes in VP children.(100, 101) 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.(102)

We recognise that measurement of SES is challenging since it can reflect a multitude of factors including social, family and parenting factors.(103) However, 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(103) which will require greater collaboration across disciplines in the design of follow-up studies. Let us consider two examples of such an approach. As described above, EP children 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 of emotional problems.(104, 105) In a recent investigation, we noted that a major part of the effect of EP birth on emotional problems was explained by EP 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 was a mediator of the effects of EP birth on emotional problems.(106) Furthermore, it has been shown that the academic achievement of healthy term born children is only minimally influenced by good or poor parenting. In contrast, VP children are strongly and adversely affected by low sensitive parenting while, on the other hand, very sensitive parenting has been found to lead to academic achievement on a par with children born at term.(107, 108)

These examples indicate that parenting and peer behaviour are important mediators or moderators of outcomes in the EP population. There is also increasing evidence that EP birth makes children more sensitive to adverse environmental risk factors.(109) This increased vulnerability leads to even worse outcomes if children are exposed to an average or poor environment, but EP survivors may attain outcomes similar to term born children when exposed to optimal environments. The effects are therefore best described using a diathesis-stress model.(110) Research that considers environmental influences from SES and parenting to peers and friendships and how these protect against, mediate or moderate the impact of EP birth on developmental outcomes is urgently needed. Understanding such developmental mechanisms will be a major step change in current research as it may point to factors that are modifiable and thus are prime targets for intervention.

Summary

EP birth places infants at high risk for attention, social and emotional problems and disorders and for academic deficits later in life. Studies of VP/VLBW cohorts have shown that these deficits persist into adult life but a greater understanding of trajectories of educational and behavioural outcomes for EP survivors are needed. These will naturally ensue as the earliest EP cohorts born in the 1990s transition through adulthood. Attempts to improve long term outcomes for EP children have typically focused on the efficacy of early parenting interventions or of training children's cognitive abilities, but these have met with little success to date. Ongoing efforts to identify effective interventions to improve outcomes for EP children need to be intensified, for which a greater focus on theory driven research may hold the answer.

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FIGURE 1a

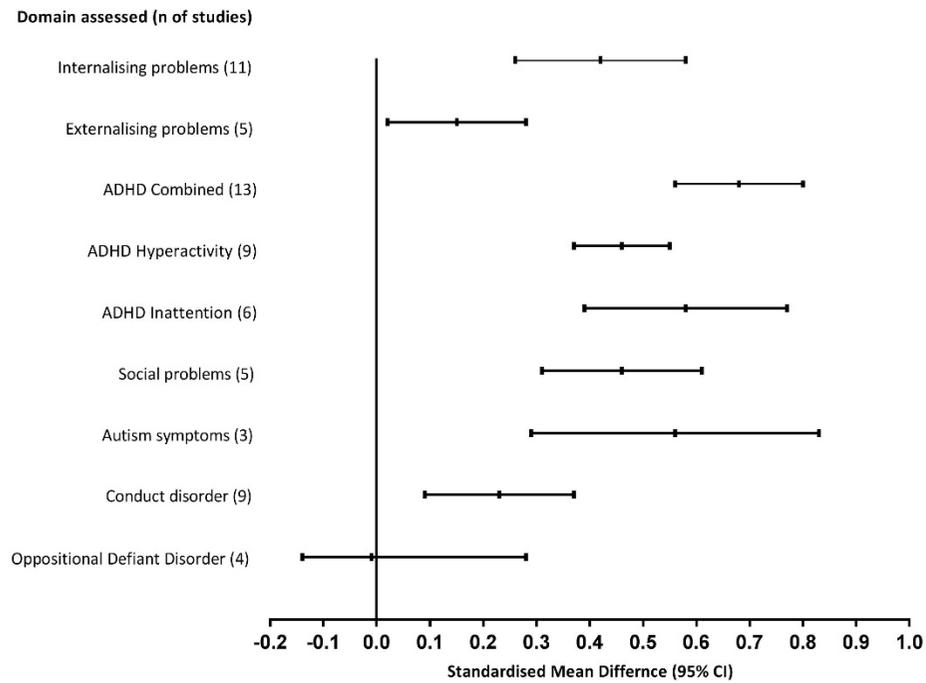


FIGURE 1b

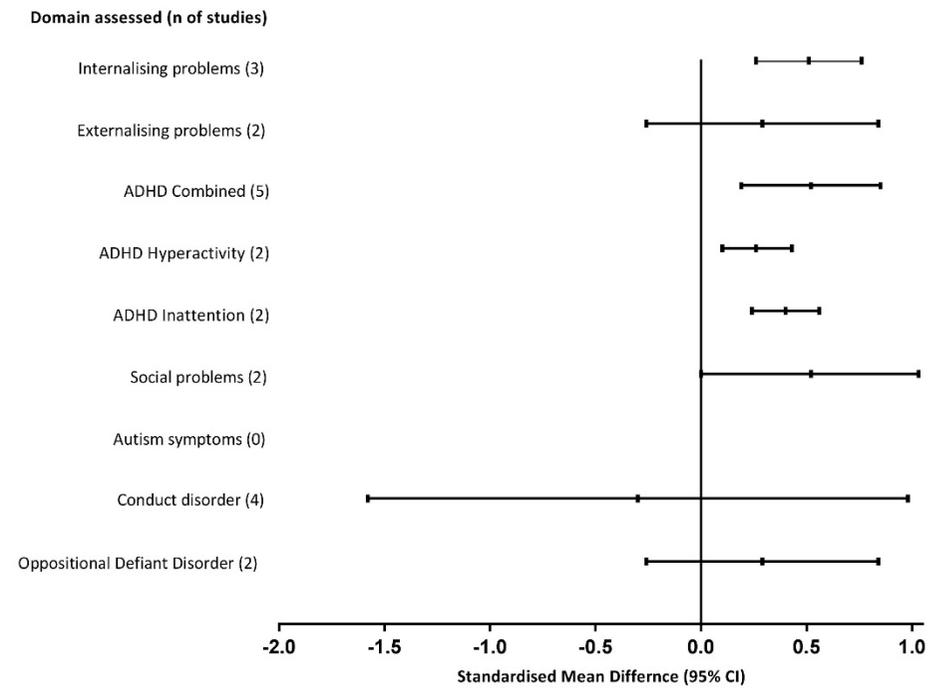


Figure 1. Results of meta-analyses of parent reports of mental health outcomes for extremely low birth weight (<1000g) survivors compared with term born (≥ 37 weeks' gestation) controls. Results are shown as standardised mean differences (SMD) and 95% Confidence Intervals (95% CI) for children aged 5 to 13 years (Figure 1a) and adolescents aged 14 to 18 years (Figure 1b). Figures created using data published by Mathewson KJ, Chow CHT, Dobson KG, Pope EI, Schmidt LA & van Lieshout RJ. Mental Health of Extremely Low Birth Weight Survivors: A systematic Review and Meta-Analysis. Psychological Bulletin 2017;143(4):347-383.

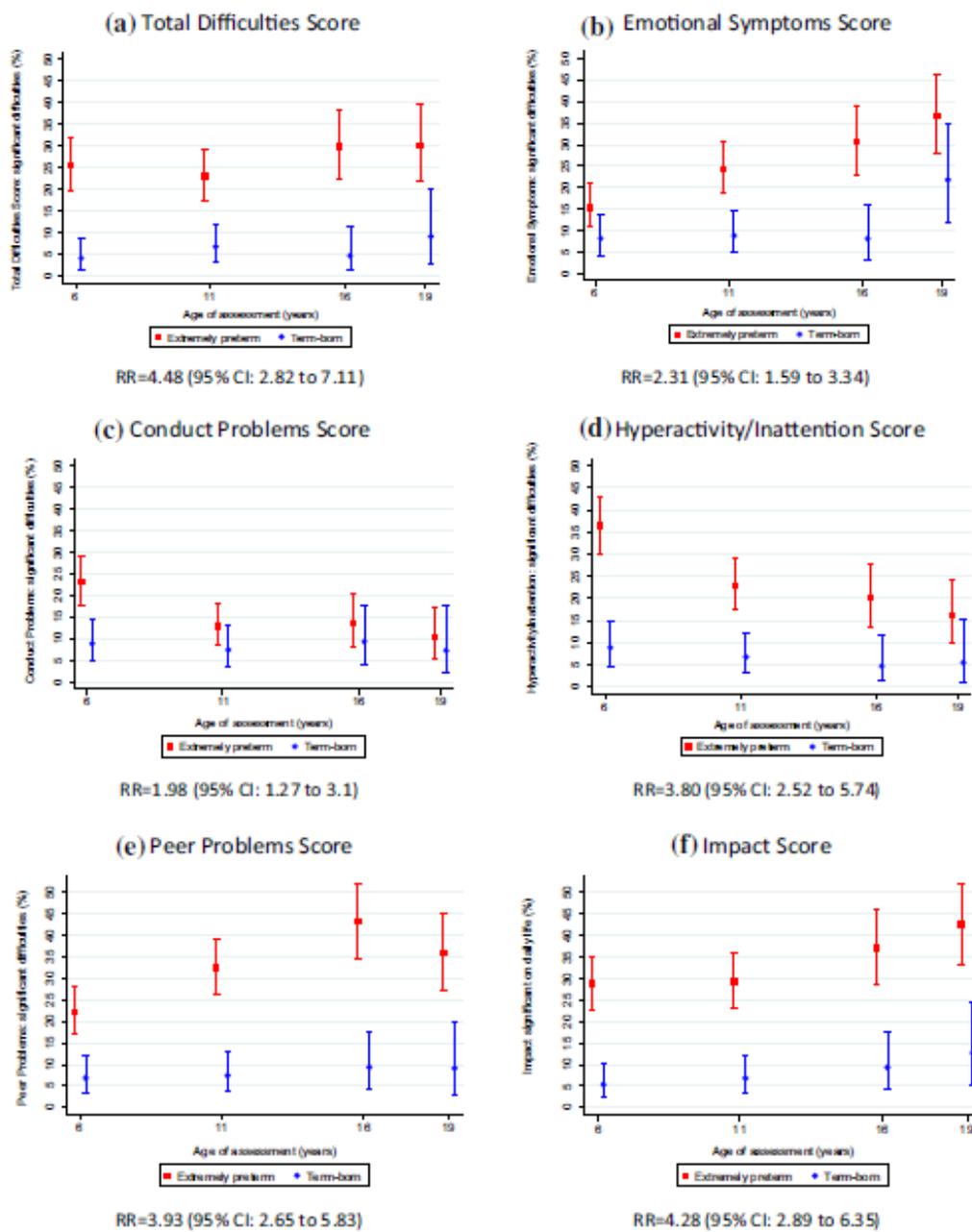


Figure 2. Percentage in the abnormal range and 95% confidence intervals for Strengths and Difficulties Total difficulties and sub-scale scores in the extremely preterm participants and term born controls at age 6, 11, 16 and 19. Figure reprinted from Linsell L, Johnson S, Wolke D, Morris J, Kurinczuk J, Marlow N. Trajectories of behaviour, attention, social and emotional problems from childhood to early adulthood following extremely preterm birth: a prospective cohort study. *Eur Child Adolesc Psychiatry* 2019;28(4):531-42.

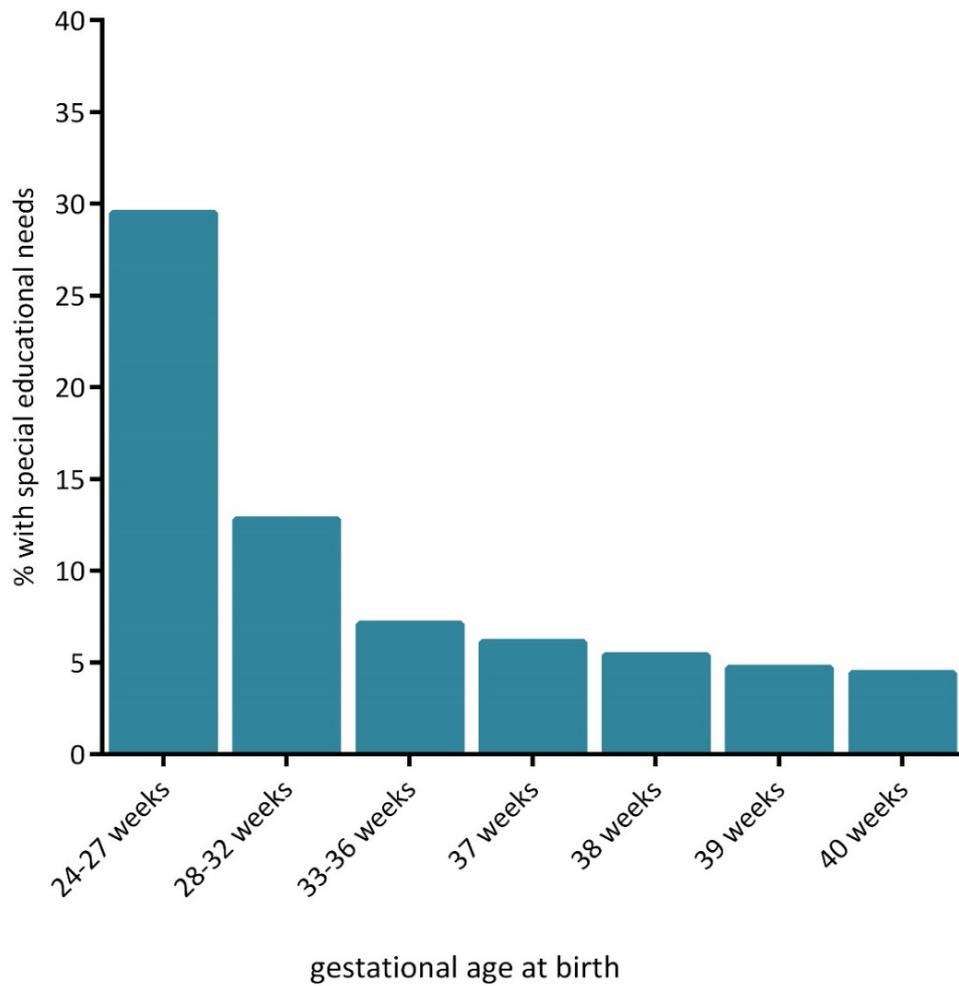


Figure 3. Prevalence of special educational needs in relation to gestational age at birth in a geographic population based cohort in Scotland. Figure created using data published by Mackay D, Smith GCS, Dobbie R, Pell JP. Gestational age at delivery and special educational need: Retrospective cohort study of 407,503 school children. PLOS Medicine 2010;7(6):e10000289.

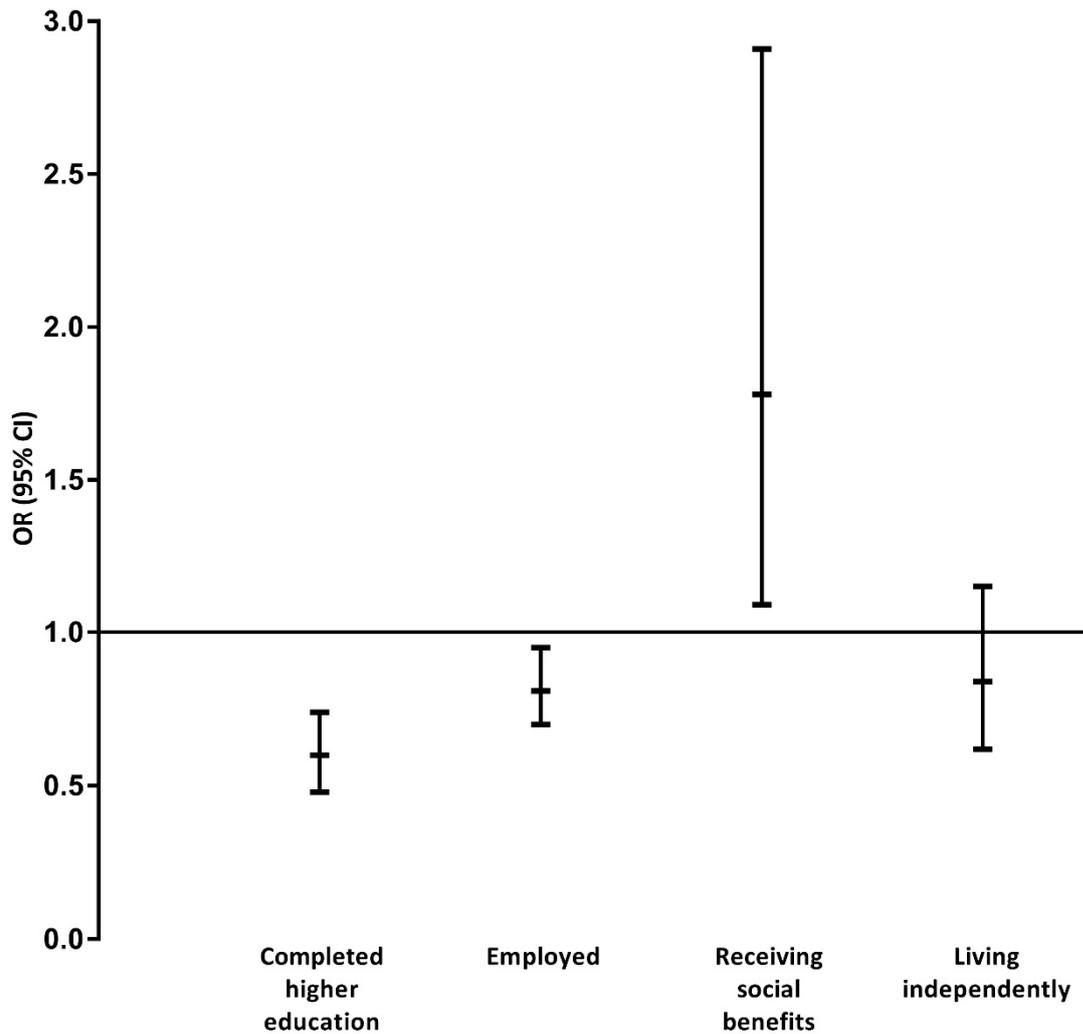


Figure 4. Meta-analysis of 23 studies of the impact of very preterm birth/very low birthweight on educational, occupational and functional outcomes in adulthood. Data shown are Odds Ratios with 95% Confidence Intervals. Figure created using data published by Bilgin A, Mendonca M, Wolke D. Preterm birth/low birth weight and markers reflective of wealth in adulthood: A meta-analysis. *Pediatrics* 2018;142(1):e20173625.