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The extremely preterm young adult – State of the art

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A B S T R A C T

Recently several studies have reported adult outcomes for individuals born at extremely low gestations, although they tend to be included as part of slightly more mature populations. The growth in collaborative studies allows greater confidence in the identification of persisting risk and allows us to have confidence in the likely outcomes in more contemporary cohorts. This review shows the persistence of adverse outcomes through to adult life and includes a range of outcomes including all body systems evaluated. Nonetheless adult outcomes demonstrate that most survivors appear to be free of major disabling conditions and demonstrate good participation in society. Several studies have reported outcomes in the third decade, but subsequent ageing trajectories have not yet been defined. The stability of many of the outcomes evaluated over childhood into adult life and the lack of improvement in prevalence of childhood impairments found in contemporary cohorts indicates persisting levels of risk.

1. Introduction

In the early 1990's, several key interventions were introduced which dramatically improved survival among populations of extremely preterm babies. Alongside this, anxieties about the high risk for long term disability and wide-ranging challenges for survivors and their families assumed greater importance among professionals and parents alike. Since this time, there has been an explosion in our knowledge and understanding of outcomes in childhood and, more recently, in adult life for this group of NICU graduates. Whilst survival continues to increase, there is, as yet little evidence that either the serious or more subtle adverse childhood outcomes are improving in parallel.

Several important questions stem from these trends:

- How do outcomes change over adolescence? One can conceive that some outcomes – such as somatic growth, for example – may demonstrate an altered trajectory through the second decade leading to reducing (or even increasing) deficits when viewed across adolescence. How important is the influence of the physiological changes that occur over this period?
- Are the reported outcomes in childhood predictive of outcomes in adult life? This is critically important as it allows clinicians to extrapolate from key childhood findings and draw conclusions about current practice.
- What are the impacts of the preterm neurocognitive, psychiatric or somatic phenotype on the attainment and life-course of extremely preterm adults and can we extrapolate outcomes for current survivors?

The UK EPICure study recruited a national cohort of births <26 weeks of gestation in 1995. This remains one of the most immature groups to be followed through to adult life and is therefore highly relevant to this issue of Seminars. It is challenging to describe outcomes for even smaller survivors - <400 g or <23 weeks of gestation at birth – as the cohorts that have now reached adult life contain very few of these individuals, who will have similar findings to those 34-25 weeks. In this paper we will review results from the EPICure cohort alongside longitudinal and cross-sectional studies of slightly more mature cohorts which help to answer the above questions and provide a broad picture of the lifecourse implications of extremely preterm birth, which are summarised in Fig. 1.

2. Cognition

Across childhood, the commonest challenges stem from altered cognitive function and reduced intelligence quotient (IQ) among survivors. Studies reporting IQ test scores in adult life vary greatly in their selection criteria leading to uncertainty as to the precise magnitude of the cognitive deficit associated with extremely preterm birth. Because of the close relationship between IQ test scores and gestational age, and to a lesser extent the relationship between weight for gestation at birth, it is difficult to provide precise estimates from single studies.

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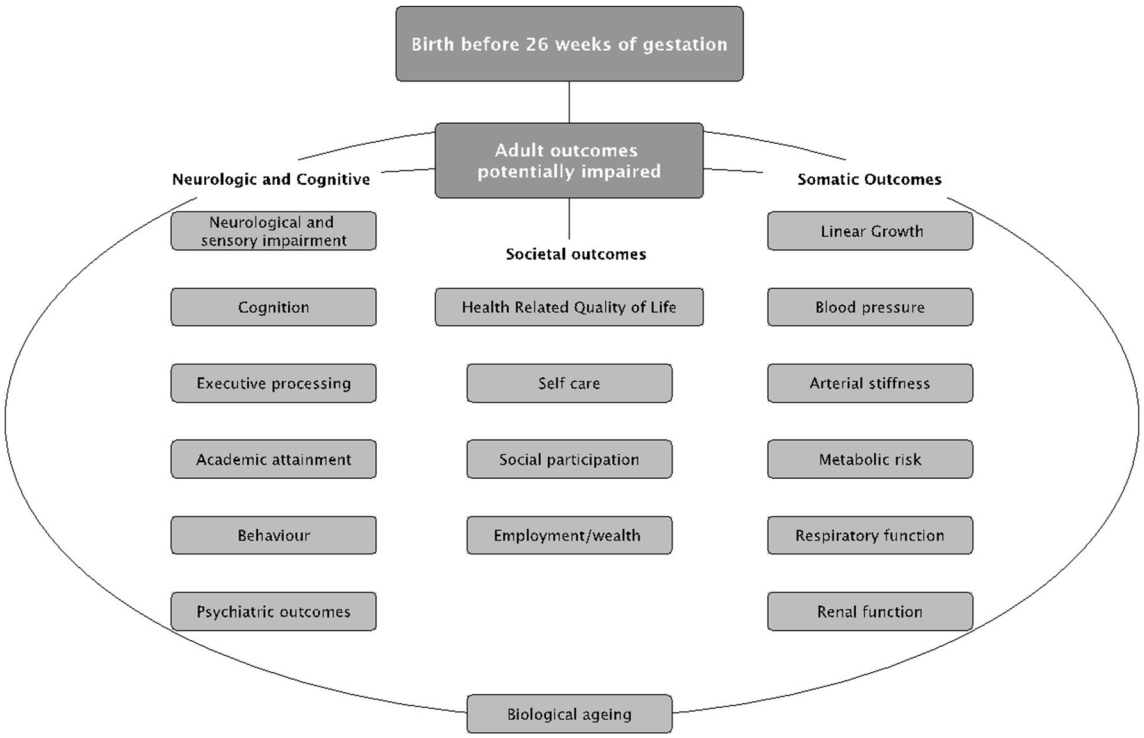

Fig. 1. Broad range of potentially impaired outcomes studied in adults who were born extremely preterm.

In a mixed individual patient data (IPD) and cohort analysis, Eves and co-authors found a 12 point deficit in IQ among very preterm (VP) adults born <32 weeks of gestation (mean gestational age 28.3 weeks) compared to term-born adults at a mean age of 24.6 years [1]. Even after excluding those with neurosensory impairment (including those with low IQ), the deficit remained at 10 points or 0.65 standard deviations (SD). Using either the IPD alone or including cohorts for whom IPD was not available, the findings did not substantially differ and were similar to the results of systematic reviews in childhood. The constituent studies included a wide range of cohort definitions – very low birthweight (VLBW; <1500 g), VP (<32 weeks), extremely preterm (EP; <28 weeks) and <26 weeks of gestation (EPICure). The importance of this is that each study comprised a unique set of gestational and/or weight defined participants. Key influences on adult IQ were found to be gestational age at birth (0.11 SD per week), birthweight for gestational age (0.21 SD per birthweight SD), and higher vs. lower maternal education level (0.26 SD difference). In addition, markers of neonatal morbidity such as supplemental oxygen use at 28 days/36 weeks postmenstrual age and the ultrasound identification of preterm brain injury were also associated with a 2–3 point decrement in IQ. In a separate meta-analysis, the effect of maternal education produced a consistent effect at different ages and in different gestational groups [2]. Reflecting the birth years of the cohorts (1978–1995), the mean age at assessment ranged from 19 to 30 years. Given the stability in findings from childhood to adulthood, one might expect the deficit to persist across the lifecourse, however longer term follow up of these cohorts is needed to determine outcomes in later adulthood and cognitive trajectories across the lifespan.

The relationship between measures made during childhood and adult life has recently been explored in single cohort studies where tighter control over the measures used may be made. Breeman and colleagues [3] evaluated a mixed VP/VLBW group at 26 years of age in relation to 5 childhood assessments between 5 months and 8 years of age. Among their index group and term-born controls, correlation with adult IQ improved between successive childhood assessments and was best for IQ tests carried out between 4 and 8 years, improving in parallel in both groups. Interestingly, whilst the correlation was consistently stronger among the index group relative to controls, the correlation in the controls was very similar to index participants who did not have other neurodevelopmental impairments despite the differences in scores referred to above. In addition, the authors noted that adult IQ could be reliably predicted from age 6 in term-born children and from as early as 20 months of age in VP children, underscoring the potential value of early cognitive assessments.

In a further analysis from the Bavarian Longitudinal Study, being small for gestational age was associated with a fixed effect on IQ through to adult life, the size of which (8 IQ points) was approximately half of that from the study group compared with controls and half of that from low versus high social class [4].

Linsell and colleagues evaluated the trajectory of cognitive test scores from 2 to 19 years of age in the EPICure cohort of EP births before 26 weeks of gestation, using hierarchical mixed modelling [5]. Despite some movement in scores over childhood, with an estimated within-individual variation of 8.7 IQ points for the EP group (compared to 5.7 points for term-born controls), the between-group deficit in scores remained similar in magnitude from 6 through 19 years with only marginal closure between the EP and control participants. There was a marked sex difference in IQ scores among the EP group with girls outperforming boys, but this was constant over the assessments and the effect of maternal education as a marker of social advantage was similar in both groups. Within the EP group, lower gestational age at birth and brain injury exerted constant deleterious effects on IQ. Thus there is no evidence that the cognitive deficits identified in childhood alter significantly over adolescence and, importantly, the findings from modelling were the same as the complete case analysis, including only those who were evaluated at all ages.

It is important to recognise that even excluding participants with brain injuries detected on ultrasound scanning in the neonatal period, significant cognitive deficits persist into adulthood in most studies. Volpe described preterm brain outcomes as a complex amalgam of destructive and developmental disturbances [6]. The processes which lead to very or extremely preterm birth bring with them their own influence on outcome, on which are superimposed neonatal determinants

of outcome such as postnatal brain injury, nutritional and physiological problems making identification of single influences difficult [7,8], and careful thought is required in developing investigations of risk factors and influences [9].

This 'encephalopathy of prematurity' [6] has wide effects on cognitive development as is shown in multiple studies of executive function [10,11]. In middle childhood these may be reflected in impairments in attention, working memory and processing speed, key processes underlying executive function [12,13]. In the EPICure cohort, extremely preterm young adults scored less optimally over a range of neuropsychological tests relative to term-born controls (with effect sizes 0.7 to 1.2 SD) and 60% had impairment in at least one domain [14]. The specific effects of very or extremely preterm birth on cognitive processes are not individually predictable and reflect other influences from fetal growth to the rearing environment. Overall, general cognitive measures reflect these differences and do show comparability between studies despite differences in the specific tests used. As yet changes over time are less obvious and changes in neonatal care are not as yet reflected in reduced proportions with neurosensory impairment [15,16] deficits in executive functions [17], or academic attainment [18].

3. Behaviour and psychiatric outcomes

Alongside cognitive outcomes, dimensional and categorical approaches to evaluating behaviour and emotions are widely studied. An emerging childhood 'preterm behavioural phenotype' has been identified, characterised by internalising symptoms, namely inattentiveness, anxiety and social interaction difficulties [19]. Behavioural scores track into adult life in a similar fashion to cognitive scores, and major influences, such as neonatal risk factors, maternal education and sex, exert similar effects over adolescence [20]. A higher prevalence of anxiety and depressive symptoms and more withdrawn or avoidant personality traits are reported by EP young adults compared with controls [21]. Five cohorts have now evaluated personality type in adulthood – individual participant data analysis confirms that VLBW adults score lower on extroversion but higher for neuroticism and agreeableness [22] than their term-born peers, paralleling the adult expression of the childhood phenotype.

Studies have shown an increased risk of autism spectrum disorders in childhood. At 19 years of age, EP adults in the EPICure Study had higher mean total and subscale scores on the Broad Autism Phenotype Questionnaire (BAPQ) with medium and large effect sizes, indicating an excess of autistic traits compared to term-born controls, with increased odds of a score in the clinical range (adjusted odds ratio 4.87; 95%CI 1.67, 14.15) [23]. Based on a clinical interview, 10% of EP young adults in this study reported a diagnosis of autism compared to 1.6% of controls. Allied with this, EP participants scored lower in terms of empathy and emotional recognition, but after adjustment for IQ, empathy and BAPQ scores were significantly correlated. Scores on the Social Communication Questionnaire (SCQ) at 11 years and BAPQ total score at 19 years showed moderate association among EP individuals and there were similar rates of scores in the clinical range among EP participants at each age [23].

Using self-report, an IPD meta-analysis using the Adult Born Preterm Consortium (APIC) VP cohorts (including EPICure) at a mean age of 23 years confirmed the increased risk for internalising problems and avoidant personality traits, with a decreased risk for externalising and related conditions [24]. In a broader IPD analysis including adolescents, Anderson and colleagues confirmed a higher rate of VP born adults met criteria for autism spectrum disorder (ASD) (OR 10.6; 95%CI 2.5, 45), ADHD (OR 5.4; 95%CI 3.1, 9.5), anxiety disorder (OR 1.9; 95%CI 1.4, 2.7) and mood disorder (1.5; 95%CI 1.1, 2.1) than term-born adults, with a similar pattern observed in VP cohorts evaluated before 18 y and after, and in males and females [25].

Similarly, in an IPD meta-analysis carried out by the RECAP-Preterm and APIC consortia, Robinson and colleagues [26] identified no significant increase in self reported Attention-Deficit Hyperactivity Disorder (ADHD) symptoms (difference in mean z-scores 0.0; 95%CI -0.07, 0.07) or scores in the clinical range (OR 1.11; 95%CI 0.8, 1.53) across 7 cohorts, although the EP group did have a higher proportion with clinical scores, mainly explained by the presence of neurosensory impairments. This report also included a population register-linkage study from Finland. In contrast to the cohort-based findings, the linkage study demonstrated an increased risk of ADHD diagnoses among adults born preterm (RR 1.26; 95%CI 1.12, 1.41), which increased further in adults born VP (<32 weeks) and was more prevalent among those born small for gestational age.

Data from other population linkage studies also suggests that there is an increased risk for psychiatric disorders among VP/VLBW individuals, reflecting the findings reported widely in childhood. However, results from several longitudinal cohort studies find no excess of mood or anxiety disorders in early adulthood [26] and it may be that the increased population prevalence reflects bias from increased referrals in populations with more frequent health service contact [21]. Alternatively, result from cohort studies may be affected by selective drop out of individuals with internalising symptoms or disorders. Other longitudinal studies emphasise the difference between self-report and parent-report formats, the latter being more likely to demonstrate differences [27].

Thus, there is some evidence for an increase in symptoms or conditions relating to internalising, attention and social cognition disorders, and probably an increase in related conditions in early adult life, but studies of mental health in later adulthood are awaited. Screening for behavioural, social and emotional challenges in childhood and awareness of the risks in transition to early adult life are important to ensure support and where possible effective interventions.

4. Quality of life and functioning in society

Social functioning may be a more ecologically valid measure of outcomes for VP or EP individuals. Here, self-report commonly identifies fewer issues compared to carer or parent report indicating that the lived experience is different from externally observed experiences. One of the commonly used measures is that of health-related quality of life. The Heath Utilities Index Mark 3 may be used to derive a multi-attribute utility score based on a community survey in Hamilton, Ontario, conducted in the 1990's. Although based on health states, this measure has been widely used with its original utility values [28]. This facilitates comparisons over time and between studies. In a recent report from the EPICure cohort (EP; <26 weeks of gestation) at 19 years, Ni and colleagues reported lower multiattribute utility (MAU) scores compared to term-born controls and lower scores from EP individuals with impairments and their parents [29]. Parent-reports led to lower MAU scores compared to self-report, and comparing with parent-report at 11 years, scores at 19 years were lower, suggesting a decline in health-related quality of life. These findings contrast with a report from Melbourne which did not demonstrate differences between EP (<28 weeks) and term-born individuals [30]. It was encouraging that generally scores were higher than the original Canadian reports and reports from the Netherlands and Bavaria [31].

Despite their popularity and utility in economic analysis, such scales remain firmly based in health and it is clear that health outcomes for EP individuals may be less optimal than term-born individuals. A further way of evaluating functional outcomes and participation is to use the classification proposed by the World Health Organisation International Classification of Functioning [32]. This uses 5 domains (cognition, executive function, self-care, academic attainment, social participation), which may be classified into three states (optimal, at risk, challenged) or combined into a whole person evaluation as able, struggling or restricted. In a study of preterm and term-born individuals at 17 years, Sullivan and colleagues identified that 65–79% of preterm young adults experienced optimal functioning compared to 66–86% of their

term-born controls [33]. Although less optimal than controls, the majority of their preterm group were functioning well in society. The Rhode Island cohort is more mature than many of the cohorts reported above and studies using this classification in more immature groups would be valuable.

Several studies have now followed populations into the third and fourth decade evaluating societal integration. Hack and colleagues [34] performed a longitudinal VLBW study on a Cleveland, Ohio population though 20 years. As anticipated, chronic health conditions were more common, educational attainment was on average lower in the VLBW group and fewer had been enrolled in post-secondary education. However, fewer VLBW adults used alcohol or marijuana/other recreational drugs. Fewer had been in contact with the police (primarily because of less truancy/alcohol or drug use). Female VLBW adults were less likely to report ever having intercourse, being pregnant or having a child. These differences persisted after exclusion of those with neurosensory impairment or low IQ. Although reassuring that VLBW birth was not associated with greater sociopathy, these findings probably also reflect the behavioural phenotype of introversion and social communication difficulties leading to a narrower social group with less peer pressure [35].

Saigal and colleagues have followed an extremely low birthweight (ELBW; < 1000 g birthweight) group from Hamilton, Ontario through to their 4th decade. At 22–25 years a higher proportion of their ELBW cohort were neither employed or in school, mainly attributable to neurosensory disabilities, and there were no significant differences in the proportions in independent living, marriage/cohabiting or with children [36]. Among unimpaired healthy Finnish VLBW young adults evaluated at 18–27 years, there was evidence that more were living in the parental home compared to controls and they were less likely to have started a sexual relationship [37]. However, by the fourth decade (30–36 years) the Hamilton ELBW group had lower levels of employment, lower incomes and fewer were married or had children although they reported fewer risk-taking behaviours compared with controls [38]. One further unexplained finding in this group is the excess of adults without disability who identified themselves as non-heterosexual compared to controls. These consistent findings too may be associated with personality type.

5. Growth

The growth of several cohorts across childhood has been reported showing reduced linear growth and relative reductions in body mass index. In the EPICure cohort, somatic growth was evaluated at each assessment (2, 6, 11 and 19 years). EP children consistently had height, weight and head circumferences below those of controls and below normative means for their age [39]. There was no catch up over childhood to 19 years in height or head circumference compared to controls. Weight showed some catch up mainly over the period 6–11 years with the result that BMI tended to rise between 6 and 19 years, although similar proportions of controls had BMI values in either overweight or obese categories.

Comparison with other longitudinal cohorts is challenging as they are based on birthweight criteria and will comprise greater proportions of more mature individuals who had fetal growth restriction, which itself may affect childhood growth. The EPICure Study findings are similar to those of the Canadian cohort of ELBW individuals [40] but show less catch up compared to the Victoria, Australia, ELBW cohort who attained average weight by adulthood [41]. In contrast, the Cleveland, Ohio VLBW cohort reported compete catch up in females but not in males [42], whereas in the more immature EPICure cohort there were few differences between males and females.

In EPICure at 11 years of age, slightly greater proportions of term-born than EP females had entered puberty, but pubertal status at 11 years was not related to height at 19 years in EP boys or girls [39]. This is consistent with other findings that suggest that the timing of puberty affects the intensity of the adolescent growth spurt but not final height [43].

6. Cardiovascular and metabolic outcomes

Higher blood pressure is found among VLBW or VP adults. In an individual patient metanalysis including 9 cohorts, systolic blood pressure was elevated by 3.4 mmHg (95%CI 2.2, 4.6) and diastolic by 2.1 mmHg (95%CI 1.3, 3.0) in a pooled sample of 1571 individuals and 777 controls [44]. This was a robust finding that was not confounded by a range of birth characteristics and contemporary measures but was exacerbated by the presence of maternal pre-eclampsia in pregnancy. Blood pressure elevation was similar in males and females and results were similar to those of two aggregate metanalyses. These are important confirmatory analyses and complement the childhood findings among generally smaller cohorts. The relationship of blood pressure with gestational age at birth and intrauterine growth was evaluated in male Swedish army conscripts – higher blood pressure was independently inversely related to gestational age at birth, birthweight for gestational age and correlated with BMI [45]. VP individuals enter adulthood with higher blood pressure and therefore increased risk for cardiovascular disease.

We have evaluated measures of arterial stiffness, associated with later cardiovascular risk in the EPICure group using Doppler measurement of the systolic augmentation pressure. In parallel with measures of blood pressure the EP participants had a clinically significant elevation in Augmentation Index (AIx) of 6% (95%CI 2.1 to 9.8) which tracked over adolescence to 19 years [46]. This was associated with increased total peripheral resistance. Other studies using cardiovascular magnetic resonance imaging (CMR) demonstrate that preterm-born adults have anatomical differences compared with those born at term, namely smaller ventricles and altered myocardial mass, with increased myocardial fibrosis, leading to impaired function (see Ref. [47] for a review). This cardiac phenotype could interact with higher blood pressures and physiological stress to accelerate progression of cardiovascular disease, but longer-term longitudinal studies are required to confirm this trajectory.

Cardiovascular risk may be assessed in other ways. Metabolic syndrome defined according to the International Diabetes Federation criteria was present in 8% of EPICure EP 19 year olds and 4% controls (not statistically significant) [48]. There was an association between size at birth and BMI at 19 years among the EP group, mediated in part by socio-economic status and weight gain between 2.5 and 6 years of age. Although BMI was higher than population norms from 1990, similar trends were seen in control participants suggesting that these differences may represent secular trends over the intervening period. Other serological markers of risk show conflicting results with little evidence of ongoing inflammation (lower fibrinogen, alpha-1-antitrypsin and ESR, with no change in CRP), raised desmosine concentrations reflecting increased elastin turnover, and higher creatinine concentrations, with estimated glomerular filtration rates inversely related to AIx and aortic pulse wave velocity [46]. Using a multiparameter cardiovascular health profile at 25 years, Cheong and colleagues demonstrated less favourable profiles amongst their EP/ELBW cohort and a relation with weight growth patterns in childhood [49].

In the Hamilton cohort at a mean age of 32 years, their ELBW participants had a higher percentage body fat and lower lean body mass compared to controls but with similar waist measurement and BMI. Following a 75 g-oral glucose load, the ELBW participants had an increased risk of dysglycaemia (OR 4.0 (95%CI 1.5–10.7). The lipid profile was similar in the two groups. These findings are consistent with the observation of increased insulin resistance [50,51] and population studies among preterm populations which show increased biomarkers for later atherogenic cardiovascular disease [52].

One needs to remember that the numbers included in the various cohorts cited are relatively small compared to population studies

showing associations between BMI or other cardiovascular disease markers and outcome in the general population and hence null conclusions may represent a type II error. However, generally the results of the two approaches concur that there is significantly increased risk in VP populations.

7. Respiratory outcomes

Whereas neuropsychological outcomes have been extensively studied there is less information concerning respiratory outcomes, mainly concentrating on those individuals with a diagnosis of bronchopulmonary dysplasia (BPD), defined by need for supplemental oxygen as below. Among EP populations, chronic oxygen dependency is a common finding and most, if not all EP survivors will have met a minimal criterion for BPD at 28 days, and a very high proportion moderate to severe criteria at 36 weeks post menstrual age. The prevalence of BPD is inversely related to gestational age at birth. More recently several cohorts have followed EP and VP individuals through into adult life.

In the EPICure cohort, compared to term-born controls, we observed poorer lung function on all spirometric parameters at 19 years– for example FEV_1 z-score was 1.08SD lower [46]. Furthermore, despite a higher proportion with bronchodilator reversibility (27% versus 6%), lower concentrations of exhaled nitric oxide (FeNO) were observed indicating lower levels of inflammation. Dichotomising the population by the use of supplemental oxygen at 36 weeks (our definition of "BPD"), all parameters were worse in the more severe group with BPD, but the less severe group also had significant reductions in spirometric measures, alongside significant reduction in the richness and diversity of the respiratory microbiome [53], which is a common finding in chronic lung diseases. The discrepancy in respiratory parameters between EP groups was similar to that at 11 years and tracked over adolescence; at both ages 19% of those evaluated showed signs of airway obstruction.

The findings from the EPICure cohort (<26 weeks of gestation at birth) were similar to those from the Victoria cohort of 25 year old EP/ELBW survivors [54] and to the results from an IPD analysis from 11 available VLBW/VP studies, although the variation in the latter findings may have been ascribed to the long time period covered by the constituent studies (births 1977–1992). Similarly other studies have failed to demonstrate any increase in FeNO although some of the studies included in the recent metanalysis comprised births <36 weeks and others simply cohorts with neonatal BPD [55].

The aetiology of lung disease in these various preterm groups is multifactorial [56] but it is likely that among EP populations it is primarily related to birth at such an immature stage of lung development and the subsequent neonatal course. The result is that individuals reach their third decade with a significant reduction in their respiratory potential. In subsequent decades there is a well described age-related decline in lung function, although it is subclinical in the vast majority of healthy individuals. One of the key uncertainties is whether there is subsequent accelerated age-related decline in particular groups leading to trajectories which develop symptomatic lung disease at earlier ages [57,58]. Our understanding of the activity of lung disease in EP survivors is limited. The high rates of airway obstruction and reversibility do indicate active respiratory problems for this group, but the lack of inflammatory markers provides some reassurance. Respiratory health is clearly a critical issue as EP individuals move through adult life and one that is poorly recognised by adult physicians [59].

8. Renal outcomes

Renal effects of prematurity have received little attention. Renal growth and final size may be reduced after birth <32 weeks [60] and <30 weeks of gestation [61]. At 23 years, renal volume was significantly decreased, with higher urine creatinine:albumin ratios, and higher circulating angiotensin II levels, although there were no differences in glomerular filtration rate compared with term born controls [61]. These differences were associated with higher blood pressure. In the EPICure cohort we did not measure renal size, and eGFR did not differ from controls, but AIx, and therefore cardiovascular risk was associated with both eGFR and BPD status [46].

9. Ageing

Finally, there is rising interest in how EP individuals may age from perspectives other than lung function. For example, from our studies cardiovascular health may resemble values for individuals 10–15 years older than tested [46]. Others have shown that preterm men have fewer long telomeres and a higher proportion of short telomeres [62,63] indicating molecular evidence for ageing. Epigenetic age may also be estimated using an epigenetic clock method, which in the Hamilton cohort was advanced by 4.6 years in preterm males but not in preterm females [64]. These markers may indicate increased susceptibility to age related diseases, particularly in males, and provide some evidence for ongoing development of morbidity in this vulnerable population.

10. Conclusions

One of the challenges in predicting outcomes for the very smallest survivors – those <400 g or <23 weeks – is that the numbers included in each study are tiny, making conclusions about these specific individuals difficult to tease out. However, most outcomes show a gradation of adverse outcomes inversely proportional to the gestational age at birth. Hence, outcomes from the EPICure studies of births (<26 weeks) tend to show more frequent adverse outcomes compared to other studies, although within the EPICure group again the numbers born at such low gestations are very small. Early childhood outcomes for more recent cohorts [65] confirm the persisting high rates of adverse outcomes in this group and the lack of improvement in outcomes at 11 years between the two EPICure cohorts [15], would indicate that adult outcomes are likely to be similar.

One of the constant features of the results of cohort studies is the marked stability in outcomes for EP individuals between childhood and adulthood. Most measures, be it cognitive scores, blood pressure or lung function, track over this period with little evidence of true or significant catch up when compared with term born controls. Whilst adolescence is associated with increased independence for these individuals, this is developing alongside what seems to be a fixed deficit in performance measures.

It is reassuring that our childhood assessments provide measurable deficits that have relevance in early adult life, underscoring their value in clinical follow up. This also provides context for studies to evaluate changing outcomes based on childhood outcomes. Despite these, a majority of individuals achieve independent functioning in society and report a good quality of life based mainly around reports of health-related measures.

The key issues that we now need to understand relate to how the altered somatic, cognitive and psychological functioning that we have comprehensively identified through these studies, plays out against ageing (Fig. 1). Future studies should prioritise these questions to shed light on biological processes as much as the influence of prematurity.

Individuals who are born at extremely low gestational ages may have multisystem problems as they enter and progress through adult life. Neonatal care has expanded into childhood by the development of paediatric follow up services but there are few resources to support this group, many of whom will clearly have continuing complex needs at later ages. Although neonatal teams have a responsibility to emphasise the need for lifelong health and educational surveillance and the adoption of a healthy lifestyle, it is also incumbent on adult services to recognise and understand these complex needs. Simply being aware of the range of potential issues and taking a perinatal/neonatal history as part of routine care [66,67] will go some way to ensuring that potential issues are sought and managed.

Practice points

- Neurosensory and somatic impairments track over adolescence into adult life, with little evidence of change
- Young adults demonstrate cardiovascular and respiratory risk factors for later adult disease often not evaluated in neonatal outcome studies
- Neurosensory and somatic impairments tend to occur together in individuals
- All adult physicians should be aware of the importance of birth at low gestations and identify individuals for longitudinal surveillance

Research directions

- Longitudinal follow up of individuals born extremely preterm is necessary into middle age and beyond, to determine the interaction with ageing processes
- Trials of perinatal/neonatal interventions must evaluate outcomes beyond two years after birth to facilitate understanding of the likely effects on adult outcomes
- Post-neonatal interventions to ameliorate effects of neonatal disease are required

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Declaration of competing interest

NM declares Consulting fees with Novartis, Takeda and InfanDx outside the published work, JRH & SJ have nothing to declare.

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