



Outcomes of Children Born Extremely Preterm

Miami Neonatology 2020—44th Annual International Conference

Overview

Children who are born extremely preterm are at risk for cognitive difficulties and disability. A common major morbidity for these infants is neurodevelopmental impairment (NDI). Susan R. Hintz, MD, MS Epi, focuses on changes in increased survival for infants born extremely preterm, modifications in resuscitation and perinatal neonatal care, as well as longer term, nontraditional NDI outcomes. She reviews studies that extend beyond 2 years of age, and how they could change the trajectory of NDI outcomes and future research. Dr. Hintz cites the importance of earlier interventions in the NICU, and better preparing families with transition-to-home care programs and excellent referral and follow-up. She concludes with quality improvement opportunities across the provider network, and discusses the importance of integrating health-related quality of life outcomes to better understand and improve long-term neurodevelopmental outcomes.

Target Audience

This activity was developed for neonatologists, pediatric physicians, nurses, nurse practitioners, dietitians, and other healthcare providers who have an interest in newborns, infants and toddlers.

Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Recognize neurodevelopmental impairment outcomes in very preterm infants and its significance beyond 2 years of age
- Review common challenges associated with neurodevelopmental impairment outcomes
- Discuss the importance of earlier interventions in the NICU and better preparing families with transition-to-home programs, as well as referrals to improve later outcomes.

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Outcomes of Children Born Extremely Preterm

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Outcomes of Children Born Extremely Preterm

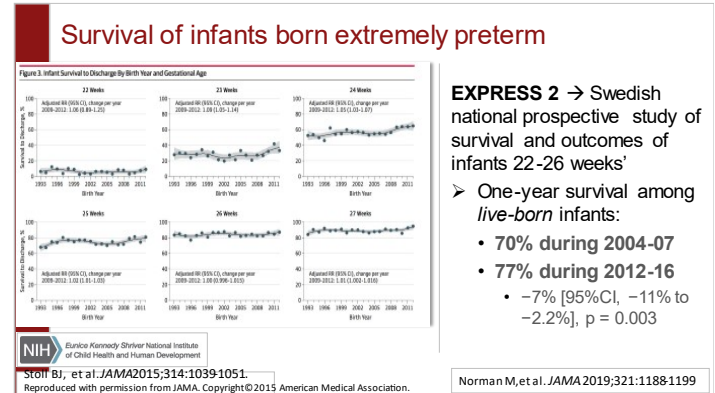
Editor's Note: This is a transcript of an online presentation on November 18, 2020, at the Miami Neonatology International Conference. It has been edited and condensed for clarity.



Susan R. Hintz, MD: I'm very honored to be asked by the organizers today to take part in this extremely successful and very well-known international conference. I was asked to speak about outcomes of children born extremely preterm, and of course that is a very, very broad topic.

I'm going to try to hit some of these concepts that are shown here in the broad overview, of course, including some information about neurodevelopmental outcomes. I am also looking forward to going a little bit beyond those traditional outcomes and exploring with you, perhaps, later outcomes and, perhaps, nontraditional outcomes and possibilities for potentially changing the trajectory of research and outcomes, we hope.

Although the focus of the discussion today was going to be on neurodevelopmental and later outcomes, of course it's important to review changes for infants born extremely preterm in terms of survival, especially in light of changes in resuscitation stance, and also in perinatal and neonatal care. Here on the left [Slide 1] is from Barbara Stoll and colleagues at the NICHD Neonatal Research Network in the US showing 20-year trends in infant survival-to-discharge, by gestational age.¹ You can see very clearly that there has been improvement in survival over those years and particularly, for 23 and 24 weeks [gestational age].



Slide 1 - Survival of infants born extremely preterm

Although other gestational ages also enjoy that increase. But now to the point that 27, and not shown 28 weeks, survival is really all but expected and has increased to 95% or more. But of course, that's a birth cohort that ended at 2012 and, as we know, the stance in terms of resuscitation has changed. For that reason and for others, I'm turning to data that you see on your right from the EXPRESS 2 cohort. This is a Swedish national prospective study.² This is the second cohort of the EXPRESS group, and they follow survival and outcomes for infants 22-26 weeks. They are following their first cohort now through young adulthood, which we will talk about a little bit later; but, as you can see here, for that most recent cohort, 2012-2016, the 1-year survival for these infants, live born, was 77%, which is a significant increase over the previous cohort.

Of course it is important for us to touch on major morbidity because of the association of neurodevelopmental impairment, especially with increasing numbers of morbidities, as was shown in Barbara Schmidt's paper that Dr. Jobe [Alan H. Jobe, MD, PhD] shared with you.³ Again, we turned to the EXPRESS 2 cohort.² They reported 1-year survival without any major morbidity for the most recent cohort at 38% and that, again, was a significant increase over the previous cohort of 2004-2007.

Outcomes of Children Born Extremely Preterm

Survival without major morbidity

EXPRESS 2 → 1-year survival without any major morbidity (22-26 weeks):

- 32% during 2004-2007
- 38% during 2012-2016
- -6% [95%CI, -11% to -1.7%], $p = 0.008$.

Norman M, et al. JAMA 2019;321:1188-1199

In California, survival to discharge without major morbidity improved among VLBW (~62% to 67%) from 2008-2017 ($p < 0.001$)

- Largest gains among infants born <27 weeks'
- Substantial variation across sites.

CPQCC
california perinatal quality care collaborative

Lee HC, Liu J, Profit J, Hintz SR, Gould J. Pediatrics 2020;146:e20193865

Slide 2 - Survival without major morbidity

In California, we have the California Perinatal Quality Care Collaborative [CPQCC], which is a population-based data set that is also linked to high-risk infant follow-up, which is also population-based, and we'll talk about that a little bit later. My colleague, Henry Lee, led this analysis that showed that survival-to-discharge without major morbidity over the last 10 years overall for VLBW [very low birth weight] infants improved from 62% to 67%,⁴ and the largest gains we're seeing in infants born less than 27 weeks.

You see here [Slide 2], one of the figures from that paper of 25–27 weekers, which shows an increase overall of survival without major morbidity adjusted rates of survival. Shown here in the dotted lines are the interquartile ranges for the NICU themselves.⁴ You see there's quite substantial variation across sites and of course opportunities for improvement, for quality improvement, across the network.

Obviously, with these increases in survival and survival without major morbidity, understandably and appropriately, I think, our focus shifts to better understanding of neurodevelopmental outcomes. That is especially true because neonatal clinical trials now frequently include 2-year neurodevelopmental endpoints as either part of the primary outcome or as a main secondary outcome.

Shifting focus to neurodevelopmental outcomes

- As the number of extremely preterm infants surviving to discharge increases, **attention has appropriately shifted to understanding neurodevelopmental outcomes.**
- Neonatal clinical trials now frequently include ~2-year neurodevelopmental endpoints as part of the primary outcome or a main secondary outcome.

Slide 3 - Shifting focus to neurodevelopmental outcomes

Measuring Neurodevelopment Outcome

How is neurodevelopmental outcome measured? This is going to be quite a review for many people on this call or in this conference. It's certainly important for us to reiterate, and I think this was touched on by Dr. Jobe, as well, that the vast majority of prospective studies and trials that follow babies in terms of neurodevelopmental follow-up pretty much stopped right around 2 years of age. At that point the exam generally includes a neurologic examination for the diagnosis of cerebral palsy (CP), assignment of severity based on gross motor function classification system level, and that's Palisano et al, and some cognitive or developmental assessment.⁵ Often, this is done by the Bayley scales of infant development, but not always. As many of you know, there have been subsequent additions to the Bayley scales of infant development. Now, we are on number 4. Then, of course, some assessment of hearing and vision.



Outcomes of Children Born Extremely Preterm

How is “neurodevelopmental outcome” measured?

Follow up *only* to ~18 months - 3 years corrected age for the vast majority trials and prospective studies.

Gross Motor function

- Neurologic examination; diagnosis of cerebral palsy, severity by Gross Motor Function Classification System (GMFCS)

Palisano R, et al. Dev Med Child Neurol 1997;39:214-223

“Cognitive” and developmental assessment

- Bayley II → Bayley III → Bayley 4

Hearing and Vision

Stanford University

Slide 4 - How is “neurodevelopmental outcome” measured?

Neurodevelopmental impairment—or NDI or neurodevelopmental disability—is very often that endpoint for prospective studies and trials. It is important to remember that it is a composite outcome. It's compliance criteria and cut points from all those domains I mentioned before, including cognitive and neurosensory. It's generally categorized by severity, but as I'll mention in the next slide, those definitions and cut points are quite variable across studies. Sometimes it is combined even with death to be a composite outcome.

How is “impairment” or “disability” defined?

- “NDI” - a **composite outcome**
 - Combines criteria and cut points from *several domains* including motor, cognitive/developmental, neurosensory.
 - Generally categorized by severity - but definitions and cut points within each component varies among studies and cohorts.
 - None, mild, moderate, severe

Stanford University

Slide 5 - How is “impairment” or “disability” defined?

I think it's also important for us to recall and to really understand what the challenges are to interpretation of these 2-year outcomes, and especially of neurodevelopmental impairment. First, the relative prevalence of each of these components within neurodevelopmental impairment is not the same, and the rates and the

responses of each of these areas within that composite outcome may respond very differently to interventions.

Challenges to interpretation

- Relative prevalence of component, response to interventions.**
Marlow N. Arch Dis Child Fetal Neonatal 2013;98:F554
- Changes in instruments e.g., Bayley II vs. III (vs. Bayley 4...)**
 - Bayley-III reported to underestimate developmental delay
Anderson PJ et al. J Pediatr. 2018;197:781, Vohr BR, et al. J Pediatrics 2012;161:222 Moore T, et al. J Pediatr 2012;160:558
- “NDI” definition and age at FU not consistent across studies.**
 - Multiple definitions across literature even in “severe NDI”
Haslam M, et al. J Pediatr. 2018;197:781
- Differing rates of NDI, death or NDI across centers with networks**
Synnes A, et al. ADC Fetal Neo 2017;102:F235; Vohr BR, et al. Pediatrics 2004;113:781
- Family and functional perspective**
Janvier A, et al. Seminars Perinatal 2016;40:571



Slide 6 - Challenges to interpretation

This has been very elegantly discussed by Neil Marlow in several papers, including the one I referenced.⁶ Also, as I alluded to before, there have been changes in instruments and versions of instruments, and particularly the move from Bayley II to Bayley III underscored some of those challenges. In that case, several studies, including some from the US, from the UK, Australia, and others, reported the Bayley III to underestimate developmental delay.^{7,8,9} As I also alluded to, NDI definition is not consistent across studies, nor is even the age at evaluation. Again, in an elegant study by the Canadian Neonatal Follow-Up Network (Haslam is the first author) underscored that even severe NDI definitions are different.¹⁰ In that study, he showed that the rate of NDI, the prevalence, can vary up to a factor of 4 across different network studies.

There are also center-to-center differences in NDI, and that has also been shown by Ann Synnes and Betty Moore.¹¹ But perhaps most importantly, these NDI definitions generally are not taking into account family and functional perspective, and Annie Janvier has published very extensively and very elegantly on this topic.¹² Having said all of that, the vast majority of extremely preterm cohorts across the world's literature do present data at around 2 years.

Outcomes of Children Born Extremely Preterm

Spectrum of Neurodevelopmental Outcome

Although we have very little time, I do want to highlight some of these results. I'm going to start by talking about findings from the NICHD Neonatal Research Network.¹³ This is research that was led by Ira Adams-Chapman, who, unfortunately, recently passed away. She was really a true pillar in follow-up research, both at Emory where she was, and also in the NICHD Neonatal Research Network. For this study that was published in 2018,¹³ she looked at all of the children born less than or equal to 26 weeks in the Neonatal Research Network that had follow-up, and that is our general capture for our routine follow-up in the network.

Spectrum of neurodevelopmental outcomes

- Children born **≤26 weeks EGA** in NICHD Neonatal Research Network
- Neurodevelopmental assessment completed **2011-2014** at 18-26 months corrected age
- 2113 children evaluated; mean GA 25+1 weeks, mean BW 760+154 g.

Overall - neurological examination findings:

•59% no abnormal or suspect findings; 19% suspect; 10% abnormal non-CP; 12% CP

Adams-Chapman I, Heyne R, DeMauro S, Duncan A, Hintz S, Pappas A, et al. *Pediatrics* 2018, 141(5):e20173091

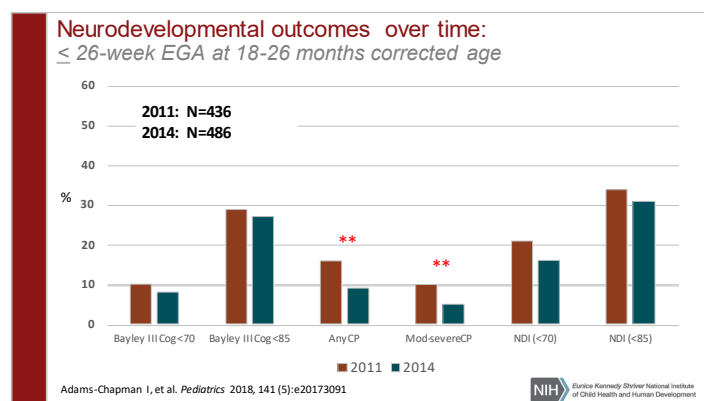


Slide 7 - Spectrum of neurodevelopmental outcomes

Neurodevelopmental assessment was done between 18–26 months during this period, where neurodevelopmental assessment was done between 2011 and 2014. Overall, the neurologic exam findings are sometimes surprising to people that at around 2 years of age, in this cohort, about 60% had no abnormal findings and not even suspect findings. About 20% had some suspect finding that didn't affect their functional capacity, and about 12% had cerebral palsy.¹³ Now, importantly, 10% also had abnormal findings that did cause functional challenges, but they were not CP. Most of those were severe hypotonia, which was not classified as CP.

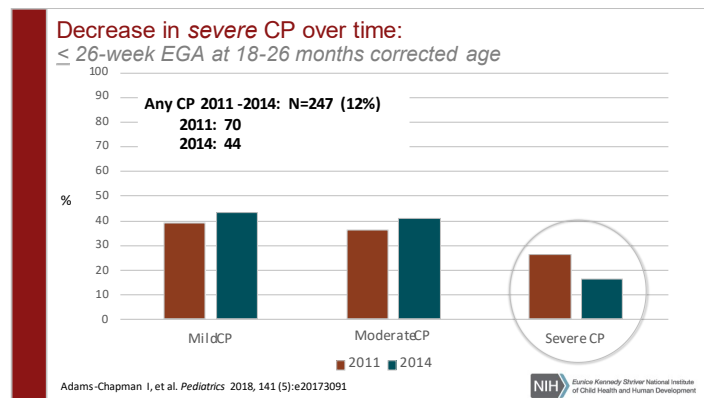
Prevalence of Cerebral Palsy

This is just showing you some findings over time [Slide 8]. Again, this is a relatively short period between 2011 and 2014. You can see for the Bayley cognitive score, less than 70, for less than 85, for NDI either defined as a cut point of cognitive, less than 70 or 85; certainly, the rates did not appear to increase.¹³ The slight decrease you see there was not significant.



Slide 8 - Neurodevelopmental outcomes over time

However, what was significant was a decrease in cerebral palsy and, particularly, moderate or severe cerebral palsy. If we look just at the patients that had cerebral palsy in that group [Slide 9], we see the explanation for that is a decrease in cerebral palsy, again, over the short period of time.

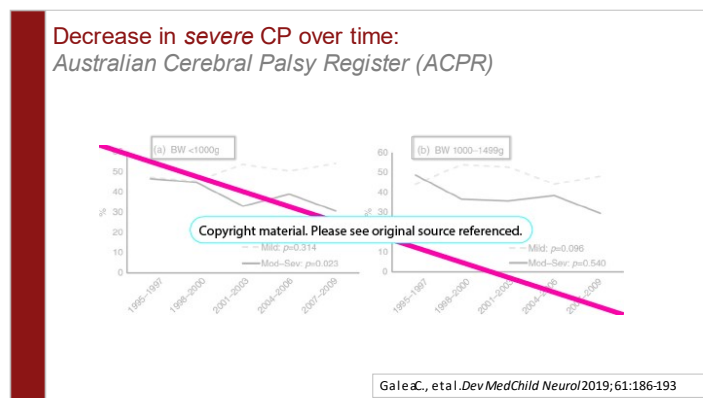


Slide 9 - Decrease in severe CP over time

This has also been noted in Australia. This is from the Australian CP register showing that across all

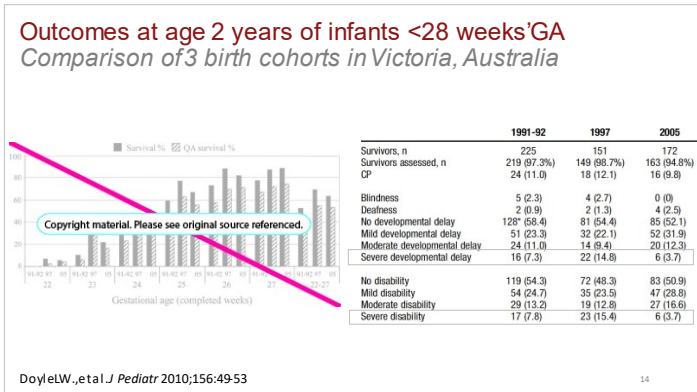
Outcomes of Children Born Extremely Preterm

sites in Australia,¹⁴ the percentage of children with CP whose disability was classified as moderate to severe—you see here in birth weight [BW], less than a 1000 g—decreased significantly over this period of time. In addition, not shown here, the 3 Australian states, including South Australia, Victoria, and Western Australia, with birth prevalence data that's collected, also showed overall decrease in prevalence of cerebral palsy.



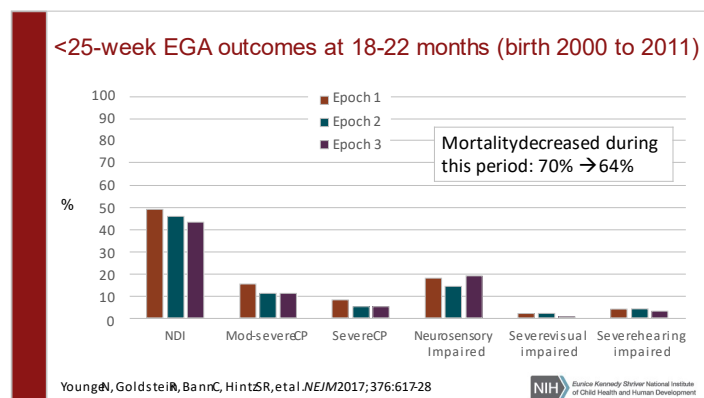
Slide 10 - Decrease in severe CP over time

These trends in outcomes at 2 years of age, were also seen in previously reported data, here from the Victoria Infant Collaborative study group led by Lex Doyle.¹⁵ We see here on the left, by gestational age [Slide 11], that survival in the dark bars has been increasing over time. We see that for all of the whole group of 22–27 weeks here as is quality adjusted survival rates, which was based on neurosensory utilities that were assigned based on severity of outcomes. As you see here on the right, that was explained basically over these 3 birth cohorts from 1991 through 2005, through a decrease in severe developmental delay and severe disability decrease.¹⁵



Slide 11 - Outcomes at age 2 years of infants <28 weeks GA

Going back to the Neonatal Research Network in the US and looking just at those children who were born less than 25 weeks EGA [estimated gestational age], which is a topic of great interest and concern, especially recently. What was found was, again, over these 3 birth epochs from 2000–2011, certainly neurodevelopmental impairment, and these components of neurodevelopmental impairment, do not appear to have increased.¹⁶ They have not significantly decreased in this particular study, but because mortality decreased during this period from 70%–64%, both survival without neurodevelopmental impairment increased from about 16%–20%,¹⁶ and the adjusted odds actually for both survival with NDI and survival without NDI, compared to death, increased over this period of time.

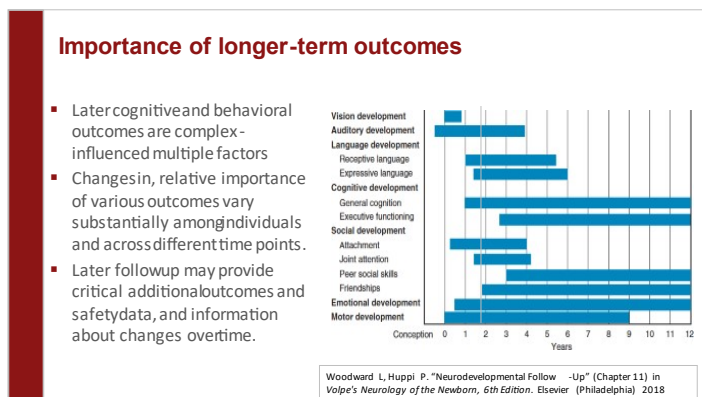


Slide 12 - <25-week EGA outcomes at 18-22 months (birth 2000 to 2011)

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Long-term Outcomes Significance

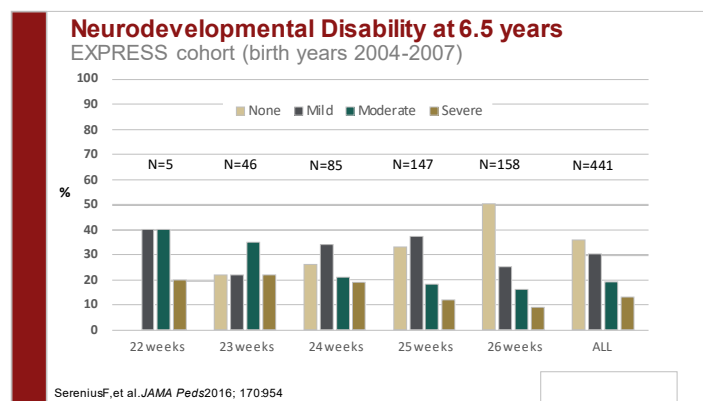
What about the later outcomes of children born extremely preterm? Well, this is one of my favorite figures,¹⁷ and I'm not just saying that because Dr. Petra Hüppi is also on this virtual platform; I think it describes very visually well the kinds of challenges we're dealing with if we stop at 2 years follow-up [Slide 13]. I'm showing you here where that would be if we stopped where most studies stop—at 2 years. As you can see, there are rich developmental and complex developmental landmarks that we would not evaluate, and we would not know about if we stopped there. I'll say, very significantly, executive functioning, which is connected with academic achievement, peer social skills, friendships, and even aspects of motor development that we will talk about later. Also, I think it's very important to recognize that the value placed on each of these developmental endpoints changes over time, changes for individuals, and also may be different for families compared with the individuals born extremely preterm.



Slide 13 - Importance of longer-term outcomes

This moves us to talking a little bit about what the outcomes are at school age. This is from Fredrik Serenius and the EXPRESS group in Sweden [Slide 14].¹⁸ This is from the first cohort EXPRESS I. This, again, is showing neurodevelopmental disability, which is also a composite outcome. In this case, the developmental, the cognitive aspect, of that was by

full-scale IQ, by the WISC [Wechsler Intelligence Scale for Children]. However, this group also had a control group that was a term control group that is followed with them. So, those cut points were based on standard deviations compared to the term control group.



Slide 14 - Neurodevelopmental disability at 6.5 years

This severe group, for instance, is greater than 3 standard deviations below the mean from that comparison term group. Indeed, it's quite severe. However, having said that, you can see, to the far right, for all of these patients from 22–26 weeks, that about 19% of them had some moderate neurodevelopmental disability, and about 13% severe.¹⁸ Now, I'm showing you the numbers that were evaluated here on top for each of these groups because, as you see, the numbers are relatively small at 22 and 23 weeks. But overall, the severe and moderate disability decreases with increasing gestational age until here, you see at 26 weeks, that about half had no developmental disability noted, not even mild.¹⁸

Dr. Jeanie Cheong and the VICS [Victorian Infant Collaborative Study] group, again, from Victoria Infant Collaborative in Australia, have been following multiple birth cohorts out to adulthood.¹⁹ These are from a study that she did that compared the outcomes at 8 years across these 3 birth cohorts [Slide 15]. I think, first note that the overall rates of disability were similar across these birth eras. You can see that death or major disability and major

Outcomes of Children Born Extremely Preterm

disability among survivors at 8 years decreased again with increasing gestational age. IQ, if we just look at another study where she really looked at the details of some of these outcomes, IQ also was similar across the birth cohorts.²⁰ This is showing in comparison to the 2005, in comparison to the earliest birth cohort, and the 1997 birth cohort—both in terms of scores and odds ratios—were in a concerning area for IQ that was not different.

VICS: Outcomes at 8 years by GA – 3 birth cohorts (1991-92, 1997, 2005)

	N	Death	Major disability	No major disability	Not assessed
22 weeks	7	5 (71%)	1 (14%)	0 (0%)	1 (14%)
23 weeks	44	23 (52%)	6 (14%)	14 (32%)	1 (2%)
24 weeks	99	44 (44%)	11 (11%)	41 (41%)	3 (3%)
25 weeks	179	57 (32%)	22 (12%)	94 (53%)	6 (3%)
26 weeks	205	41 (20%)	27 (13%)	126 (61%)	11 (5%)
27 weeks	217	35 (16%)	18 (9%)	138 (64%)	25 (12%)
Total	751	205 (27%)	88 (11%)	413 (55%)	47 (6%)

Data are n (%). Gestational ages are in completed weeks.
Table 3: Outcomes at 8 years by gestational age at birth

Major disability among survivors
23 weeks—29%
24 weeks—20%
25 weeks—18%
26 weeks—17%
27 weeks—10%

Rates of major disability were similar across birth eras:
• 1991–1992, = 18%; 1997 = 15%; 2005 = 18%

Cheong JLY, et al. *Lancet Child Adolesc* 2018;2(12):872879
Cheong JLY et al. *Pediatrics* 2017;139(6):e20164086

Slide 15 - VICS: Outcomes at 8 years by GA

But when we look at academic achievement, there was some evidence that these scores, especially for reading and math, were lower in 2005 compared to either of the earlier eras, as were the odds of having an academic problem in those areas.²⁰ This is an area of concern, and it's also consistent with work that was done by Alicia Burnett from the same group, which showed increasing concern over the birth cohorts for executive function challenges,²¹ which as I mentioned before, is important, obviously, for academic achievement.

Predicting School-Age Outcomes

If it is so difficult and these assessments are so complex at school age, can we not just predict school age outcomes from toddlerhood? The short answer is no, we can't. This is data from the EXPRESS cohort again;¹⁸ showing that about only 47% remained in the same category from the 2005 disability assignment to the 6½-year disability assignments. This is just as an example, showing

you for those children that were considered to have mild disability at 2½ years, at 6½ years, about 37% of them had gone into either the moderate or severe category. If we don't continue following these children, there may be things that we are missing, both in terms of research and being able to identify where we might do a better job, but also in terms of interventions.

Predicting school age from toddlerhood??
Importance of longer-term outcomes

Table 5. Change in Classification of Overall Disability From 2.5 to 6.5 Years for Children Born Extremely Preterm and Assessed at Both Ages^a

Disability at 2.5 y Corrected Age	Disability at 6.5 y, No. (%) of Children				Total No.
	None	Mild	Moderate	Severe	
None	108 (58.4)	52 (28.1)	19 (10.3)	6 (3.2)	185
Mild	36 (27.1)	48 (36.1)	42 (31.6)	7 (5.3)	133
Moderate	12 (16.9)	27 (38.0)	17 (24.3)	14 (20.0)	70
Severe	1 (2.2)	4 (8.9)	11 (24.4)	29 (64.4)	45
Total	157 (36.3)	131 (30.3)	89 (20.6)	56 (12.9)	433

Only 47% remained in the same category →
• 21% moved to a better category, 32% moved to a worse category.

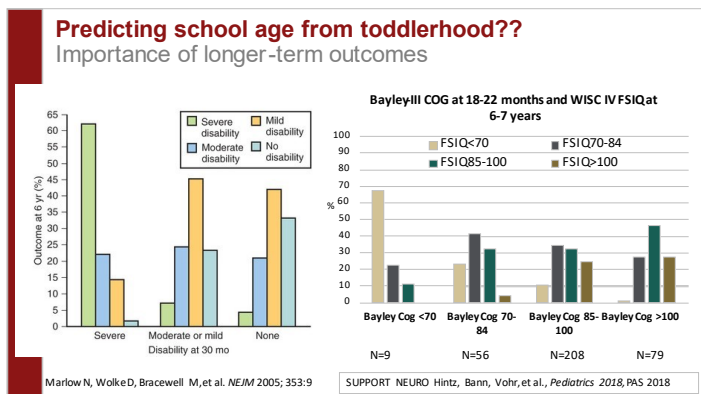
Serenius F, et al. *JAMA Peds* 2016; 170: 954

Slide 16 - Predicting school age from toddlerhood?

On the left is from the EPIcure I cohort [Slide 17]. I think Dr. Jobe mentioned this to you, as well, from Neil Marlow.²² Again, showing disability at 30 months here, and then the percentage with the outcome that's shown here at 6 months. We see that although the majority of those children who were considered severely disabled at 30 months remained in that category, about 15% of them moved to either the mild- or the no-disability category by 6 years. So, again, that's something we wouldn't have seen.

This is from the SUPPORT trial NEURO cohort, which was a subcohort within the trial that had serial neuroimaging.²³ This is showing, again, the variation or the instability across these categories between the 18–22-month assessment and the 6–7-year assessment. If we stopped looking at Bayley cognitive of 85–100, as with this group, we may not have recognized that a number of them fell into a different category over time.

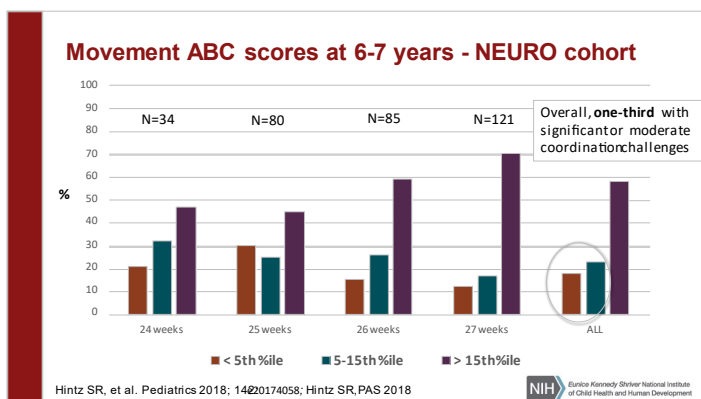
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Slide 17 - Predicting school age from toddlerhood?

As I mentioned before, there are also issues that we can't assess even until the child gets older. We tend to focus on cerebral palsy as the motor outcome, but in fact, issues around coordination and balance, including developmental coordination disorder are really much more prevalent for children who were born preterm than cerebral palsy.

This is showing you [Slide 18], from the NEURO cohort,²³ movement ABC scores at 6–7 years. Overall, about 1/3 of these children had significant or moderate coordination challenges that were not cerebral palsy. This kind of issue can be connected also with challenges with academic achievement, but also with behavior and other outcomes. Again, you can see there is a relative trend associated with gestational age.



Slide 18 - Movement ABC scores at 6-7 years - NEURO cohort

All these studies, I would say, address important questions about outcomes and important

outcomes, but I think really, we need to ask ourselves, **are we really asking all the right questions?** And are we asking the right questions that will lead us to outcomes that are really the most important outcomes to families, to parents and to, increasingly, those individuals who were born extremely preterm?

Outcomes Important to Families

Annie Janvier is really an extraordinary researcher. I think she's going to have a huge amount to say about this. In general, I'll just highlight a few things that have been published,^{16,24,25,26} that families are oftentimes interested in real-life endpoints that we may not be providing to them. The usual research outcomes may be confusing or may not really even be what they want to hear about.

What about outcomes important to families?

- **“Real life” endpoints**
 - Usual research/ trial outcomes confusing, or only short-term endpoints; personalize data
- **Functional outcomes**
 - Concept of child's health and well being in terms of function, activities, participation
- **Parent and child well-being**, family impact and interactions.
- **Daily life factors**

Janvier A et al. *Semin Perinatol* 2016, 40: 571; Petty J, et al. *NCYP* 2018, e1084; Cantor, Msall ME. *Clin Perinatol* 2018, 45: 501; Kilbride W, et al. *Clin Perinatol* 2018, 45:467

Slide 19 - What about outcomes important to families?

Many families are interested in functional outcomes, their relationship with their families, their participation in activities, their own sense of wellbeing, and also the parents and the family's sense of wellbeing. On daily life factors, which Dr. Jobe mentioned before, we don't always do a great job of talking to families about all different kinds of outcomes.

Better Preparing Families

Some of the simplistic outcomes that can be important to families are issues around hospitalization after going home and other kinds of

Outcomes of Children Born Extremely Preterm

impacts that may affect their child and their family. This is data from 2013–2016 birth cohort [Slide 20], again from the NICHD Neonatal Research Network. This is unpublished at this moment, but this is showing you at 22–26 weeks, [and] at 22–26 months, about half of these children have been rehospitalized at least 1 time with a median of twice. You can see that number varies across gestational ages. You can also see that there are a number of equipment or assistive devices that are being used by these children at 22–26 months. I'm just showing you some numbers here, but again, these are issues families express that perhaps they were not prepared for, and that we certainly could do a better job of talking to them about.

Re-hospitalizations and medical equipment: Birth years 2013-2016, follow up at 22-26 months CA

	22 weeks	23 weeks	24 weeks	25 weeks	26 weeks	22-26 weeks
Hospitalized since discharge, N (%)	20 (64.5)	171 (59.0)	311 (54.9)	360 (49.2)	415 (44.1)	1277 (49.9)
If yes, median (IQR)# times	3 (2-4)	2 (1-3)	2 (1-3)	2 (1-3)	1 (1-3)	2 (1-3)
Selected equipment/assistive devices (%)						
Gastrostomy tube and/or tube feeding	6 (19.4)	52 (17.9)	81 (14.3)	75 (10.2)	80 (8.5)	294 (11.5)
Oxygen	3 (9.7)	33 (11.4)	33 (5.8)	36 (4.9)	30 (3.2)	135 (5.3)
Tracheostomy	1 (3.2)	19 (6.6)	29 (5.1)	23 (3.1)	22 (2.3)	94 (3.7)
Braces/orthotics	7 (22.6)	60 (20.7)	88 (15.5)	80 (10.9)	93 (9.9)	328 (12.8)

NICHD
NEONATAL RESEARCH NETWORK

Slide 20 - Rehospitalizations and medical equipment

Service Utilization

This is from the CPQCC high-risk infant follow-up program [Slide 21], the California population-based program that I talked to you about.⁴ This is all California. Another issue we maybe don't talk to families a lot about is service utilization. How many medical specialties and special services will they be seeing? This is at the first High-Risk Infant Follow-Up visit in California at about a median of 6 months, showing you that about 60% of these children are seeing at least 1 medical specialty, some many more, and about 30% are already seeing special services like PT [physical therapy] and OT [occupational therapy]. I will, however, tell you that

at this first visit, our data shows in California that about 30% of the children who come to their first visit require even more referrals, both for medical and special services at that time point.

• Service Utilization at 1st HRIF Visit

VLBW = very low birth weight; HIE = hypoxic ischemic encephalopathy



	VLBW N=4900	HIE N=193
Medical specialties - currently receiving	n (%)	n (%)
0	1845 (38%)	68 (35%)
1 to 2	2502 (51%)	90 (47%)
3 to 4	477 (10%)	30 (16%)
5 or more	76 (2%)	5 (3%)
Special services - currently receiving		
0	3369 (59%)	105 (54%)
1 to 2	1344 (27%)	65 (34%)
3 to 4	168 (3%)	21 (11%)
5 or more	19 (0.4%)	2 (1%)

Median age at follow up = 6 months

CALIFORNIA PERINATAL QUALITY CARE COLLABORATIVE



Slide 21 - Service utilization at 1st HRIF visit

Impact on Parents and Family

We need to be thinking about the impact and the outcomes of families, as well as the children. As many will be aware, parents of NICU babies are at extremely higher risk for depression, anxiety, and trauma symptoms. These may persist for years. Certainly, in the work that has been done at Stanford with our partnership and our partners in pediatric psychiatry, including Richard Shaw, about 1 in 3 of the mothers of babies in the NICU (of babies who are very low birth weight) meet criteria for post-traumatic stress disorder by about a month after discharge.²⁷ Maternal NICU and trauma anxiety symptoms are also linked to other outcomes. They're linked to dysfunctional coping.^{28,29} There is data to show that they're linked to cognitive and behavioral and motor challenges in toddlerhood, and that they may affect parents and infant engagement.^{30,31,32} These all open themselves up to interventions for the families, for the mothers and for the parents. It actually contrasts what we think of early intervention as being quite significant.^{33,34}

Outcomes of Children Born Extremely Preterm

The Impact to the Parent and Family – Depression, anxiety, trauma

- Parents of NICU babies at ↑↑ **risk for depression, anxiety, trauma** – may persist for years.
 - ↑ stress, anxiety, trauma significantly associated with **dysfunctional coping, cognitive and behavior/ motor challenges in toddlerhood**Shaw RJ, et al. *J Clin Psych Med*2013; Greene M, et al. *Early Hum Dev* 2017, Zelikowitz P, et al. *Acta Paediatr* 2011
- Maternal NICU trauma and anxiety symptoms linked to later ↑ perception of **child vulnerability, affect parent-infant engagement.**
Horwitz SM, et al. *J Dev Behav Ped* 2015; Zelikowitz P, et al. *Early Hum Dev* 2009; Landry SH, et al. *Dev Psych* 2006
- **Protective** effects of positive home environment on EPT/ VPT outcomes; **negative** effect of parental stress and family dysfunction.
 Treyvaud K, et al. *J Exp Child Psych* 2012; *Semin Fetal Neonatal* 2014

“Early Intervention”

- “Early intervention” may encompass many different components, services, disciplines –



SpittleA, et al. *Cochrane Database of Systematic Reviews* 2015, Issue 11. Art. No.: CD005495.

- Concluded that early intervention **has a positive influence on cognitive outcomes through preschool and motor outcomes to ~ 2 years.**
- Early diagnosis and intervention for cerebral palsy – both child *and* parents.

Novak, et al. *JAMA Pediatr* 2017; 171: 897907; Maitre NL, et al. *Pediatrics* 2020; 145: e20192126; Irwin L, et al. *Research in Developmental Disabilities* 2019; 100: 3511

Slide 22 - The impact to the parent and family - Depression, anxiety, trauma

Slide 23 - “Early Intervention”

Early Intervention

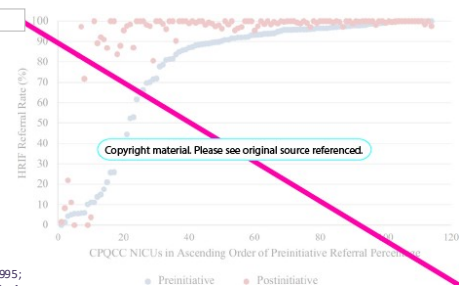
We think of early intervention and usually, early intervention is considered an umbrella term of postdischarge interventions and multidisciplinary programs. The heterogeneity of these postdischarge programs makes it very difficult to combine and assess how well they are doing or if they're having an impact. But Alicia Spittle did an outstanding Cochrane database systematic review,³⁵ and the authors concluded that early intervention, sort of writ large, of postdischarge interventions, have a positive influence on cognitive outcomes through preschool for children and motor outcomes up to 2 years. But, of course, there are a number of specifically targeted interventions for motor issues, such as cerebral palsy, and these include interventions that are focused on early diagnosis and treatment of cerebral palsy, as has been noted by Iona Novak in this recent review, and also, as has been demonstrated by Nathalie Maitre and colleagues, to be deployable across a wide variety of even diverse US network high-risk infant follow-up clinics.^{36,37,38}

This would point to the need to have really excellent referral and follow-up. What we found, however, in California, is that it's not necessarily always the case that these children who are high risk even get referred to high-risk infant follow-up. What we found [Slide 24] is the blue from our pre-intervention period showing very low birth weight referral from NICU discharge to a high-risk infant follow-up.^{39,40} I will say, a very low birth weight is an automatic mandate from the California Children's Services to refer to high-risk infant follow-up. But we found that the rate was only right about 80% for all of those children. Very unfortunately, we found sociodemographic factors and other disparities, as well as NICU-level factors that you see there and other clinical factors to be associated with nonreferral.

Getting to follow up: Improved Referral of VLBW to HRIF in California after QI Initiative

- **Pre-intervention** period - birth 1/10-6/13: **83% referred**
- **Post-intervention** period - birth 7/13-12/16: **95% referred**

Substantial ↑ in referral rates by sociodemographic and program-level factors - - but **disparities remain.**



Hintz SR, et al. *J Pediatrics* 2015; 166: 28995; Pai V, et al. *J Pediatrics* 2020; 216: 101108.e1

california perinatal quality care collaborative

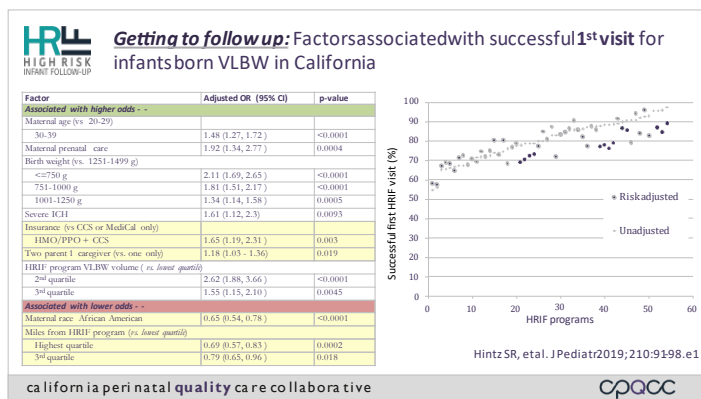
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Slide 24

Outcomes of Children Born Extremely Preterm

First Visit

These kinds of disparities we felt were very important to try to ameliorate. We instituted an intervention statewide, which I'm very happy to say improved referral dramatically to more than 95% for very low-birth-weight infants, which ameliorated the sociodemographic disparities, but it did not completely eliminate them. That's just getting in the door of referral. What about getting to the first visit? This is really only getting to the first visit. Again, in California we found that even for those that have been successfully referred, only about 76%–77% of these children get to their first high-risk infant follow-up visit. As you can see here [Slide 25], a list of adjusted odds ratios, factors associated with higher odds and lower odds, there certainly are some clinical factors, but I think what really pops out are the sociodemographic factors and the program-level factors.⁴¹



Slide 25

Associated with higher odds, and this is again in the United States, is having private insurance compared to only public insurance. Having 2 parents or 2 primary caregivers in the house is associated with a higher chance of getting to that first visit. Very unfortunately, getting to that first visit, lower odds are associated, again, with socioeconomic and sociodemographic factors, including maternal African American race and miles away from the high-risk infant follow-up clinics.

Earlier Intervention

Again, we are talking now about postdischarge implementation when really, we need to be thinking about intervention as much earlier intervention. Dr. Jobe would say even earlier than in the NICU, certainly in terms of the fetal environment, but what we can do in the NICU, I think, is very important. There are innovative transition-to-home programs, including those at Brown, that have decreased ER visits, rehospitalizations, and healthcare use.^{42,43} Also, important interventions starting in the NICU include that PPP or Positive Parenting Program. That has shown improved Bayley cognitive and motor scores at 2 years.⁴⁴

Interventions and outcomes – Engagement in the NICU → home and community

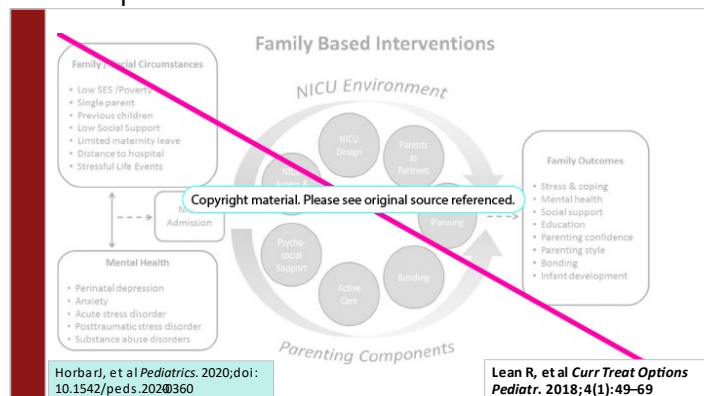
- Innovative transition to home program (Brown): ↓ ER visits, rehospitalizations, health care use.
Vohr BR et al. *J Perinatol* 2017 & 2018, *Early Hum Dev* 2012
- Interventions beginning in NICU and continuing after DC, including “Triple P” (Brisbane) - improved Bayley III cognitive and motor score at 2 years.
Colditz PB, et al *J Pediatr* 2019; 210:48
- Family Integrated Care intervention (25 NICUs) → ↓ parent stress/anxiety, ↑wt gain and breast feeding at discharge.
O’Brien K, et al *Lancet Child Adolesc Heal* 2018; 2: 245
- Rethinking intervention – supporting parent mental health, responsive parenting
Van Wassenauer-Leemhuis AG, et al, *DMCN* 2016; 58(suppl 4): 473

Slide 26 - Interventions and outcomes - Engagement in the NICU → home and community

Family-integrated care intervention, and again, this is showing some very interesting outcomes, including decreased parents’ stress and anxiety, as well as increased weight gain and breastfeeding.⁴⁵ As many authors, including Van Wassenauer-Leemhuis have said, we really need to be rethinking intervention to be a parent-integrated, a family-integrated, approach.⁴⁶ Rachel Lean did a very nice review, demonstrating all of the many components that are necessary.⁴⁷ This is just in the NICU environment, for family-based interventions that will hopefully have family outcomes and that will be able to improve children's outcomes through

Outcomes of Children Born Extremely Preterm

follow-ups.



Slide 27 - Family based interventions

We really need to be thinking about these interventions as a continuum, starting in the NICU through transition to home and for longer follow-up, as well.⁴⁸

We also need to be thinking about other outcomes, including health-related quality of life outcomes, which Saroj Saigal has done amazing work in publishing.^{49,50} She has shown that even in comparing extremely low-birth-weight with normal-birth-weight children at young adulthood, there was no difference between self-reported health-related quality of life despite the fact that the extremely low-birth-weight young adults self-reported sensory and cognition challenges, as well as more likely not [to be] in perfect health. If one uses indirect methods, it really makes assignments based on population perspectives on indirect community preferences.

Health-related QoL

Saigal S, et al. *J Pediatr* 2016;179:687-3; *Pediatrics* 2006;118:1140; *Semin Perinatol* 2016; 40:571-577;

Quality of life at adolescence and adulthood for ELBW

- *Self-perceived HRQoL for NBW and ELBW*
- Fewer ELBW than NBW respondents (24% vs 46%) reported "perfect health".
- **Young adulthood: NO difference between NBW and ELBW in HRQoL (0.85 vs 0.88).**
- *Using indirect methods only*
- ELBW with lower HRQoL teens → mid 30's, especially among those with neurosensory impairments

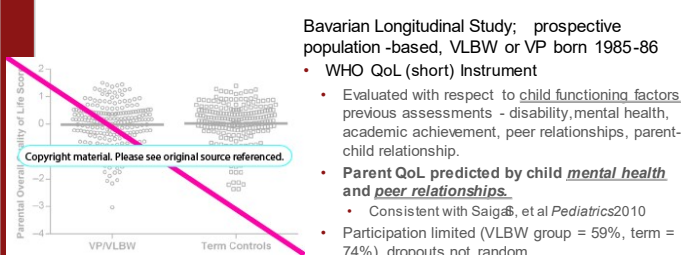
Stanford University

Slide 28 - Health-related QoL

You can see here that over time, from adolescence to adulthood, extremely low-birth-weight individuals decrease in terms of their health-related quality of life and those who have a neurosensory impairment, shown here, are significantly decreased.

It's also important for us to look at quality of life for parents. This is from the Bavarian Longitudinal Study that shows compared to term-control parents of adult individuals, very low-birth-weight and term-control parents really had no difference in their self-reported quality of life.⁵¹ Interestingly, parents reported that the factors that predicted these quality-of-life outcomes were not disability, were not academic achievement, but were child mental health and peer relationships, which I think also really underscores the importance of integrating psychosocial support to our interventions.

Quality of Life for parents of adults born very preterm



Bavarian Longitudinal Study; prospective population-based, VLBW or VP born 1985-86

- WHO QoL (short) Instrument
- Evaluated with respect to child functioning factors previous assessments - disability, mental health, academic achievement, peer relationships, parent-child relationship.
- Parent QoL predicted by child mental health and peer relationships.
 - Consistent with Saigal S, et al *Pediatrics* 2010
- Participation limited (VLBW group = 59%, term = 74%), dropouts not random.

→ Importance of integrating psychological support and interventions

Wolke D, Baumann N, Busch B et al. *Pediatrics* 2017;140:e20171263

Slide 29 - Quality of life for parents of adults born very preterm


Outcomes of Children Born Extremely Preterm

Finally, touching on something that Dr. Jobe mentioned about the need to look far beyond childhood to adulthood, this is from *Nature* and this was highlighting the work of Casey Crump, which was looking at a Swedish national birth database that went all the way back to the 1970s.⁵² What was found here was that for those adults born at 22–27-weeks' gestation, about 75% of them had at least 1 chronic condition in adulthood. Now, I might turn that around and say, that means that 25% did not have any chronic condition, and furthermore, that if you look over birth cohorts, there is an improvement, over time, or an apparent improvement, over time, in survival without major morbidities.

Fortunately, the APIC, or Adults Born Preterm International Collaboration, is looking at these important adult outcomes.⁵³ You can see [Slide 30], as was touched on by Dr. Jobe, cardiometabolic measures as well as respiratory outcomes—this was also discussed by Lex Doyle—are being targeted, but so is health-related quality of life, relationships, independent living, and other issues.

I would also say that Saroj Saigal's, *Preemie Voices*⁵⁴ serves as a very good flag post for us to think about other things, including coping and resilience, and the adult's born extremely preterm, focus on gratitude and living with different abilities.

Common Core Assessments in follow-up studies of adults born preterm—Recommendation of the Adults Born Preterm International Collaboration



Eero Kajantie^{2,3,4} | Samantha Johnson⁵ | Kati Heinonen⁶ | Peter J. Anderson^{7,8} | Dieter Wolke^{9,10} | Kari Anne I. Evensen^{11,12,13} | Katri Räikkönen⁶ | Brian A. Darlow¹⁴ | Sylvia van der Pal¹⁵ | Marit S. Indredavik³ | Julia Jaekel^{16,17} | Petteri Hovi^{18,17} | Katherine Morrison¹⁹ | Erik Verrips²⁰ | Lex W. Doyle^{21,22} | APIC Adults Born Preterm International Collaboration

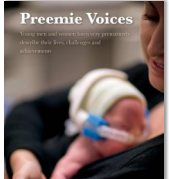
Paediatr Perinat Epidemiol 2020 (ahead of print)

- *Cardiometabolic measures*
- *Respiratory outcomes*
- *Motorchallenges*
- *Mentalhealth*
- *HRQoL*
- *Relationships*
- *Independent living...*
- *Others*

• *Preemie Voices - themes...*

- Importance of emotional, personal, psychological support; coping and resilience.
- Gratitude and living with "different abilities".

Saigal S. *PreemieVoices* Friesen Pres 2014



Slide 30

I thank you very much. I think we all would agree that with a huge amount that's been invested in the survival of our tiniest and highest-risk babies, it really is time for us to pivot looking at truly life-course outcomes, investing in that kind of research, and investing in frameworks that will support the family and these children beyond the NICU exit doors.

Challenges to reshaping the future

- Much is invested in the survival of the tiniest and highest risk babies.
 - › We must now invest in the best possible **life course outcomes** for them and their families.
- *Truly* long-term research must be a priority.
- Pursue innovative research and intervention frameworks with outcomes important to families
→ **beyond the NICU exit doors.**

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Slide 31 - Challenges to reshaping the future

Outcomes of Children Born Extremely Preterm

Abbreviations

ABC	Activities-Specific Balance Confidence	HIE	hypoxic ischemic encephalopathy
APIC	Adult Born Preterm International Collaboration	HRIF	high-risk infant follow-up
BSID	Bayley Scales of Infant Development	HRQoL	health-related quality of life
CI	confidence interval	IQR	interquartile range
COG	cognitive	NBW	normal birth weight
CP	cerebral palsy	NICHD	National Institute of Child Health and Human Development
CPQCC	California Perinatal Quality Care Collaborative	NDI	neurodevelopmental impairment
CPR	cerebral palsy register	NICU	neonatal intensive care unit
EGA	estimated gestational age	PPP	Positive Parenting Program
ELBW	extremely low birth weight	QI	quality improvement
EPT	extremely preterm	SES	socioeconomic status
EXPRESS 2	Extremely Preterm Infants in Sweden Study	VLBW	very low birth weight
FISIQ	full-scale IQ	VP	very preterm
GA	gestational age	VPT	very preterm
GMFCS	gross motor function classification system	WISC®-I	Wechsler Intelligence Scale for Children

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Outcomes of Children Born Extremely Preterm

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