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Outcomes of Children Born Extremely Preterm

Miami Neonatology 2020
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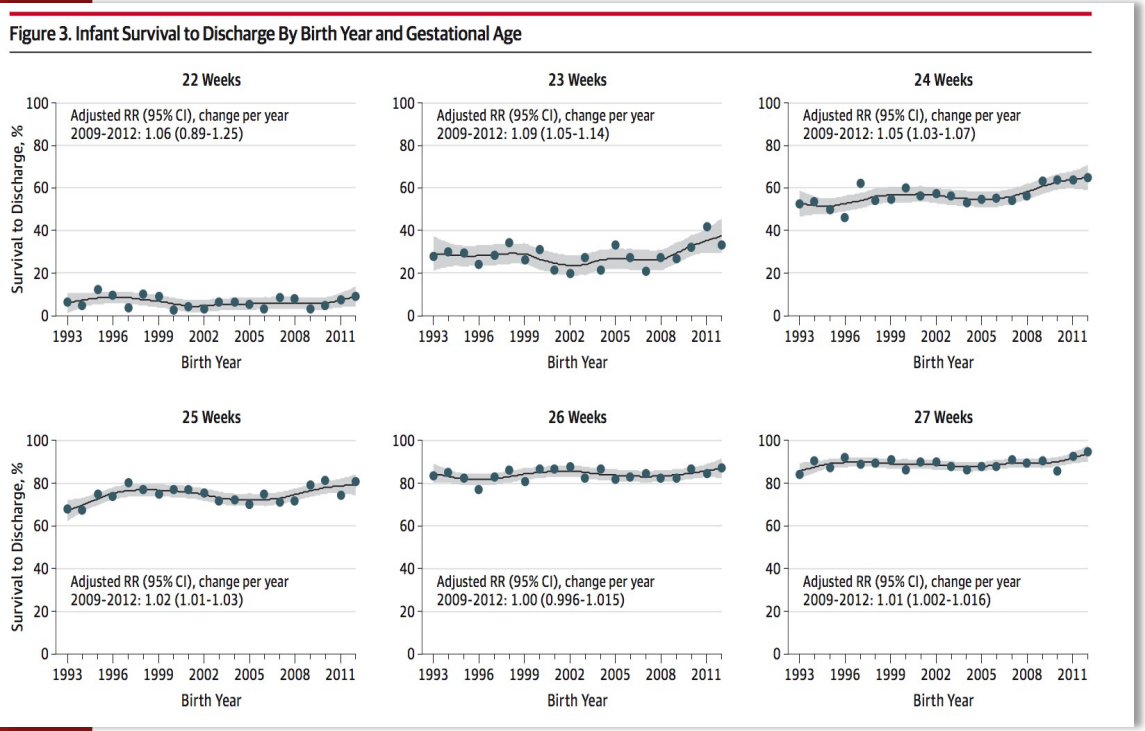
Outline -

- Changes in survival and survival without major morbidity
- Neurodevelopmental outcomes of children born extremely preterm -
  - Toddlers, children, and challenges to interpretation
- Are we asking the right questions?
  - Beyond traditional outcomes -
- Possibilities for changing the trajectory of research and outcomes

Dr. Susan Hintz has no conflicts of interest or financial disclosures.

Survival of infants born extremely preterm



EXPRESS 2 → Swedish national prospective study of survival and outcomes of infants 22-26 weeks'

- One-year survival among *live-born* infants:
  - **70% during 2004-07**
  - **77% during 2012-16**
    - −7% [95%CI, −11% to −2.2%], p = 0.003

NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

Stoll BJ, et al. *JAMA* 2015;314:1039-1051.

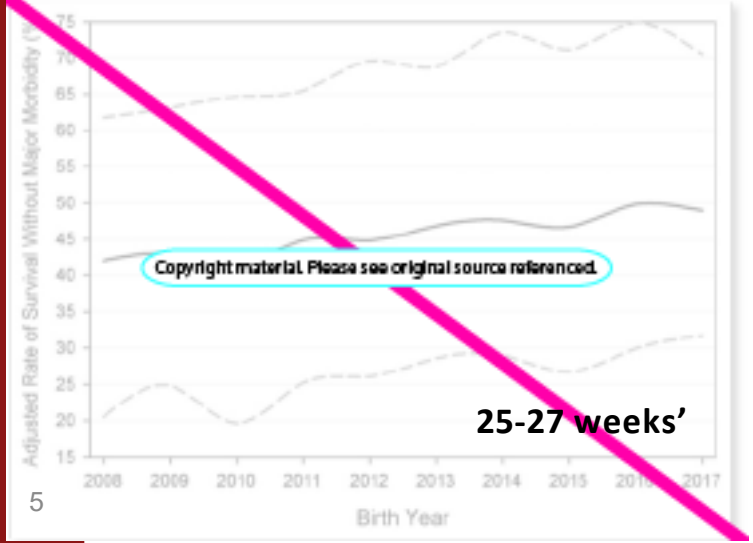
Norman M, et al. *JAMA*. 2019;321:1188-1199

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

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.

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

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

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;197:75-81, Vohr BR, et al *J Pediatrics* 2012; 161:222
    Moore T, et al. J Pediatr 2012;160:553-8

- **"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;197:75-81

- **Differing rates of NDI, death or NDI across centers *within networks*.**

  Synnes A, et al *ADC Fetal Neo* 2017; 102: F235; Vohr BR, et al. *Pediatrics* 2004; 113: 781

- **Family and functionalperspective**

  Janvier A, et al. *Seminars Perinatol* 2016, 40: 571

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

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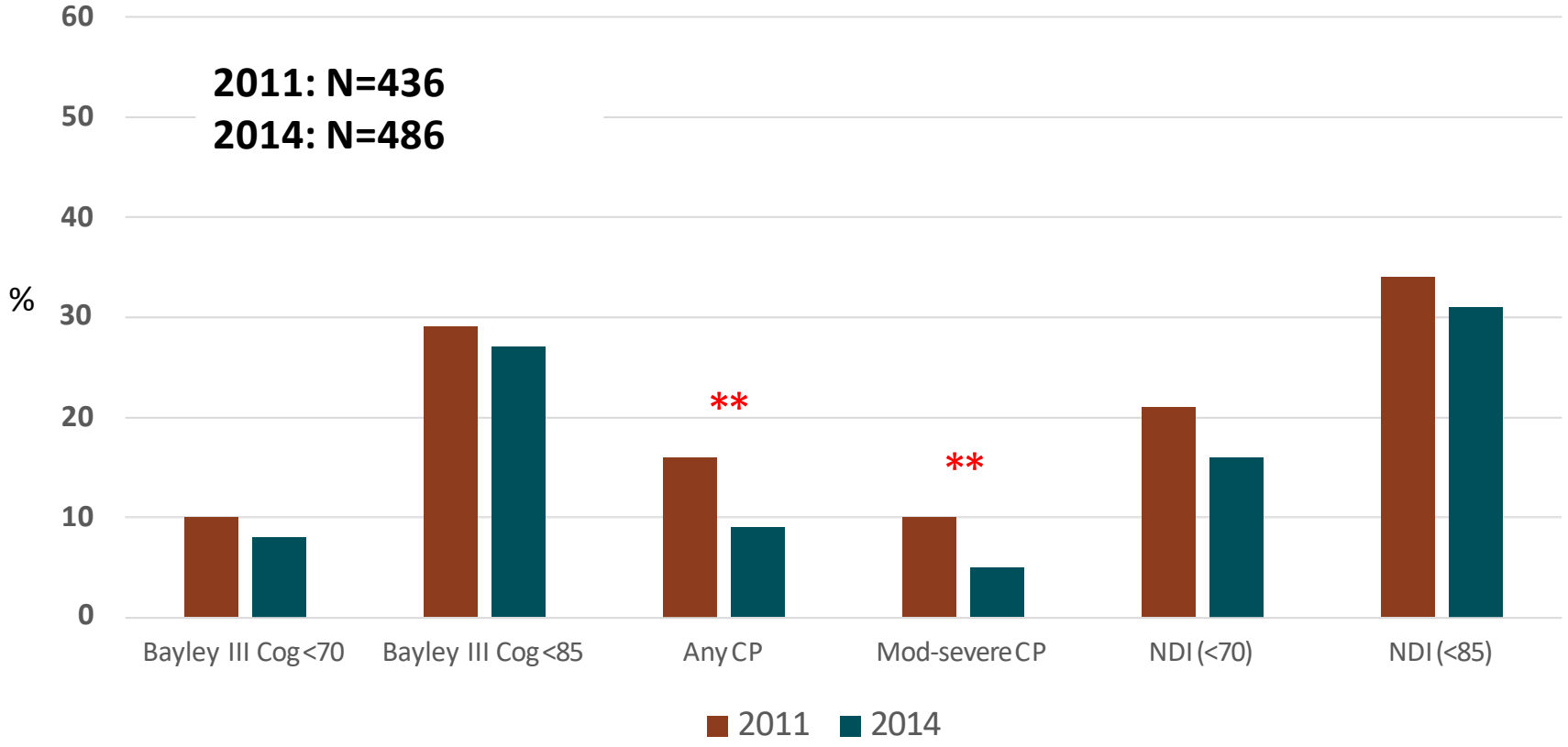
Neurodevelopmental outcomes over time:
≤ 26-week EGA at 18-26 months corrected age



Adams-Chapman I, et al. *Pediatrics* 2018, 141 (5):e20173091

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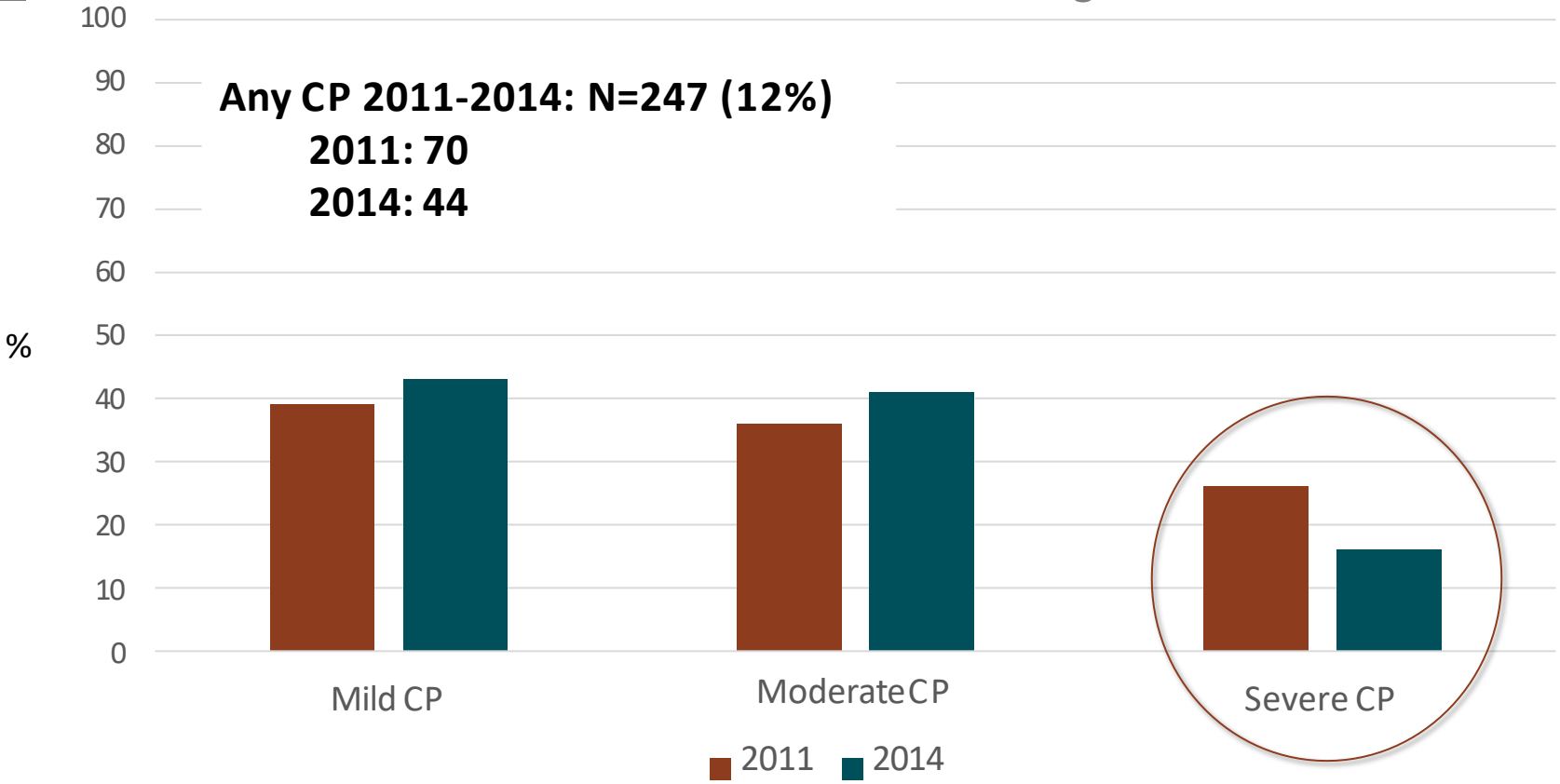
Decrease in *severe* CP over time:

≤ 26-week EGA at 18-26 months corrected age



Adams-Chapman I, et al. *Pediatrics* 2018, 141 (5):e20173091

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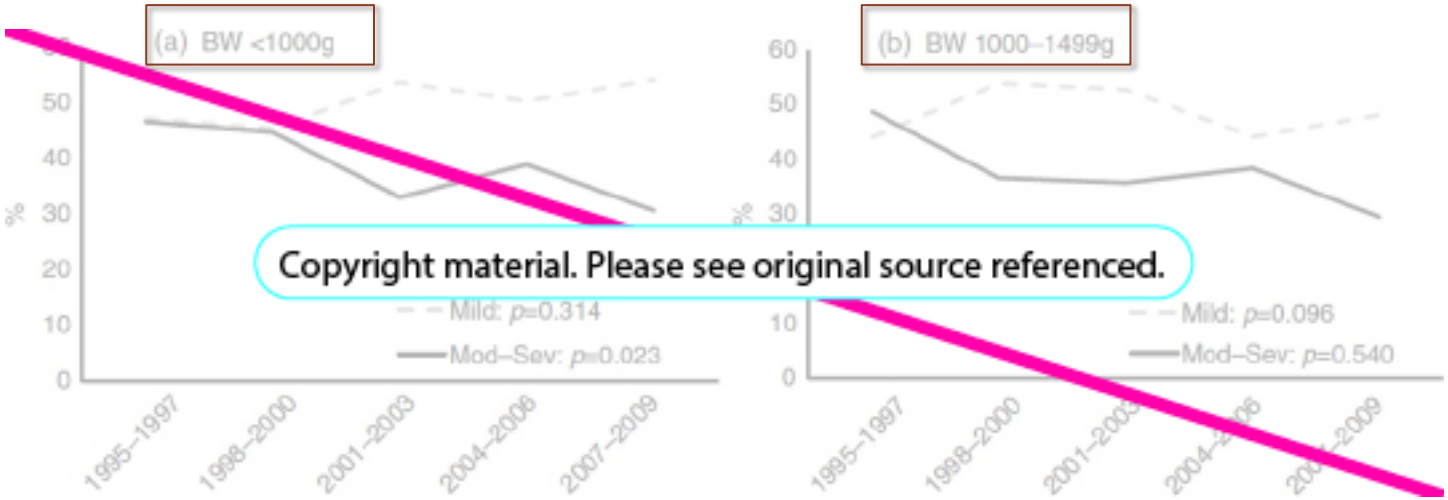
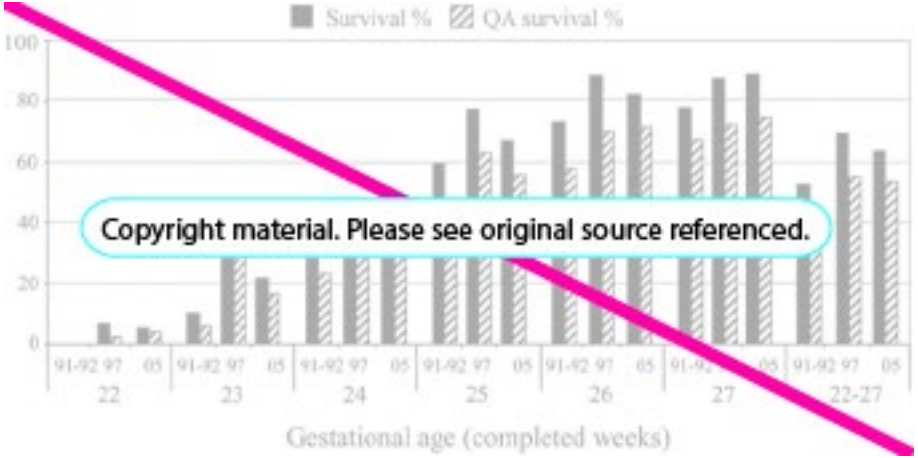
Decrease in *severe* CP over time:
Australian Cerebral Palsy Register (ACPR)



Galea C., et al. *Dev Med Child Neurol* 2019; 61:186-193

Outcomes at age 2 years of infants <28 weeks' GA

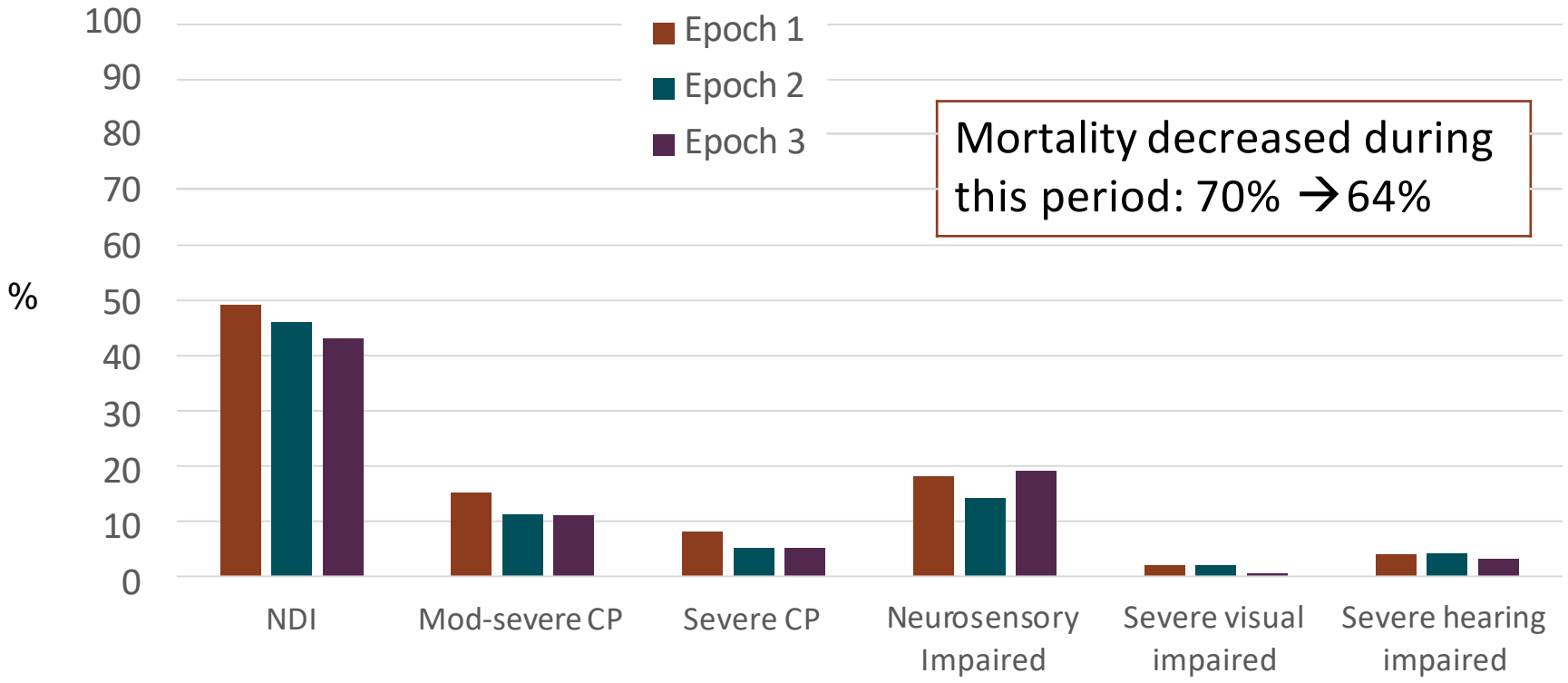
Comparison of 3 birth cohorts in Victoria, Australia



	1991-92	1997	2005
Survivors, n	225	151	172
Survivors assessed, n	219 (97.3%)	149 (98.7%)	163 (94.8%)
CP	24 (11.0)	18 (12.1)	16 (9.8)
Blindness	5 (2.3)	4 (2.7)	0 (0)
Deafness	2 (0.9)	2 (1.3)	4 (2.5)
No developmental delay	128* (58.4)	81 (54.4)	85 (52.1)
Mild developmental delay	51 (23.3)	32 (22.1)	52 (31.9)
Moderate developmental delay	24 (11.0)	14 (9.4)	20 (12.3)
Severe developmental delay	16 (7.3)	22 (14.8)	6 (3.7)
No disability	119 (54.3)	72 (48.3)	83 (50.9)
Mild disability	54 (24.7)	35 (23.5)	47 (28.8)
Moderate disability	29 (13.2)	19 (12.8)	27 (16.6)
Severe disability	17 (7.8)	23 (15.4)	6 (3.7)

Doyle LW., et al. *J Pediatr* 2010;156:49-53

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



Younge N, Goldstein R, Bann C, Hintz SR, et al. *NEJM* 2017; 376:617-28

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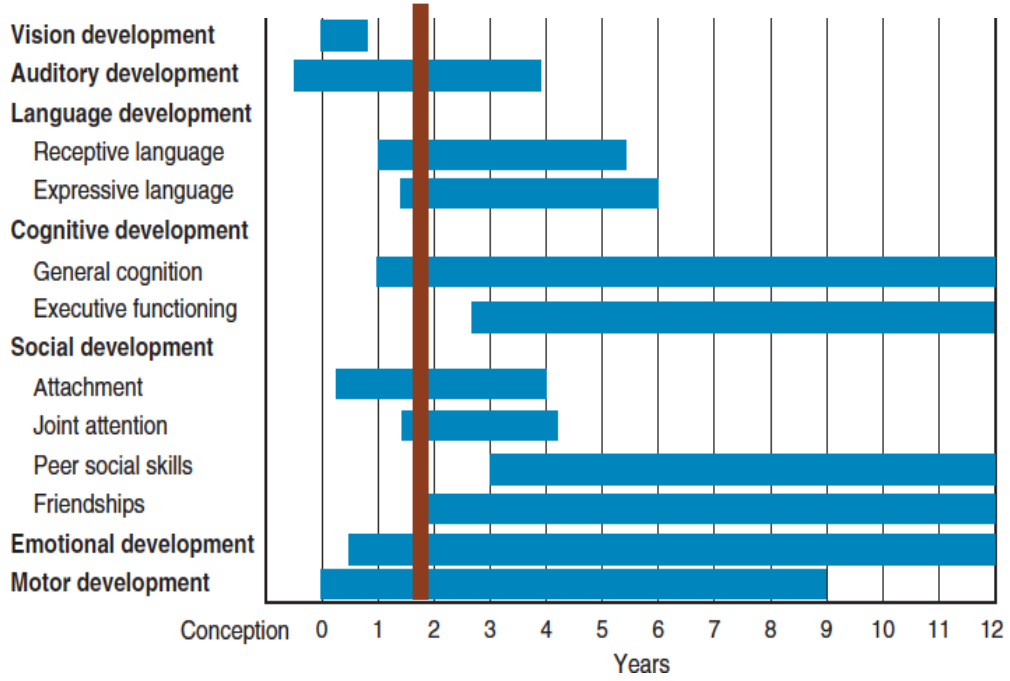
What about *later* outcomes of children born extremely preterm?

Importance of longer-term outcomes

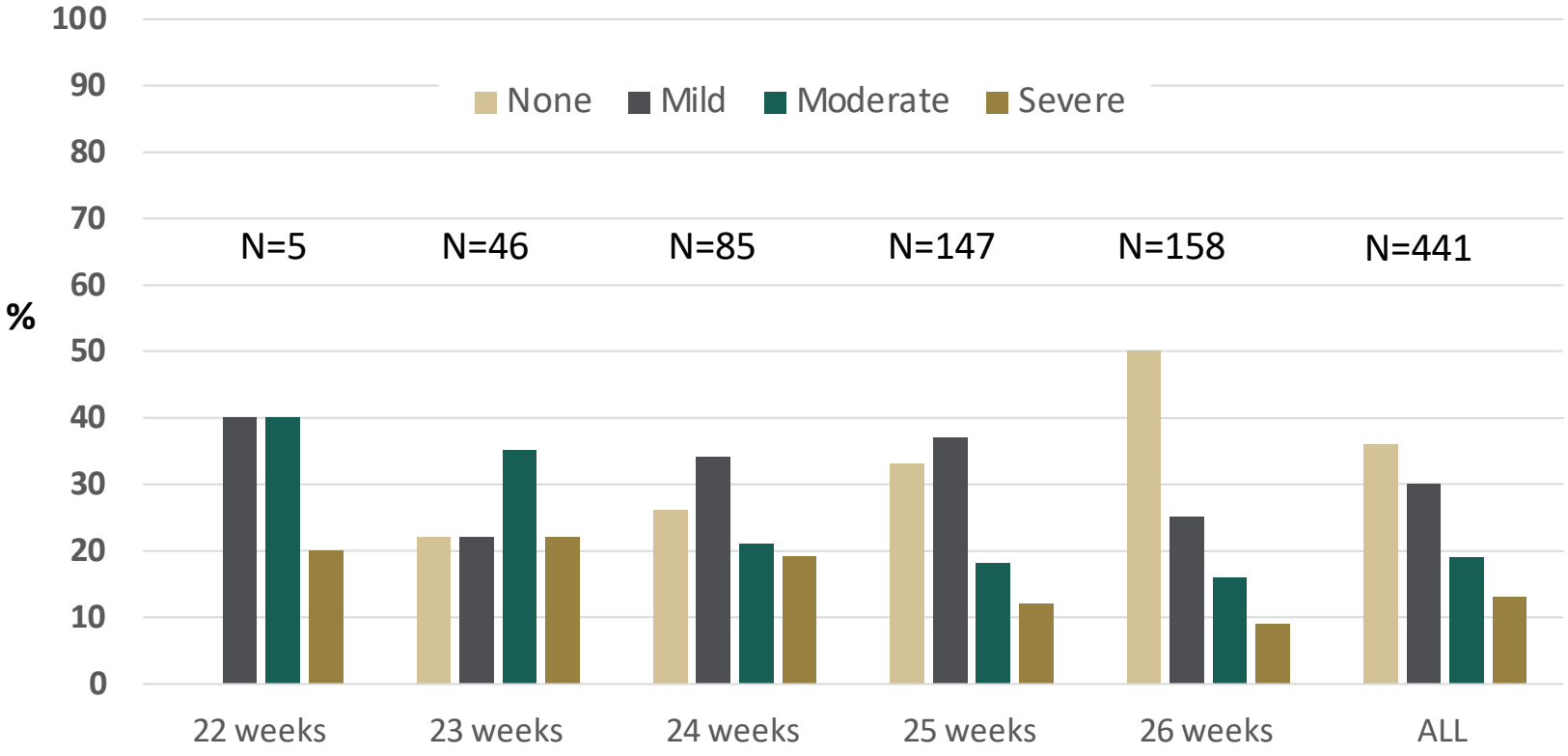
- Later cognitive and behavioral outcomes are complex - influenced multiple factors
- Changes in, relative importance of various outcomes vary substantially among individuals and across different time points.
- Later follow up may provide critical additional outcomes and safety data, and information about changes over time.



Woodward L, Huppi P. "Neurodevelopmental Follow-Up" (Chapter 11) in *Volpe's Neurology of the Newborn, 6th Edition*. Elsevier (Philadelphia) 2018

Neurodevelopmental Disability at 6.5 years

EXPRESS cohort (birth years 2004-2007)



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

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%)	19 (9%)	138 (64%)	25 (12%)
Total	751	205 (27%)	86 (11%)	413 (55%)	47 (6%)

Data are n (%). Gestational ages are in completed weeks.

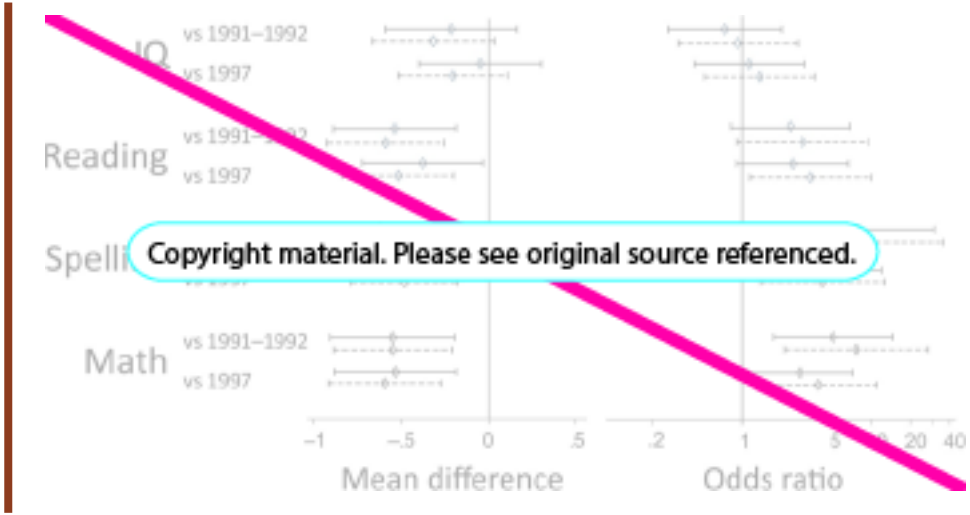
Table 3: Outcomes at 8 years by gestational age at birth

Rates of major disability were **similar** across birth eras:

- 1991–1992, = 18%; 1997 = 15%; 2005 = 18%

Major disability **among survivors**

23 weeks –29%
24 weeks –20%
25 weeks –18%
26 weeks –17%
27 weeks –10%



Cheong JLY, et al. *Lancet Child Adolesc* 2018; 2(12):872-879

Cheong JLY, et al. *Pediatrics* 2017;139(6): e20164086

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				
	None	Mild	Moderate	Severe	Total No.
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

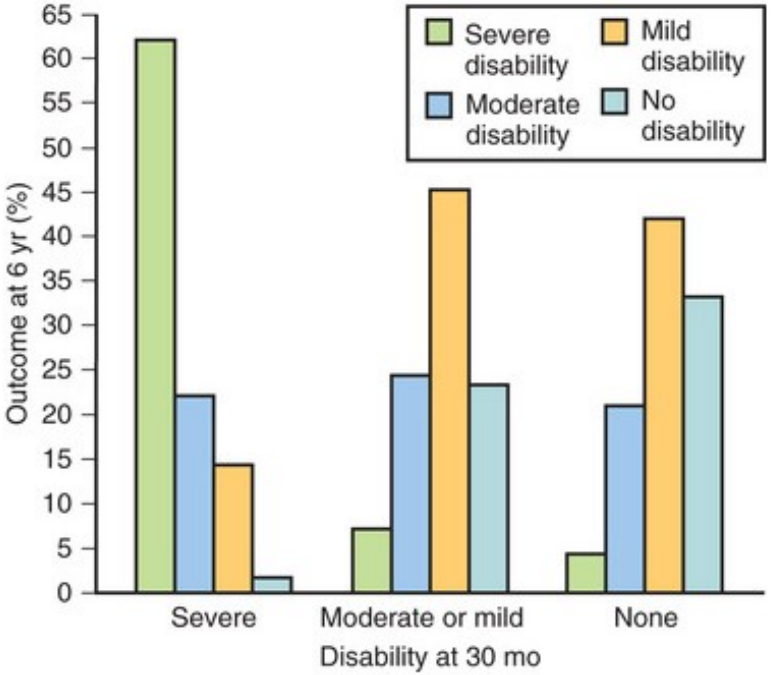
Only 47% remained in the same category →

- **21% moved to a better category, 32% moved to a worse category.**

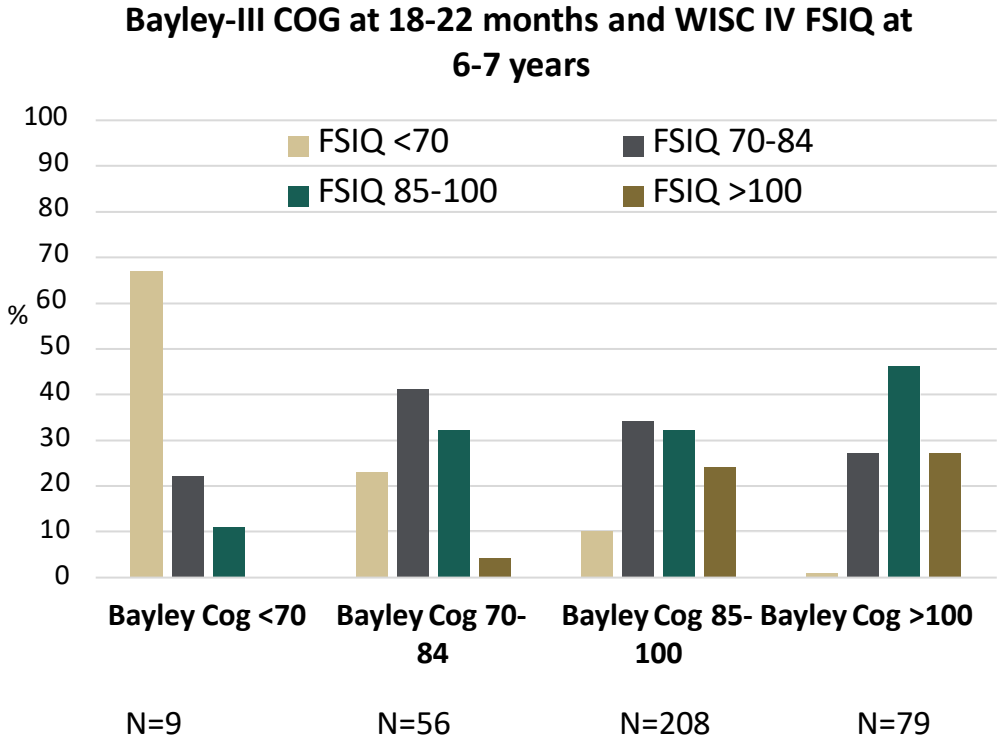
Serenius F, et al. JAMA Peds 2016; 170: 954

Predicting school age from toddlerhood??

Importance of longer-term outcomes

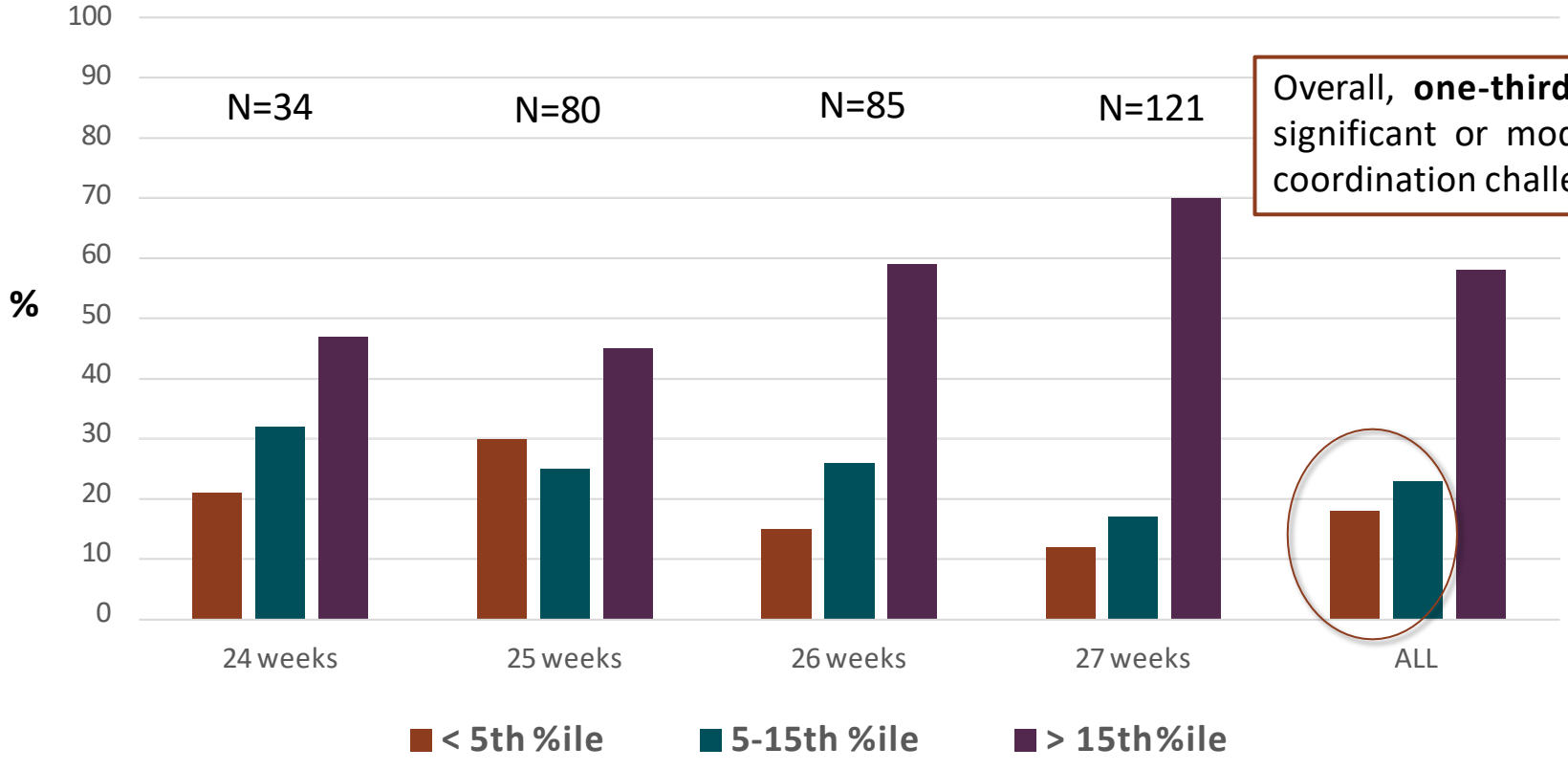


Marlow N, Wolke D, Bracewell M, et al. *NEJM* 2005; 353:9



SUPPORT NEURO Hintz, Bann, Vohr, et al., *Pediatrics 2018,* PAS 2018

Movement ABC scores at 6-7 years - NEURO cohort



Overall, **one-third** with significant or moderate coordination challenges

Hintz SR, et al. Pediatrics 2018; 142: e20174058; Hintz SR, PAS 2018

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Are we asking all the right questions?

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; Carter F, Msall ME. *Clin Perinatol* 2018, 45: 501; Kilbride HW, et al. *Clin Perinatol* 2018, 45: 467

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 n (%)						
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)

• Service **Utilization** at 1st HRIF Visit

HIGH RISK INFANT FOLLOW-UP

***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

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, Zelkowitz 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; Zelkowitz 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 Chid Psych* 2012*; Semin Fetal Neonatal* 2014

“Early Intervention”

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

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

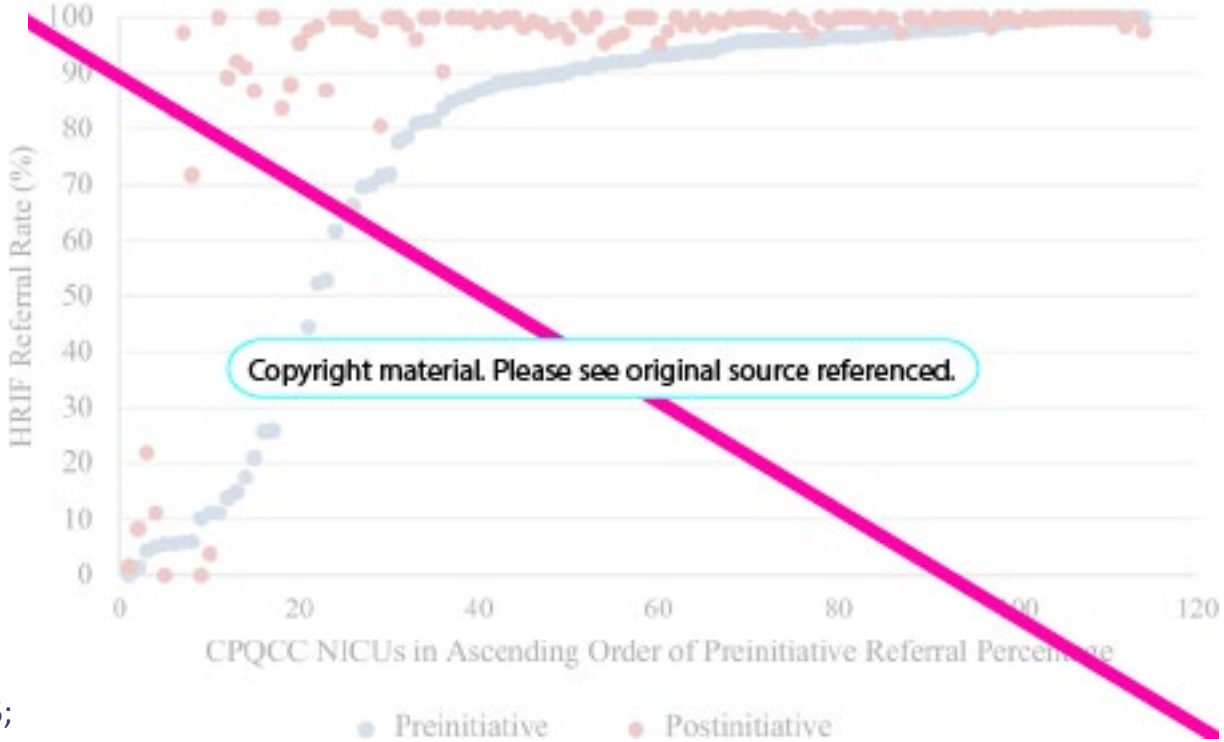
  - Concluded that early intervention **has a positive influence on *cognitive* outcomes through preschool and *motor* outcomes to ~ 2 years.**
  - Early diagnosis and intervention for cerebral palsy – both child *and* parents.

Novak I, et al. *JAMA Pediatr* 2017; 171: 897-907; Maitre NL, et al. *Pediatrics* 2020; 145: e20192126; Irwin L, et al. Research in Developmental Disabilities 2019; 19: 103511

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**

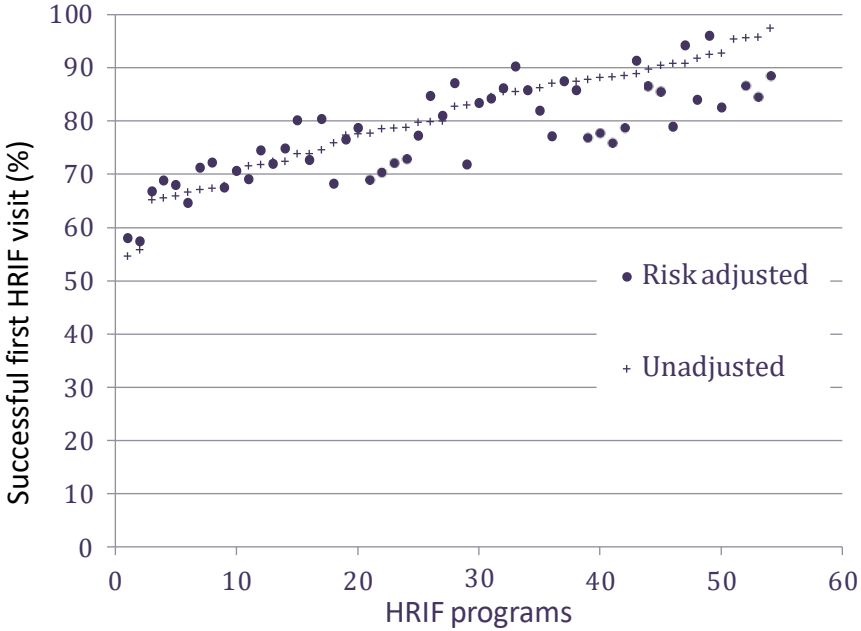
Substantial ↑ in referral rates by sociodemographic and program-level factors - - *but disparities remain.*



Hintz SR, et al. *J Pediatrics* 2015;166:289-95;
Pai V, et al *J Pediatrics* 2020;216:101-108.e1

Getting to follow up: Factors associated with successful **1st visit** for infants born VLBW in California

Factor	Adjusted OR (95% CI)	p-value
Associated with higher odds - -		
Maternal age (vs 20-29)		
30-39	1.48 (1.27, 1.72)	<0.0001
Maternal prenatal care	1.92 (1.34, 2.77)	0.0004
Birth weight (vs. 1251-1499 g)		
<=750 g	2.11 (1.69, 2.65)	<0.0001
751-1000 g	1.81 (1.51, 2.17)	<0.0001
1001-1250 g	1.34 (1.14, 1.58)	0.0005
Severe ICH	1.61 (1.12, 2.3)	0.0093
Insurance (vs CCS or MediCal only)		
HMO/PPO + CCS	1.65 (1.19, 2.31)	0.003
Two parent 1 caregiver (vs. one only)	1.18 (1.03 - 1.36)	0.019
HRIF program VLBW volume (*vs. lowest quartile*)		
2nd quartile	2.62 (1.88, 3.66)	<0.0001
3rd quartile	1.55 (1.15, 2.10)	0.0045
Associated with lower odds - -		
Maternal race African American	0.65 (0.54, 0.78)	<0.0001
Miles from HRIF program (*vs. lowest quartile*)		
Highest quartile	0.69 (0.57, 0.83)	0.0002
3rd quartile	0.79 (0.65, 0.96)	0.018



Hintz SR, et al. J Pediatr. 2019; 210:91-98.e1

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.

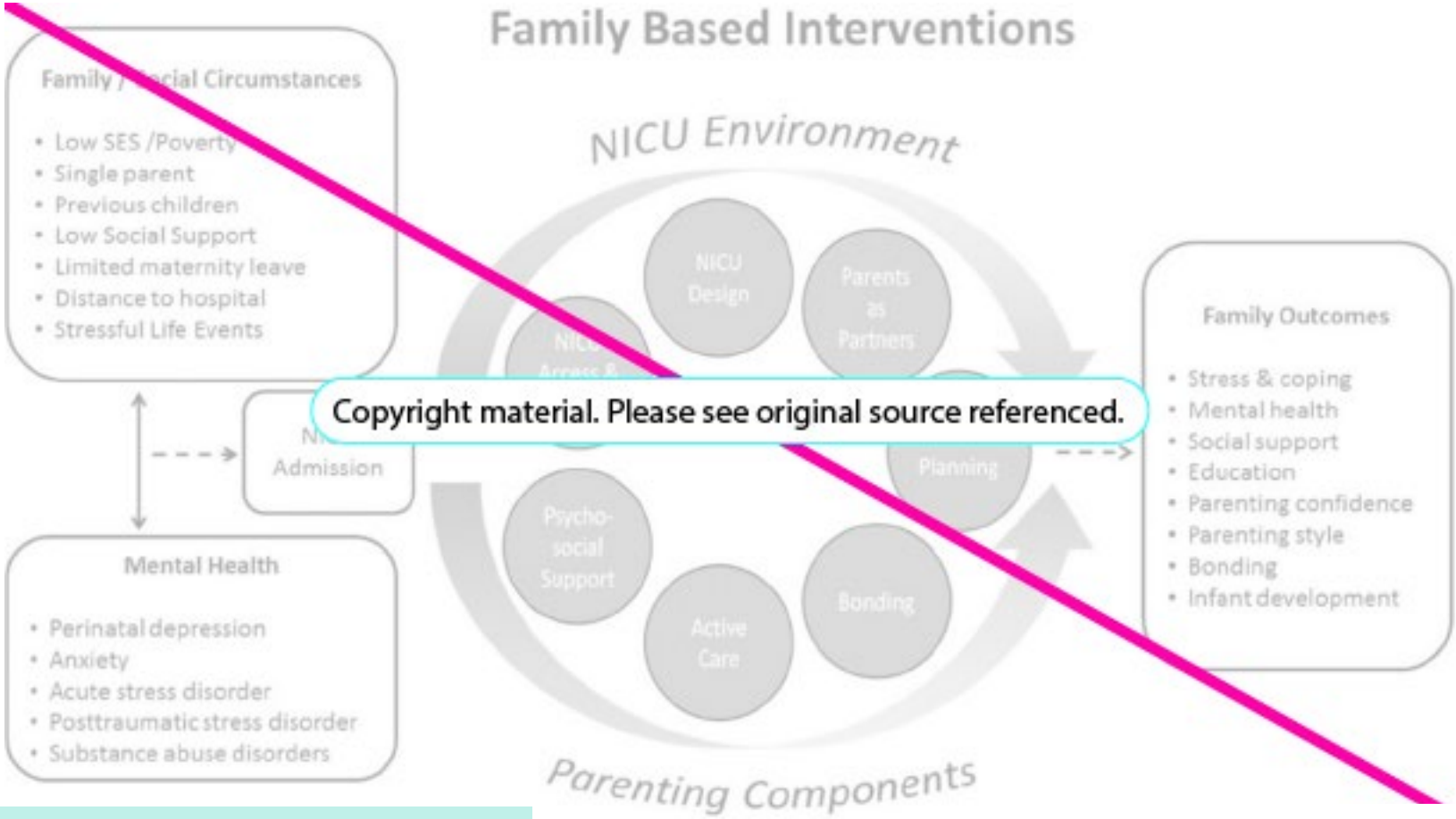
  Colditz PB, et al. *J Pediatr* 2019; 210: 48

- Family Integrated Care intervention (25 NICUs) → ↓ **parent stress/anxiety, ↑wt gain and breast feeding** at discharge.

  O'Brien K, et al, *Lancet Child Adolsc Health* 2018; 2: 245

- ***Rethinking* intervention** – supporting parent mental health, responsive parenting

  Van Wassenauer-Leemhuis AG, et al, DMCN 2016; 58(suppl 4): 67-73



Horbar J, et al *Pediatrics.* 2020; doi: 10.1542/peds.2020-0360

Lean R, et al *Curr Treat Options Pediatr*. 2018; 4(1):49–69

Health-related QoL

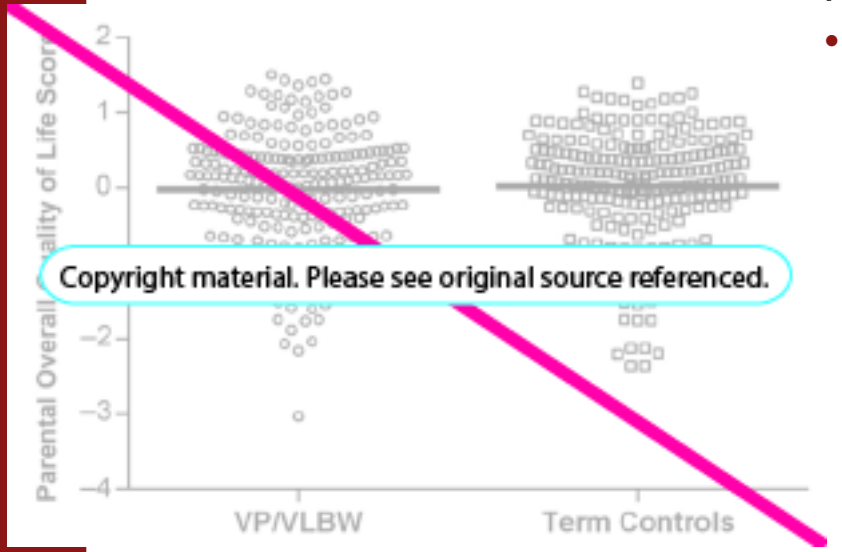
Saigal S, et al. *J Pediatr* 2016;179:68-73; *Pediatrics*. 2006;118:1140; *Semin Perinatol* 2016; 40: 571-577;

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: <u>NO difference</u> 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

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

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

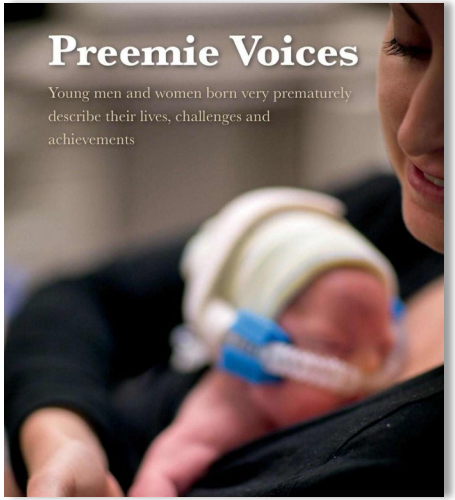
Eero Kajantie[1,2,3,4] | Samantha Johnson[5] | Kati Heinonen[6] | Peter J. Anderson[7,8] | Dieter Wolke[9,10] | Kari Anne I. Evensen[3,11,12,13] | Katri Räikkönen[6] | Brian A. Darlow[14] | Sylvia van der Pal[15] | Marit S. Indredavik[3] | Julia Jaekel[1,9,16] | Petteri Hovi[1,4,17] | Katherine Morrison[18] | Erik Verrips[15] | Lex W. Doyle[8,19] | APIC Adults Born Preterm International Collaboration

Paediatr Perinat Epidemiol 2020 (ahead of print)

- *Cardiometabolic measures*
- *Respiratory outcomes*
- *Motor challenges*
- *Mental health*
- *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. Preemie Voices, Friesen Press, 2014



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.**