Neurodevelopmental Outcomes after Perinatal Brain Injury

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Contents

- **Neurodevelopmental outcomes** after perinatal brain injury in **Preterm** infants

1) Prevalence
2) Predictors
3) Clinical recommendations

Classification of Preterm

The classification based upon GA is as follows:

- Late preterm birth — GA between 34 and less than 37 weeks
- Very preterm birth — GA less than 32 weeks
- Extremely preterm birth — GA at or below 25 weeks

Prematurely born infants are also classified by birth weight (BW):

- Low birth weight (LBW) — BW less than 2500 g
- Very low birth weight (VLBW) — BW less than 1500 g
- Extremely low birth weight (ELBW) — BW less than 1000 g

Institute of Medicine(IOM) committee on understanding preterm birth (2007)

steady increase in preterm birth

& remarkable improvements in survival

(by antenatal steroids, artificial surfactant etc.)

outpacing

any concomitant decrease in long-term neurodevelopmental disability rates.

Importance of Preterm birth

- 64-75% of infant death
- 42-47% of CP
- 27% of cognitive impairment
- 37% of visual impairment
- 23% of hearing impairment

->Attributed to preterm birth

Pathogenesis of Prematurity

- not a single disease, but a common complex condition

- **multiple gene-environmental interaction**
  - biological markers, maternal medical conditions, genetics ,environmental exposures, assisted reproductive technology, behavioral and psychosocial factors and neighborhood social characteristics,
  - Prior preterm birth
  - Inflammation, uterine distention, deteriorating fetal or maternal health

Trends of Preterm outcome studies

- Past 50yrs

- cerebral palsy, intellectual disability, sensory impairment

- More recent studies

- school and behavior problems(minor neuromotor dysfunction, specific learning disability and language, visual- perceptual and attention deficits)
- Contributions of preterm complications
- Treatments to neurodevelopmental outcomes

Caution needed in interpretation of studies

- Time of study as practice changes occur
- Population study based upon BW or GA
- Assessment tools used for evaluation
- Length of follow-up(age at assessment)

Neurodevelopmental disability

- **Major disabilities**
  - Cerebral palsy
  - Mental retardation
- **Sensory impairment**
  - Visual impairment
  - Hearing impairment
- **More subtle disorders of CNS function**

More subtle disorders of CNS ft

- Language disorder
- Learning disability
- Attention deficit- hyperactivity disorder
- *Minor neuromotor dysfunction*

or developmental coordination disorders

- Behavioral problems
- Social-emotional difficulties

Minor Neuromotor Dysfunction

- mild but persistent abnormalities (asymmetries, tight heel cords)
- motor planning problems and/or sensorimotor integration problems leading to functional impairment(tying shoelaces)
- academic difficulty(writing)
- social emotional problems

  (poor self esteem, peer relationships)

Neurosensory Disability

Motor outcomes

- **Transient neuromotor abnormalities**

- 17-48% of preterm infants

- some develop significant neuromotor abnormalities & motor delays that signify **CP**, but most do not.

- associated with increased risk of later school and behavioral problems

Vohr et al. 2005

Cerebral palsy

- Many preterm have neuromotor abnormalities on examination, but do not develop CP.

- **Rate of CP after 1990s**

- 4-12% below 1000g
- 6-20% before 27wks
- 21-23% before 25wks

Trends in the prevalence of CP in Northern Ireland, 1981-1997

Northern Ireland, 1994-1997

- **CP prevalence** (**2.2**/1000 live birth)
- **1.2** over 2499g
- **11.3** 1500-2499g
- **44.5** below 1500g
- **47.0** below 1000g (**99.5** in survivors)

- Increase in CP with decreasing BW

Helen et al. DMCN 2006

Cognitive impairment

In Preterm

- More common cognitive impairments and academic difficulties
- More common than motor, visual, hearing impairment.

Cognitive deficits in PVL

- **Peritrigonal region**

- interhemispheric associative fibers
- ascending and descending projection fibers

- **Gray matter injury associated with PVL**

- neuronal loss: thal 38%, G. pallidus 33%, hippocampus 33%, Cbll cx 24%
- gliosis: Caudate 60%, Thal 50%,putament 50%, G. pallidus 60%, basis pontis 100%

Intellectual function in Preterm infant

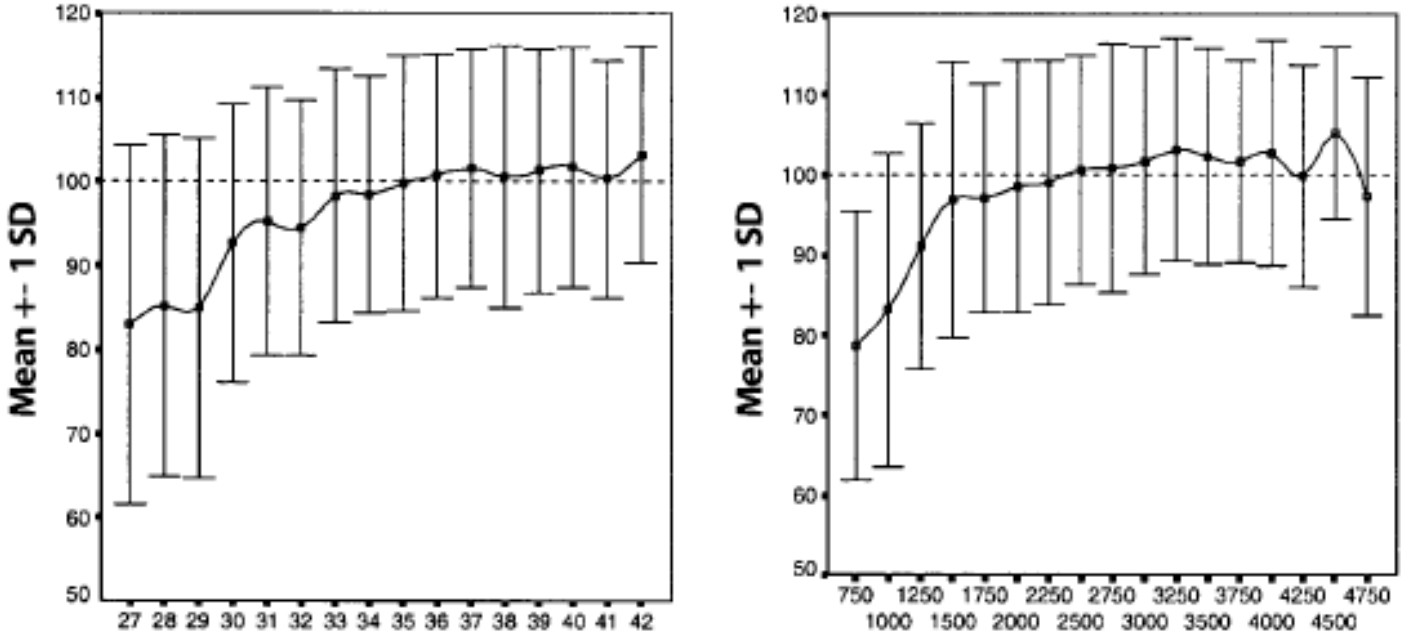
	Spastic Diplegia	Spastic Quadriplegia
Normal or IQ≥70	68	14
Moderate MR	15	21
Severe MR	17	54

Pharoah et al 1987

IQ correlation with GA & BW

- Bavarian longitudinal study
- for infants born before **32wks GA**
- **Cognitive and school** outcome **at 4yr 8mo**

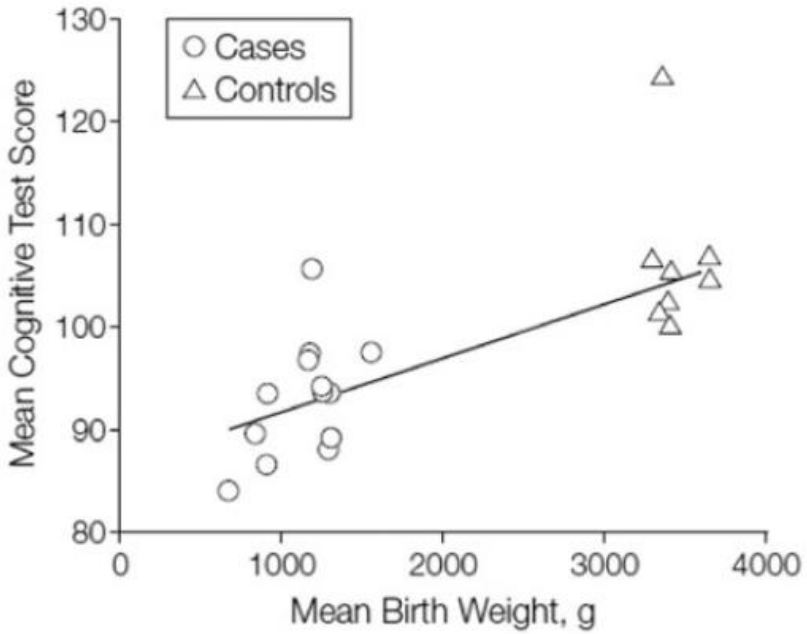
–better predicted by **neonatal risk** than social factors

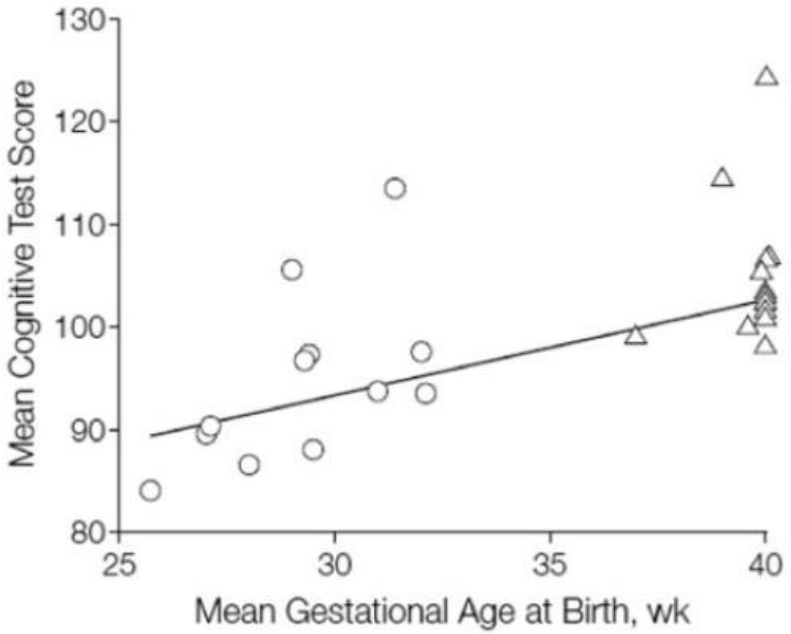


Wolke et al. 2001

Cognitive and behavioral outcomes of school-aged children who were born preterm : a meta-analysis

- 15 case-control studies, 17 groups of children (1556 vs 1720 controls)
- Evaluated After **5 years** old





1. Correlations between mean cognitive scores, birth weight and gestational age.

Bhutta et al. JAMA 2002

Factors associated with cognitive outcomes

- Birthweight
- Gestational age
- Neuroimaging evidence of brain injury
- Neuromotor abnormalities on exam
- Male gender
- Some factors related to severity of neonatal illness or chronic lung disease

Extremely Preterm infants

EPICure study

- Great Britain and Ireland
- 308 survivors born in 1995 <25wks GA
- Disability : Bayley-II MDI & PDI <-3SD, CP, blindness, and/or hearing loss

- At 30 months- 283 of 308 **(Wood et al.2000)**
- At 6yrs- 241 of 308 **(Marlow et al. 2005)**
- At 11yrs-219 9f 308 **(Johnson et al.2009)**

NEUROLOGIC AND DEVELOPMENTAL DISABILITY AFTER EXTREMELY PRETERM BIRTH

NICHOLAS S. WOOD, M.B., CH.B., NEIL MARLOW, D.M., KATE COSTELOE, M.B., B.CHIR., ALAN T. GIBSON, PH.D., AND ANDREW R. WILKINSON, M.B., CH.B., FOR THE EPICURE STUDY GROUP*

At 30 months

- **Developmental delay 30%**
  -severe 19%
  -moderate 11%
- **Severe neuromotor impairment 10%**
- **Hearing loss 3%**
- **Visual impairment 2%**

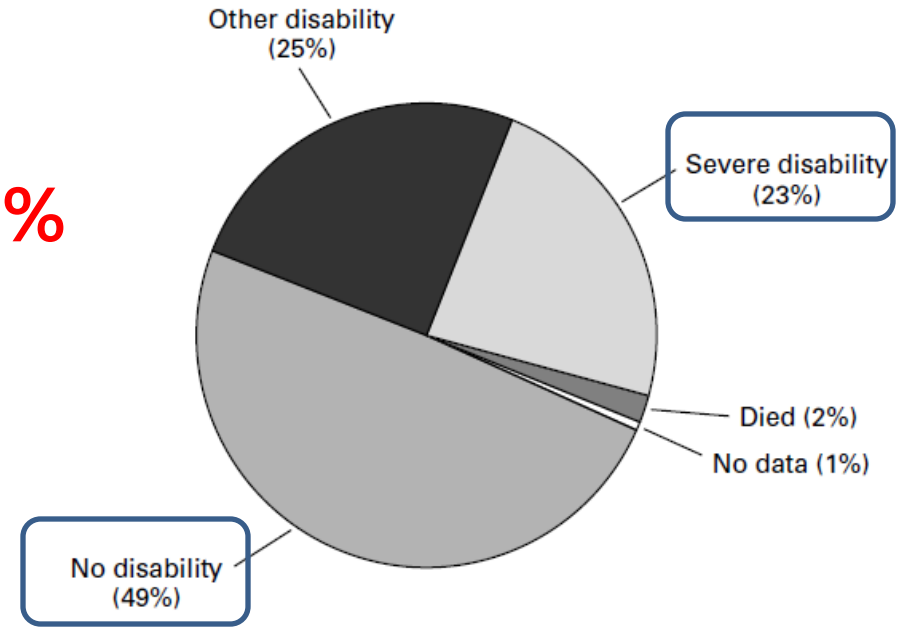


Figure 1. Summary of Outcome with Respect to Overall Disability at 30 Months for 314 Children Born at 22 through 25 Weeks of Gestation.

Wood et al. NEJM 2000

Neurologic and Developmental Disability at Six Years of Age after Extremely Preterm Birth

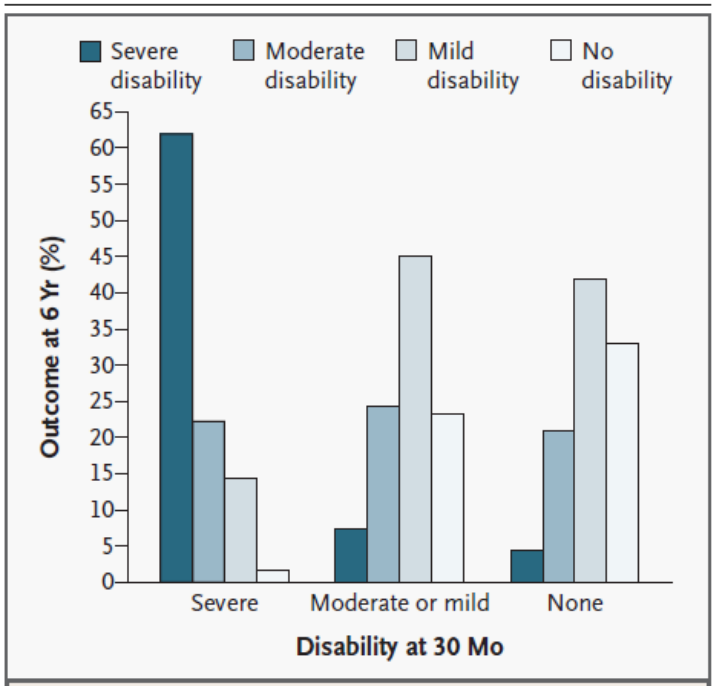
At 6 yrs old

- **Disabilities**

  Severe 22%

  Moderate 24%

  Mild 34%



- **86%** of **severe** disability at **30mo**

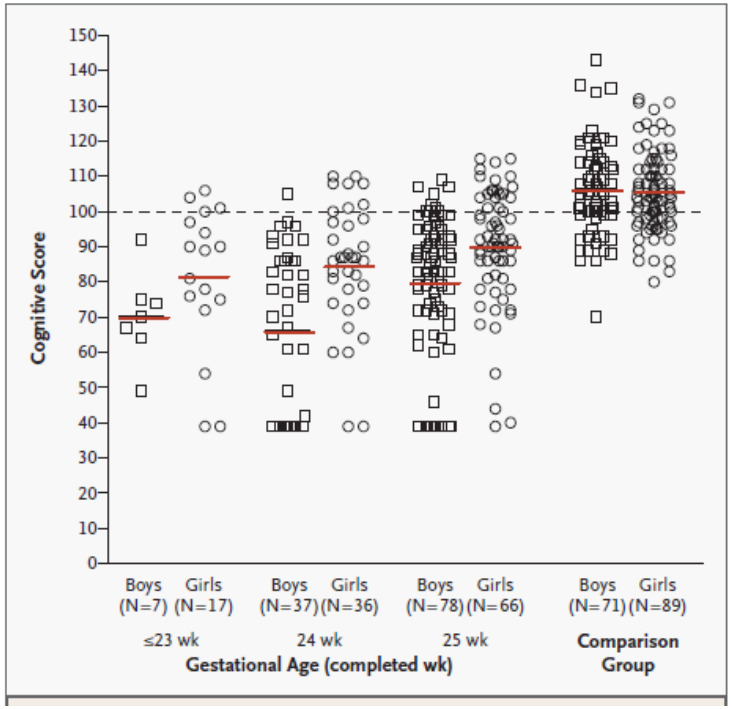
- **moderate to severe** disability at **6rys**

Marlow et al. NEJM 2005

Neurologic and Developmental Disability at Six Years of Age after Extremely Preterm Birth

- **Cognitive impairment 41%**
  - **82.1**+19.2 vs **105.7**+11.8

- **Linear relationship between IQ & GA in EP**



Marlow et al. NEJM 2005

Neurologic and Developmental Disability at Six Years of Age after Extremely Preterm Birth

	Hearing impairment		Visual impairment	
Severe	**3%**	**0**	**2%**	**0**
Moderate	**3%**	**1**	**5%**	**0**
Mild	**4%**	**1**	**29%**	**4**

Marlow et al. 2005

Neurodevelopmental and Functional Outcomes of Extremely Low Birth Weight Infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993–1994

NICHHD
Multicenter cohort study, US
1151 ELBW(401-1000g) in 12 centers
Functional assessment at 18-22mo CA

- Abnormal neurologic examination 25%
- MDI<70 37%
- PDI<70 29%
- Vision impairment 9%
- Hearing impairment 11%

Pediatrics. 2000

Factors associated with Neurodevelopmental morbidity

Increasing factors

- chronic lung ds, IVH Gr3-4/PVL, steroid for chronic lung ds, NEC, male gender

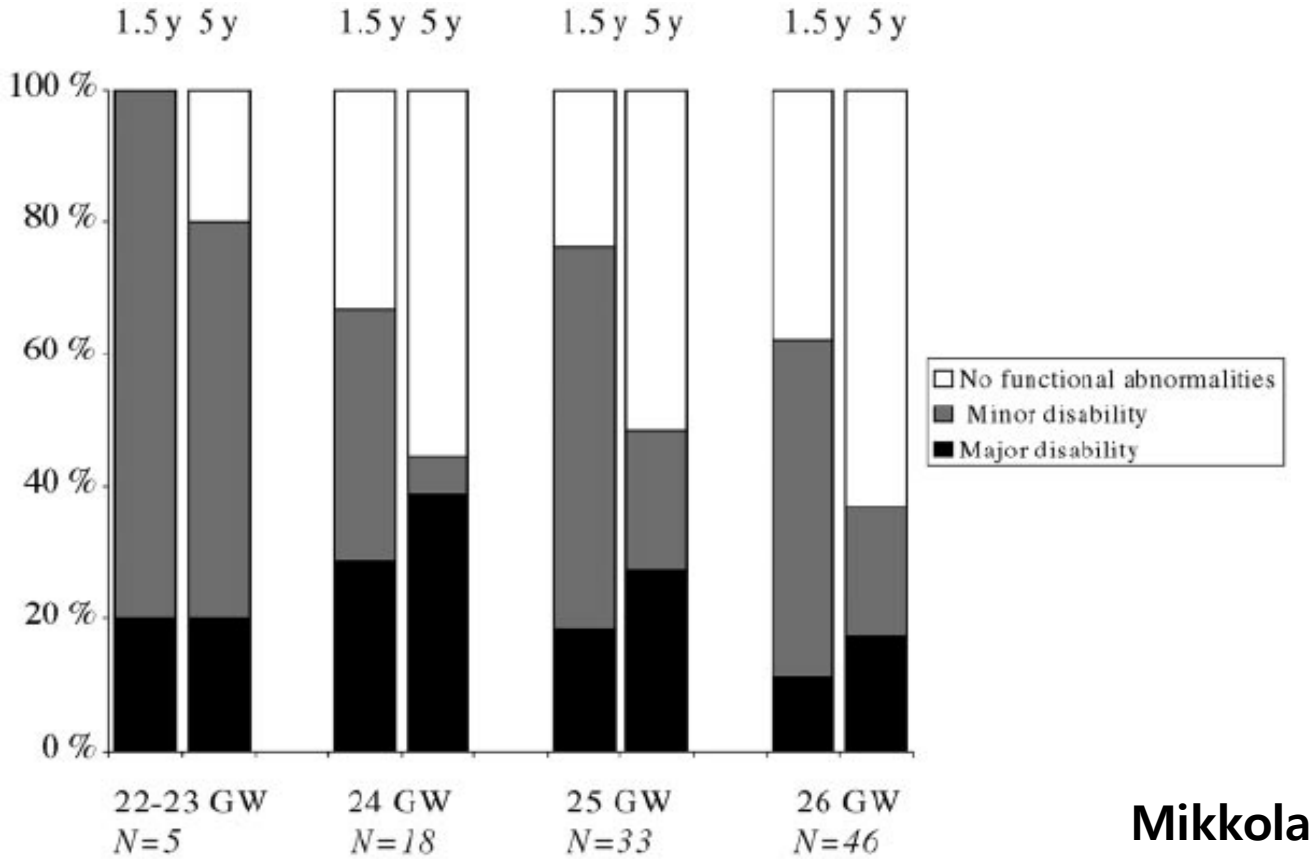
Decreasing factors

- increased birth weight, female gender, higher maternal education, white race

Pediatrics. 2000

Neurodevelopmental outcome at 5 years of age of a national cohort of extremely low birth weight infants who were born in 1996-1997

- 5-year outcome of a prospectively followed national **ELBW** infant coh ort in **Finland**, 172 children were assessed with neurocognitive test**.**



Mikkola et al. 2005

Neurodevelopmental outcome at 5 years of age of a national cohort of extremely low birth weight infants who were born in 1996-1997

- **cerebral palsy 14%**
  (19% of ELBW infants <27 GW)
- **cognitive impairment 9%.**
- **Attention, language, sensorimotor, visuospatial, and verbal memory values of NEPSY assessment were significantly poorer**
- **Hearing impairment 4%**
- **Visual impairment 30%**

Mikkola et al. 2005

Neurodevelopmental outcome at 5 years of age of a national cohort of extremely low birth weight infants who were born in 1996-1997

41 **(20%)** exhibited **majo**r disabilities,

38 **(19%)** exhibited **minor** disabilities,

124 **(61%)** showed development with no functional ab normalities but **subtle** departures from the norm.

26% (Only one fourth) of the ELBW normally devel oped at age 5.

- increased risk for learning difficulties that needs to be evaluated at a later age.
- Extended follow-up should be the rule in outcome st udies of ELBW infant cohorts to elucidate the impact of immaturity on school achievement and social beh avior later in life.

Mikkola et al. 2005

Rate of ELBW without any impairment is very low

- **NICHHD** neonatal research network
- 5250 ELBW born in 1998-2001
- At 18-22 months CA

40% died

16% no impairment (26% of survivor)
(BSID≥85, normal N/E, vision, hearing, walking)

22% mild impairment (BSID 70-84, mild)

22% moderate to severe impairment
(BSID<70,mod/severe CP, bilateral blindness or hearing impairment requiring amplification)

Gargus et al. Pediatrics 2009

Factors associated low Mortality & better ND outcome

- **Body weight**
- **Maternal factors**
  - age, marital status, private insurance
- **Infant factors**
  - female, singleton, SGA, white
- **Perinatal & delivery care**
  - antenatal steroid, C/S
- **Absence of major neonatal morbidities and interventions**

Gargus et al. Pediatrics 2009

Prediction of ND and sensory outcome at 5 yrs in Norwegian Children born extremely preterm

- 239 with 22-27wks GA, 500-999g BW born in 1999-2000 **, Norway**
- At 5yrs

Mean IQ 94

CP 11%

Risk of mod/severe disability

- **32**%(<25wks) vs **8**%(26-27wks)

Leversen et al. Pediatrics 2011

Neurodevelopmental disability through 11 yrs of age in children born before 26 weeks of gestation

- **EPICure group, At 11yrs**

	Classmates N = 153		Extremely Preterm N = 219	
	N	%	N	%
Cerebral palsy	0	**0**	39	**17.8**
Hearing loss	0	**0**	4	**1.6**
Impaired vision	0	**0**	19	**8.7**
No communication or sign language only	0	**0**	11	**5.0**
IQ > 2 SD below mean	2	**1.3**	90	**41.1**
Any severe or moderate disability	2	**1.3**	99	**45.2**

Johnson et al. Pediatrics 2009

Neurodevelopmental outcome after EP: a review of the literature

Mortality>50% in 22-25wks GA

Short-term f/u(at 18-22 or 30mo)

- ND disability **17-59**% among survivors
- Unimpaired or minimally impaired
  - 6-20% in ≤25wks GA vs ≤5% at 22-23wks GA

Long-term F/U(at 4-35yrs)

- **Intellectual disability 5-36%**
- **CP 9-20%**
- **Blindness 0.7-9%**
- **Deafness 0-4%**
- Milder degree of disability(cognition, behavior, learning) in older children, teens, young adults

Imad TJ. Pediatric neurology 2015

Short-term ND outcome after **EP**

	(%)
No NDI	9.8-30
NDI	17-59
CP	7-25
MDI<70 or PDI<70	8.9-51
Blindness	0-11
Deafness	0.9-4.3

Long-term ND outcome after **EP**

	(%)
No NDI	16-62
Mod/severe NDI	17-46
Mild NDI	19-42
CP	9.1-20
IQ<70	4.4-36
Blindness	0.7-9
Deafness	0-4

No NDI (1/4) Significant NDI (1/2) CP 15%

Very Preterm infant

Less at risk for NDI compared with EPI or ELBW, but significant numbers have NDI

ND disabilities and special care of 5-yr-old children born before 33 wks of GA

- French **EPIPAGE** study

  (The Etude Epidemiologique sur les Petits Ages Gestationnels)
- 2901 22-32wks GA in 1997 vs 667 control
- Only 12% <25wks, ELBW

- At 5yrs, 2357(70%) vs 396(60%)
  - N/E,
  - Kaufman assessment battery

    (Mental Processing Composite(MPC) score)

Larroque et al. Lancet 2008

ND disabilities and special care of 5-yr-old children born before 33 wks of GA

CP 9%

MPC score 70-84(OR 3.0), 55-69(OR 3.4)

Severe bilateral vision impairment 1%

(10% <26wks)

Special health care service

- 40%(24-28wks) vs 30%(29-32wks)

Larroque et al. Lancet 2008

Australian cohort of VP(≤32wks)

- born 2003-2006
- **Bayley MDI & PDI** at 1yr old

	<85	<70
PDI	**27%**	**8%**
MDI	**18%**	**3%**

Kiechl-Kohlendorfer U et al. Acta paediatr 2009

Meta-analysis in VP(≤33wks) and/or VLBWI 1

Literature 1998-2009

- more behavioral problems(inattention)
- Poorer executive function(verbal fluency, working memory, cognitive flexibility)
- Lower test scores in math, reading, spelling
- Poor outcomes –lower BW, GA
- Persisted through adulthood

Aarnoudse-Moens et al. Pediatrics 2009

Meta-analysis in VP(≤33wks) and/or VLBWI 2

Literature 1992-2009

- greater motor impairment from infancy to 15yrs
- Poorer motor development at 1yr
  - lower GA, BW
  - persist though adolescence

-> affect balance skills, ball skills, manual dexterity, fine & gross motor development

de Kieviet et al. JAMA 2009

Functional Outcomes and Participation in Young Adulthood for VPI and VLBWI

Dutch 705 of 959 survivors born in 1983

- Born before the use of antenatal corticosteroids and surfactant
- at19yrs

- **Mod/severe disability 12.6%**

  Neuromotor disablity 8.1%
  Cognitive impairment 4%
  Visual 1.9%
  Hearing 1.8%

- **Poorly educated (x 2)**
- **Not employed (x 3)**

Elysee et al. Pediatrics 2007

Long-term ND outcome after VP

	VP	EP
Mod/severe NDI	13	17-46
CP	5-14	9.1-20
IQ<70	3-8	4.4-36
Blindness	1-5	0.7-9
Deafness	1-5	0-4

Less at risk for NDI compared with EPI or ELBW, but significant numbers have NDI

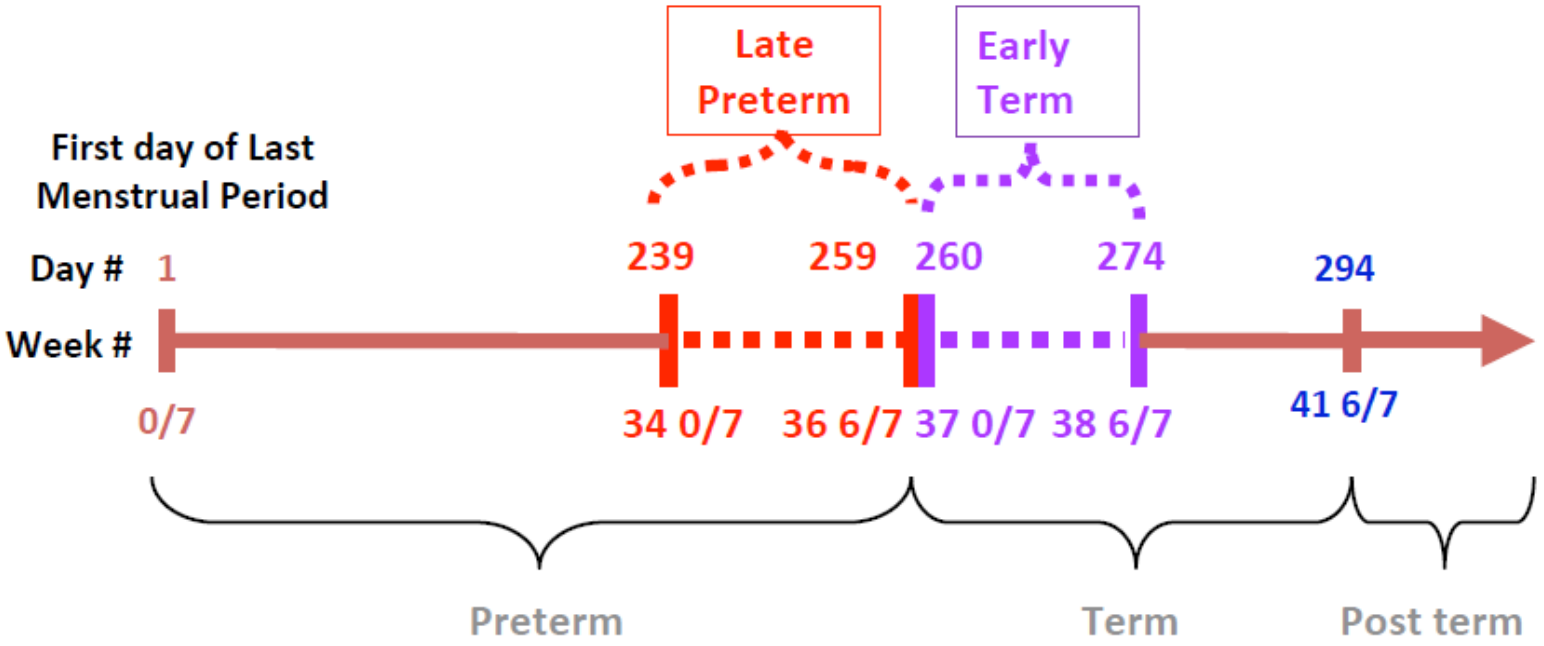
Late Preterm Infant

instead of

Near Term infant

Poorer ND outcomes compared with term infant

"Late Preterm" and "Early Term" Definitions



* "completed" weeks' gestation = # 7-day intervals from 1st day of LMP. Ex: 34 completed weeks is 34wk 0/7 days and 34wk 1/7 days is the first day of the 35th week of gestation.

Kominiarek M, Engle W. Clin Perinatol, 2008

Percent Distribution of Births by Gestational Age: United States, 1990 and 2004

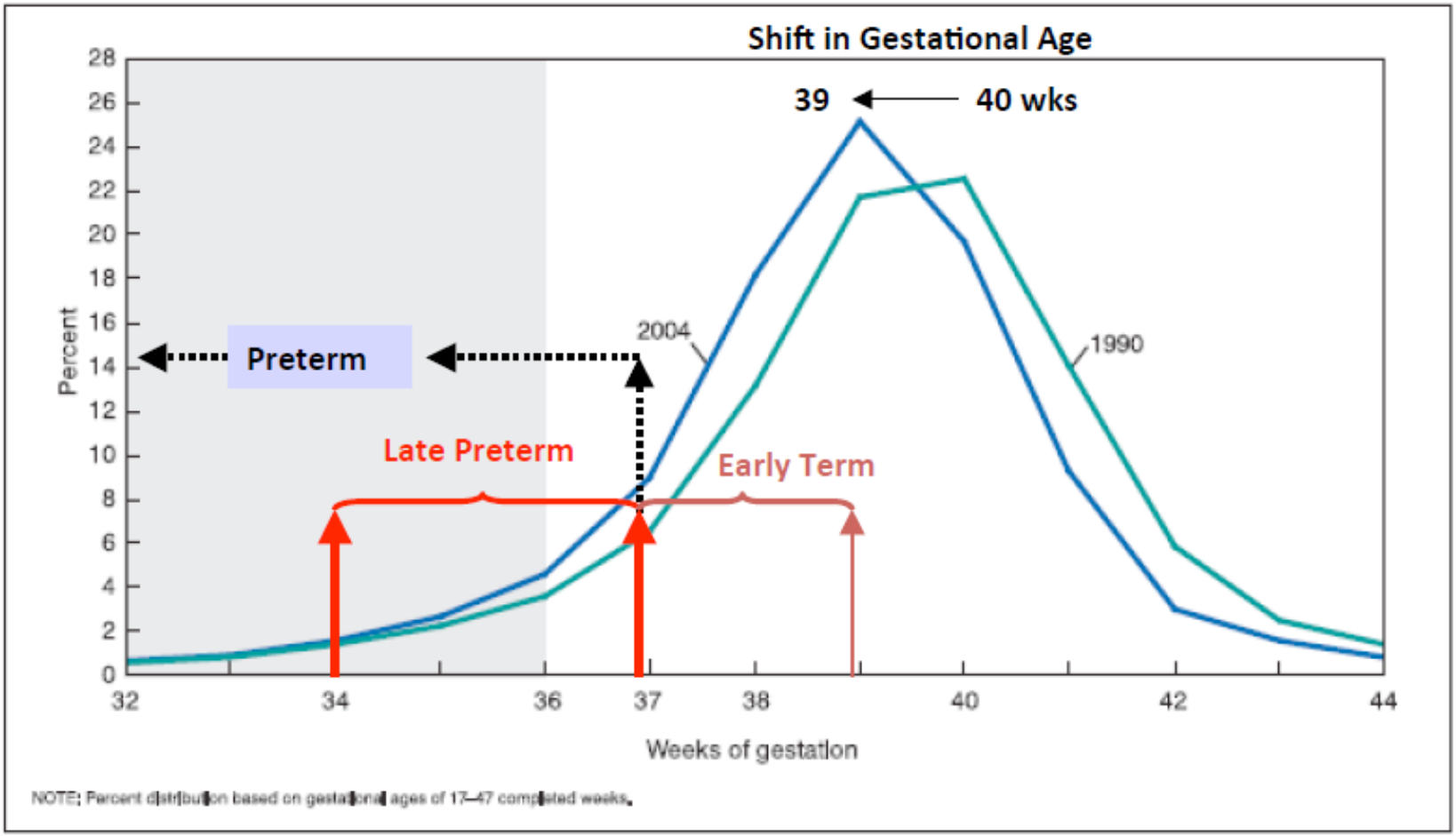


Figure 12. Percent distribution of births by gestational age (32–44 weeks): United States, 1990 and 2004

CDC, NCHS final Natality Data 2004

Increase in CP with decreasing BW and GA

- consistent, not limited to ELBW infants

Marret et al. (2007)

-Increase in CP with each preterm week

-0.7%, 3.7% 4.1%, 8.7% 6.3% in 34,33,32,31,30wks, respectively($p<0.01$)

Himmelmann K et al.(2005)

- 7/1000 vs 1.1/1000 in 32-36wks vs term baby

Medical Outcomes in 20 to 36 Year Old Norwegian People By Gestational Age

	Gestational Age (%)					
	23-27 N=362	28-30 N=1 686	31-33 N=6 591	34-36 N=32 187	≥37 N= 853 309	Relative Risk 95% CI 34-36 vs ≥37
Cerebral Palsy	9.1	6.0	1.9	0.3	0.1	2.7(2.2-3.3)
Mental Retardation	4.4	1.8	1.0	0.7	0.4	1.6 (1.4-1.8)
Schizophrenia	0.6	0.1	0.2	0.2	0.1	1.3 (1.0-1.7)
Disorders of psychological development, behavior, and emotion	2.5	0.7	0.3	0.3	0.2	1.5 (1.2-1.8)
Other major disabilities	4.1	2.2	0.5	0.3	0.2	1.5 (1.2-1.8)
Any disability affecting working capacity	10.6	8.2	4.2	2.4	1.7	1.4 (1.3-1.5)

Moster D et al. NEJM.2008

Social Outcomes in 23 to 29 Year Old Swedish People By Gestational Age

	Gestational Age (%)					
	24-28 N=317	29-32 N=2630	33-36 N=19 166	37-38 N=68 541	39-41 N= 431 656	P value
Post secondary education	26	34	36	38	40	.001
Employed in 2002	68	70	73	73	74	.001
Social welfare in 2002	5.0	3.0	2.8	2.2	1.8	.001
Lives with parents	18	18	17	17	15	.001
Disability (sickness pension, disability allowance, disability assistance)	13.2	5.6	2.7*	1.9*	1.5	.001

* Attributable risk for disability: 74% of all disability is associated with birth at 33-38 weeks' gestation due to large N (vs high incidence in more preterm infants). n=522,310, 23-29 years old

Lindstrom K et al. Pediatrics 2007;120:70-77,

Functioning at school age of moderately preterm children born at 32-36wks GA

Retrospective Dutch study of 377 (32-36wks) at 8 yrs of age

	Late preterm	control
Special education	**7.7**	**2.8**
Repetition of a grade in mainstream school	**19**	**8**
IQ	**105**	**108**

- **More behavioral problems & ADHD**

Van Baar et al. Pediatrics 2009

"Late preterm" infants : a population at risk

American academy of pediatrics (AAP) committee on Fetus and New-born

- guidelines for evaluating and managing late preterm infants born at 34-36+6wks gestation.

Behavioral
&
Psychological problems

Behavioral and psychological effects

ELBW& VLBW compared with NBW
- specific behavioral & psychological problems

- ADHD
- General anxiety
- Depression
- Poor social interaction with peers
- Premature adolescent and young adult survivors - less-risky behavior, shyer

Pervasive behavior problems at 6 yrs of age in a total-population sample of children born≤25wks of GA

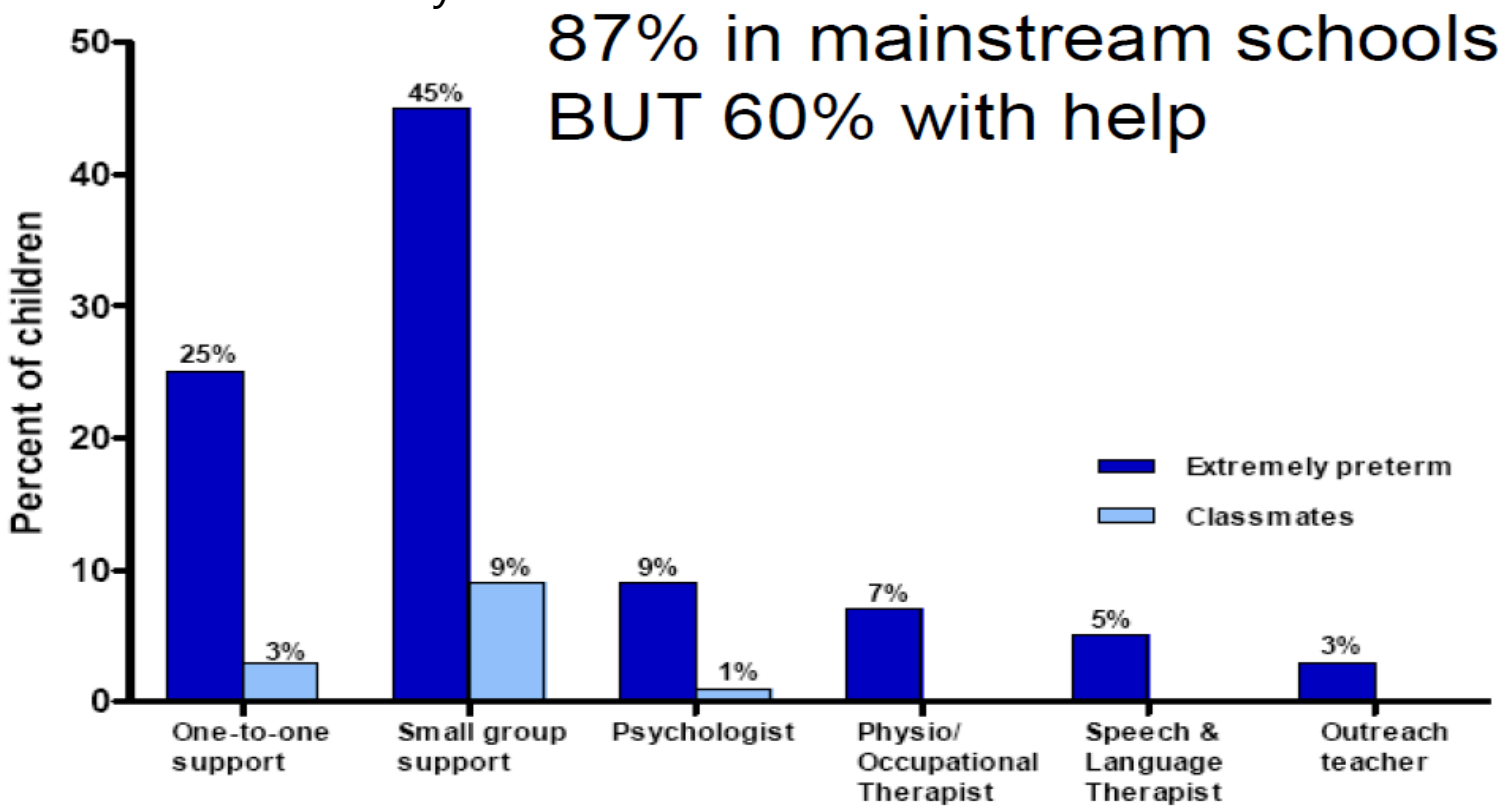
- **EPICure** study
- GA ≤25wks, more behavioral problems **at 6 yrs** compared with term by reports from parents and teachers

(%)	EP	Term
Attention	33	7
Peer interaction	25	5
Hyperactivity	30	9
Emotional problems	14	4
Conduct problems	13	5

Samara M et al. Pediatrics 2008

Academic attainment ad special educational needs in extremely preterm children at 11yrs of age

EPICure at 11yrs



- **Survivor in mainstream school**

-10-fold greater use of special education resources

Johnson et al. ADCFNE 2009

Mental health and social competencies of 10- to 12-yr old children born at 23-25wks of GA in the 1990s

Swedish prospective report of 86 born at **GA<26wks** by parent and teacher **at 11yrs**

- 85% functioning in mainstream schools without major adjustment disorder

- ELBW compared with full term children

- Internalizing behavior(anxiety, depression, withdrawn, somatic complaint)
- Attention deficit
- less well adjusted at school

Farooqi A et al. Pediatrics 2007

ELBW at risk for Autistic Spectrum Disorders

- **M-CHAT** (Modified check list for Autism in Toddlers)
  - 21% of <28wks GA survivors screened positive for autism **at 24mo (Kuban KC et al. 2009)**
  - 25% of 23-30wks GA (**Limperopoulos C et al.2008)**

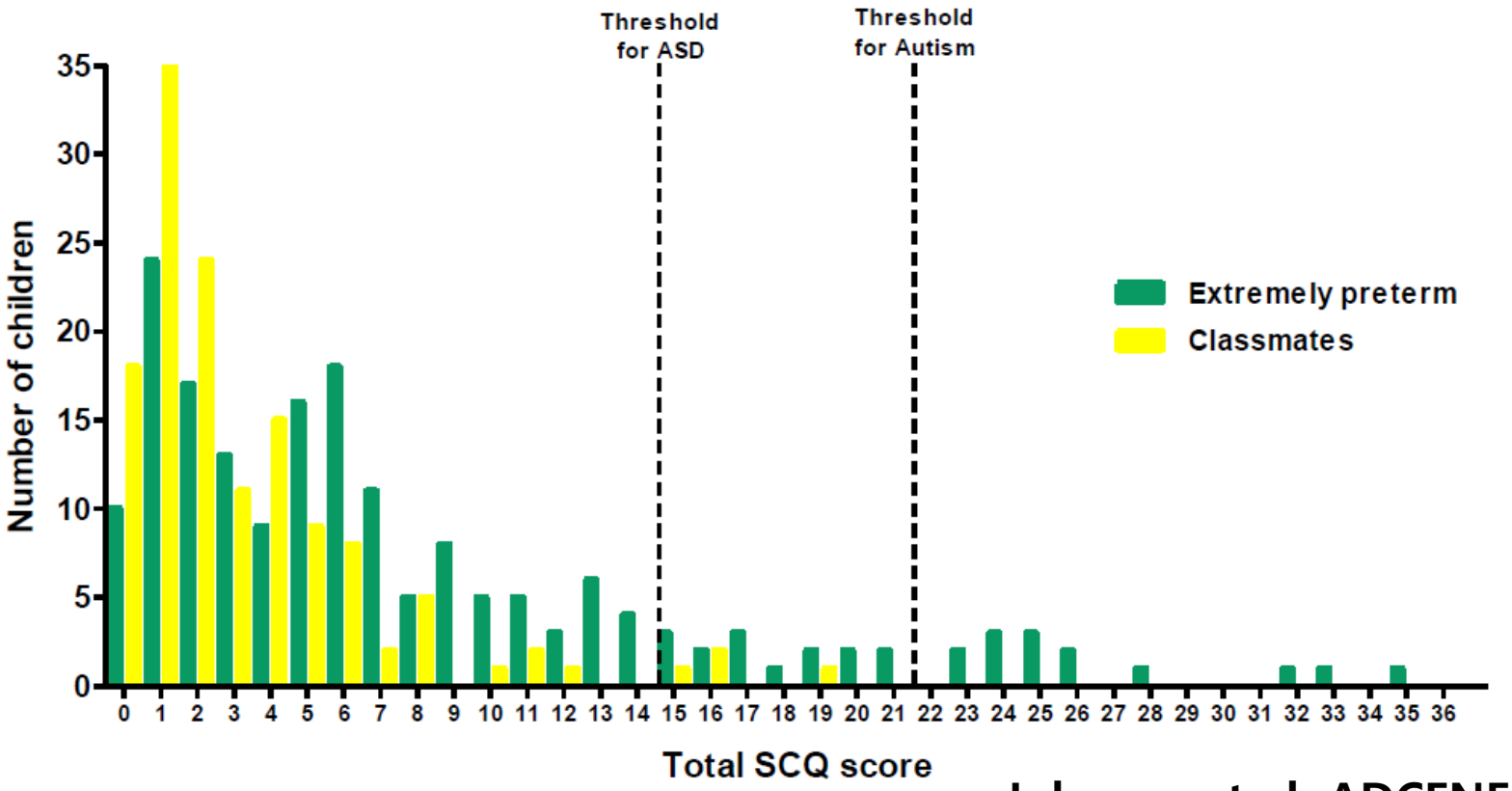
  : caution in interpretation d/t
  low specificity in children with high NDI

- 219 **ELBW** born 1992-1995, **at 8 yrs**, compared with children born at term
  - more hyperactivity, anxiety,
    Sx associated with Asperger syndrome and autism

Hack M et al. Pediatrics 2009

ELBW at risk for **Autistic Spectrum Disorders**

EPICure at 11yrs, 16 of 219 surviors (**7%**)



Johnson et al. ADCFNE 2009

VLBW at risk for Behavioral and psychological problems

EPIPAGE study(<33wks GA)

- 1102 **LBW** survivors **at 5yrs** old have more behavioral problems compared with term (OR 1.8)
- hyperactivity, conduct problems, emotional Sx, problems with peer

Delobel-Ayoub M et al. Pediatrics 2009

242 **VLBW** born 1977-1979 compared with NBW

- Male –fewer delinquent behavior,
  more frequent thought problems
- Female- fewer delinquent behavior,
  more withdrawn and internalizing behavior, anxiety, depression, withdrawal, attention problems

Hack M et al. Pediatrics 2004

VPT at risk for Behavioral and psychological problems

- **UK** study, 108 born **VPT(<33wks)**

67 controls at term 1979-1981 , At 18-19yrs

More introverted and anxious, moody, depressed, lower self-esteem

Allin M et al. Pediatrics 2006

- **VPT<32wks GA or <1500g(OR 2.84)**

Greater in boys(OR 3.85)

28 NICU graduates diagnosed as ASD

– asymmetric visual tracking and arm tone deficits at 1 month

Karmel VZ et al. 2010

- Population based Swedish study
  - 5.2% in 24-28wks GA (HR 1.68)
  - 3.5% in 29-39wks GA (HR 1.21)

Lindstrom K et al. Pediatrics 2009

Adult outcome

Young adult attainments of preterm infants

Cleveland, Ohio
219 ELBW survivors born in 1992-1995 vs 176 NBW controls

(%)	ELBW	control
Poor motor skills	47	10
Cerebral palsy	14	0
Intellectual quotient<85	38	14
Visual impairment	10	3
Limited academic skills	37	15

Hack et al. JAMA 2006

Long-term medical and social consequence of preterm birth

- Norway study, born in 1967-1983 f/u though 2003

(%)	23-27wks	Term(≥37wks)
Medical disability	**10.6**	1.7
CP	**9.1**	0.1
Intellectual disability	**4.4**	0.4
Other major disability (blindness, hearing loss, epilepsy)	**4.1**	0.2
schizophrenia	**0.6**	0.1
Autism spectrum disorder	**0.6**	0.1
Other psychological, behavioral, emotional ds	**2.5**	0.2

Moster D et al. NEJM.2008

OUTCOMES IN YOUNG ADULTHOOD FOR VERY-LOW-BIRTH-WEIGHT INFANTS

MAUREEN HACK, M.B., CH.B., DANIEL J. FLANNERY, PH.D., MARK SCHLUCHTER, PH.D., LYDIA CARTAR, M.A., ELAINE BORAWSKI, PH.D., AND NANCY KLEIN, PH.D.

242 **VLBW**(<1500g, 1977-1979) vs 233 controls
Evaluation at **20yrs**

TABLE 2. CHRONIC CONDITIONS AT 20 YEARS OF AGE AMONG VERY-LOW-BIRTH-WEIGHT AND NORMAL-BIRTH-WEIGHT PARTICIPANTS.*

- **Neurosensory impairment 10% vs <1%**
  - **CP 6%, hydrocephalus 2%, blind 2%, epilepsy 2%**
- **Fewer graduated high school(74% vs 83%)**
- **VLBW men –less likely to be studying**
- **lower mean IQ 87 vs 92**
- **Shorter height(<-3SD) 10% vs 5%**

Other††	0	0	1 (1)	2 (2)
Height <3rd percentile‡‡	9 (8)	5 (5)	14 (11)	6 (5)
Total with at least one condition	36 (31)	23 (21)	45 (36)	25 (20)§§

NEJM.2002

Preterm birth, social disadvantage, and cognitive competence in Swedish 18- to 19- yr-old men

- Lower rate of educational achievement, independent living, lower net income, permanent employment in premature survivors compared with full term
  - d/t poor cognitive skills leading to impaired learning, especially in adults with BW<1500 or <32wks GA

- Higher socioeconomic status –decrease the effect of GA upon cognitive test score

Ekeus C et al. pediatrics 2008

Preterm survivors may overcome NDD

- Longitudinal **Canadian** study of 166 ELBW born 1977-1982 compared with 145 matched controls with NBW
- At **23yrs**

	ELBW	NBW
Neurosensory impairment	27	2
High school graduation	82	87
Pursuing postsecondary education	32	33
Employment	48	57
Independent living	42	53
Married or cohabiting	23	25
parents	11	14

Saigal S et al. JAMA 2008

Preterm survivors may overcome neurodevelopmental disability

- In UK study, no difference btw VPT in school achievement, enrollment in postsecondary education, employment rate, more educational assistance than control

Allin M et al. Pediatrics 2006

- In New Zealand study (31 yr long-term)

  no differences btw 126 adults born in mean 34wks GA(mod preterm) and full term in marital status, educational attainment, socioeconomic status, cognitive function, working memory, attention or psychological changes

Dalziel SR et al. DMCN 2007

Trends over time

Trends over time

Neonatal care has changed over time, resulting in **improved survival**, and possibly **improved neurodevelopmental outcomes**

- **Antenatal glucocorticoids**
- **Surfactant**
- **Breast milk**
- the **decreased** use of **Postnatal Glucocorticoid therapy**

ND outcomes of ELBW infant<32wks GA,1993-1998

NICHHD Neonatal Research Network
3785 ELBW(BW 401-1000g, GA 22-32wks)
During 3 period
: 1993-1994, 1995-1996, 1997-1998
At 18-22 mo

- **Improved Survival & ND outcomes**
- Decreased risk of blindness, lower scores on cognitive and psychomotor testing (PDI/MDI<70)

Vohr BR et al. Pediatrics 2005

Improved Neurodevelopmental Outcomes for Extremely Low Birth Weight Infants in 2000–2002

Deanne Wilson-Costello, MD, Harriet Friedman, MA, Nori Minich, MA, Bonnie Siner, RN, Gerry Taylor, PhD, Mark Schluchter, PhD,

- 1478 ELBW(500-999g BW)

Period I (1982-1989)

enhanced assisted ventilation

Period II (1990-1999)

introduction of surfactant & antenatal and postnatal steroid tx

Period III (2000-2002)

routine antenatal steroid tx with decreased postnatal steroid use,

sepsis prevention initiatives

Peadiatrics. 2007

Improved Neurodevelopmental Outcomes for Extremely Low Birth Weight Infants in 2000–2002

Deanne Wilson-Costello, MD, Harriet Friedman, MA, Nori Minich, MA, Bonnie Siner, RN, Gerry Taylor, PhD, Mark Schluchter, PhD,

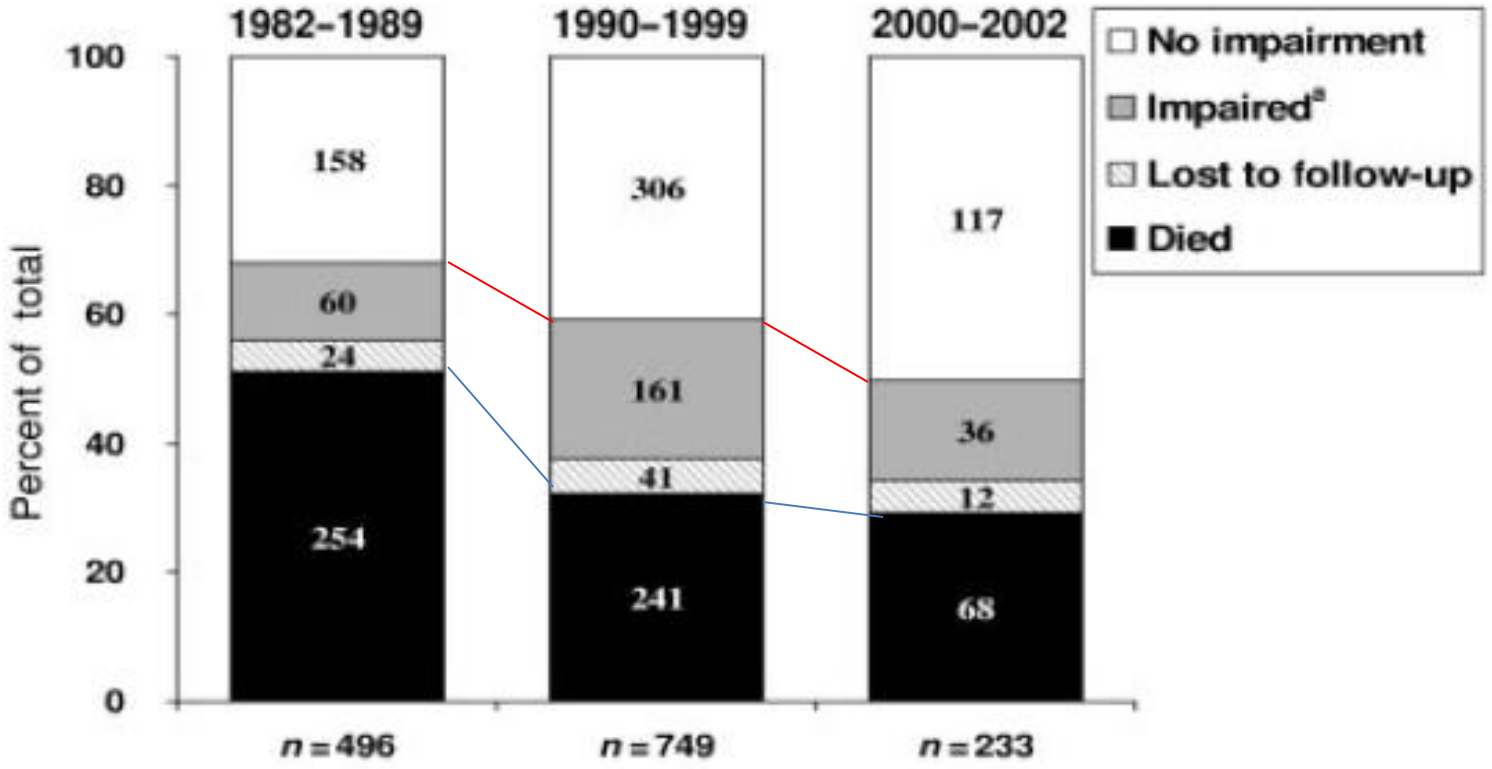


FIGURE 1

Comparison of death and survival with and without neurodevelopmental impairment at 20 months' CA for 500- to 999- g birth weight infants born during 3 periods: 1982–1989; 1990–1999, and 2000–2002. [a] Neurosensory abnormality and/or MDI <70.

Peadiatrics. 2007

Improved Neurodevelopmental Outcomes for Extremely Low Birth Weight Infants in 2000–2002

Deanne Wilson-Costello, MD, Harriet Friedman, MA, Nori Minich, MA, Bonnie Siner, RN, Gerry Taylor, PhD, Mark Schluchter, PhD,

	Period I	Period II	Period III
Survival rate	49	68	71
Neurosensory abnormalities	18	23	9
CP	8	13	5
Blindness	5	1	1
Deafness	3	6	1
MDI<70	20	24	21
PDI<70	15	22	15

Outcomes at age 2 yrs of infants<28wks GA born in Victoria in 2005

Victorian infant collaborative study group

Compared with cohorts born in 1990s.

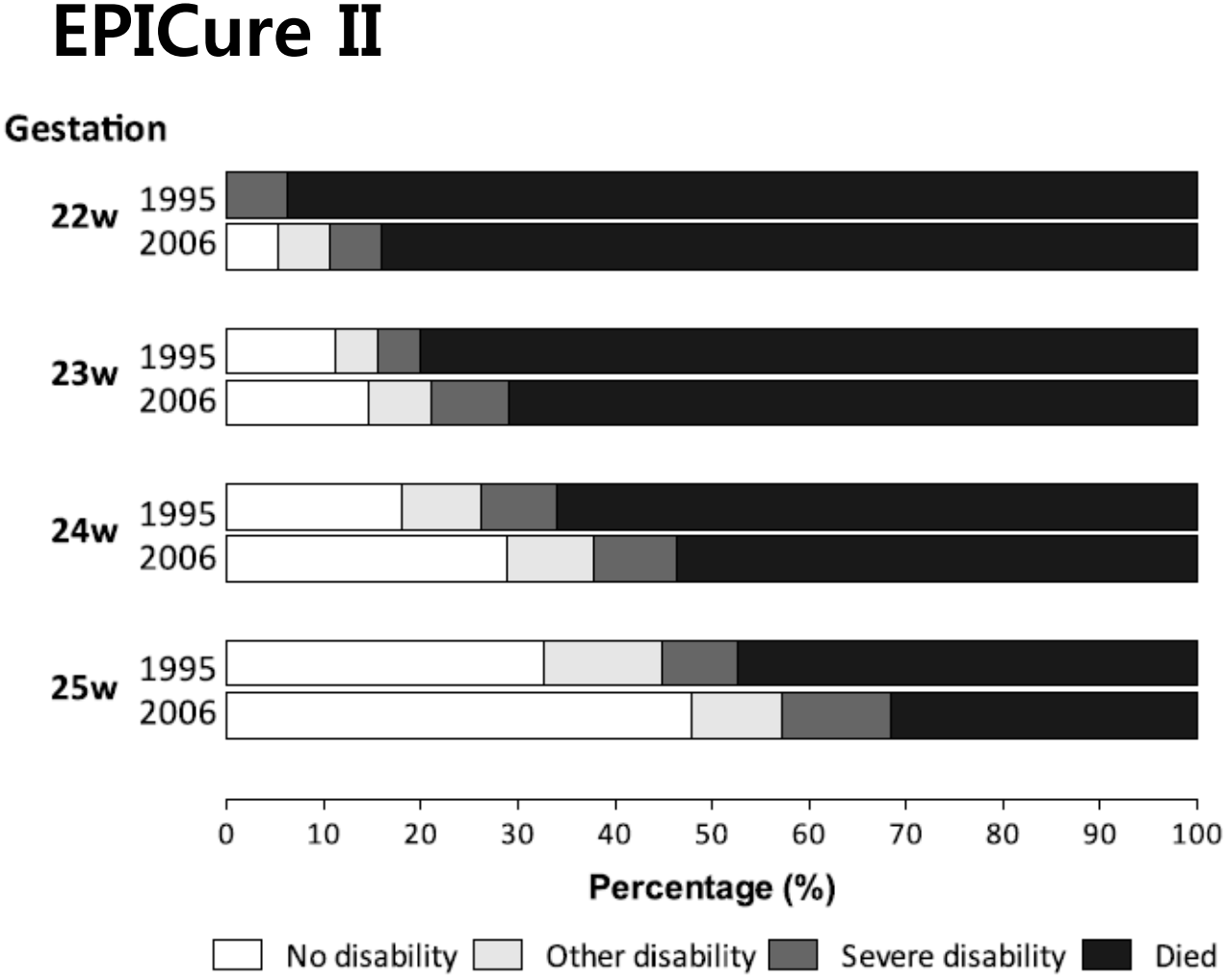
At 2 yrs

- Severe developmental delay 3.7 vs 14.8%
- Severe disability 3.7 vs 15.4%
- Survival rates 64 vs 70% (not different)

Doyle LW et al. J Pediatrics. 2010

Changes in outcome for babies <26w in England 30 – 36m

EPICure II



Gestation	Change between 1995 and 2006 Severe disability OR (95%CI):	No disability OR (95%CI):
22w	-	-
23w	1·9 (·67 to 5·2)	1·4 (·68 to 2·7)
24w	1·2 (·68 to 2·1)	1·8 (1·2 to 2·7)
25w	1·4 (·87 to 2·4)	1·9 (1·4 to 2·6)

T Moore et al BMJ 2012

Increased survival but sustained ND outcomes in Infant<25wks and/or BW<800g

- NICHHD<25wks –no difference in mortality, rate of CP, NDI, MDI<70 comparing (2002-2004) with (1999-2000)

  Hintz SR et al. Pediatrics. 2011

- In ELBW<800g, no change in NDI, improved survival, increased cognitive and hearing impairment, decreased visual impairment, lower CP over 20 yrs period(1983 vs 2003)

  Synnes AR et al. J Pediatrics. 2010

- BW≤750g in Netherlands- increased survival, risk of NDI(2001-2005) than (1996-2000)

  Claas et al. ADCFNE 2011

Q> direct effect of intervention (postnatal corticosteroid) or indirect makers for severity of illness(prolonged ventilation)?

Predictors of Neurodevelopmental Outcome

Prediction of ND outcomes

- **Radiologic evaluation**
  - Ultrasound(US)
  - Conventional MRI
  - Diffusion tensor MRI(DTI)

- **Neonatal illness**
  - chronic lung disease
    /bronchopulmonary dysplasia
  - necrotizing enterocolitis

Neuroimaging

MRI & US

– high predictive value of severe NDD, CP of 24mos

- Good specificity, poor sensitivity

: Negative US or MRI- not always good outcomes

- **Cystic PVL** – strong predictor for CP
- **Ventriculomegaly,**
  - mod/severe psychomotor delay(x4), mental delay(x3)

Cranial Ultrasound

- Bedside tool in sickest preterm infants
- Reliably detect GM and IVH, PVL
- Not as sensitive as MRI in diffuse white matter abnormalities or Cbll lesion
- EP infants with normal US at term
  -unlikely mod/severe WM or GM on MRI

Intraparenchymal hrr on US

- strong predictor, not diagnostic
- 28-30% with hrr below 1000g
  have no impairment at 18-22mo
- 39% with normal US have ND impairment

Periventricular/Intraventricular Hemorrhage and Neurodevelopmental Outcomes: A Meta-analysis

Amit Mukerji, MD[a], Vibhuti Shah, MD[b], Prakesh S. Shah, MD[b]

- **PIVH**
  - 25-30% in VLBW(<1500g)
  - 45% in ELBW(<1000g)

- **Papile classification**
  - Mild(1&2) vs Severe(3&4)

- **Primary & Secondary** (among survivors) **outcome**
  - death or mod to severe NDI at 18-24months (CP, cognitive delay, visual impairment, hearing impairment)

Mukerji et al. 2015

Periventricular/Intraventricular Hemorrhage and Neurodevelopmental Outcomes: A Meta-analysis

Amit Mukerji, MD[a], Vibhuti Shah, MD[b], Prakesh S. Shah, MD[b]

Both mild & severe PIVH –adverse long-term outcomes

- **Severe PIVH-** worse long- term ND outcomes (aOR 3.43)
- **Mild PIVH**

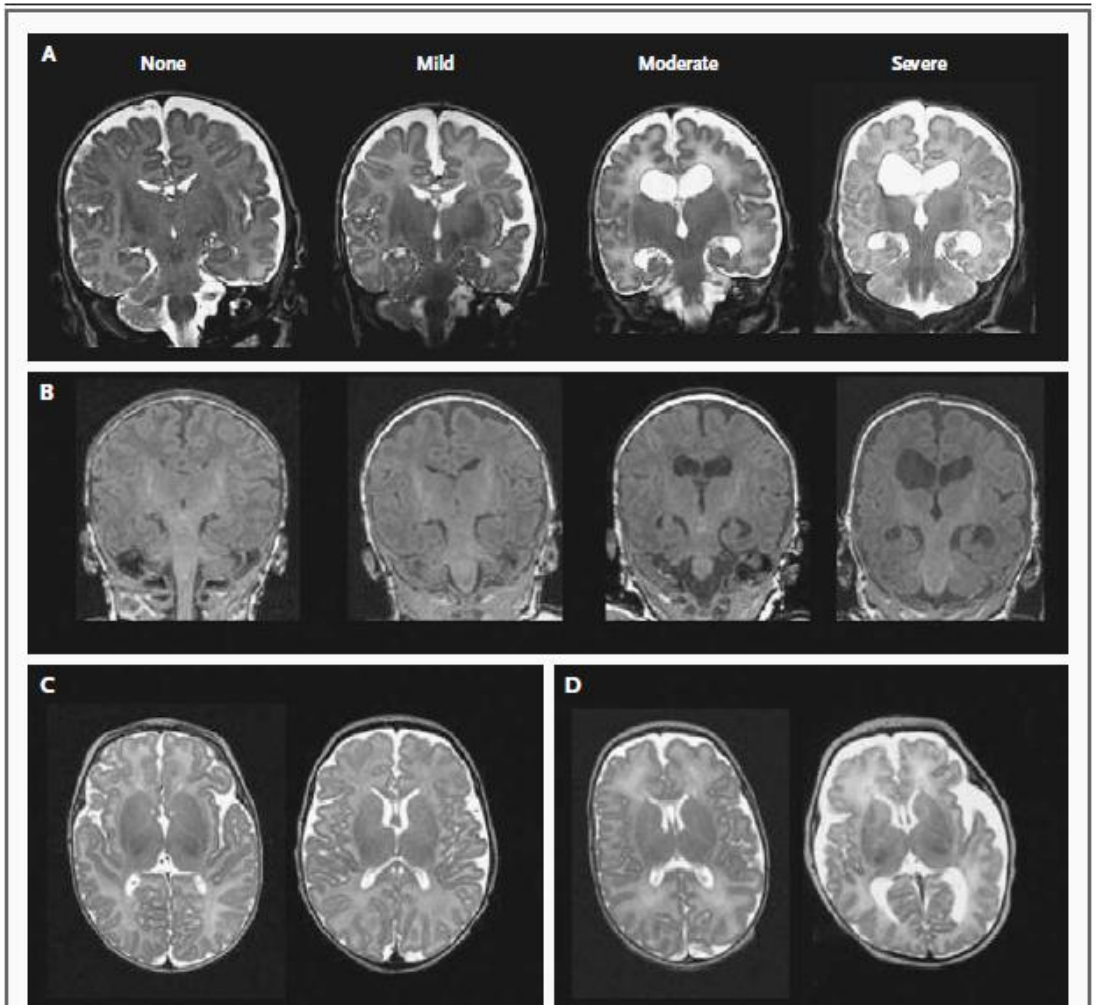
- higher odds of death or mod-severe NDI, may not benign ds need for closer surveillance for NDI, interventions, f/u
- d/t Reduced cortical volumes at term, possible combined parenchymal lesions undetected by US

- No significant OR in Cognitive delay

-Consider poor correlation of BSID score btw 18-24mo & school age **(Hack et al.2005)**

Mukerji et al. 2015

Neonatal MRI to Predict Neurodevelopmental Outcomes in Preterm Infants



Woodward LJ et al. NEJM 2007

Neonatal MRI to Predict Neurodevelopmental Outcomes in Preterm Infants

(OR)	Severe cognitive delay	Severe motor delay	Cerebral palsy	Neurosensory impairment
Mod/severe WMI	3.5	10.3	9.6	4.2
GM abnormality	3	3.8	3.8	2.5
Cystic PVL	2.6	19.5	19.9	4.0
IVH(Gr3or4)	4.6	2.7	2.7	4.4
Postnatal corticosteroid use	3.2	6.2	10.0	4.2

Abnormal findings on MRI & US
- equivalent in VP strongly predict adverse ND outcomes at 2 yrs of age.

Predictors of neurodevelopmental outcome for preterm infants with brain injury: MRI, medical and environmental factors

Lina Kurdahi Badr[a,*], Susan Bookheimer[b], Isabell Purdy[c], and Mary Deeb[d]

- **Best predictors for NDI in** 59 preterm
- **Head circumference, N/E, MRI results**

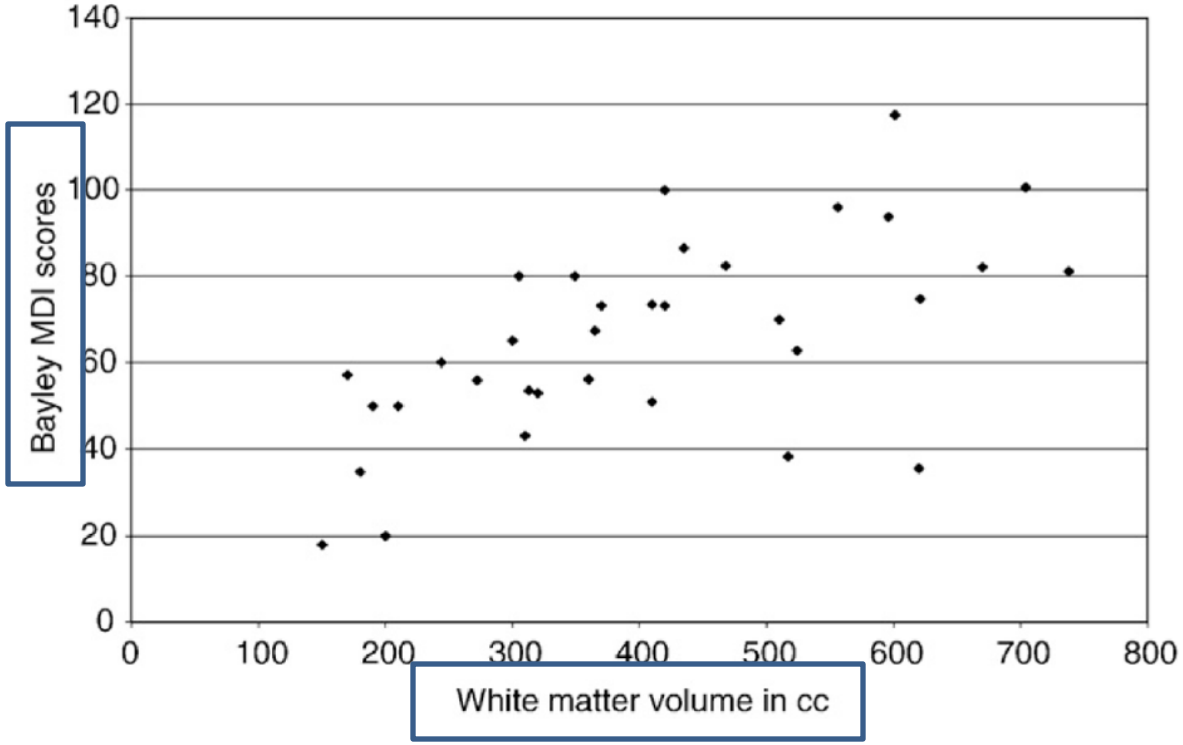


Fig. 2.
White matter total volume (cm^3) and MDI scores at 18 months (N=33).

Quantitative MRI

- Diminished volumes of **caudate** and **hippocampu**s – lower IQ, learning disorder, attention deficit disorder

  Abernethy et al 2003,2004

- Quantitative abnormalities –related to immaturity at birth

  Inder et al.1999

- Preterm assessed at term –reduced myelination

  Inder et al. 1999,2005

Brain MRI Measurements at a Term-Equivalent Age and Their Relationship to Neurodevelopmental Outcomes

H.W. Park, H.-K. Yoon, S.B. Han, B.S. Lee, I.Y. Sung, K.S. Kim, and E.A. Kim

90 preterm

(mean GA 27wks, BW 805.5g)

At 2yrs assessed by Bayley II

- **Short Corpus callosum**
  - MDI<70, high risk CP,
- **Small transcerebellar diameter**
  - PDI<70, MDI<70, major neurologic disabilitiy

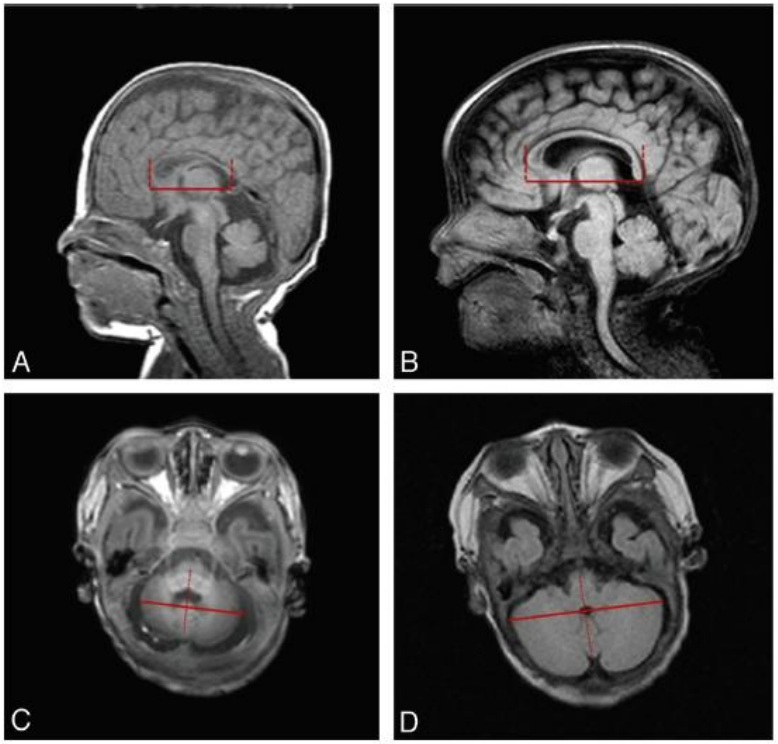


FIG 1. Linear measurements of anteroposterior length of corpus callosum (*A* and *B*) and transcerebellar diameter (*C* and *D*) and intraclass correlation coefficients (ICCs) for interobserver and intraobserver reliability. *A*, Short anteroposterior length of corpus callosum (34.1 mm); *B*, longer anteroposterior length of corpus callosum (44.4 mm); *C*, short transcerebellar diameter (36.2 mm); *D*, longer transcerebellar diameter (58.4 mm).

Diffuse excessive high signal intensity (DEHSI)

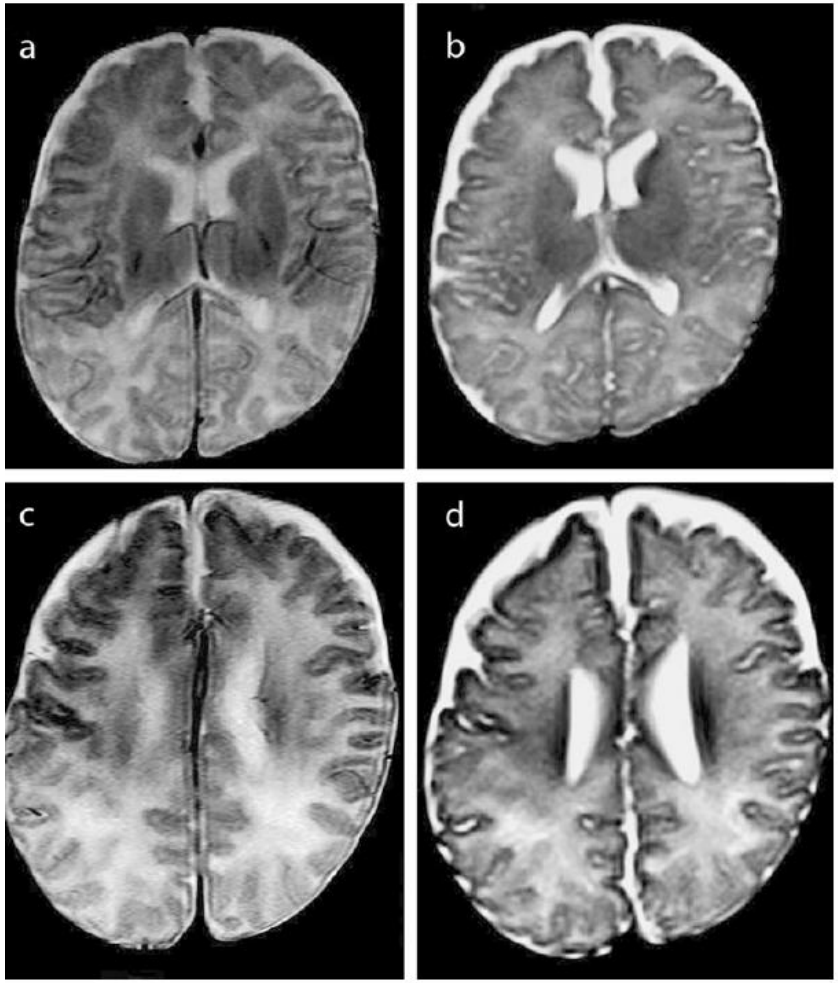
- not associated with BSID-III or with CP

  De Bruine FT et al. 2011

- Lack of correlation btw DEHSI & outcomes

  Skiold B et al. 2012

->maybe Prematurity-related developmental phenomenon



Diffusion Tensor Imaging

- 24 infant with bw below 1500g
- 37wks

- Low fractional aniostropy values in the **posterior limbs of the internal capsule**

  ->Diagnosis of CP,

  severity of gait problems at 4yrs

Rose J et al. 2007

Perinatal conditions

Conditions associated with an increase risk of poor ND outcome

- Bronchopulmonary dysplasia(BPD)
- Necrotizing enterocolitis(NEC)
- Retinopathy of prematurity(ROP)
- Postnatal use of glucocorticoids to treat BPD – increased risk of **CP**
- Intraventricular hemorrhage
- Poor growth
- Congenital anomalies
- Twin gestation

Neonatal illness

- **Chronic lung ds/bronchopulmonary dysplasia**

- Risk factor for

  CP and cognitive impairment & Language delay, visual motor impairment, low av intelligence, academic difficulties, attention and behavior problems, memory deficits and executive dysfunction

Anderson & Doyle(2006)

- **Necrotizing enterocolitis**, especially with surgical intervention

- increase risk for CP, cognitive and visual impairment

Rees CM et al (2007)

Poor growth

- In **VPT**, growth impairment
  – impair cognitive and motor performance at 7 yrs of age

Cooke RW et al. ADC 2003

- **NICHHD** Neonatal Research Network
  - increasing wt gain during NICU
  -> decreasing CP, MDI and PDI<70, abnormal N/E, ND impairment, need for rehospitalization at 18-22mo

Ehrenkranz RA et al. pediatrics 2006

NICU care

- **Hypotension**

  - unclear Tx effect of Inotropes or hydrocortisone

- **Neurodevelopmental disability**

  -lower(caffeine tx for apnea)

  -unchanged(method of ventilation, methods of ventilation, positive airway pressure or lucinactant surfactant)

  -higher (adverse effect of inhaled NO, postnatal corticosteroid)

- Newborn individualized developmental care and assessment program(**NIDCAP**)

Better outcomes in Extreme Prematurity

- **Perinatal factors**
- maternal white ethnicity
- higher level of education
- private insurance
- being married

- **Infant-related factors**
- female
- higher BW or GA,
- lager head size
- white ethnicity
- absence of neonatal morbidities and interventions

Gargus RA et al. pediatrics. 2009

Predicting neurodevelopmental outcomes at preschool aged for children with VLBW

- 126 Taiwanese 5-yr-olds

- **4 factors to predict ND outcomes in VLBW**
- medical complications at birth
- maternal education
- early motor assessments
- early cognitive assessment

- 40-70% of preterm infants : cognitive delay, mild motor problems, lower adaptive behavior
- Tend to have lower adaptive behavior at 5 yrs old
  -reflection of a child's overall integrated abilities

Howe et al. Res Dev disabil.

Neurodevelopmental outcome in ELBW infants : what is the minimum age for reliable developmental prognosis?

German 129 BW <1000g , At 6-10yrs

17% major impairment
42% minor impairment
41% normal

- Proportion of assessments that concurred with 6-10yrs outcomes

- **49%, 59%, 68%, 70%, 70%**
  at term, 1,2,3,4yrs

-> **Importance of long –term f/U**
But, CP – accurately identified by 2 yrs old

Voss W et al. Acta paediatr 2007

Clinical neurodevelopmental assessments

- Clinical risk index for babies score(CRIB-II)
- Early Motor Pattern Profile
- Griffith Scales
- Bayley Scales of Infant Development-II & III
- Cognitive Adaptive Test/Clinical Linguistic and Auditory Milestone Scale
- Gestalt evaluation
- Alberta Infant Motor Scale(AIMS)
- Neurosensory Motor Development assessment(NSMDA)
- Prechtl general movement assessment(GMs)

A systematic review of the clinimetric properties of neuromotor assessments for preterm infants during the first year of life

	Validity	Predicting abnormality	Before Term	Early Month	Later Month
AIMS	O				O
NSMDA		O			O
TIMP	O	O	O		
GMs			O	O	

AIMS(Alberta Infant Motor scale) –best psychometric properties & clinical utility
NSMDA(Neuro Sensory Motor Development Assessment)
TIMP(Test of Infant Motor Performance)-Predicting abnormal motor development
GMs(Prechtl's Assessment of General movements)
- best combination of sensitivity & specificity for predicting CP in early mo.
AIMS or NSMDA- best predictors of atypical motor development in later months
TIMP- only tool with adequate validity, reliability along with AIMS

Spittle et al.DMCN 2008

Bayley-III compared with II

- Underestimation of DD by new Bayley III scale.

  Anderson PJ et al. APAM 2010

- Measuring outcomes after EP with the Bayley-III scales of infant and toddler development: a cautionary tale from Australia.

  Msall ME. APAM 2010

- Bayley III cognitive& language scores<85 =MDI<70

  Johnson et al. 2014

Assessment

- **Comprehensive P/E including N/E** to detect motor deficits and CP

  poor postnatal head growth is associated with poor ND outcome and CP
- **Bayley mental developmental indexes** in infants and toddlers is best available tool for cognitive function, despite poor correlation with cognitive testing at school age
- In older children, **IQ, academic achievement, neurophysiologic evaluation**

Interventions

- Early interventions for
  Cognitive function & Cerebral palsy
- Pharmacological interventions
- Nutrition
- The endocrine milieu(steroid, thyroxine)

Summary 1

- Risk for impaired ND outcome(cognitive, motor, visual & hearing loss) increased with shorter GA & lighter BW
- Specific psychological and behavioral problems(ADHD, anxiety, depression)
- VLBW

  –greater risk for poor academic performance
- May overcome NDD & get high QOL

Summary 2

- Neonatal complication(BPD, NEC,ROP, IVH, poor growth, congenital anomaly) are associated with NDD
- Changing Neonatal care
  - improving survival & ND outcome
- Recommendation for screening, evaluation, referral for hearing and vision loss, neurodevelopmental disorder
- Decision of early intervention


Thank you
for your attention