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International comparisons of neurodevelopmental outcomes in infants born very preterm

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ABSTRACT

We summarise rates of survival and neurodevelopmental impairment in very (<32 weeks' gestation) and extremely (<28 weeks' gestation) preterm infants using data from recent meta-analyses. Methodological issues that require consideration when comparing international data are highlighted using examples of population-based or multi-centre cohorts of children born extremely preterm. The impact of baseline population, outcome definition, gestational age assessment, age at neurodevelopmental assessment, year of birth and follow-up rates are discussed. The impact of the intensity of perinatal care and of post-discharge management on survival and neurodevelopmental outcomes is also discussed. There is a future need for harmonisation of data collection and for more accurate and standardised reporting of neurodevelopmental outcomes in very preterm children.

1. Introduction

Babies born very (<32 weeks of gestation) or extremely (<28 weeks of gestation) preterm are at high risk for death and short, medium and long-term complications, including neonatal morbidities as well as neurodevelopmental impairments (NDI) which only become apparent when the child is older. These problems are multifactorial in origin and may result from antenatal, perinatal and/or postnatal insults, possibly in combination with pre-existing inherited susceptibilities. Although definitions vary across studies, the composite outcome of NDI generally includes motor, sensory and cognitive function and is the longer term outcome most frequently used for comparisons both within and between countries.

In this review, we first provide an overview of survival and global NDI rates for very preterm infants, predominantly using data from recent meta-analyses. We then dissect some of the methodological issues about these comparisons using more detailed examples from recent, large, population-based or multi-centre cohorts, following which the impact of perinatal care and post-discharge management on outcome differences between countries is discussed.

2. Overview of survival and neurodevelopmental impairment in very preterm children

2.1. Survival

In recent years, survival of babies born extremely preterm has been studied most. A meta-analysis of survival to hospital discharge for deliveries occurring at 22–27 weeks' gestational age (GA) included 27 cohorts of babies born after 1998 in high income countries with a low risk of bias [1].

Using all births as a denominator, survival rates were 0.1% (95% confidence interval (CI) 0–37%) for infants born at 22 weeks, 9% (95% CI 5–15) at 23 weeks, 30% (95% CI 23–38) at 24 weeks, 51% (95% CI 43–59) at 25 weeks, 64% (95% CI 56–70) at 26 weeks and 82% (95% CI 75–88) at 27 weeks' gestation. When using only live births as a denominator, rates were 7% (95% CI 4–13), 26% (95% CI 20–32), 54% (95% CI 48–60), 74% (95% CI 69–79), 84% (95% CI 81–87) and 90% (95% CI 87–92) at 22, 23, 24, 25, 26 and 27 weeks' GA, respectively. These figures hide wide differences between studies. For example, survival rates related to live births ranged from 0% to 40% at 22 weeks

Abbreviations: 95% CI, 95% confidence interval; GA, gestational age; GMFCS, Gross Motor Functional Classification System; IQ, Intellectual Quotient; NDI, neurodevelopmental impairment; SD, standard deviations; US, United States

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and from 0% to 63% at 23 weeks' GA in the included cohorts [1].

Above 27 weeks' GA, mortality is lower and absolute differences between countries are smaller – but still exist. In the EPICE study, which included all births between 22 and 31 weeks' GA occurring in 2011–2012 in 16 European regions, survival (related to all births) was 70% at 26–27 weeks, 85% at 28–29 weeks and 91% at 30–31 weeks' GA [2]. Results from 25 perinatal centers in the United States (US) using a different baseline population (singleton neonates without major congenital anomalies born in 2008–2011) and denominator (live births) demonstrated survival rates of 92% at 27 weeks and 98% or above at 28–31 weeks' GA [3].

2.2. Moderate and severe neurodevelopmental impairment

Although we focus next on overall NDI, the burden of individual components of this composite outcome varies – in terms of both the prevalence and the impact on the child and her or his family's quality of life. These points are discussed in more detail elsewhere in this issue of the journal.

A meta-analysis of 15 prospective high quality cohorts (follow-up rates above 65% with standardised neurodevelopmental assessments between 4 and 10 years of age) of children born between 22 and 25 weeks' GA after 1995 [4] defined severe NDI as an IQ score more than 3 standard deviations (SD) below the mean, non-ambulant cerebral palsy (Gross Motor Functional Classification System (GMFCS) 4 or 5), visual impairment (<20/200) and/or deafness despite amplification, and moderate NDI as an IQ score between 2 and 3 SD below the mean, ambulant cerebral palsy (GMFCS 2 or 3), visual impairment (<20/40) or hearing impairment restored by amplification.

Rates of severe NDI were 17% (95% CI 6–37%), 19% (95% CI 14–25%), 17% (95% CI 13–22%) and 11% (95% CI 8–15%) of assessed children born at 22, 23, 24 and 25 weeks' GA, respectively, and rates of moderate to severe NDI were 42% (95% CI 23–64%), 41% (95% CI 31–52%), 32% (95% CI 25–39%) and 23% (95% CI 18–29%) for assessed children born at the same gestations [4]. As well as the high prevalence of NDI, the authors highlighted the variability in the results, stating these likely reflect differences in the management of extremely preterm infants. Moreover, the generalisability of results at 22 weeks' GA was limited by small numbers and the weight of a single cohort which accounted for nearly half of the included children.

After 26–27 weeks' GA, to our knowledge no systematic reviews have been performed and very few geographically-based cohorts have followed children up longer term. One example is provided by the EPIPAGE cohort of children born in France in 1997 in whom the rates of severe NDI (at least one of: non-ambulatory cerebral palsy, mental processing composite score more than 3 SD below the mean (<55) using the Kaufman Assessment Battery for Children, bilateral visual impairment (<3/10), uni- or bilateral hearing loss >70 dB) at 5 years were 3–5% in children born at 29–32 week' GA [5].

3. NDI rates in population-based cohorts of extremely preterm children born in the 2000s

For both survival and NDI, the meta-analyses described above demonstrated high rates of heterogeneity between individual studies. Next, we examine neurodevelopmental outcomes by week of gestation in large population-based or multicentre cohorts of extremely preterm children born after 2000; the results provide examples to discuss methodological issues in comparing results.

These studies were conducted in Japan [6], the US [7], The Netherlands [8], Switzerland [9], England [10] and Sweden [11] with assessments occurring around 2 years corrected age; loss-to-follow-up rates ranged from 3% to 27%. Survival rates with and without NDI among live births and among survivors are shown in Table 1; Supplemental Table 2 provides information about each cohort and definitions of impairment used: although similar, direct comparisons are not always possible due to differences in categorisation.

Overall, survival without NDI (among live births) was poor at 22 and low at 23 weeks' GA. Variability between countries remained high at 24–26 weeks' GA. Survival without NDI was higher in Japan, Sweden and the US – countries with more active perinatal management at low gestational ages – than elsewhere. Rates of moderate to severe impairment among survivors were also extremely variable. Differences appear lower when comparing outcomes among survivors (Table 1); however, several methodological issues need to be considered when making these comparisons.

4. Methodological issues in international comparisons

4.1. Baseline population

Long-term consequences of preterm birth can be estimated using different baseline populations. *Survival without NDI*, taking into account both mortality and impairments, can be estimated using a denominator of all births, live births or babies admitted to neonatal intensive care. It is useful to evaluate the impact of perinatal practices. Indeed, interventions are only valuable if they improve survival without increasing severe neonatal or long-term morbidities. The impact of the baseline population on survival differences between countries, studied for children born at 22–25 weeks' GA in seven countries with inclusion periods between 2009 and 2015, demonstrated large differences [12]. Variation was highest when comparisons were based on live births, especially for those born at 22–23 weeks' GA, and lower when including stillbirths. Variability in rates of survival without NDI may thus be partly explained by variation in baseline survival (Supplemental Table 1). In contrast, rates of *NDI among survivors* provide information on the prognosis of children surviving to follow-up. This still requires interpretation in respect to perinatal practices due to their impact on survival. It is therefore helpful if the total numbers of births (including stillbirths), live births and survivors are reported concurrently when describing long-term outcomes of preterm children.

4.2. Outcome definition

Definitions of NDI used in the example cohorts are detailed in Supplemental Table 2. Although the same domains are assessed, reference tests and cut-offs differ between studies. Such differences have an important impact on reported NDI rates and can hinder comparisons. For example, among children born between 2009 and 2011 at 23–28 weeks' GA and included in the Canadian Neonatal Network, severe NDI ranged from 3.5 to 15.0% depending upon which of seven commonly reported definitions was used [13]. An agreed definition would greatly facilitate within- and between-country comparisons.

4.3. Gestational age assessment

Most publications report outcomes based on GA, thus it is crucial to ensure that GA assessment is comparable between studies. Pregnancy duration is usually estimated from the first day of the last menstrual period or from early fetal crown-rump length ultrasound measurement. However, the hierarchy of the method, the timing of ultrasound examination (e.g. first or second trimester) and the reference chart used may all impact the estimates [14,15]; Supplemental Table 3 highlights the variability of definitions used in our example studies. The impact of such differences on observed results is difficult to assess but is important to bear in mind.

4.4. Age at neurodevelopmental assessment

Neurodevelopmental outcomes in larger cohorts have most frequently been reported before 3 years of age and are relatively scarce at school age. However, visual examination and cognitive assessment in

Table 1
Neurodevelopmental outcomes of extremely preterm children in multicenter and population-based cohort studies.

	22 WG	23 WG	24 WG	25 WG	26 WG
	% (n/N)	% (n/N)	% (n/N)	% (n/N)	% (n/N)
Japan [6] (multicentre cohort)					
Live births (N)	75	245	332	405	–
Survival without NDI*	17.8%	27.7%	48.7%	54.1%	–
Survival with severe NDI*	11.3%	25.4%	12.6%	14.5%	–
Severe NDI among survivors	30.4% (7/23)	39.5% (45/114)	16.2% (23/142)	17.0% (36/212)	–
United States [7] (multicentre cohort)					
Live births with available outcome	234	450	664	–	–
Survival without NDI	1.3% (3/234)	13.1% (59/450)	32.2% (214/664)	–	–
Survival with any NDI	2.1% (5/234)	11.3% (51/450)	23.3% (155/664)	–	–
Any NDI among survivors	62.5% (5/8)	46.4% (51/110)	42.0% (155/369)	–	–
Sweden–EXPRESS [11] (geographically-based cohort)					
Live births (N)	51	101	144	204	206
Survival with no/mild NDI*	3.9%	25.7%	44.2%	60.2%	71.1%
Survival with moderate / severe NDI*	5.9%	26.8%	22.5%	21.7%	14.3%
Moderate / severe NDI among survivors	60.0% (3/5)	51.1% (24/47)	33.7% (29/86)	26.5% (40/151)	16.8% (28/167)
Severe NDI among survivors	40.0% (2/5)	21.3% (10/47)	12.8% (11/86)	9.9% (15/151)	7.2% (12/167)
Great Britain–EPICURE [10] (geographically-based cohort)					
Live births (N)	152	339	442	521	580
Survival with no/mild NDI*	7.8%	28.4%	49.5%	61.5%	
Survival with moderate / severe NDI*	6.3%	11.9%	16.9%	15.7%	
Moderate / severe NDI among survivors	44.7% (17/38)	29.6% (29/98)	25.4% (48/189)	20.3% (51/251)	
Severe NDI among survivors	26.3% (10/38)	15.3% (15/98)	14.8% (28/189)	9.6% (24/251)	
The Netherlands [8] (geographically-based cohort)					
Live births (N)	–	15	45	95	121
Survival without NDI*	–	0.0%	4.4%	37.1%	53.3%
Survival with moderate / severe NDI*	–	0.0%	0.0%	9.8%	6.2%
Moderate / severe NDI among survivors	–	–	0.0% (0/3)	17.0% (9/53)	8.8% (7/80)
Switzerland [9] (multicentre cohort)					
Live births (N)	–	–	210	271	346
Survival with no / mild NDI*	–	–	14.5%	33.0%	50.0%
Survival with moderate / severe NDI*	–	–	15.0%	23.4%	25.7%
Moderate / severe NDI among survivors	–	–	50.9% (29/57)	41.5% (54/130)	34.0% (72/212)
Severe NDI among survivors	–	–	19.3% (11/57)	13.8% (18/130)	9.9% (21/212)

NDI: neurodevelopmental impairment (see definitions in Supplemental Table 2).
When the combined outcomes were not explicitly described in the cohorts, numbers were extracted and percentages were calculated from available information.
* Except for the United States where raw data were not available, rates of survival without NDI was calculated as follows: survival rate (= number of survivors/number of live births) x rate of children without NDI among assessed children.
The same equations were used for survival with no/mild, moderate/severe and severe NDI.

infants can be challenging, and early findings are not always predictive of later disability.

Results from the EPICure study (births at 22–25 weeks' GA in the United Kingdom and Ireland in 1995) [16] and from the EXPRESS study (births at 22–26 weeks' GA in Sweden in 2004–2007) [11,17] showed that severe NDI at 2.5 years has good specificity but low sensitivity for diagnosing moderate or severe disability at 6–6.5 years. Definitions of NDI from these cohorts are provided in Supplemental Table 4. Among children assessed at both ages and classified as having severe NDI at 2.5 years, 86% (54/63) in the EPICure study and 88% (40/45) in the EXPRESS study had moderate to severe NDI at 6–6.5 years. Conversely, 24% of infants classified as having no NDI in the EPICure study and 23% (74/318) of those with no or mild NDI at 2.5 years in the EXPRESS study had moderate to severe NDI at 6–6.5 years. Moreover, in both studies, NDI rates among extremely preterm children were quite different according to the reference distribution used for the cognitive evaluation test. For example, of the children born at 22–26 weeks' GA in the EXPRESS study, 32% had moderate to severe NDI when compared with a control group of contemporary term-born children, but only 19% were described as such when using the pre-defined (WISC-IV) test norms. Despite these differences, neurodevelopmental assessment at different ages is important as capabilities evolve with age. Developmental trajectories should also be contextualised alongside factors such as family environment and intervention programmes. In summary, comparability of the age at assessment and of tests performed should be checked carefully before drawing conclusions from international comparisons.

4.5. Year of birth

Survival of very preterm babies has reportedly increased in many developed countries in recent decades [7,18–21]. In parallel, increases

in survival without NDI have also been reported [7,10,22]. It is less certain whether disability rates have decreased among survivors: no decrease was seen in NDI rates among survivors born extremely preterm in the US or in the UK [7,10] and in Victoria, Australia, rates of severe NDI in children born at 22–27 week's GA decreased at 2 years of age between 1991 and 1992 and 2005, but no difference was seen at 8 years of age [23,24]. However, the temporal evolution of outcomes within and between countries should be interpreted in the light of other changes that may also have happened. These include changes in population demographics (e.g. in maternal age, socioeconomic status, ethnicity or country of origin), clinical management (e.g. increased rates of antenatal steroids, Caesarean delivery and use of continuous positive airway pressure, or decreased rates of surfactant and postnatal steroids) [20,25,26] and health policies (e.g. regionalisation of perinatal care, rates of outborn children) [27–29].

4.6. Follow-up rates/missing data

Understanding long-term outcomes of children born preterm necessitates standardised assessments years after children were first recruited, but achieving high follow-up rates can be difficult. In our six examples, loss-to-follow-up rates at 18–42 months ranged from 3 to 27% (Supplemental Table 2). This attrition may bias the study in different ways as children lost to follow-up may be either healthier or have worse outcomes than those assessed. A meta-analysis of studies reporting neurodevelopmental outcomes at 18–24 months of infants born before 28 weeks' GA or with a birth weight below 1000 g found a correlation between dropout rates and NDI rates: the lower the follow-up, the higher the NDI rate [30]. Other studies have found the opposite, with higher NDI rates in late- or non-responders than in children who were followed-up easily [31,32]. Furthermore, when comparing preterm with term-born children, selection mechanisms - and consequent biases - can be different depending if both groups are followed from birth or if the control group is recruited at the time of follow-up evaluation. Demographic, social, economic, environmental and health system factors may also differentially impact lost-to-follow-up populations according to the country [33]. Although statistical methods like multiple imputation can be used to account for missing data, they make assumptions about data missingness (e.g. missing at random) and cannot replace the gold standard of complete follow-up. Therefore, the lower the follow-up rate, the less confidence one might have in the results.

4.7. Are international comparisons possible at all?

One could conclude at this point that comparison of neurodevelopmental outcomes of very preterm children internationally is hindered by too many methodological issues to be useful. However, such comparisons, if performed well, offer the opportunity to learn from differences and generate hypotheses for improvement. One way of further exploring international variations is to standardise information collection. The EPICE study, for example, assessed neurodevelopmental outcomes at 2 years of age in 3294 children born at 22–31 weeks' GA in 2011–2012 in 15 regions across 10 European countries. Information about demographics, pregnancy, neonatal care and developmental outcomes were collected through standardised tools [34]. Moderate to severe NDI was defined as severe hearing, vision or gross motor impairment and using the parentally reported non-verbal cognition scale of the PARCA-R (Parent Report of Children's Abilities-Revised) questionnaire [35]. Follow-up rates ranged from 47% to 99%. Wide variations in moderate to severe NDI rates were seen, ranging from 10 to 26%; these were reduced but still evident after adjustment for maternal demographic, pregnancy and infant factors. Despite difficulties in data harmonisation, international comparisons of outcomes in very preterm children are crucial to understand and evaluate the impact of quite different perinatal practices and post-discharge management.

5. Impact of perinatal and post-discharge management in neurodevelopmental outcomes

Highlighting the variability of neurodevelopmental outcomes in very preterm children leads us to question to what extent this is due to differences in perinatal care and decision-making, or in post-discharge management. In turn, we must ask, “what lessons can be learned from these differences?”.

5.1. Intensity of perinatal care and neurodevelopmental outcomes

International variations in perinatal care at very low gestational ages are described repeatedly. For example, the MOSAIC study examining births before 30 weeks' GA in ten European regions in 2003 showed large differences between regions in antenatal transfers, antenatal steroids and Caesarean section rates [36], with important correlations between intervention rates and survival – particularly below 26 weeks' GA. Three recent studies demonstrated improvements in survival for children born extremely preterm without differences in morbidity when considering only those children surviving [37–39]. The first study, based in the US, showed that between-hospital variation in survival and survival without severe impairment at 18–22 months were largely explained by hospital rates of postnatal treatments [37]. A similar result was found in Sweden, with survival and survival without NDI at 2.5 years for births at 22–24 weeks' GA being higher in regions with the highest intensity of perinatal care [38]. In France, survival without sensorimotor disability at 2 years for births at 22–26 weeks' GA was increased in high-intensity compared to low-intensity hospitals [39]. These studies suggest that active perinatal management at extremely low gestational ages improves the rates of survival and survival without sensorimotor and/or cognitive disability without increasing the risk of impairment in survivors. This leads to more children surviving without impairment, albeit also more children surviving with impairment.

5.2. Impact of post-discharge management on neurodevelopmental outcomes

Developmental interventions post-discharge aim to improve outcomes of preterm children; however their impact is uncertain. A meta-analysis including 25 randomized trials (about 3600 children) compared any intervention starting before 1 year corrected age and involving a health professional to standard follow-up care in preterm children born before 37 weeks' GA [40]; interventions focused on the parent-child relationship and/or on child development. Preterm children receiving early interventions had slightly higher developmental scores before 3 years of age but effects were not sustained, with no differences in motor scores at 3–5 years of age or in IQ at 5–18 years. However, there was great heterogeneity between interventions, and too few data for subgroup analysis of very or extremely preterm children.

6. Discussion

Knowledge of neurodevelopmental outcomes of very and extremely preterm children is essential for families and health care professionals as well as for policy makers. International comparisons, by highlighting differences in practices and outcomes, can improve our understanding of the impact of perinatal interventions, guide clinical decision-making and health policies and provide prognostic information for families.

Data from population-based or multi-centre cohorts suggest high variability exists in survival without NDI between countries, especially for the most prematurely born children. This is largely explained by variations in survival – itself highly correlated to intensity of perinatal management at very low gestational ages. However, methodological issues such as differences in the age and rate of follow-up, the assessment tools used, and the definition or reporting of outcomes inhibit

detailed analysis of differences between countries.

Recommendations for standardised reporting include precise description of the source population, outcome definitions and the timing of assessment, stratifying outcomes by gestational age and reporting the statistical uncertainty of results (for example, using 95% confidence intervals) [41]. Core outcome sets in neonatology have been proposed, particularly for clinical trials [42]. Several current initiatives aim to harmonise data collection and federate databases across countries: for example, the 'Research on European Children and Adults Born Preterm' project (RECAP preterm) [43], the 'Adults Born Preterm International Collaboration' (APIC) [44], the International Network for Evaluating Outcomes of neonates (iNeo) [45] or the International Neonatal Consortium (INC) [46]. Beyond direct comparison and benchmarking, pooling data with potential for successful harmonisation may allow studies of rarer complications [46].

There are many potential pitfalls when comparing outcomes of very preterm children but also many potential advantages. Differences in populations, variable definitions, denominators used or age at assessment must be taken into consideration when interpreting results. We discussed neurodevelopmental outcomes primarily assessed in early childhood because these are the end-points most frequently published. There are still too few data on outcomes in later childhood and adulthood, and on the perception of patients and their families about their health and quality of life. Large population-based cohorts have much to teach us about these issues as well, although similar considerations to those presented here will be essential to their interpretation.

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Appendix A. Supplementary data

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