

Advances for Children with Cerebral Palsy: Understanding Neuroprotection and Optimizing Function and Participation

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**LaRabida Symposium: A Collaborative Approach
to Cerebral Palsy**

**University of Chicago Gleacher Center
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Historical Milestones

- Little – 1862 (difficult labor due to ricketic pelvis, newborn encephalopathy, orthopedic deformities)
- Osler – 1889 (upper motor neuron disorder of hemiplegia, diplegia, and quadriplegia)
- Freud – 1897 (multicausal neuropathological classification)

Historical Milestones

- Phelps – 1932 (neurodevelopmental and habilitative intervention)
- Rh incompatibility – 1940 (maternal-fetal incompatibility, encephalopathy, DKCP)
- Regionalization of neonatology - 1975
- Non invasive neuroimaging – 1980
- Neuroprotection and neuro-optimization–
Current era

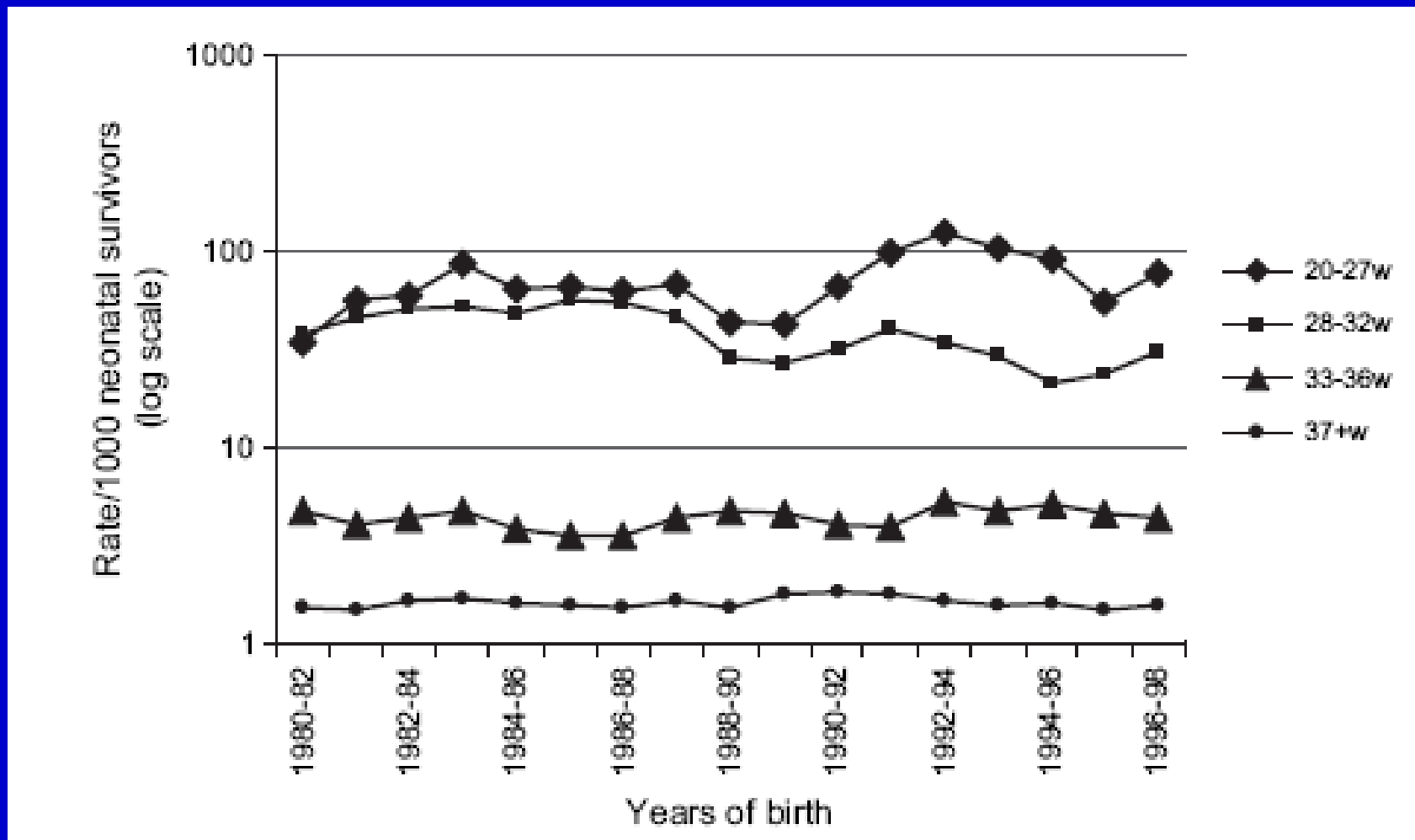
Definition of Cerebral Palsy

- A disorder of movement and posture due to a lesion or dysfunction in the developing central nervous system
- Though delay in achieving motor milestones may be the initial symptom, there is a continuum of CNS effects on developmental processes underlying balance, coordination, manipulation, communication, perception, learning and behavior.

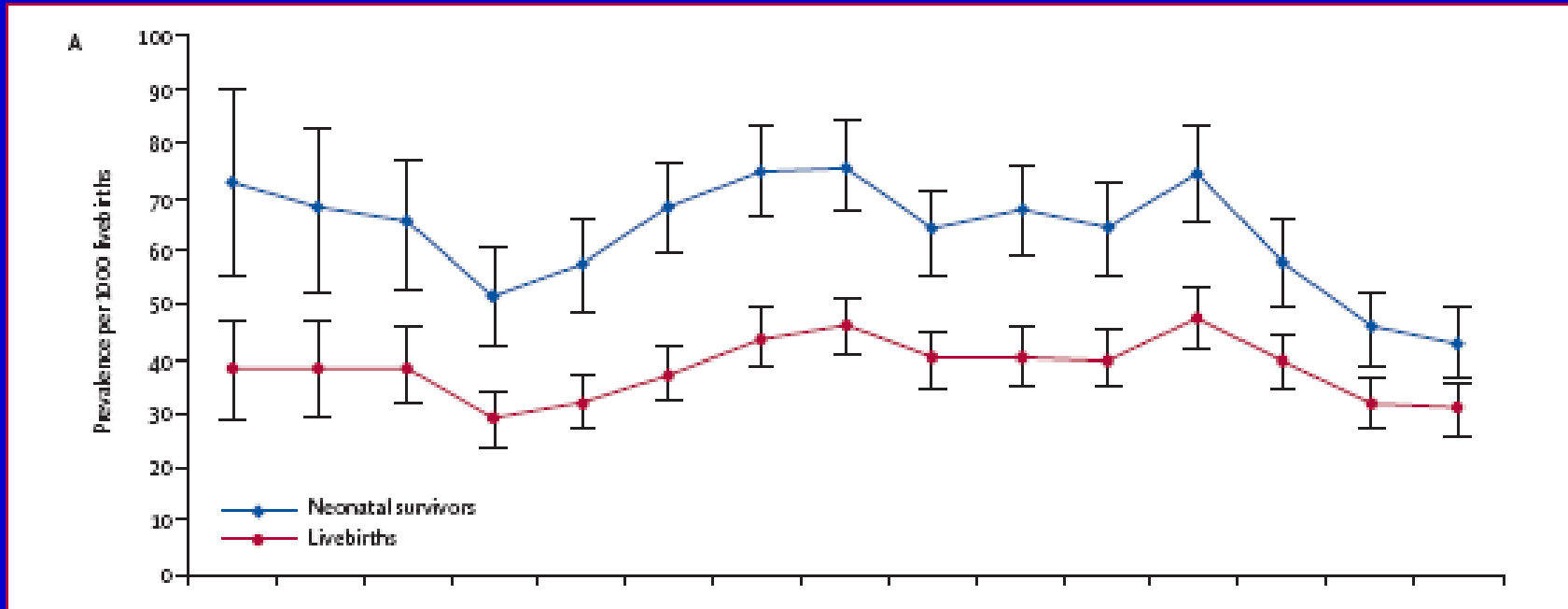
Core features of Cerebral Palsy

- Non progressive
- Evolving neurological signs
- Evolving orthopedic deformity
- Onset in early childhood
- Detected in preschool years
- Long term developmental impact
- Co morbidities include learning, attention, seizures, dysphagia, deformity, visual and hearing disorders

Trends in Gestational-age-specific CP rates (3-year moving averages), Western Australia, 1980-1998

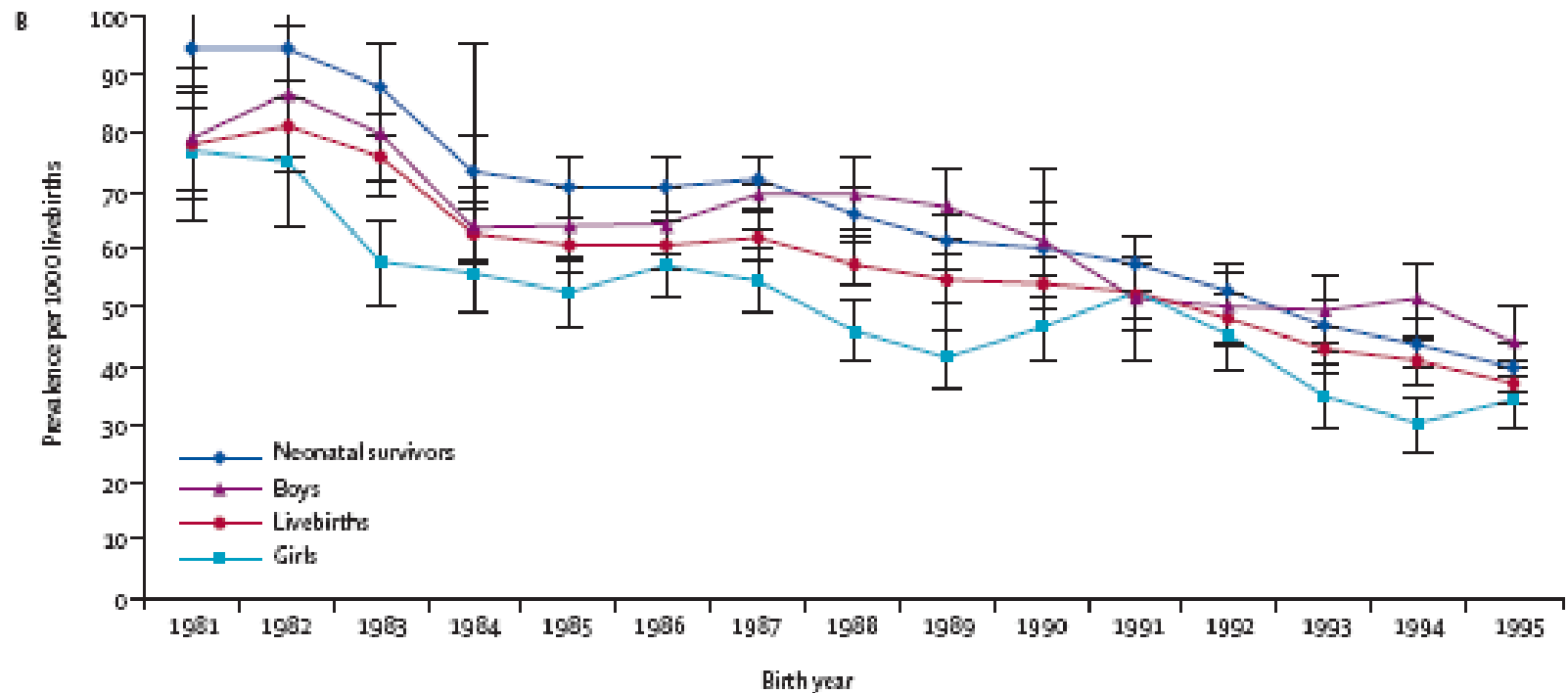


CP rates among infants of birthweight of <1000g from nine European centers, 1980-96



Platt MJ, Cans C, Johnson A, Surman G, Topp M, Torrioli MG, Krageloh-Mann I. [Trends in cerebral palsy among infants of very low birthweight \(<1500 g\) or born prematurely \(<32 weeks\) in 16 European centres: a database study.](#) Lancet. 2007 Jan 6;369(9555):43-50.

CP rates among infants of birthweight of 1000-1499g from nine European centers, 1980-96



Platt MJ, Cans C, Johnson A, Surman G, Topp M, Torrioli MG, Krageloh-Mann I. [Trends in cerebral palsy among infants of very low birthweight \(<1500 g\) or born prematurely \(<32 weeks\) in 16 European centres: a database study.](#) Lancet. 2007 Jan 6;369(9555):43-50.

Epidemiology of Cerebral Palsy I

- Term: 1 per 1000
- Preterm 32-36 wks: 10 per 1000
- Very Preterm 28-32 wks: 70 per 1000
- Extreme preterm 23-27 wks: 100-160/1000

Epidemiology of Cerebral Palsy II

- Singleton: 2 per 1000
- Twins: 50 per 1000
- Triplets: ~100 per 1000

COLLECTOR'S EDITION

LIFE

BORN TOO SOON

The high-tech, high-risk drama of keeping the tiniest babies alive



Jason Michael Waldmann Jr., who weighed only 1.1 pounds at birth

MAY 2000/\$3.99 05
0 70989 10099 2
DISPLAY UNTIL MAY 30

Myths versus Realities after Extreme Prematurity Pretest

- 1. A child is born weighing 900 grams at 27 weeks gestation. The chance that this child at age 4.5 years will walk, communicate basic needs, see, hear, understand requests, and learn in a group of peers is:**
- 2. A child is born at 28 weeks gestation to a mother with household income of <\$10,000 US. The chance that this child at age 4.5 years will have intellectual disability (IQ<70) is:**
- 3. A child weighs 800 grams at birth. Mother's education is less than high school. The chance for early childhood education experiences prior to kindergarten is:**

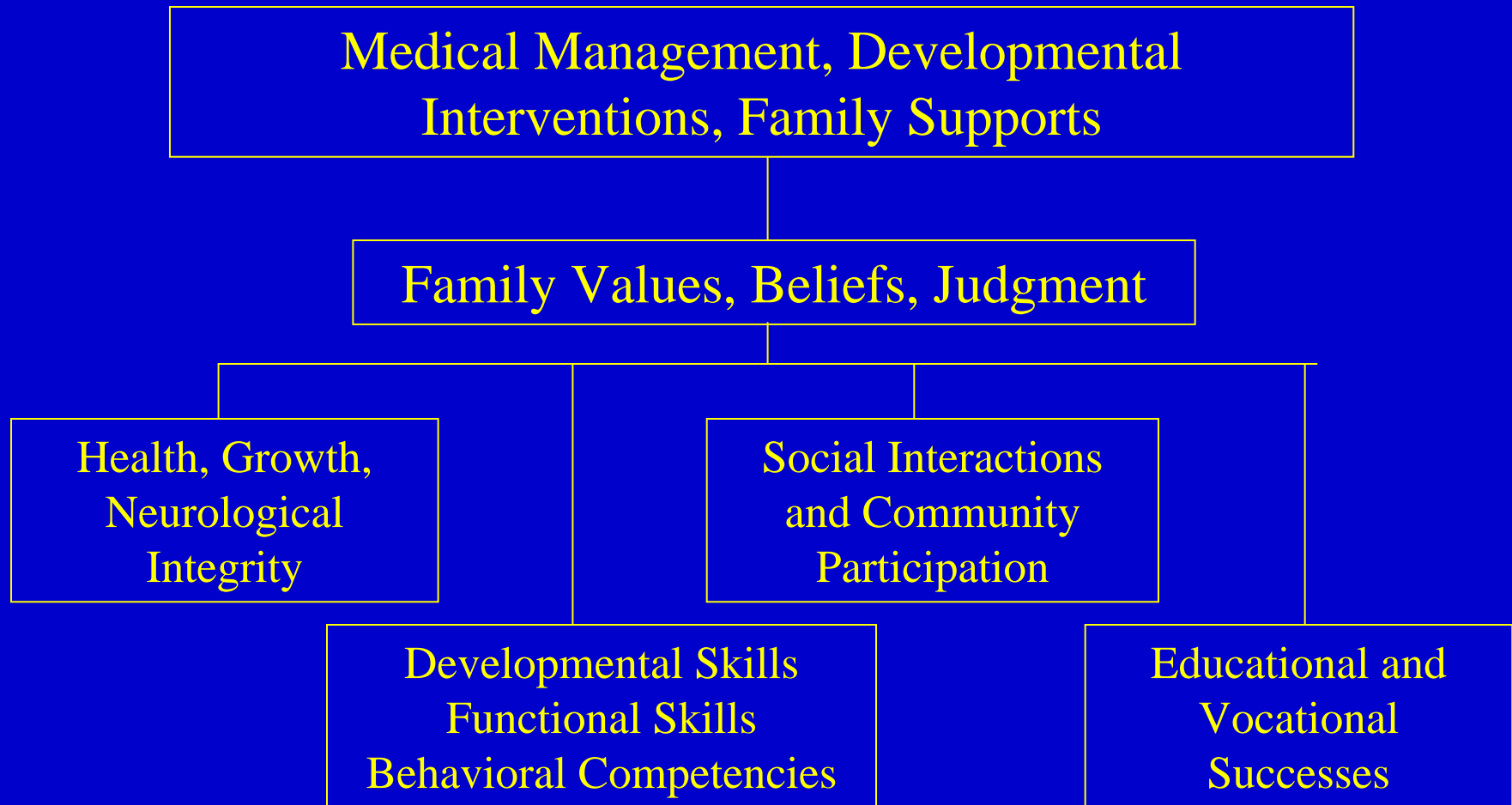
1) 5% 2) 10% 3) 25% 4) 50% 5) 75% 6) >90%

Myths versus Realities after Extreme Prematurity Pretest

4. A child is born at 26 weeks gestation and weighs 800g. The chance that this child will meet criteria for Autistic spectrum disorder at age 10 is:
5. A boy is born at term to a single mother who lives in a neighborhood of concentrated poverty and social disadvantage. The chance that this boy will graduate from college with a BA degree or an associate's degree by age 25 is:

1) 5% 2) 10% 3) 25% 4) 50% 5) 75% 6) >90%

Measuring Quality of Life in Child Neurodisability



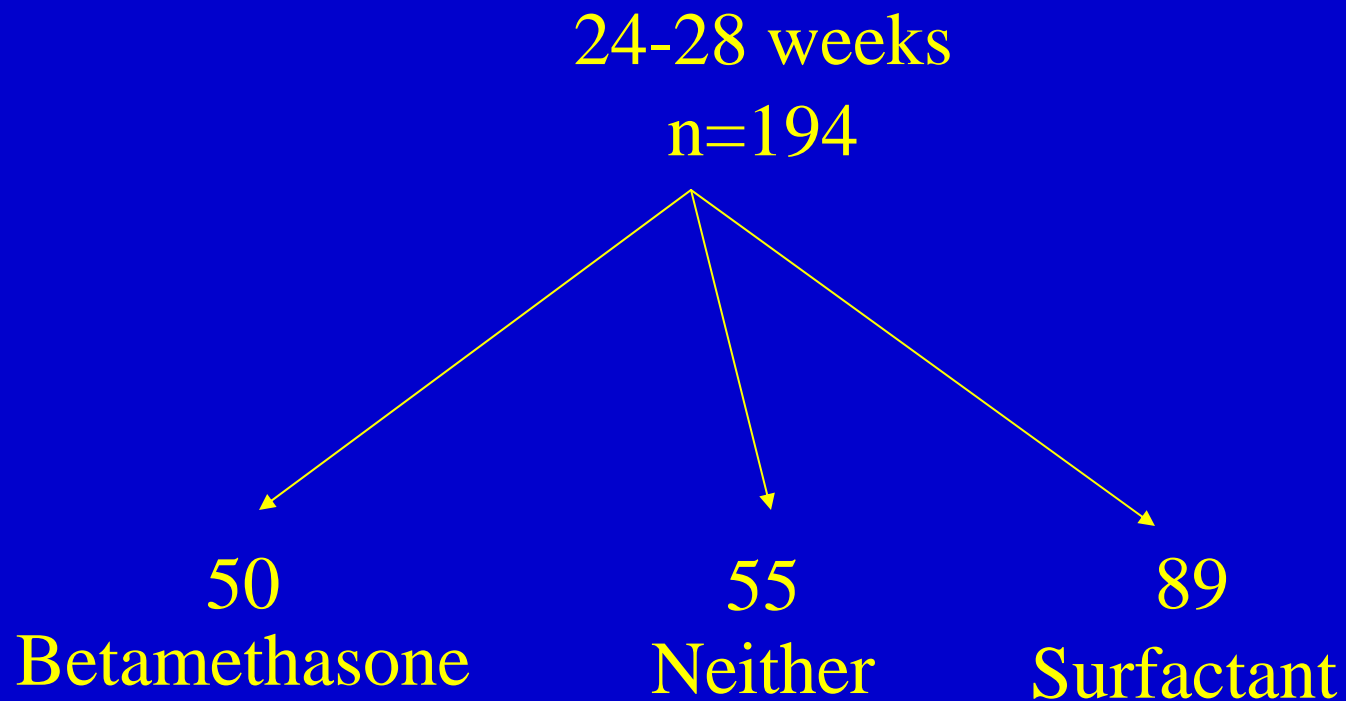
-Adapted from Spilker

Parental Concerns About Preschool Functioning

- Will my child be healthy?
- Will my child walk?
- Will my child talk?
- Will my child learn self care?
- Will my child learn at school?



1983-86 RCT + Open Infasurf^R



Kwong, et al. Pediatrics 1985; 76: 585-92 and 1986;78: 767-74

Demography

< High School 18%

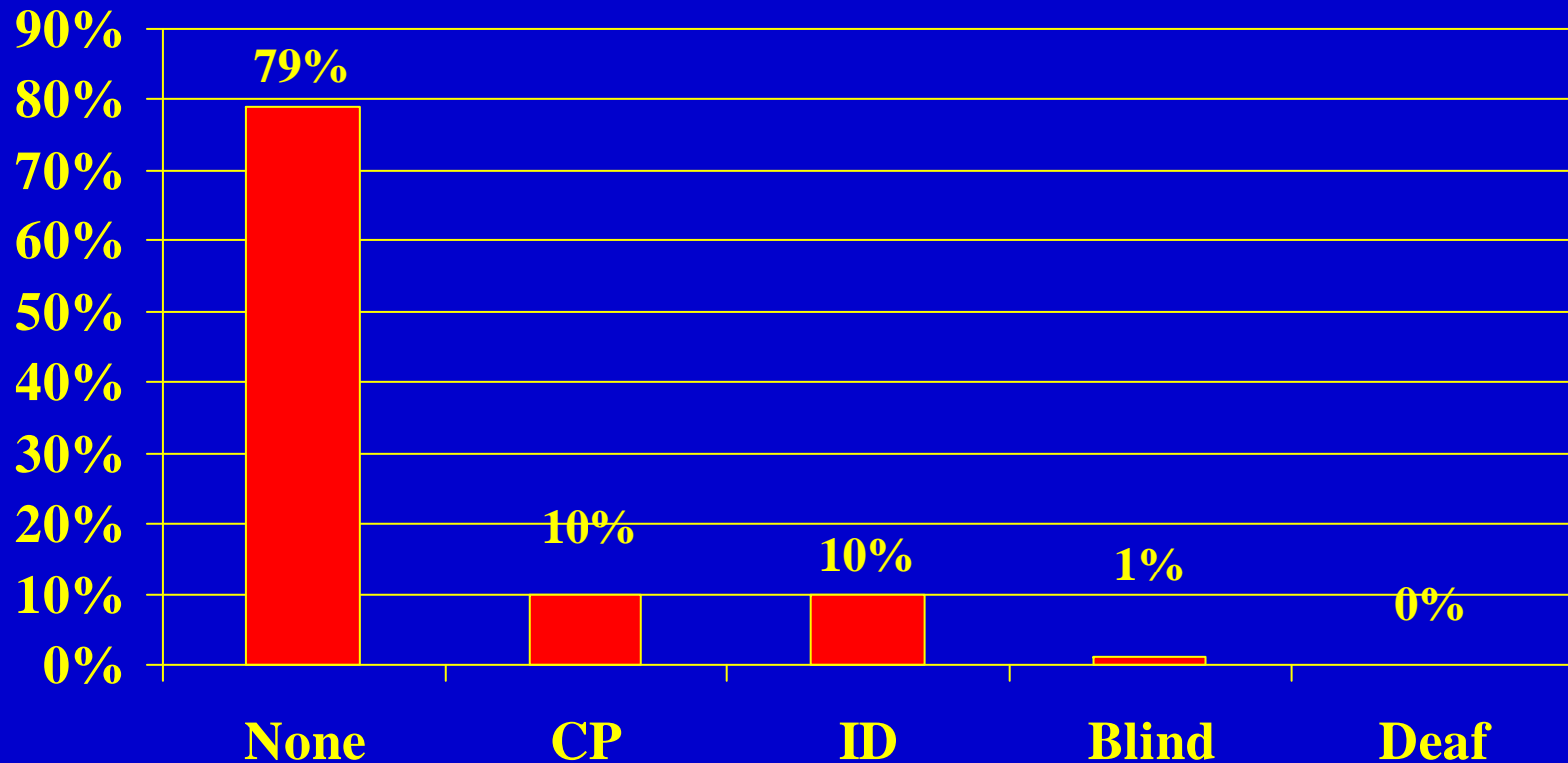
< 20 Years Old 17%

Poverty 78%

Minority 40%

Msall et al. J Perinatology 1994; XIV: 41-47

Neurodevelopmental Disabilities



Neurodevelopmental morbidity among survivors (N=149).
CP = cerebral palsy; ID = intellectual disability

Predictors of NDD

Cerebral Palsy:

- Ventriculomegaly RR7 (3-18)
- IVH3/4 RR 5 (2-13)

Intellectual Disability:

- Ventriculomegaly RR4 (2-10)
- Sepsis RR4 (2-8)
- Seizures RR3 (1.2-8)
- Minority RR3 (1.3-6)

Functional Status at Kindergarten Entry

Walks 150 Feet	97.3%
Talks in Sentences	96.6%
Toilets Self	95.9%
Self-Care/ADL	95.9%

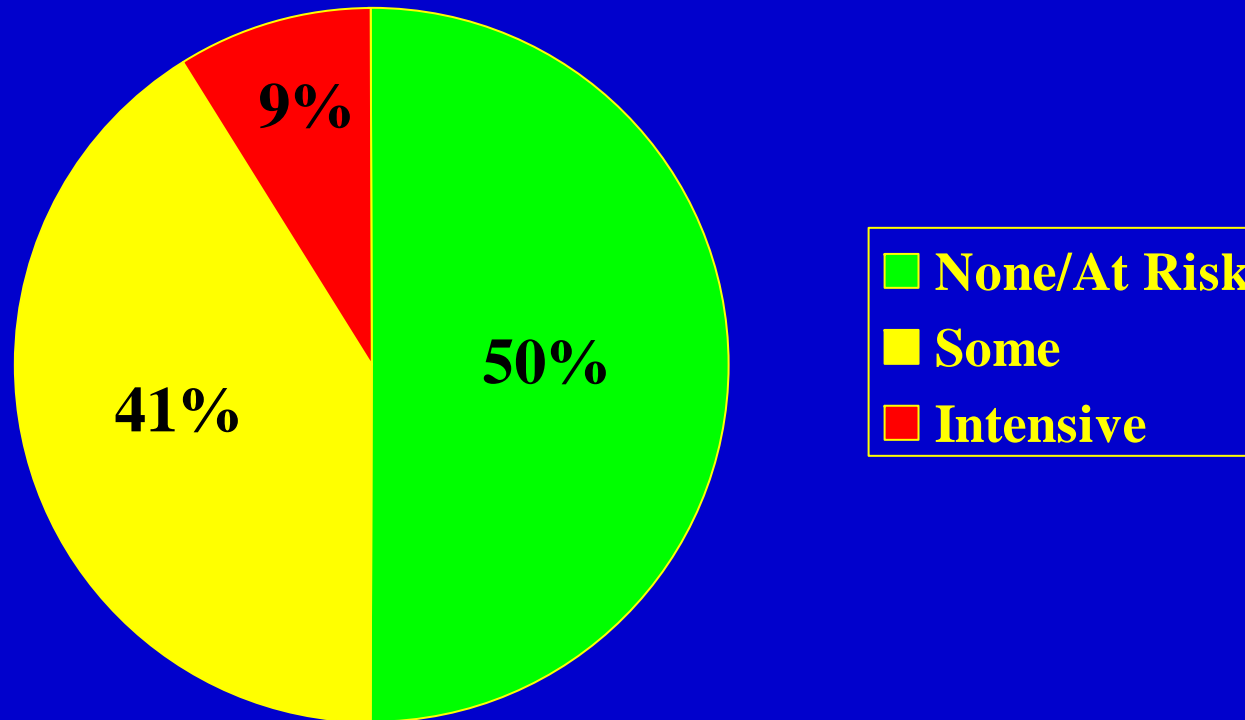
Msall et al. J Perinatology 1994; XIV: 41-47

Functional Outcomes and Neurodevelopmental Disability

Walks 150 Feet	87%
Talks in Sentences	84%
Toilets Self	81%
Self-Care/ADL	81%
Understands Request	94%

Msall et al. J Perinatology 1994; XIV: 41-47

Kindergarten Readiness Status



Requirements for special education resources among survivors of extreme prematurity (N=149)

Predictors of Special Education Resources at Kindergarten Entry

	<u>RR</u>	<u>95% CI</u>
Poverty	7.3	2.5 - 21.4
Minority status	2.5	1.2 – 5.3
Male gender	2.4	1.1 – 5.0

Msall et al. AJDC 1992; 146:1371-1375

The longtime standard of surfactant efficacy

[Mollie, age 12]

[Mollie, newborn]



Time and kids like Mollie are showing Survanta works safely and effectively in the treatment of children born with, or at risk for, respiratory distress syndrome (RDS). Mollie was one of the first Survanta patients. Only 880 grams at birth and given little chance of survival, she was included in an early Survanta study. Today, Mollie's growing up healthy and active, and the record of Survanta safety and efficacy keeps growing. **Proven. Reliable. Time-tested.**

* More infants treated by hospitals nationally than any other surfactant. IMS America DDD Lung Surfactant Market Purchases 12 months ending September, 2000. On file, Ross Marketing Research.

Please see the adjacent page for a brief summary of prescribing information.

SURVANTA CAN RAPIDLY AFFECT OXYGENATION AND LUNG COMPLIANCE. During controlled clinical trials, the most commonly reported adverse experiences were associated with the dosing procedure: Transient bradycardia 11.9% of doses; oxygen desaturation 9.8% of doses; ETT reflux, fewer than 1% of doses.

**Over 500,000
infants treated
shows...there's safety
in numbers.***



SURVANTA®
(beractant)
intratracheal suspension
bovine pulmonary surfactant

ROSS ROSS PRODUCTS DIVISION
ABBOTT LABORATORIES INC.
COLLINGSBURG, OHIO 43015-1724

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B1005/0090

Parental Concerns about Middle Childhood Functioning

- Will my child succeed in academic skills such as reading, writing and math?
- Will my child succeed in extracurricular activities?
- Will my child succeed in social relationships with family and peers?

Study Purpose

- To assess the impact of extreme prematurity as a risk factor for grade repetition, special education placement, and resource room services.

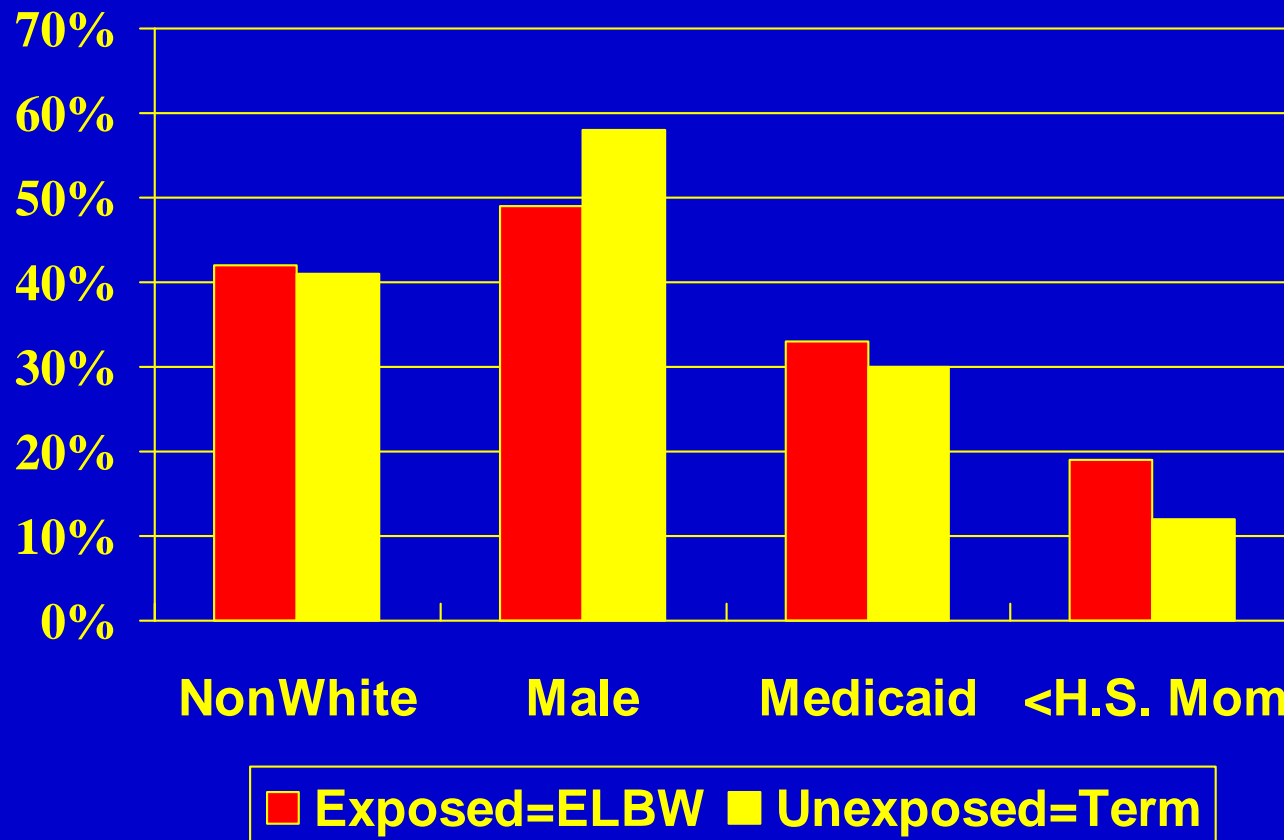
Study Sample

- Exposed group:
 - ≤ 28 completed weeks gestation, singleton infants
 - Born at one regional NICU, 1983-1986 (n=138).
- Excluded 26 children with NDD at age 4.5Y
- Unexposed matched control group:
 - ≥ 37 completed weeks gestation, singleton infants
 - Frequency matched to cases on date-of-birth, zip code, and type of health insurance (n=219).

Outcomes

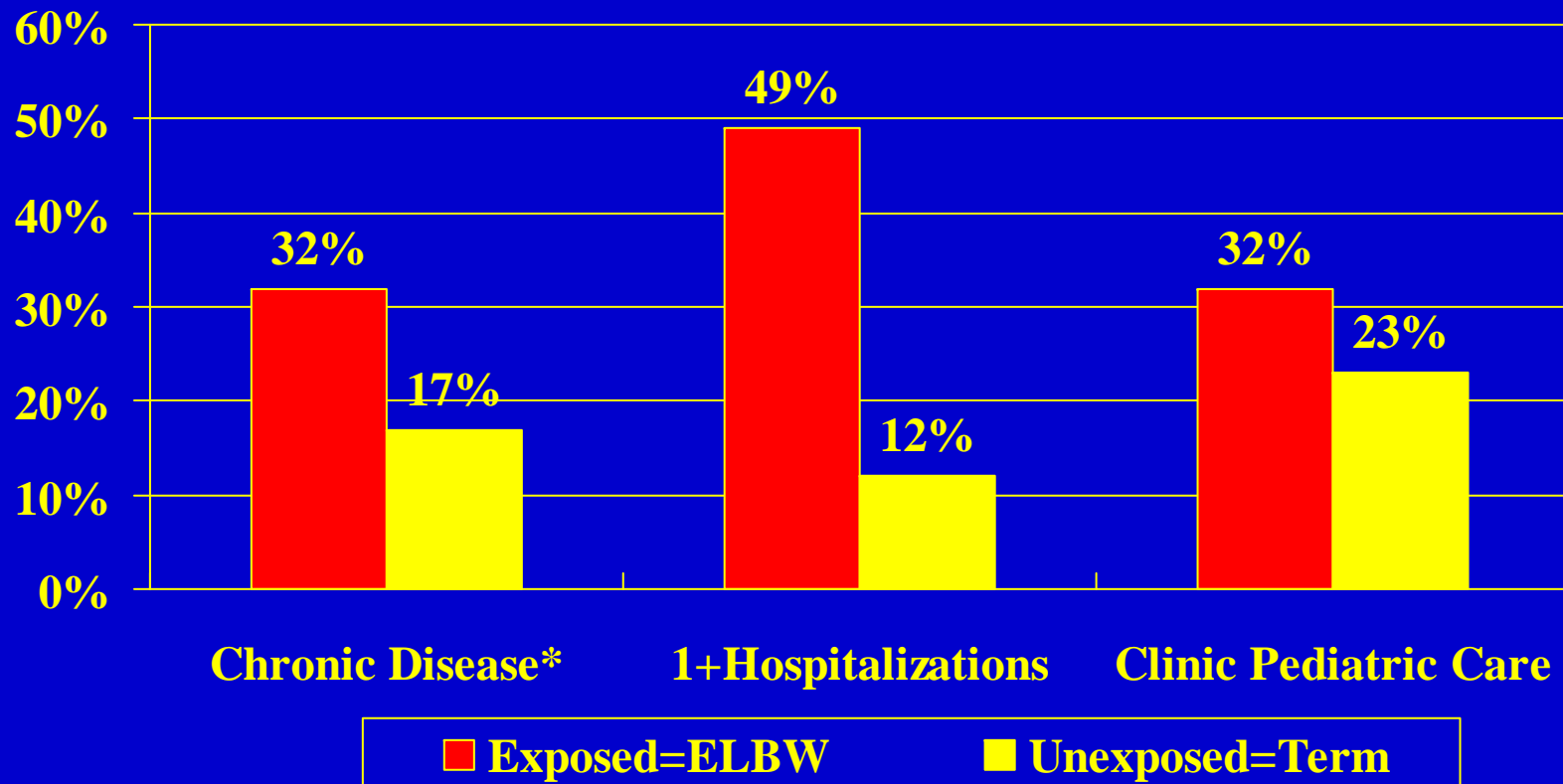
- Grade repetition: Repeating the same grade
- Special education placement: Ratio of 12 or fewer students to 1 teacher
- Resource room: Tutoring for reading, spelling, or math
- Logistic Regression Analyses

Sociodemographic Description of Study Sample (n=327)

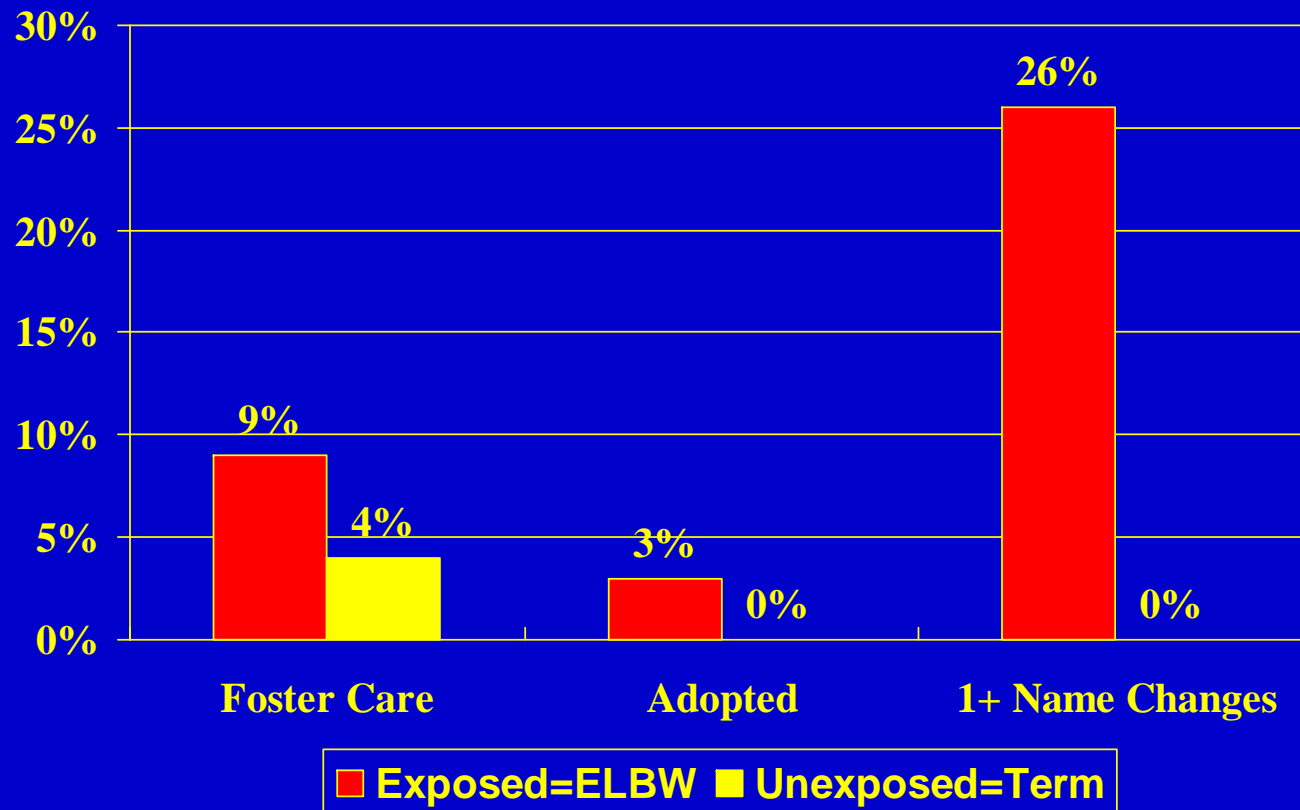


*Unexposed frequency matched to exposed on date of birth (\pm 1 month), mother's zip code and type of health insurance at birth

Description of Children's Health Status at Follow-Up (n=327)



Name Changes and Living Arrangements of Children (n=327)



Family Resources

	ELBW	CONTROL
Mom employed	55%	55%
Dad employed	75%	80%
Mom college	41%	51%
Dad college	36%	46%
Hollingshead I-III	38%	41%

School Based Therapies

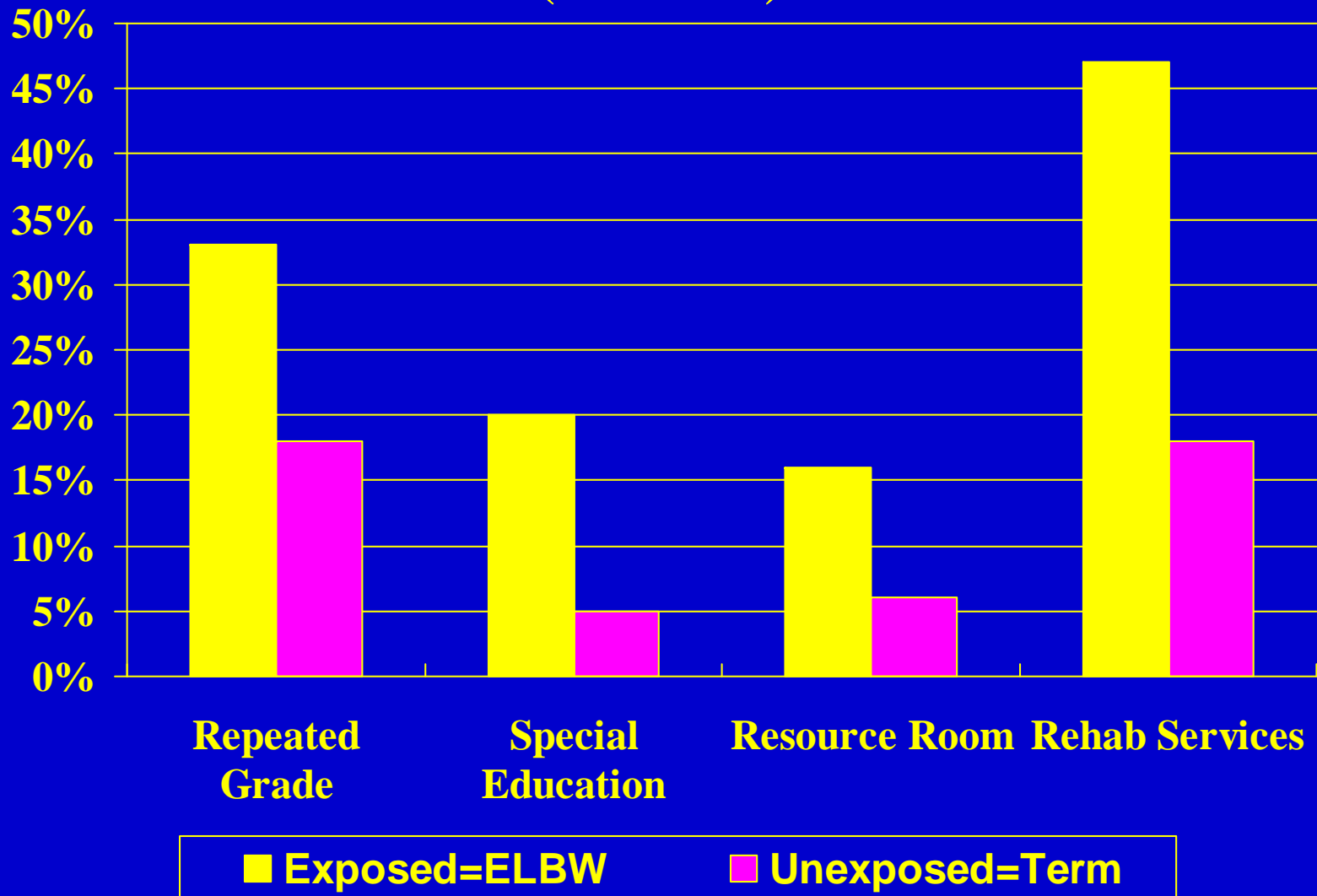
	ELBW (N=108)	Controls (N=219)
Any	47%	18%
Speech-Language	28%	11%
Occupational	18%	1%
Physical	12%	0.5%
Psychological	15%	7.3%

Remedial Services

	ELBW (N=108)	Control (N=219)
Any	23%	17%
Math	11%	4%
Reading	6%	6%
Both/Other	8%	8%

School Outcomes by Status

(n=327)



Summary

- Extreme prematurity was a significant risk factor for grade repetition (OR=3.2), special education placement (RR=3.2) and use of resource room (RR=4.6).
- Male gender (RR=2.0) and Medicaid- or no health insurance (RR=2.2) were significant risk factors for grade repetition
- Child's age significantly increase risk for resource room utilization (RR=1.9)

Conclusions

- Extremely premature infants born in the surfactant era of neonatology remain at risk for educational underachievement.
- Low maternal education, foster care placement, male gender and Medicaid/no health insurance may increase risk.
- Interventions aimed at reducing school failure should address both biomedical and social risks.

Lessons

1. Optimizing endogenous surfactant or early surfactant replacement increases survival.
2. There are low rates of neurosensory disability.
3. There are high rates of intellectual, communicative, and learning disabilities.
4. Optimizing outcomes requires combination of prenatal, perinatal, and postnatal status.

Predicting School-Readiness from Two Year Neurodevelopmental Assessments



Athena I. Patrianakos, Michael E. Msall, Jeremy D. Marks,
Karen Mestan, Dezheng Huo, Grace Yoon, and Michael D. Schreiber

AACPDM Atlanta 2008



COMER CHILDREN'S HOSPITAL
THE UNIVERSITY OF CHICAGO



207 Infants in Original Cohort

168 Surviving Children
At 2 years (corrected)

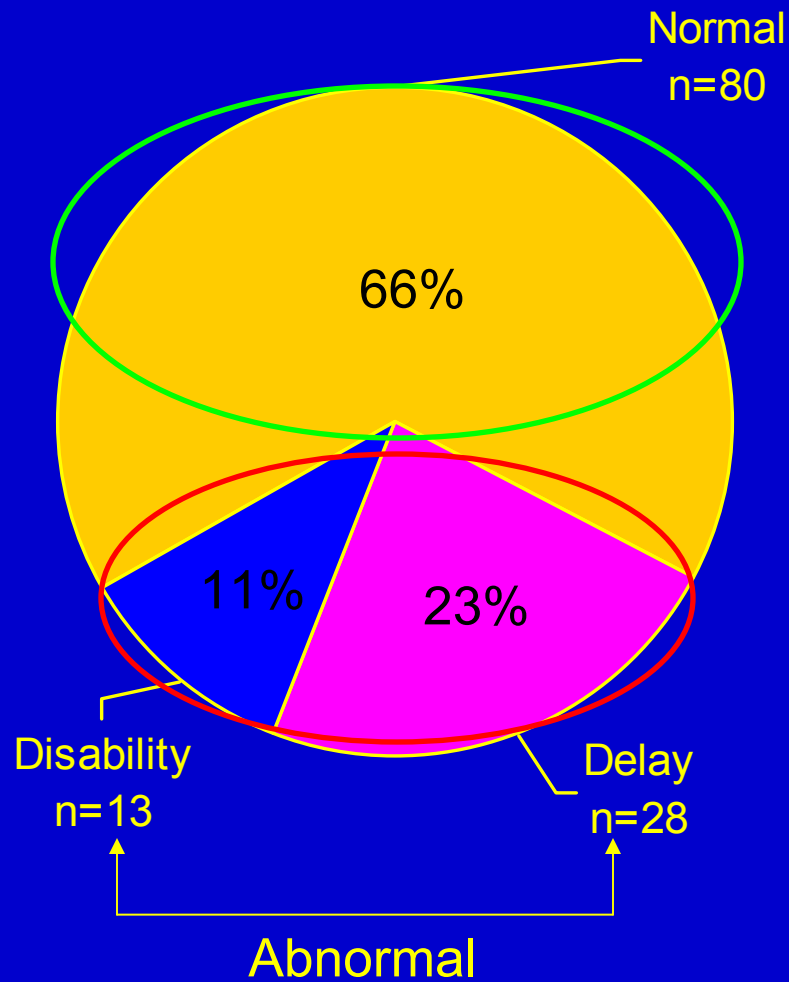
138 Children Evaluated
At 2 years

121 Children Evaluated
At Both 2 years and 5 ½ years
(88%)

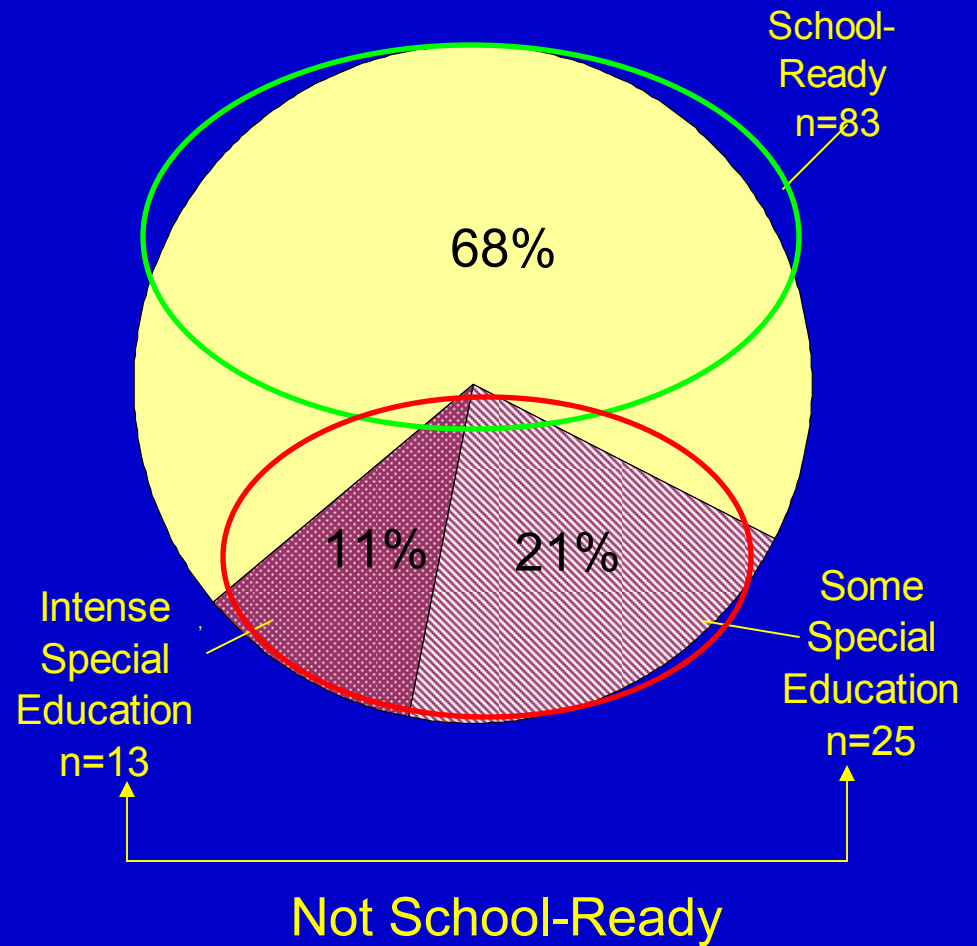
Characteristics	n = 121
Birth Weight (grams)	987 ± 374
Gestational age (weeks)	27.3 ± 2.6
Male, n (%)	57 (47%)
Median Apgar Scores	
- 1 minute (IQR)	5 (3-6)
- 5 minute	7 (6-8)
Race/Ethnic Group (Self-Reported)	
- African-American	85 (70%)
- White	21 (17%)
Hollingshead Index of Social Position	
- Levels I-III	51 (42%)
- Levels IV-V	70 (58%)
Neonatal Morbidities	
- Chronic Lung Disease	56 (46%)
- Severe IVH/PVL	20 (17%)

Similar Distribution of Outcomes at 2 and 5 1/2 Years

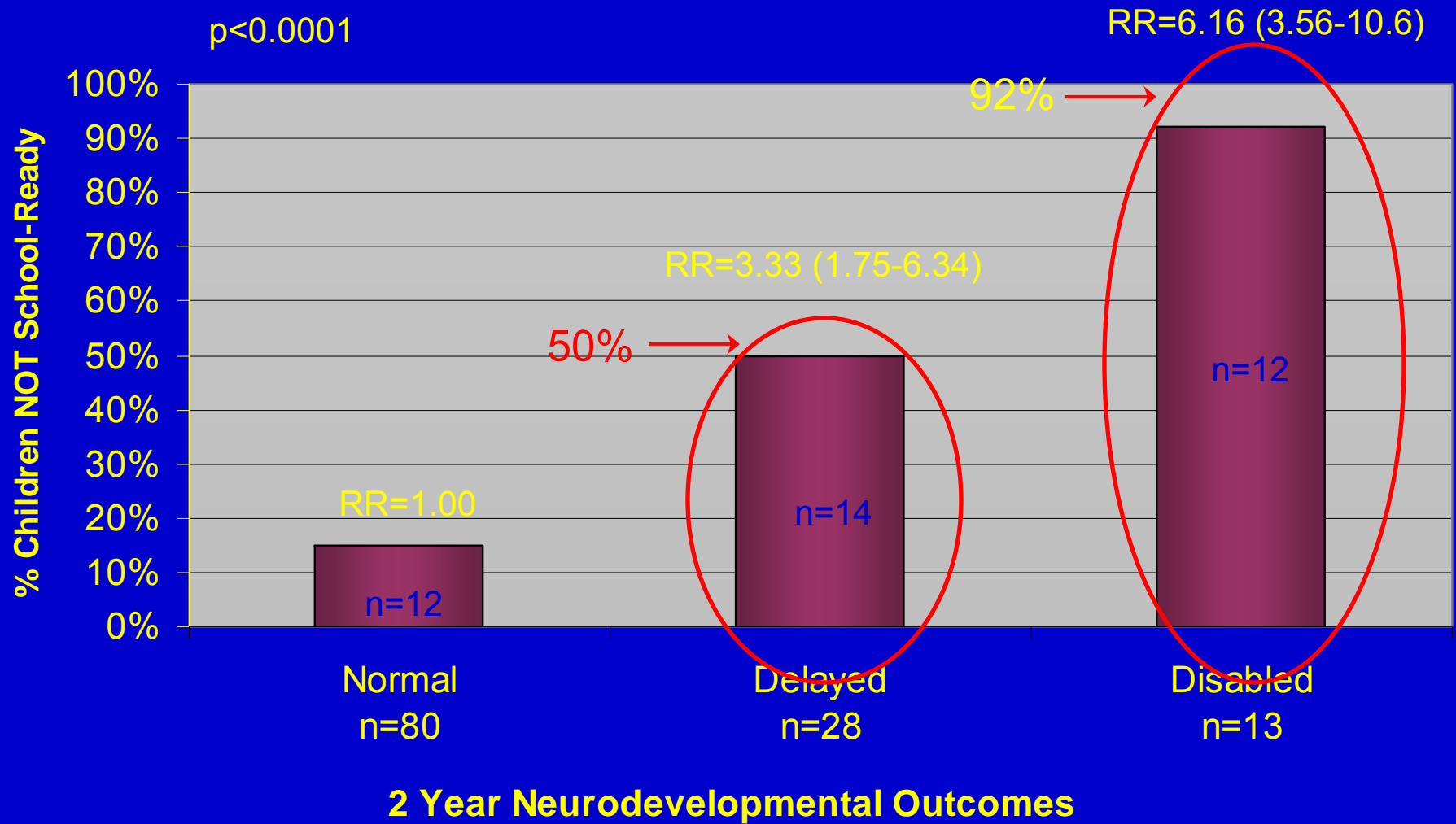
2 year Outcomes



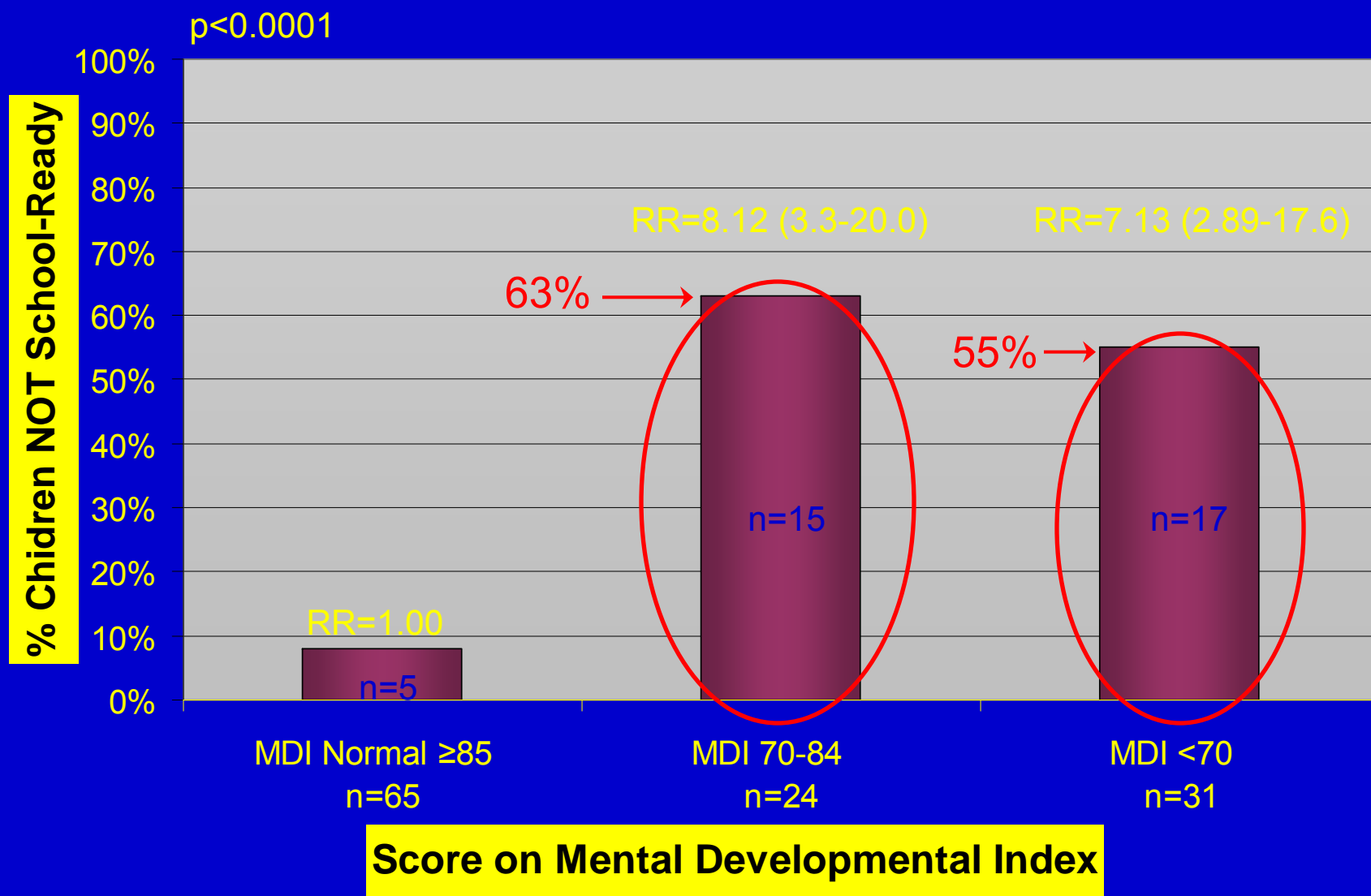
5 1/2 Year Outcomes



Disability at 2 Years is Associated with Lack of School-Readiness at 5 ½ Years

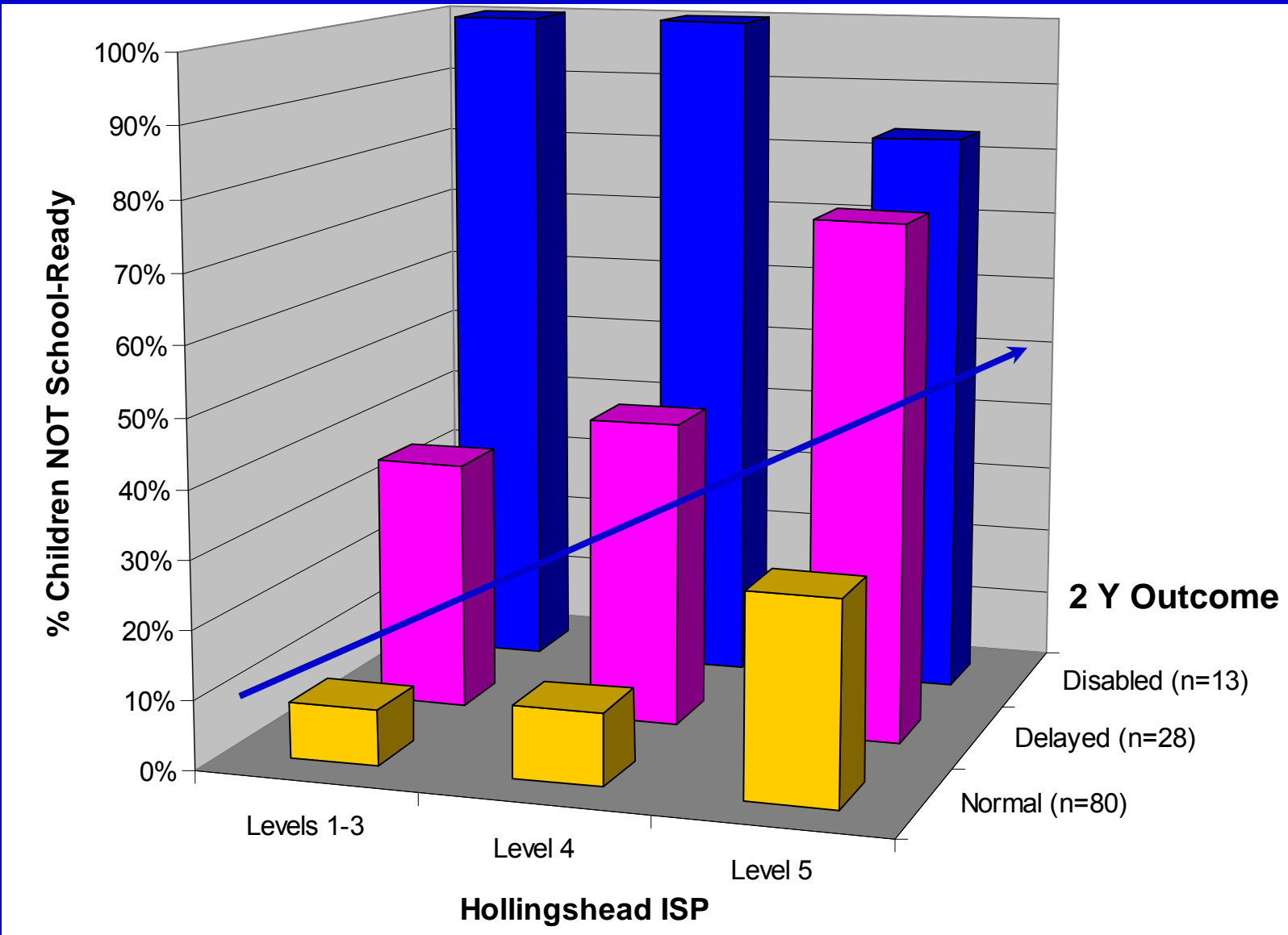


Low Score on MDI at 2 Years is Associated with Lack of School-Readiness at 5 ½ Years



Poor Social Position Negatively Impacts School-Readiness

5 1/2 Year Outcome



2 Y Outcome

Disabled (n=13)

Delayed (n=28)

Normal (n=80)

Levels 1-3

Level 4

Level 5

Hollingshead ISP

Conclusions

- Normal neurodevelopment at 2 years is 85% predictive of school-readiness
- Disability at 2 years is 92% predictive of lack of school-readiness
- Delay at 2 years is 50% predictive of lack of school-readiness
- School-Readiness is adversely affected by:
 - Delay or disability at 2 years
 - An MDI greater than 1 SD below the mean at 2 years
 - A PDI greater than 1 SD below the mean at 2 years
 - Adverse early childhood environments

Process of Learning to Read

- Unlike oral language, reading is not a natural process
- Requires systematic and explicit instruction
- Begins very early in child's development
 - Amount and quality of early language and literacy interactions
 - Oral vocabulary development
 - Exposure to oral reading and language play (rhyming)

Learning to Read

- Language is a hierarchical structure made up of increasingly complex parts:
 - Phonology (sound elements)
 - Semantics (word meaning)
 - Syntax (grammatical structure)
 - Discourse (connected sentences)

How does reading work?

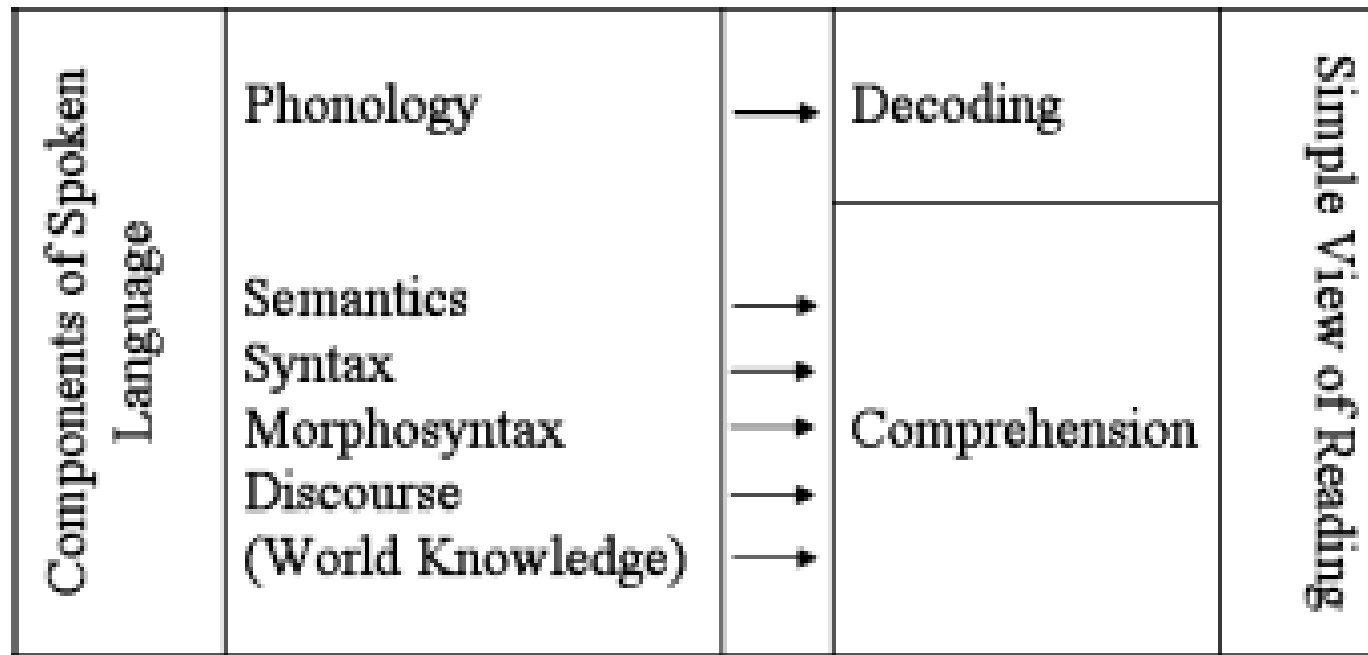


Figure 1. The Simple View. Reprinted with permission from Shaywitz (2003).

What Skills are Needed?

- Reading requires the acquisition of phonemic awareness
 - Words and syllables used in oral language are composed of phonemes
 - “CAT” = 3 phonemes: “C”, “A”, and “T”
- Letters need to be linked to phonemes
 - 26 letters and 44 phonemes in English

What Skills are Needed?

- Understanding the alphabetic principle
 - Words can be broken down into smaller units of sound
 - Letters on page represent these sounds
 - Written words have the same number and sequence of sounds heard in the spoken word

Comprehension

- Integration of the meanings of spoken or written words
- Leads to understanding of sentences whether spoken or written
- Allow understanding of broader topics represented by those sentences

Vellutino, 2004

What is Phonologic Deficit?

- Single word reading problems
 - Problems segmenting words and syllables into phonemes
 - This is true in virtually all poor readers, including children, adolescents, and adults
 - At all levels of IQ
 - In socially disadvantaged children and adults.

What is Phonologic Deficit?

- Normal reading: decoding must be accurate, fluent, and automatic
- Limitations in phonological awareness lead to slow, labored, and inaccurate decoding of words
- Inaccurate decoding leads to poor reading comprehension and impede the acquisition of reading skills

The Myths of Dyslexia

- Mirror writing is a symptom of dyslexia
- Eye training is a treatment for dyslexia
- More boys than girls are dyslexic
- Dyslexia can be outgrown
- Smart people cannot be dyslexic

Scientific American, Nov. 1996

Clues to Dyslexia

- History
 - Delayed language
 - Problems with the sounds of words
 - Expressive language difficulties
 - Difficulty naming
 - Difficulty learning to associate sounds with letters
 - History of reading and spelling

Dyslexia

- Results from a deficit in the phonologic component of language
- Unexpected difficulty in reading in children who otherwise possess the intelligence and motivation necessary for accurate and fluent reading
- Neurobiological in origin
- Estimated to occur in 10-15% of school-aged children
- Affects boys and girls equally

Effective Intervention

- Systematic and explicit instruction in:
 - Phonemic awareness
 - Decoding
 - Spelling
 - Reading sight words
 - Comprehension strategies
- Practice
- Fluency training
- Enriched language experiences: listening to, talking about, and telling stories

Challenges to Intervention

- Identification of children with LD at the school level exhibits great variability.
- Schools have opted to ignore exclusionary criteria
- One-time assessments based on assumptions that LD is caused by intrinsic neurological difficulty as opposed to poor instruction.

Trajectory of Reading Skills over Time

- Persistent, chronic condition; not a developmental lag:
 - Poor readers and good readers tend to maintain their relative positions along the spectrum of reading ability
- No support for classification based on IQ discrepancies

Lyon et al 2003; Vellutino 2004

Intervention for Reading Disorders

- Children selected by phonological awareness scores in kindergarten (N=180)
- Children had VIQ ≥ 75
- Random assignment to 4 curricula:

Torgesen et al, J of Learning Disabilities 27: 276-287 ,1994

Intervention for Reading Disorders

- Phonological awareness at oral/motor level plus synthetic phonics (PASP)
- Implicit phonological awareness training plus phonics instruction of read word reading and spelling (Phonics)
- Regular classroom support groups receiving individual instruction to support classroom reading (Resource)
- No treatment control group (Control)

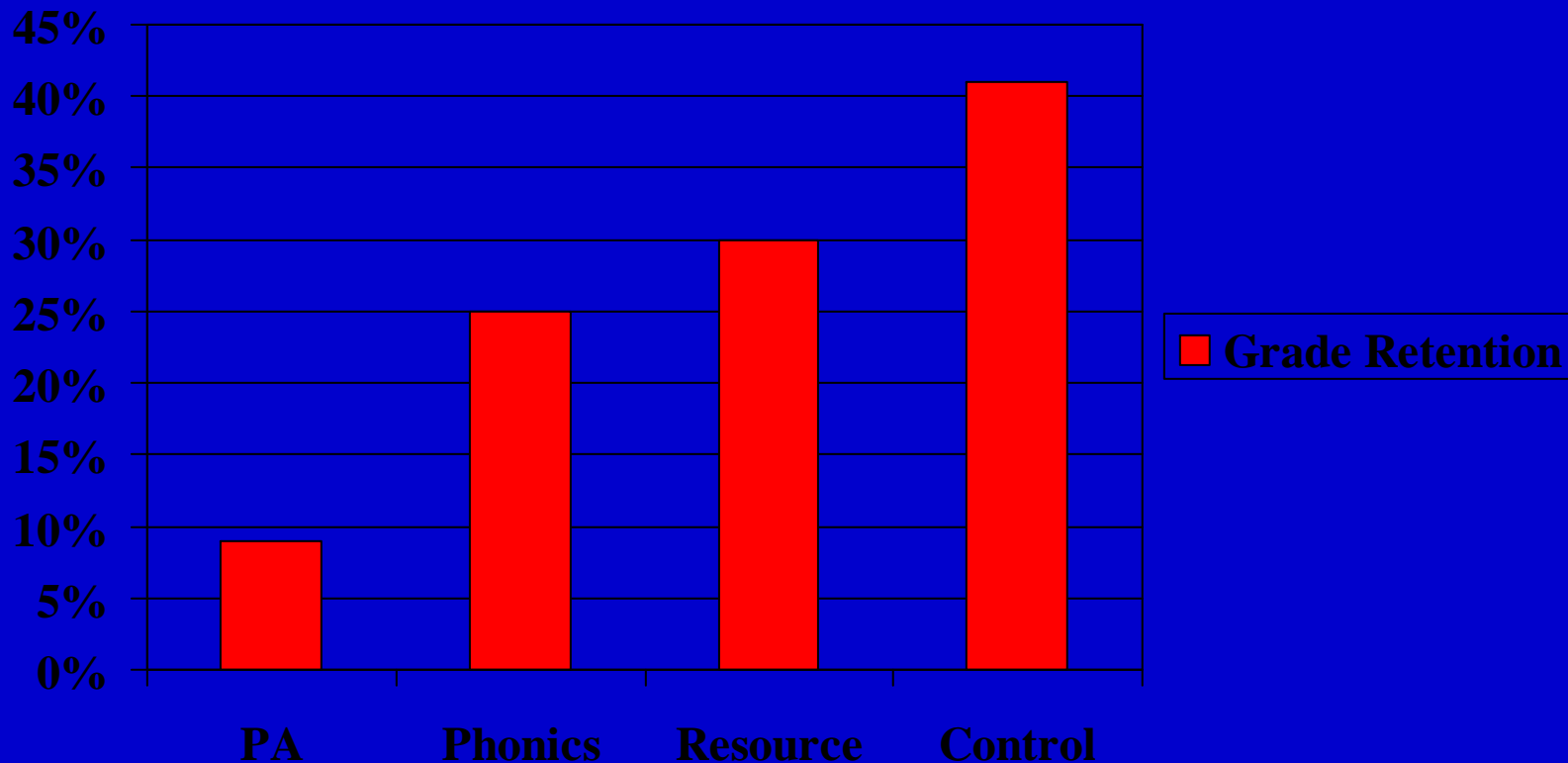
Intervention for Reading Disorders

- Each instructional group received 20 minutes 1:1 instruction in reading, 4 times per week x 2.5 years
- Over 2.5 years, 88 hours of supplemental instruction (47 from tutors, 41 from aides)

Results at End of Grade 2

	Phonological Awareness (N=33)	Phonics (N=36)	Resource (N=37)	Control (N=32)
Word Attack	99.4	86.7	86.7	81.6
Word ID	98.2	92.1	92	86.3
Passage Comp.	91.5	87.4	86.4	85.2

Results at End of Grade 2



Intervention for Reading Disorders

- Longitudinal study; tracked K-4th
- Intervention initiated in mid-first grade for impaired readers (daily 1:1 tutoring) for up to 2 terms
- Remediation focusing on emergent literacy skills:
 - Knowledge of print concepts, letter identification, phonologic awareness, listening

Intervention for Reading Disorders

- Relative to normal readers
 - Letter-naming and phonological awareness deficient in kindergarten
 - 67% of tutored children brought to within the average range in only 1 semester (majority maintained to 4th grade)
 - Difficult to remediate scored well below normal readers and easy-to-remediate on phonological tests at K, 1st , 3rd grade
 - IQ-achievement discrepancy did not predict outcomes

Intervention for Reading Disorders

- Disabled readers : 9% of population
- After 1 semester : 1.5% of the population
- Very similar results noted with 2nd study that intervened in K and 1st grade
- Lesson: comprehensive and well-balanced reading instruction can prevent long-term reading difficulties who would otherwise qualify for a Dx of RD

Functional Brain Imaging

- Temporo-parietal reading system (angular gyrus)
 - Critical for analyzing the written word
- Left occipito-temporal area
 - Critical for development of skilled reading
 - Functions as automatic word recognition system: visual word form area
- Inferior frontal gyrus (Broca's area)
 - Associated with articulation
 - Important in silent reading and naming

Functional Brain Imaging: Intervention

- Shaywitz et al 2004
- 2nd and 3rd graders recruited into 3 groups
 - Experimental intervention, n= 37
 - Community intervention, n=12
 - Community controls, n=28

Functional Brain Imaging: Intervention

- Community intervention: met criteria for RD and received interventions commonly found in school
 - Not explicit phonologically-based interventions
- Experimental
 - 50 minutes daily, individualized tutoring
 - Explicit, systematic focus on understanding alphabetic principle
- Imaged pre, post, and 1 year later

Functional Brain Imaging: Intervention

- EI group improved reading accuracy, fluency and comprehension
- Compared to Community intervention both EI and CC demonstrate
 - Increased activation of left hemisphere regions
 - After intervention: increased bilateral inferior frontal gyri, left superior temporal gyrus, occipital temporal region

Functional Brain Imaging: Intervention

- The nature of remedial educational intervention is critical to successful outcomes
- Use of an evidence-based phonological reading intervention facilitates development of neural systems that underlie skilled reading

Challenges to Intervention

- Converging evidence indicates that the majority of children who struggle to read early on can learn to read at average levels or above
- If they receive evidence-based instruction by 9
- If not, they will have reading problems until adulthood

Shaywitz, Pediatrics 2002

Performance of NAEP Reporting Groups in Chicago: 2005, 4th Grade Reading

Reporting Group	%Total Students	Below Basic	Above Basic
Male	52	62	38
Female	48	57	43
White	9	30	70
Black	48	69	31
Hispanic	41	57	43
Free/reduced lunch	84	65	35
Not eligible	16	32	68

What can we do?

- Long term strategies to enhance functional outcomes, literacy, academic competencies, and social successes are required for children at biomedical and social risks.
- Predictors of literacy are quality early child experiences, maternal literacy, and close attention to learning letters and numbers by kindergarten.
- The task of pediatrics is to combine the best of medical and developmental science in our daily practices.

DBP Chicago Model

Examine sequential outcomes after implementing translational science and community interventions so that disability is prevented, function optimized, and we create systems of care that strive to eliminate health care disparities for vulnerable children.