Lessons Learned From The Follow-up Of Children After Life-saving Therapies

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UNIVERSITY OF ALBERTA

Capital Health

Disclosure Statement

- The Neonatal and Infant Follow-up Program began in 1974 as part of the Northern and Central Alberta Perinatal Program with program funding until 1986 and since under of the global funding of Glenrose Rehabilitation Hospital.
- The Western Canadian Registry and Follow-up of Complex Pediatric Therapies Program began in 1996 with funding as follows: (1)1996-99, Glenrose Rehabilitation Hospital Trust Fund, 1999-2006, Alberta Health and Wellness- special research fund, (3) 2006-present, Child Health.
- Drs Y Yasui and I Dinu, School of Public Health, preformed the statistical analyses to be presented.

Acknowledgements

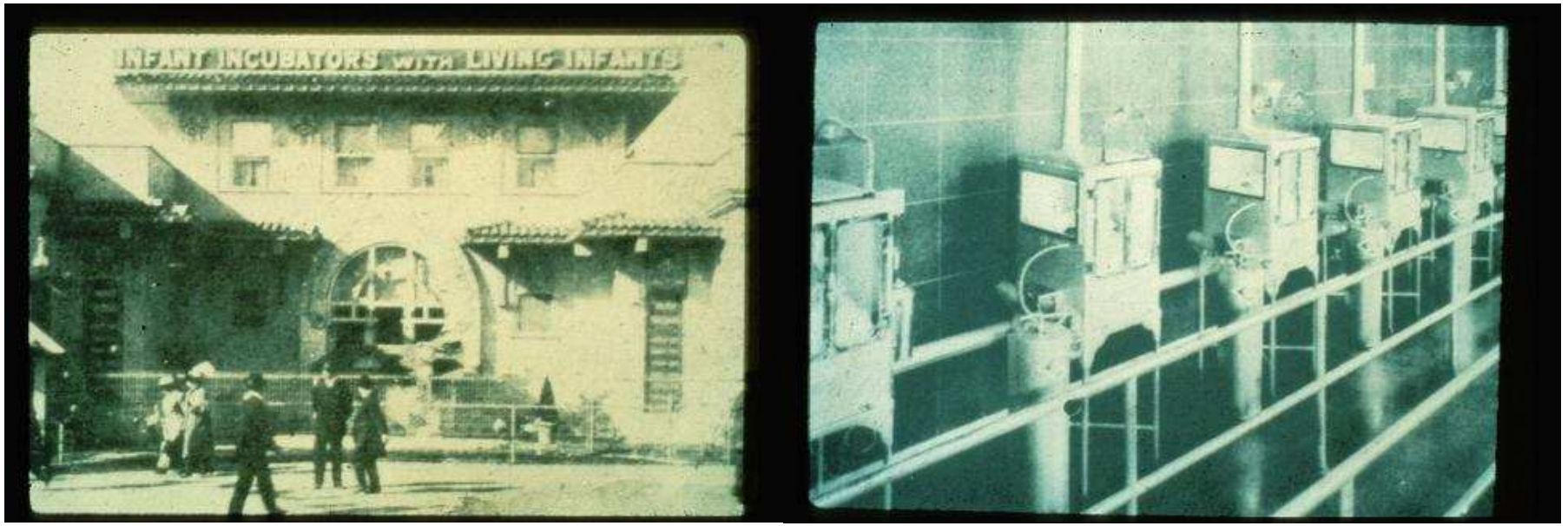
- We thank the children and their parents for attending follow-up.
- We are indebted to the Glenrose Rehabilitation Hospital, Edmonton, AB for encouraging both service and audit to be part of follow-up.
- We thank Dr. G. Eddy, former director of the Glenrose School Hospital, and Dr. E. Gauk, Pediatric Neurologist, for their vision of follow-up for children surviving life-threatening events.
- We thank Drs A Joffe, SCH, and R Sauve, U of C, as co-chairs of The Registry of Complex Pediatric Therapies Program and the interprovincial members of the Steering Committee for making this a successful follow-up including service, audit and research.

Learning Objectives

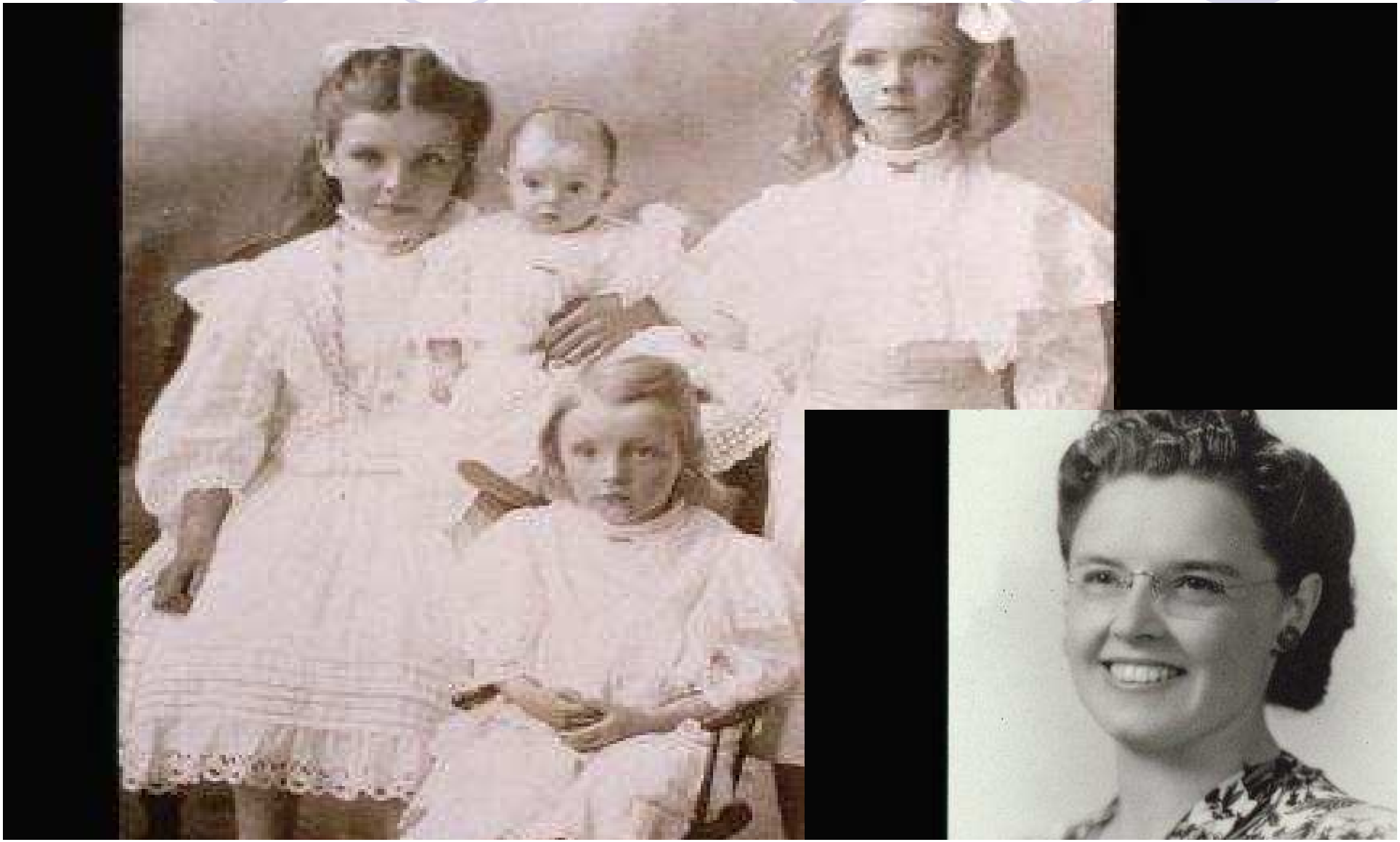
- To demonstrate a working model of Outcomes Research as part of follow-up of at-risk children.
- To understand how the documentation of consistently determined outcomes helps to relate outcomes to treatment era and identify modifiable factors that can lead to changes in acute care.
- To be aware of the current outcomes of children surviving select life-saving treatments. A comparison of outcomes of children after newer treatments with outcomes of extremely preterm infants is given to help to understand the risk of major disability among these survivors.

Setting the stage: Care of the preterm infant 100 years ago

- Infant Incubators with Living Infants



Farm Home Birth of a preterm :1909



Longitudinal Follow-up: Background

- early 1900s,- low, but intact survival for <2500g BW;
- 1950s-1960s,- higher survival, iatrogenic handicaps; long-term follow-up reports in the literature
- early 1970s,- improved survival, fewer disabilities for < 1500g BW
- mid 1970s, ability to ventilate extremely preterm babies---threshold of viability---
- mid 1980s, beginning of major corrective repair of congenital heart defects and solid organ transplantation for children

Groups for outcomes

- Extremely preterm, ≤28w GA and <1250 g BW
- Complex cardiac surgery at ≤6 weeks of age: (1) Arterial switch operation for transposition of the great arteries, (2) Norwood-BT and RVPA modification for hypoplastic heart syndrome, (3)Total Anomalous Pulmonary Venous Connection Repair, (4) Interrupted Aortic Arch Repair
- Cardiac Extracorporeal Life Support (ECLS)
- Solid Organ Transplantation at ≤5years of age: Heart and Liver

Decision Making based on data about survival free of major disability: determinants of bias

- Disability rates depend on – definition of disability, era of treatment, % of follow-up and to what age, BW or GA groupings,% malformations, % SGA, SES, and the denominator (population-, regional-,or hospital- based).
- Reflects -past decision making about the initiation or continuation of intensive care.
- Opinions and attitudes.

Example of definitions of disability : Preterm outcome table (POT): Bolisetty S. 2006 (Australia)

- **Impairment at 2-3 years corrected age (CA):**
- **Severe:** non-ambulatory cerebral palsy (CP), bilateral blindness, and/or mental developmental quotient (MDQ) under 3 SD below mean- (<55=0.13% of normative data)
- **Moderate:** hearing loss (aids/cochlear implant), CP walking with aids, and/or MDQ 2 to ≥ 3 SD below mean- (55-69=2.14% of normative data).
- **Mild:** CP walking without aids, and/or MDQ 1 to ≥ 2 SD below mean- (70-84 =14% of normative data).

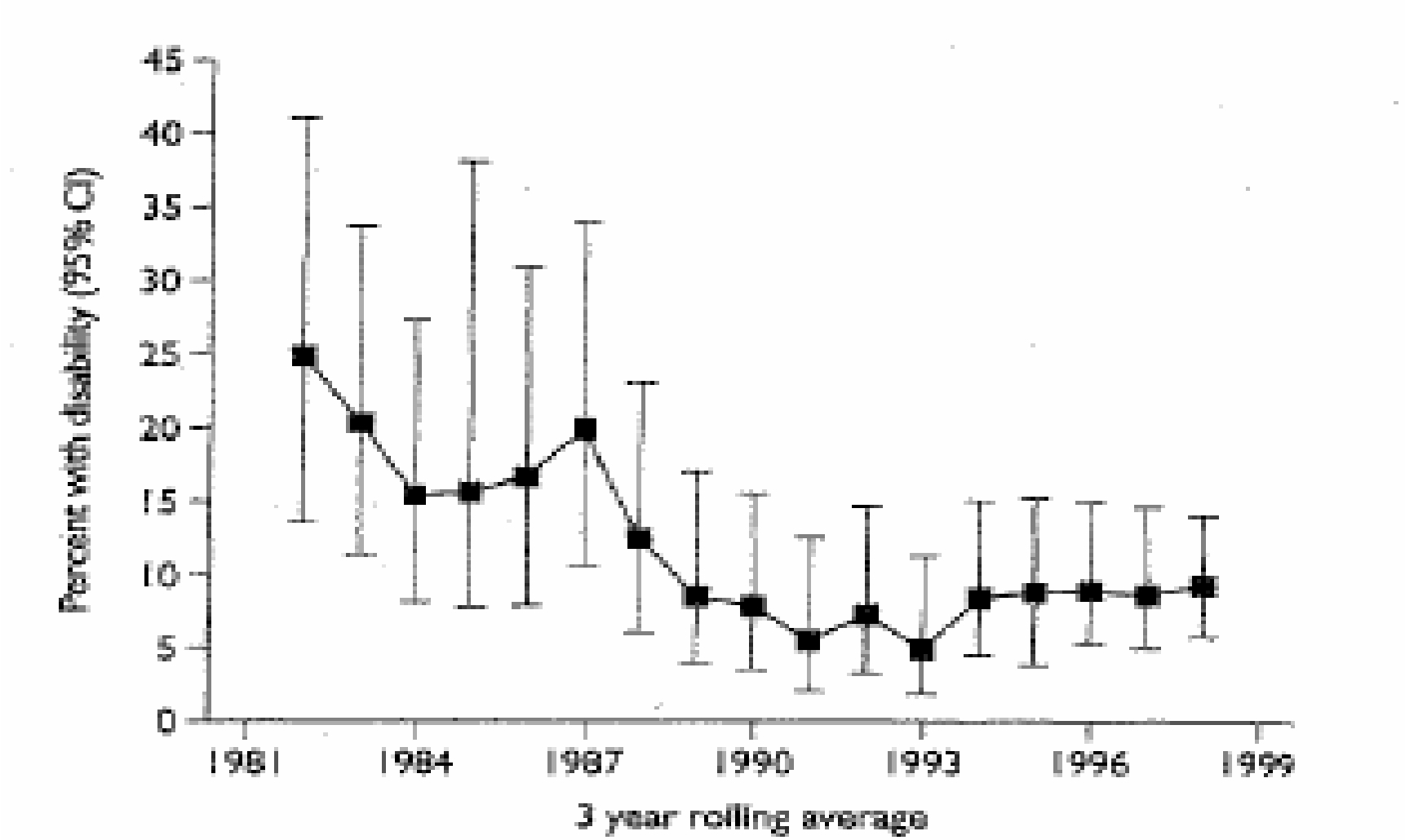
Concerns about major disabilities as outcome measures at 18-24 months

- Predictive validity and permanency of outcomes in early childhood remain questionable.
- Threshold cerebral palsy is difficult to diagnose.
- Mental impairment may be over or under diagnosed.
- Important behavioral and language diagnoses are missed.
- Inability to report school-related outcomes.
- Lack of consideration of function.

Survival free of major disability: controversy

- Increase in survival rates have been associated with increasing, unchanging, and decreasing disability rates. An increase in the proportion of survivors after extreme prematurity are free from major disability. (Marlow N, 2005; Wilson-Costello D,2007).
- **Key Questions!!!** What disabilities occur after select life-threatening events? How do they compare? Are major disability rates decreasing?

Improving Disability Rates for <1000g BW survivors:1981-99,England, Marlow, 2005



Definition of 18-24m Disability in NAB as established in 1974; Impairments that are likely Permanent: One or more of:

- **CP** (all types and severity), confirmed by one pediatric physiatrist after age 3 years.
- **vision loss** (legal blindness, visually impaired) (pediatric ophthalmologists).
- **hearing loss** (>40dB HL loss in voice range) (pediatric audiologists).
- **mental impairment** (under 3 SD below mean) (pediatric psychologists)- cut-off level based on positive predictive value of very low scores (Honzik MP, 1976).

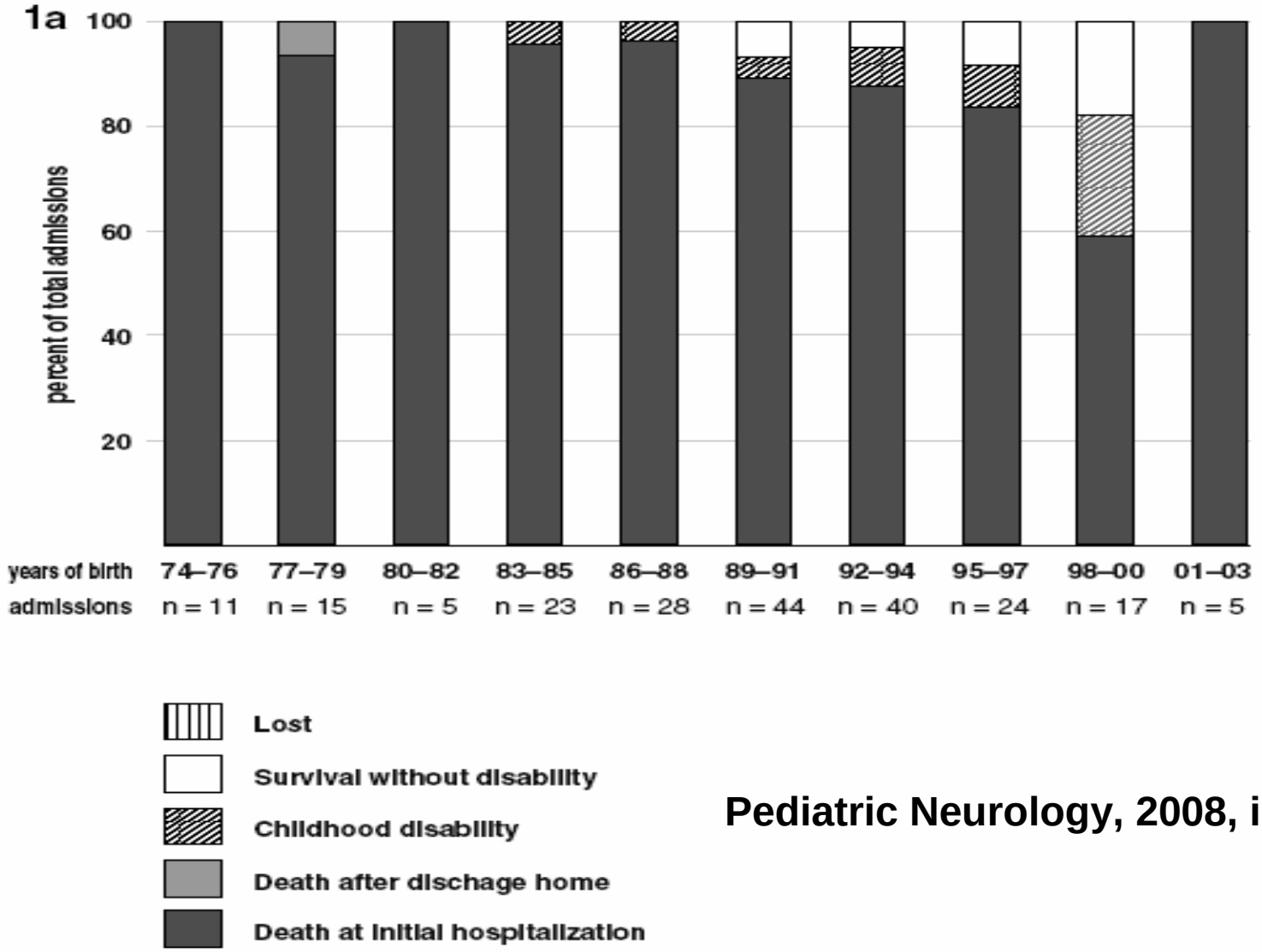
Trend Statistics

- To assess changes in percentages of disabilities among survivors, logistic regression models were used with mid points of the **10 3-year periods** as continuous covariates.
- Logistic regression with linear-spline was used to assess changes, expressed as **log- odds slope per 10 years (95% confidence intervals),** P value.

2 y outcome of 2463 infants of Albertan parents admitted to NICU of ≤28 w GA and<1250g BW, N Alberta:1974-2003

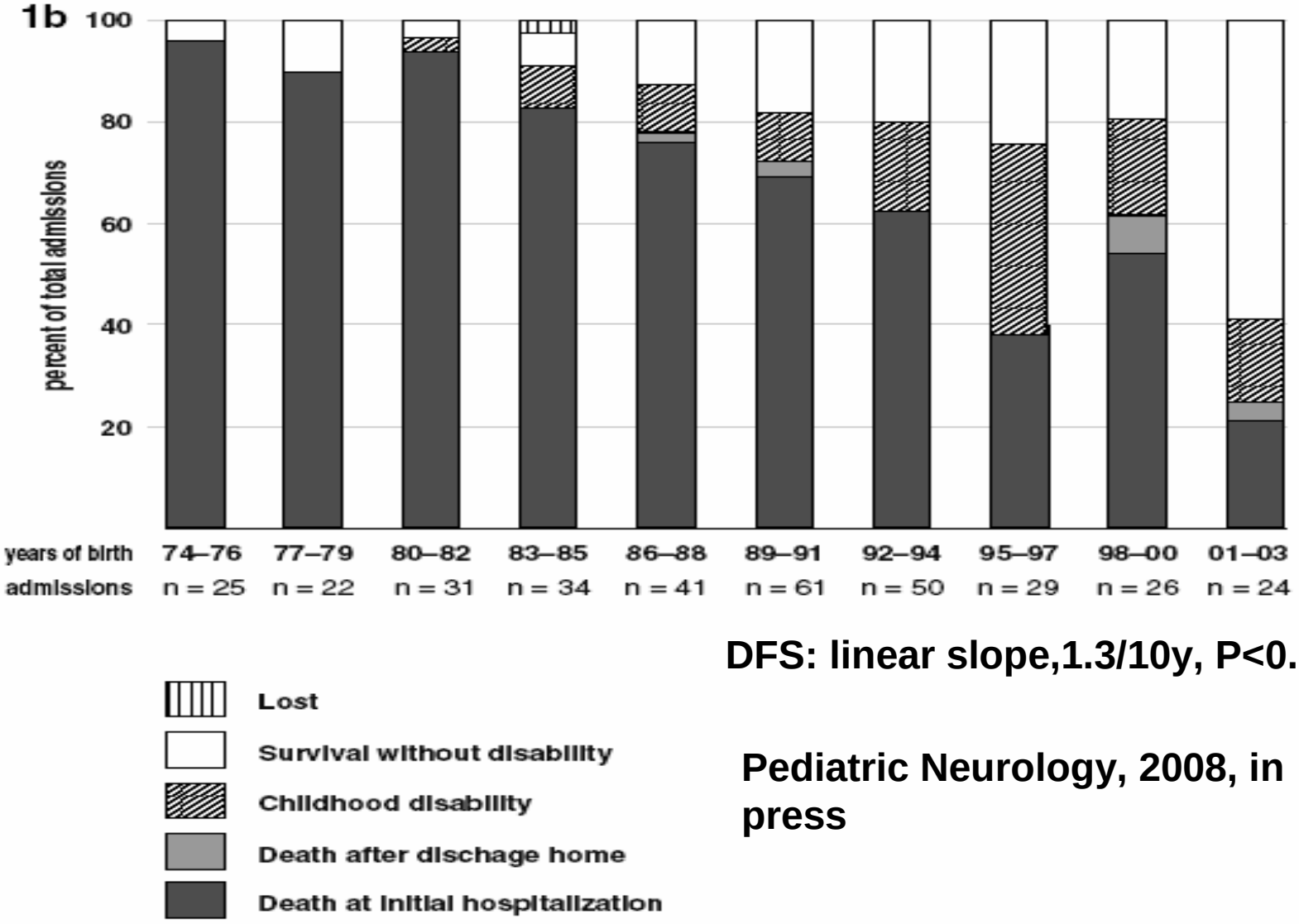
- Death in NICU: 1095 (45%)
- Death post-discharge: 29(1%)
- Survival increased : 26%-88%
- Loss to follow-up: 60(2%)
- Survivors with outcome: 1279
- Disabled: 304(12%); disability-free: 975(40%)
- Disability-free survivors: 38(1974) to 163(2003)
- Disability-free survival:22-77%,log odds P<0.001

Disability-free survival: 212 infants of ≤23 w GA and <1250g BW: 1974-2003, P=ns



Pediatric Neurology, 2008, in press

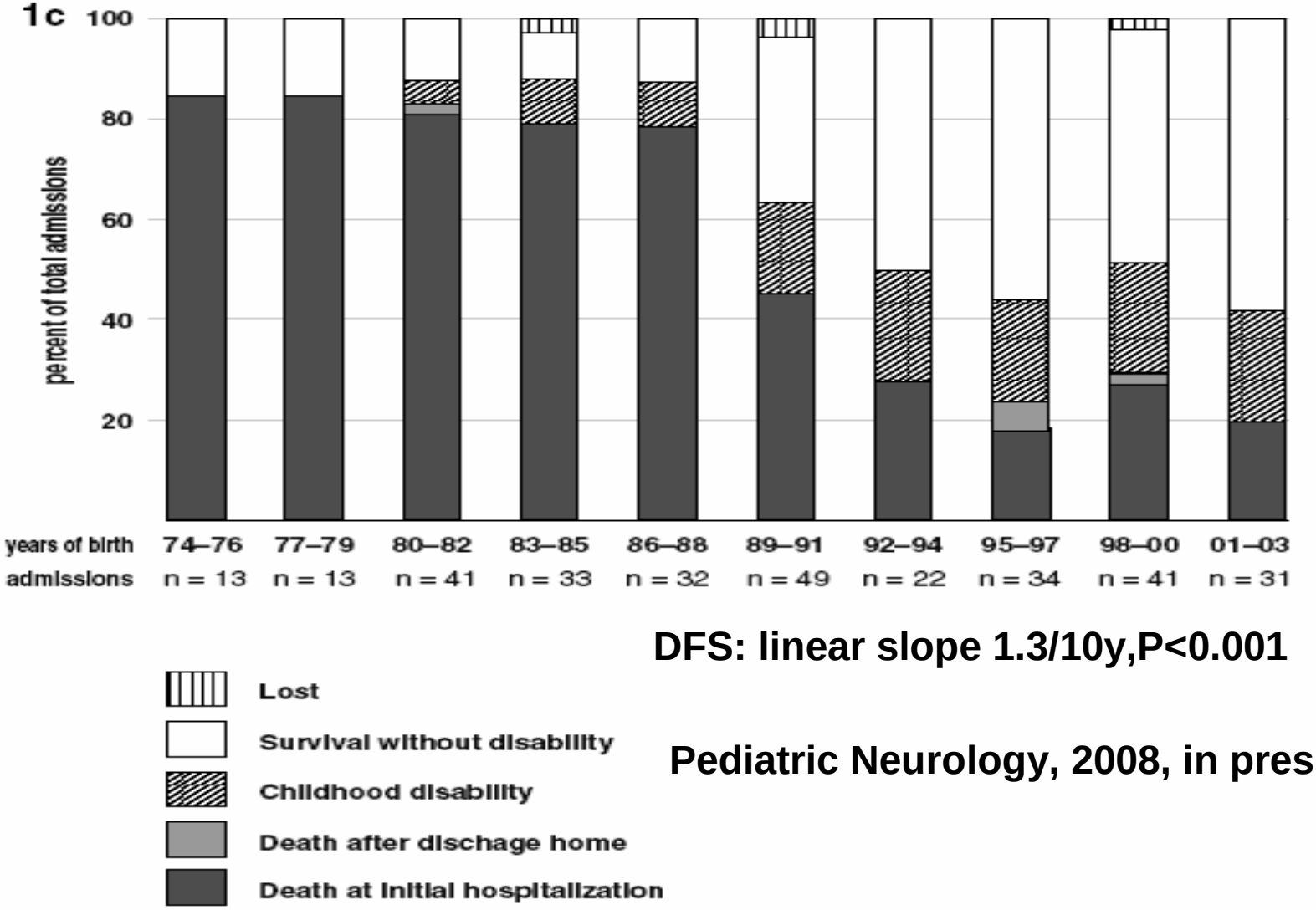
Disability-free survival trend: 343 infants 24w GA and <1250g BW: 1974-2003



DFS: linear slope,1.3/10y, P<0.001

Pediatric Neurology, 2008, in press

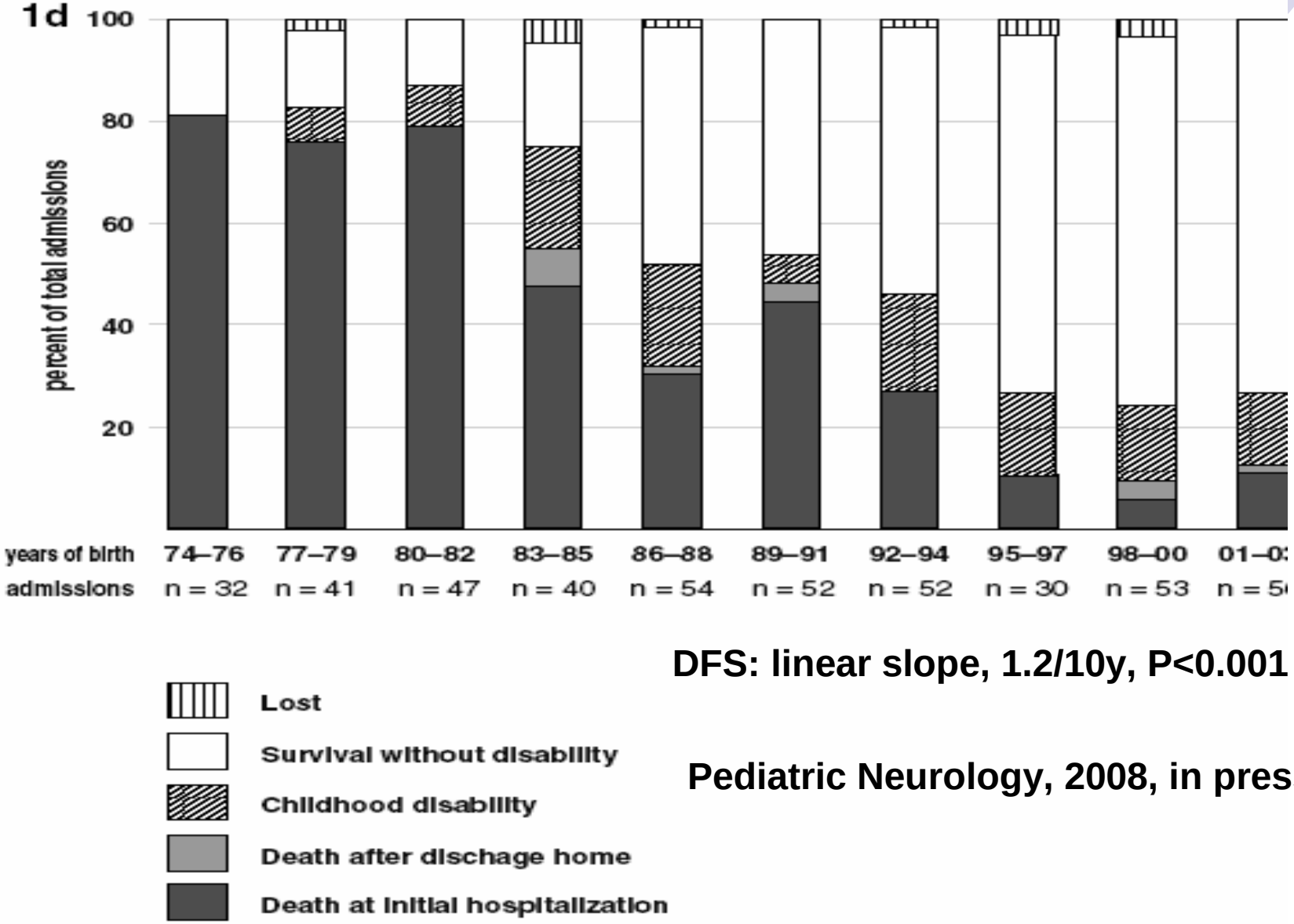
Disability-free survival trend: 309 infants of 25 w GA and <1250g BW: 1974-2003



DFS: linear slope 1.3/10y,P<0.001

Pediatric Neurology, 2008, in press

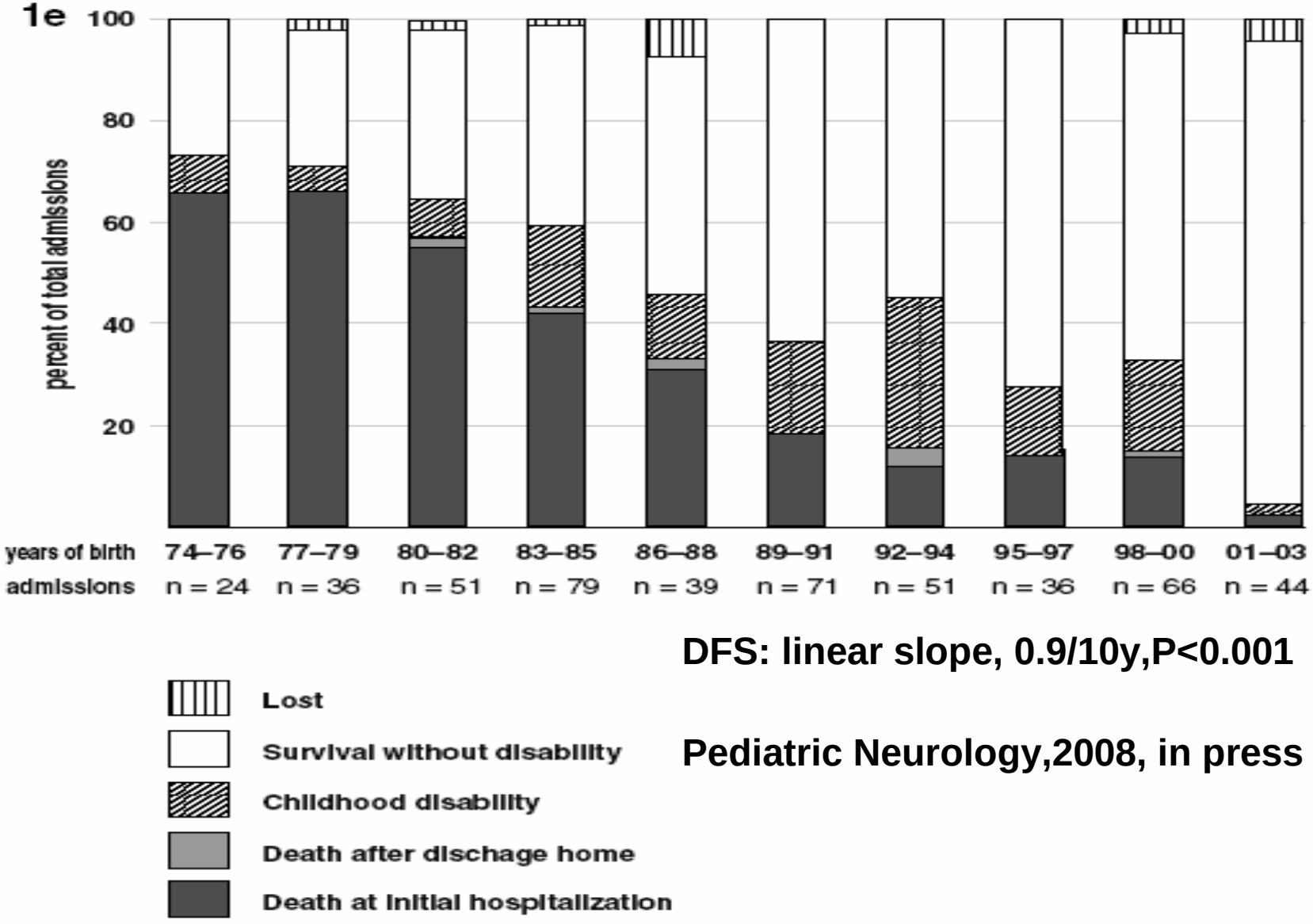
Disability-free survival trend: 457 infants of 26 w GA and < 1250g BW: 1974-2003



DFS: linear slope, 1.2/10y, P<0.001

Pediatric Neurology, 2008, in press

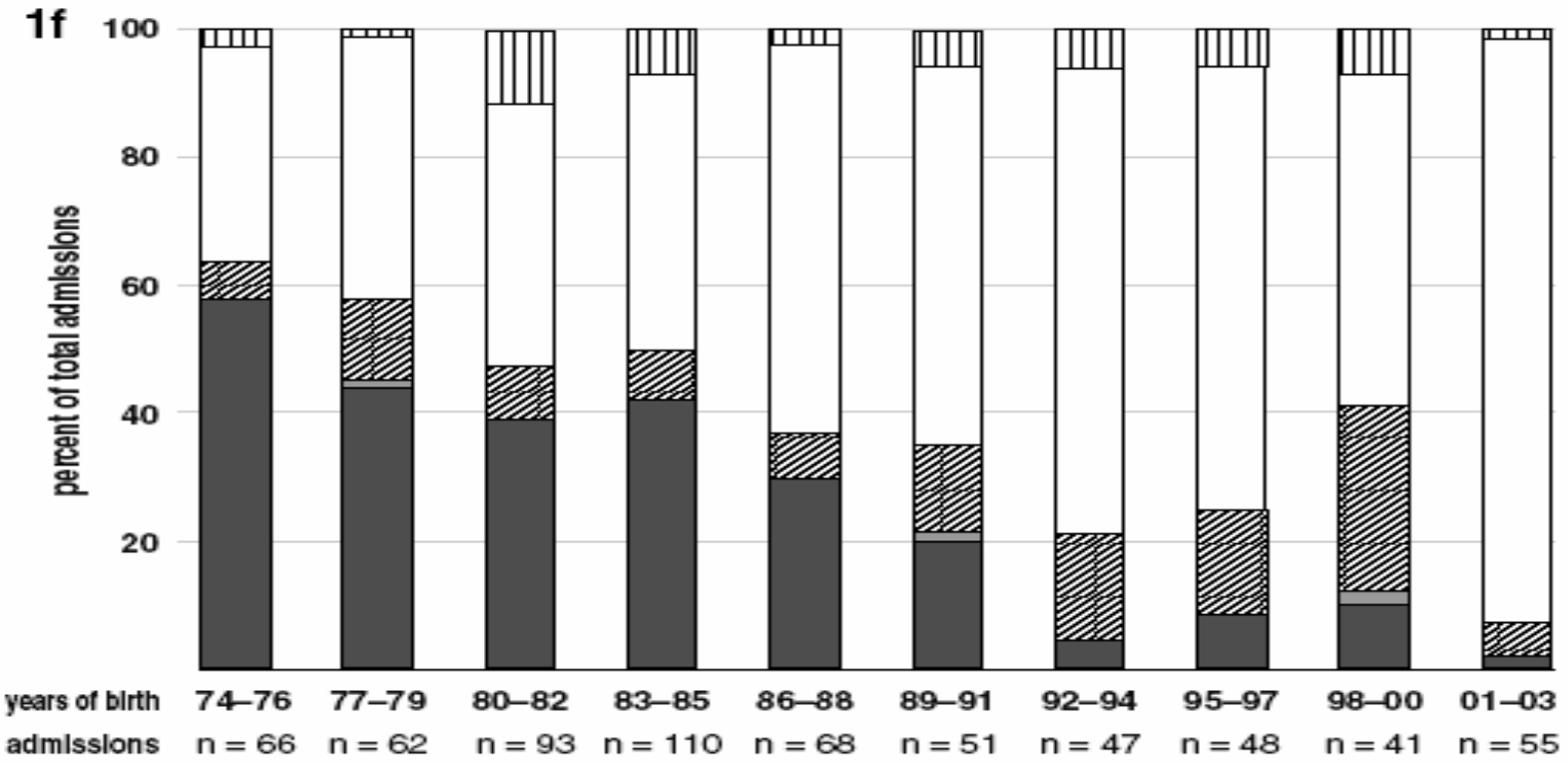
Disability-free survival trend: 501 infants of 27 w GA and < 1250g: 1974-2003



DFS: linear slope, 0.9/10y,P<0.001

Pediatric Neurology,2008, in press

Disability-free survival trend: 641 infants of 28 w GA and < 1250g BW: 1974-2003



DFS: linear slope, 0.8/10y,P<0.001

Pediatric Neurology, 2008, in press

Predictors of Disability among 1279 survivors of ≤ 28 w GA and <1250g BW : 1974-2003

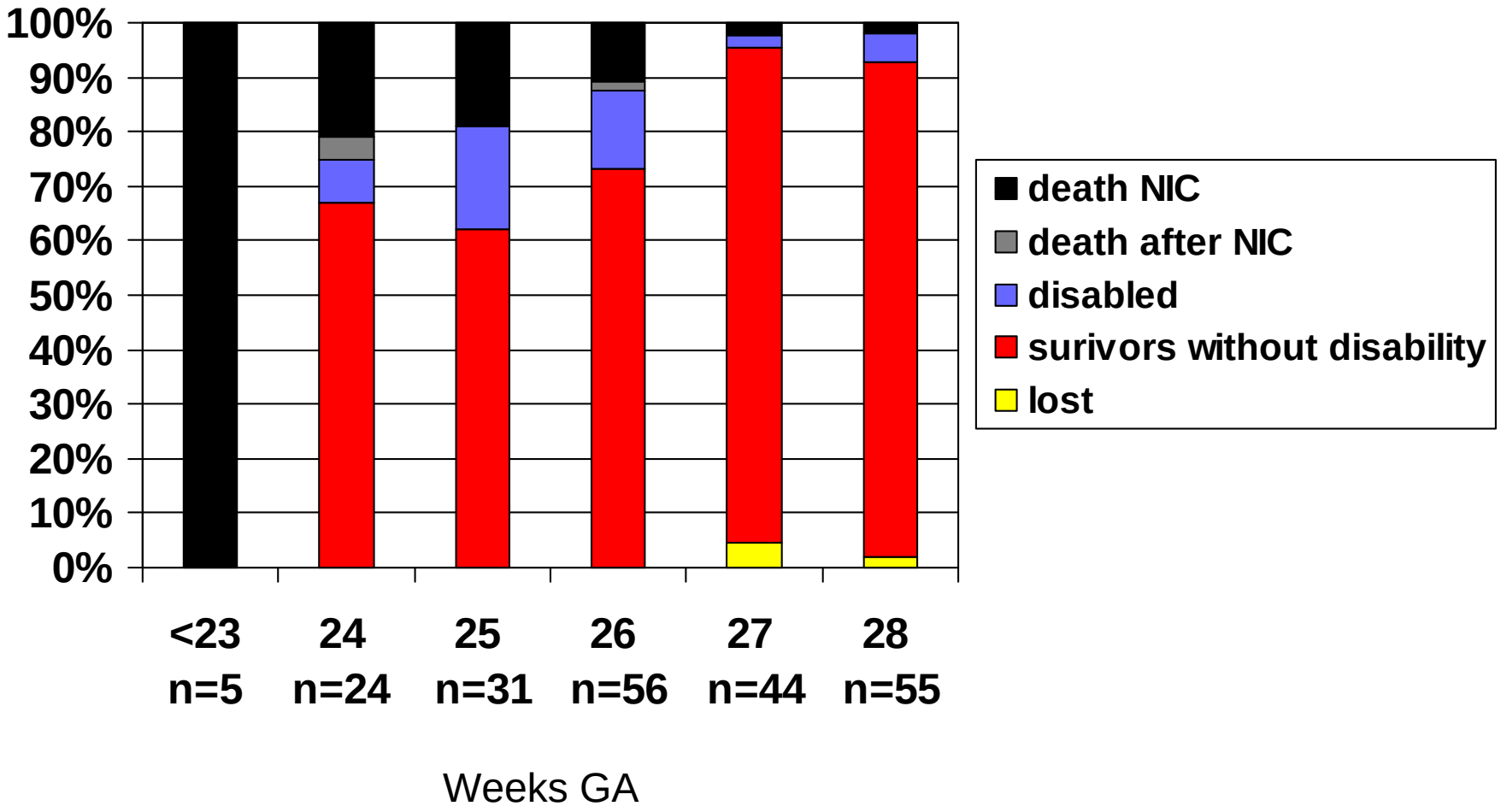
Descriptor	No N = 975	Yes N =304	P T-test
SES Index	37(13)	33(13)	<0.001
GA-weeks	26.7(1.3)	26.2(1.5)	<0.001
BW-grams	945(117)	869(185)	<0.001

SES-Blishen Index: mean=43(13)(range18-102)

Predictors of Disability among 1279 survivors of ≤ 28w GA and <1250g BW: 1974-2003: Odds Ratios(95%CI)

- ICH,g 3/4 5.7 (4.2,7.6)
- Lazer/Cryo 4.3 (2.8,6.5)
- BPD-O2,36w 3.1 (2.4,4.0)
- CPR(birth) 2.3 (1.5,3.6)
- GI- surgery 2.2 (1.4,3.4)
- Malformations 2.0(1.5,2.8) (56/236 FASD)
- PDA-ligation 1.7 (1.2,2.5)
- Vaginal delivery 1.3 (1.09,1.6)
- Sex-male 1.2 (1.03,1.4)
- Outborn, SGA, multi births ns

% overall outcome by GA for 215 preterms admitted to NIC by each GA of ≤28w and <1250g BW: 2001-2003



Cerebral Palsy (CP): Definition

Rosembaum P et al: Dev Med Child Neurol

2007; 49: Supp #109: 8-14

- group of permanent disorders of movement and posture
- causing activity limitation
- attributed to non-progressive disturbances of fetal/ infant brain

Prevalence of Cerebral Palsy depends upon:

- Diagnostic accuracy
- age of child
- Population-, regional-, or hospital-based denominator
- Years of birth
- Inclusion/exclusion of post-neonatally derived cases and/or congenital brain malformation

Cerebral Palsy- severity

- **Gross Motor Function Classification System** for Cerebral Palsy (Palisano R, et al, 1997) with motor developmental curves, level I, II, III predict independent walking (Rosenbaum P et al, 2002)
- Non-ambulation determined by level IV/V – transported or power mobility (Rosenbaum P et al, 2002)
- Good reliability over age 2 years

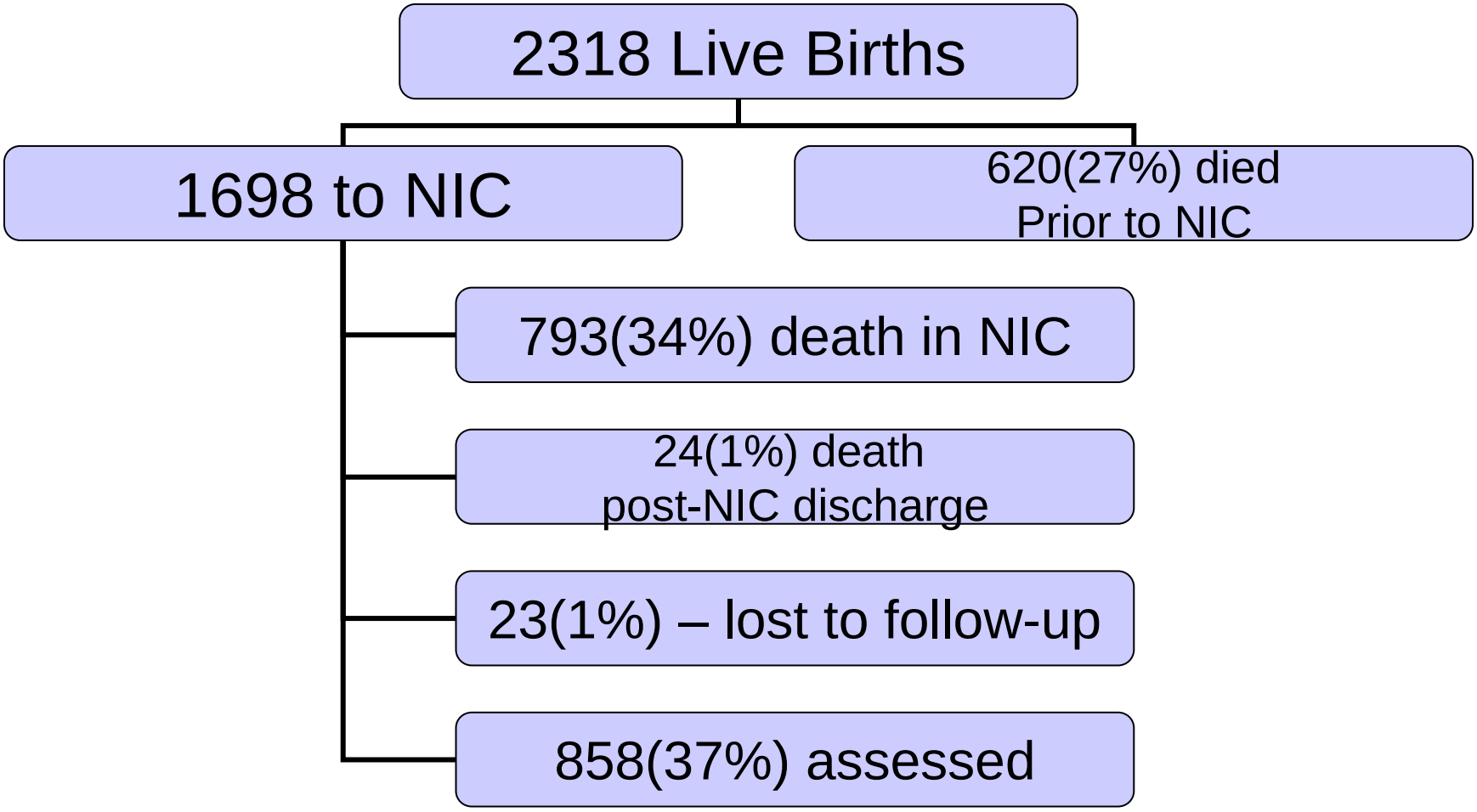
Cerebral Palsy Prevalence: preterms

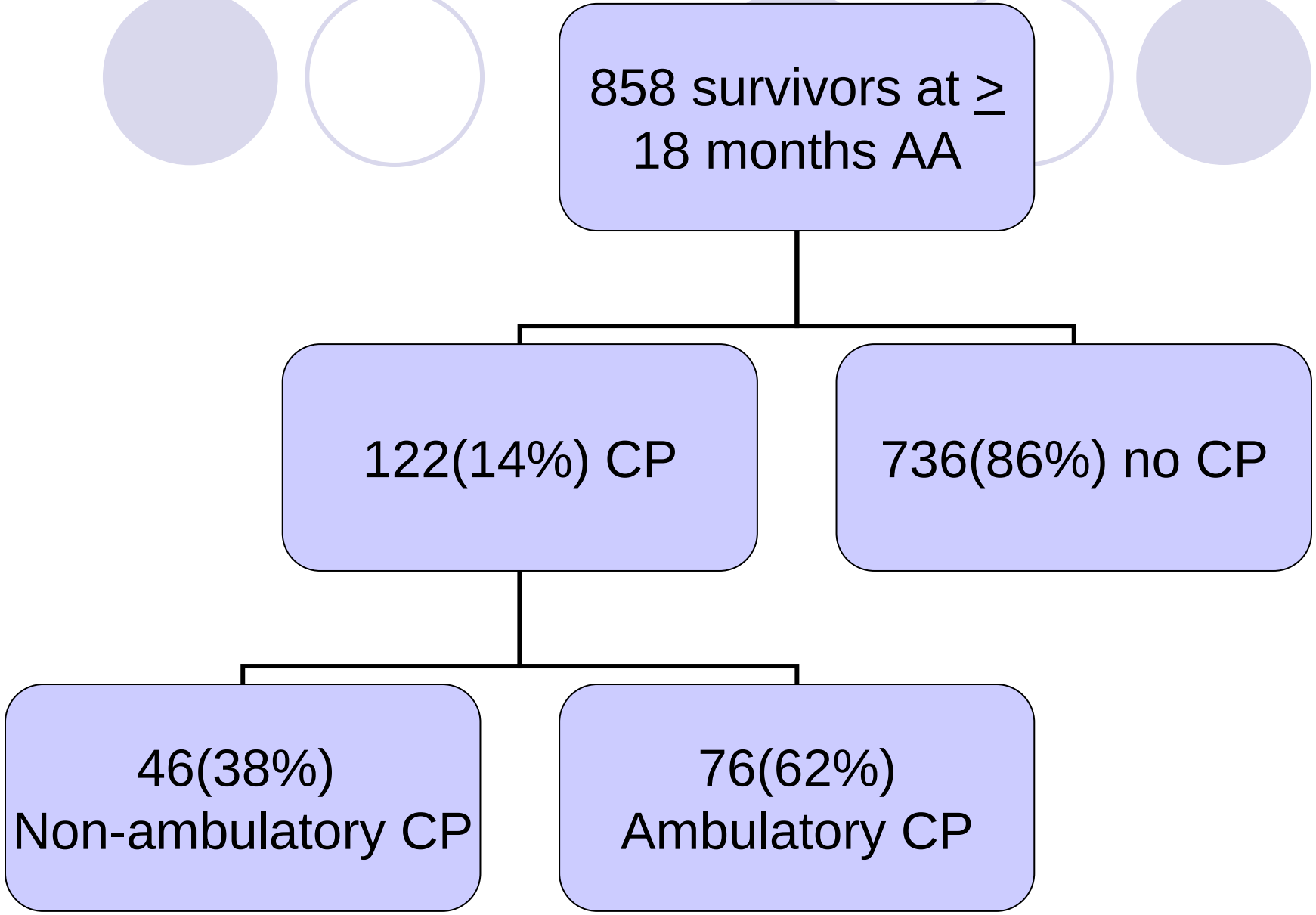
- Population-based GA- or BW- specific CP rates in extreme prematurity vary depending on birth years: from 40-152/1000 live births.
- Europe for 1996,<1000g BW, - 39.5/1000 (Platt MJ, 2007)
- Sweden for 1995-8, 28 w GA,- 77/1000 (Himmelmann K, 2005)
- USA for early 2000s (Perinatal center-based cohort) for <1000g BW, -5% of survivors (Wilson-Costello D, Pediatrics, 2007)

Our Study: JAMA, 2007

To present a unified assessment of change in population-based GA-specific prevalence rates of CP among extremely premature infants.

Live Births to Alberta residents in NAB of 20-27 weeks GA and 500-1249 g BW: 1974-2003




858 survivors at ≥ 18 months AA
122(14%) CP
736(86%) no CP
46(38%) Non-ambulatory CP
76(62%) Ambulatory CP

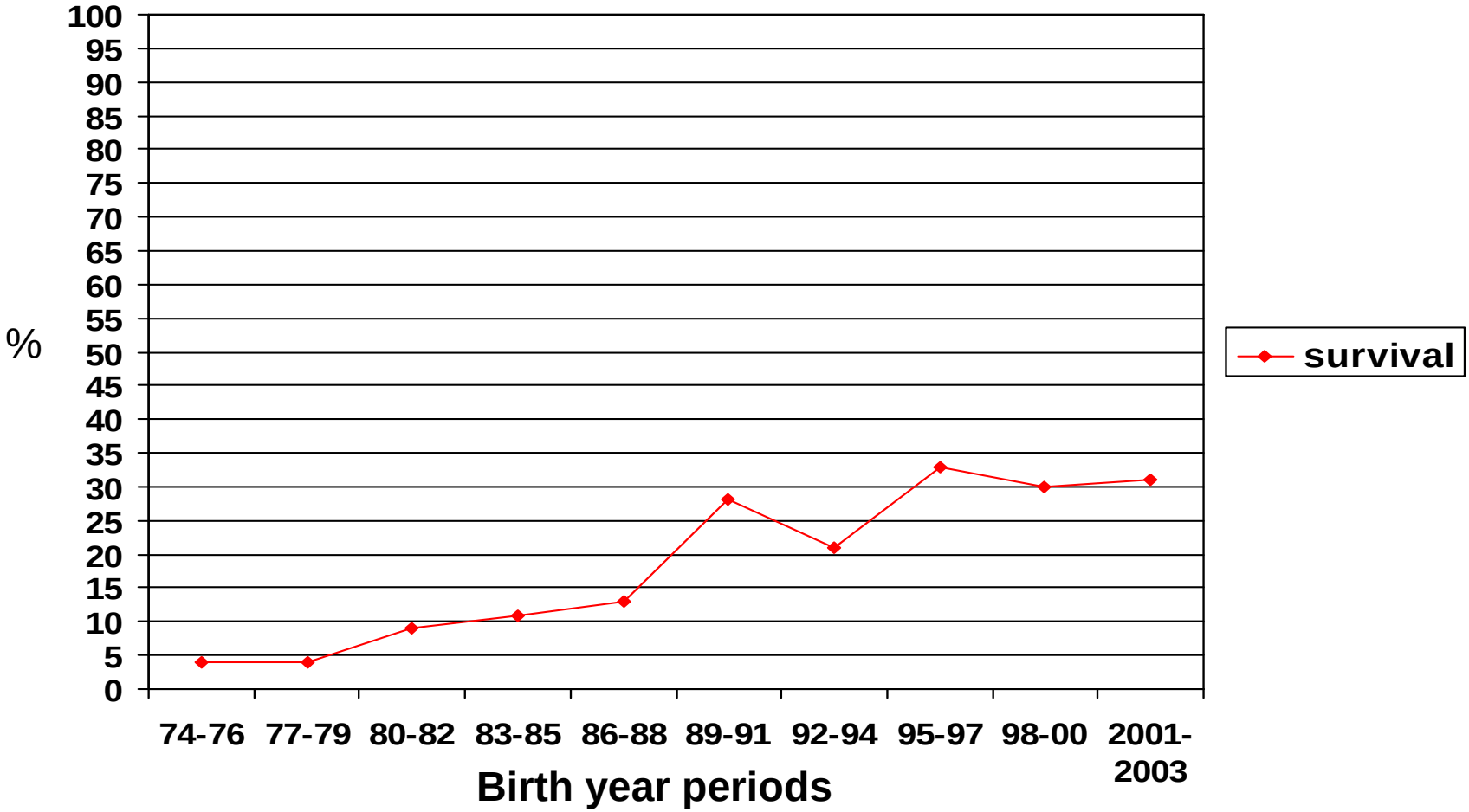
GA- specific population-based CP prevalence rates for preterms of 20 to 27 w GA and 500-1249 g BW:1974-2003

1974-03: Population-based survival increased, 12-51%;
Hospital-based survival increased, 18-84%
(Congenital Malformations not excluded)

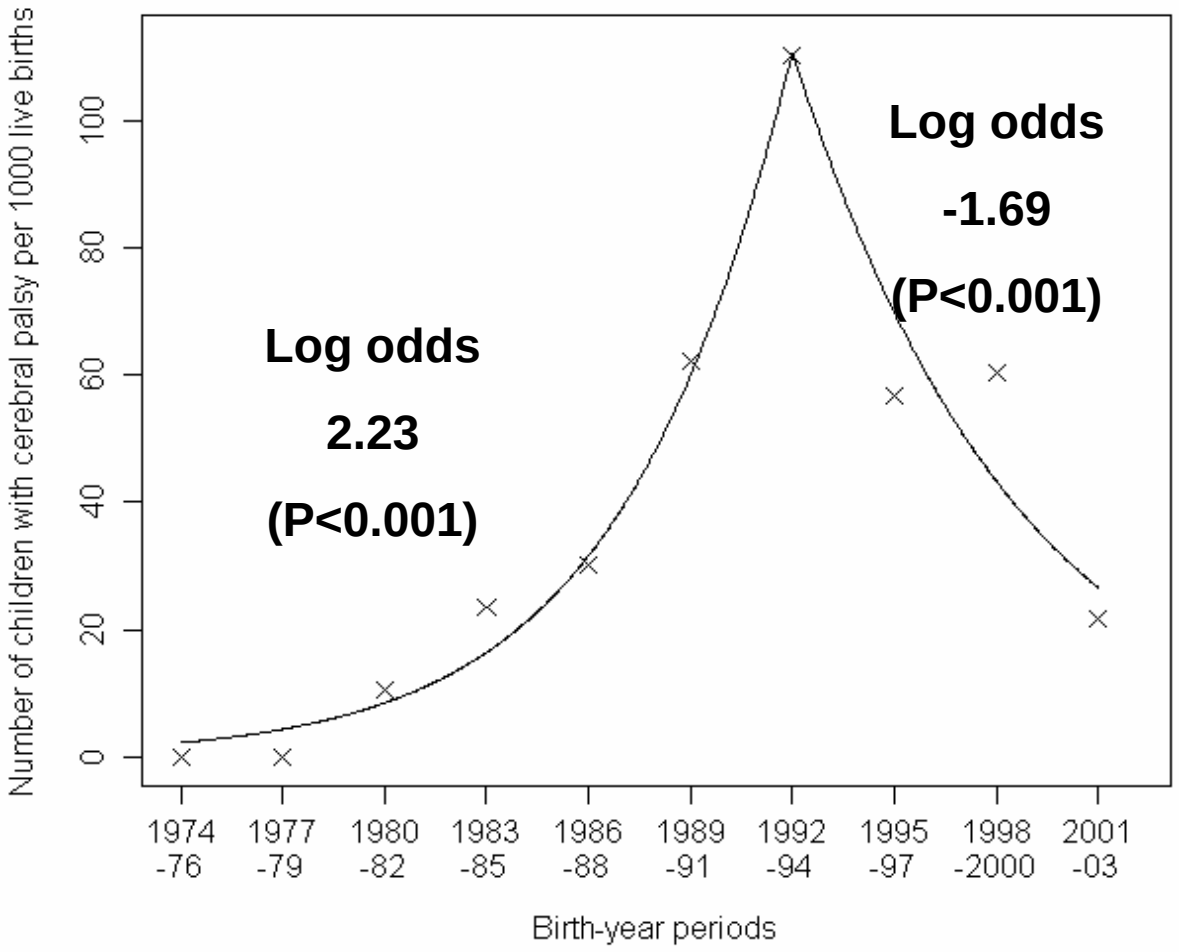
1992-94: CP rate peaked, 131/1000 LBs;
non-ambulatory CP rate peaked, 59/1000 LBs

2001-03: CP rates, 19/1000 LBs;
non-ambulatory CP, 8/1000 LBs

2 year population-based survival for LBs of 20-25w GA and 500-1249g BW over 10 birth-year periods: 1974-2003

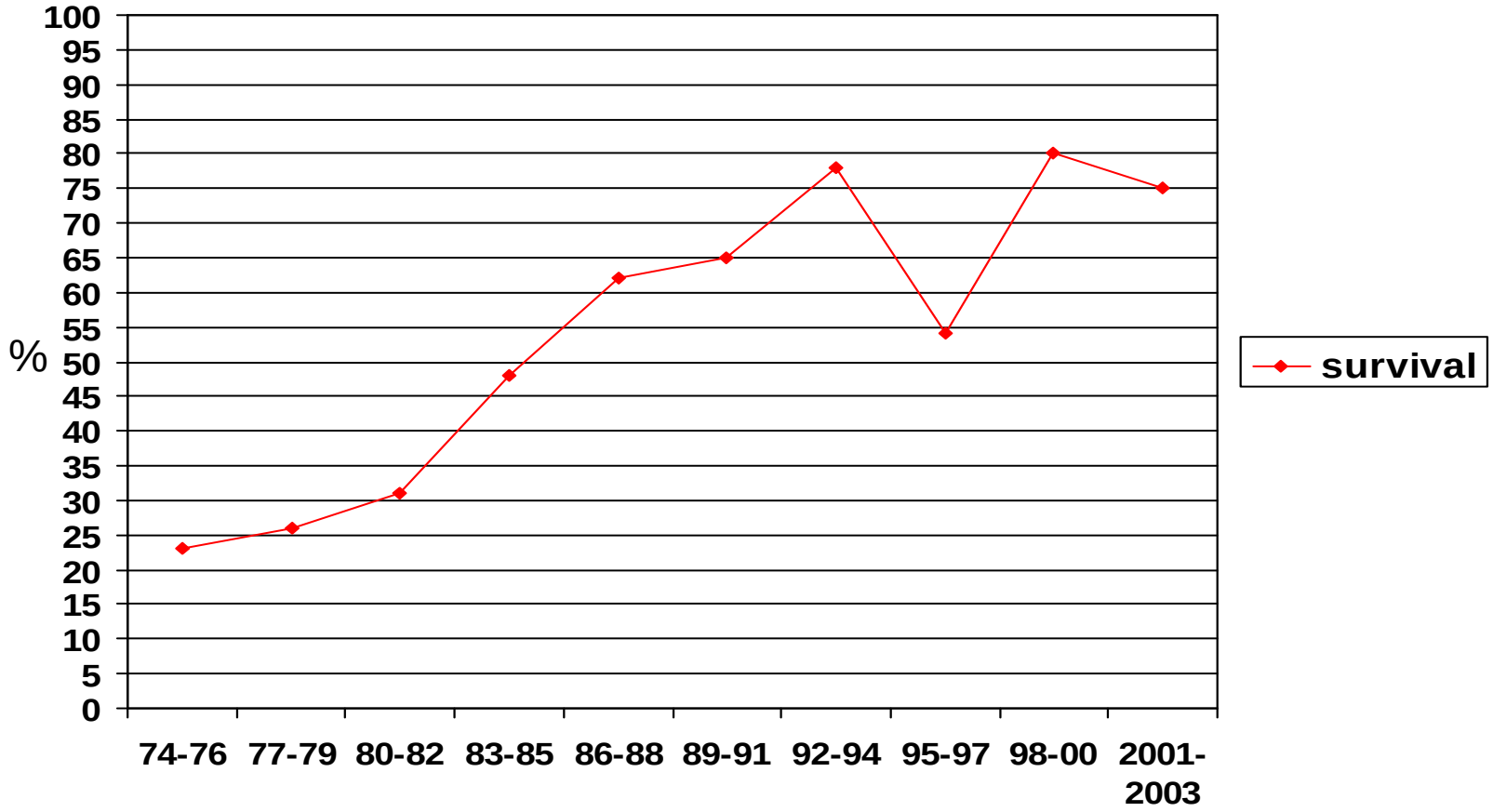


GA-specific population-based CP rates for 20-25w GA and 500-1249g BW: 1974-2003: JAMA, 2007;297:2733-40

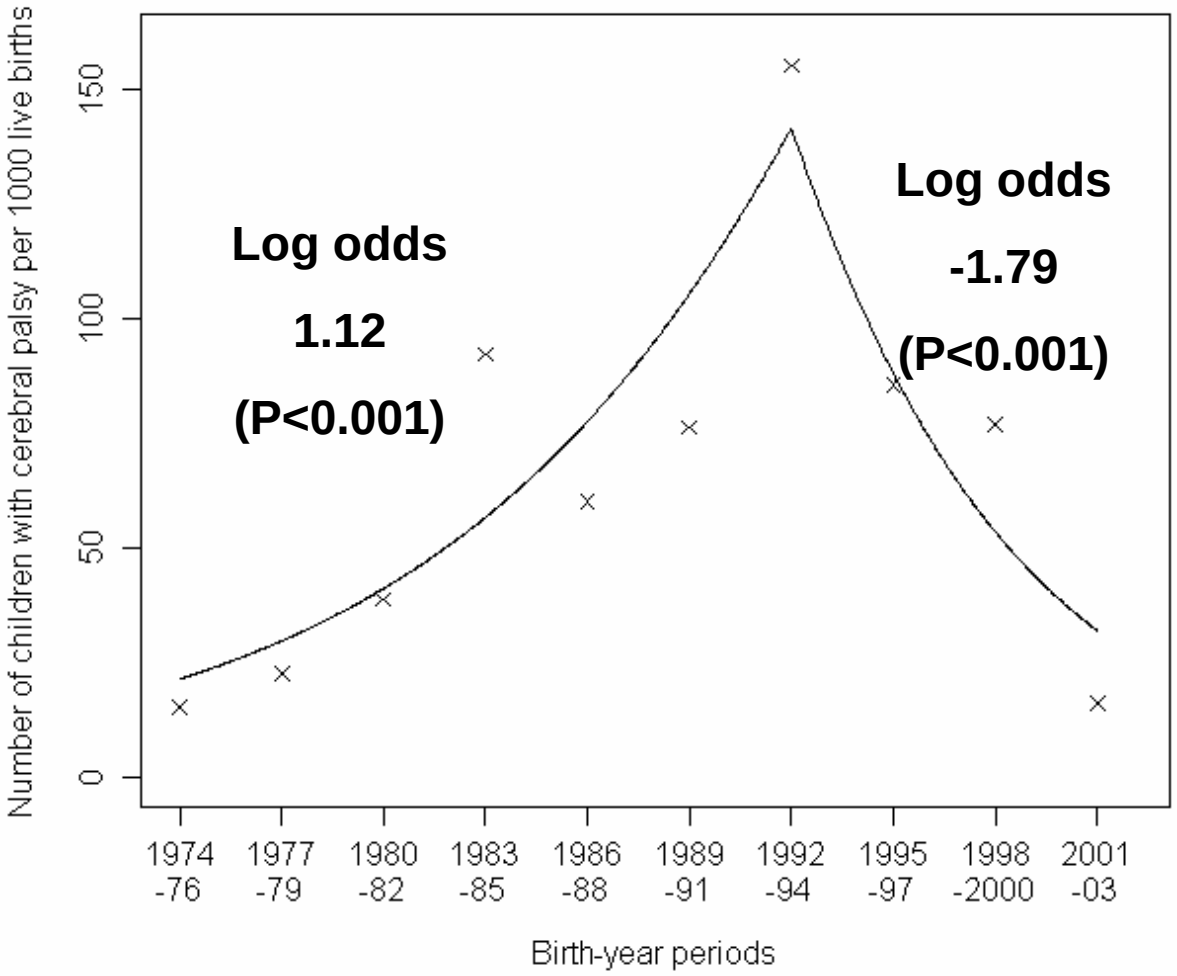


22/1000 (01-03)

2 year population-based survival for LBs of 26-27w GA and 500-1249g BW over 10 birth-year periods: 1974-2003



GA-specific population-based CP rates for 26-27w GA and 500-1249g BW: 1974-2003: JAMA, 2007;297:2733-40



16/1000 (01-03)

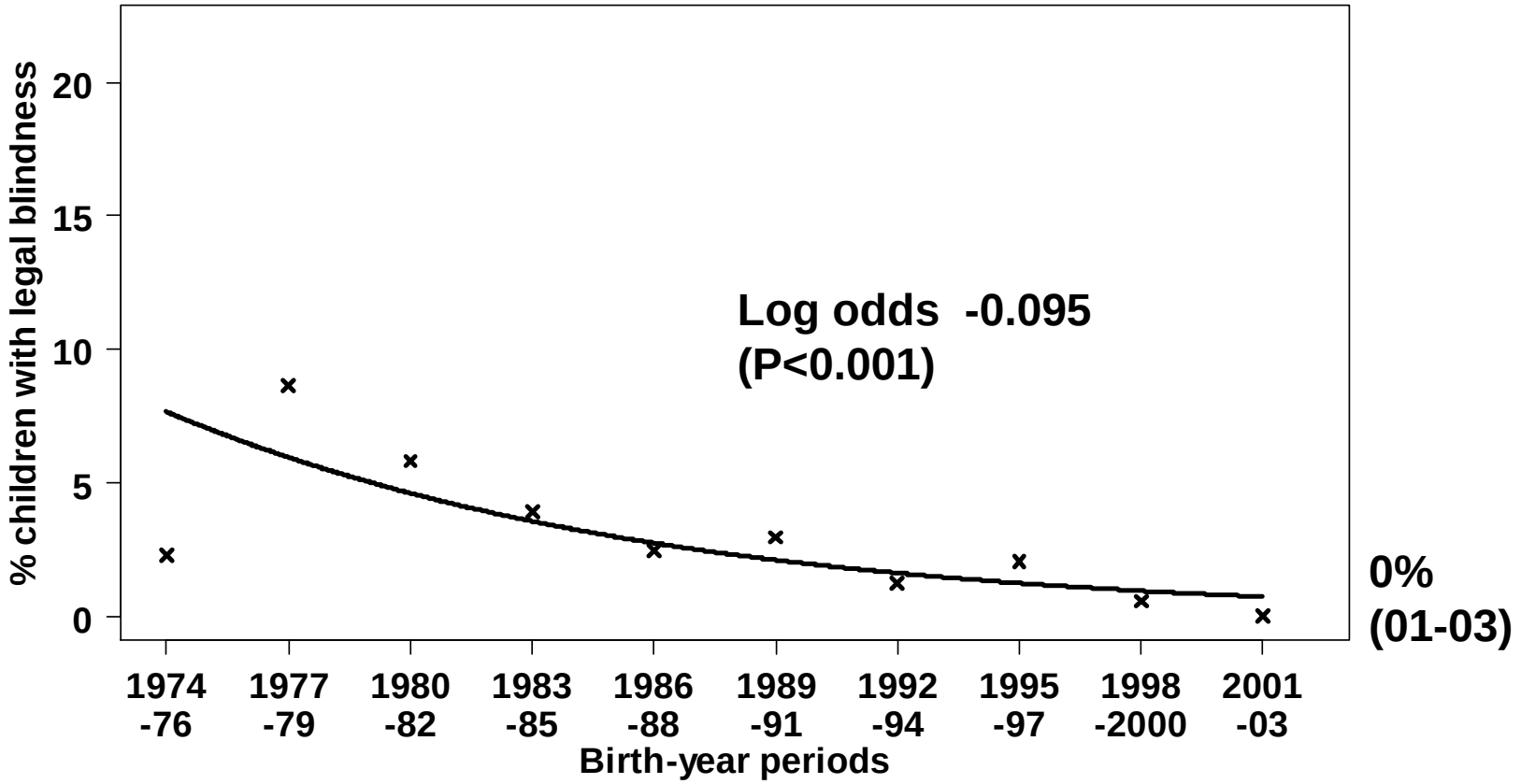
Cerebral Palsy at 2 y after Complex Therapies:

- Complex cardiac surgery at ≤ 6w of age: 2(1.02%) of 195, one child -3 limbs, another- 2 limbs- both spastic and ambulatory
- Cardiac ECLS at <5y of age: 2(13%) of 16, both 2 limbs-spastic, same side
- Cardiac Transplantation at ≤ 5 y of age: 1(5.9%) of 17, 4 limbs-spastic
- Liver Transplantation at ≤ 5y of age: 1(2.6%) of 39, 4 limbs-spastic

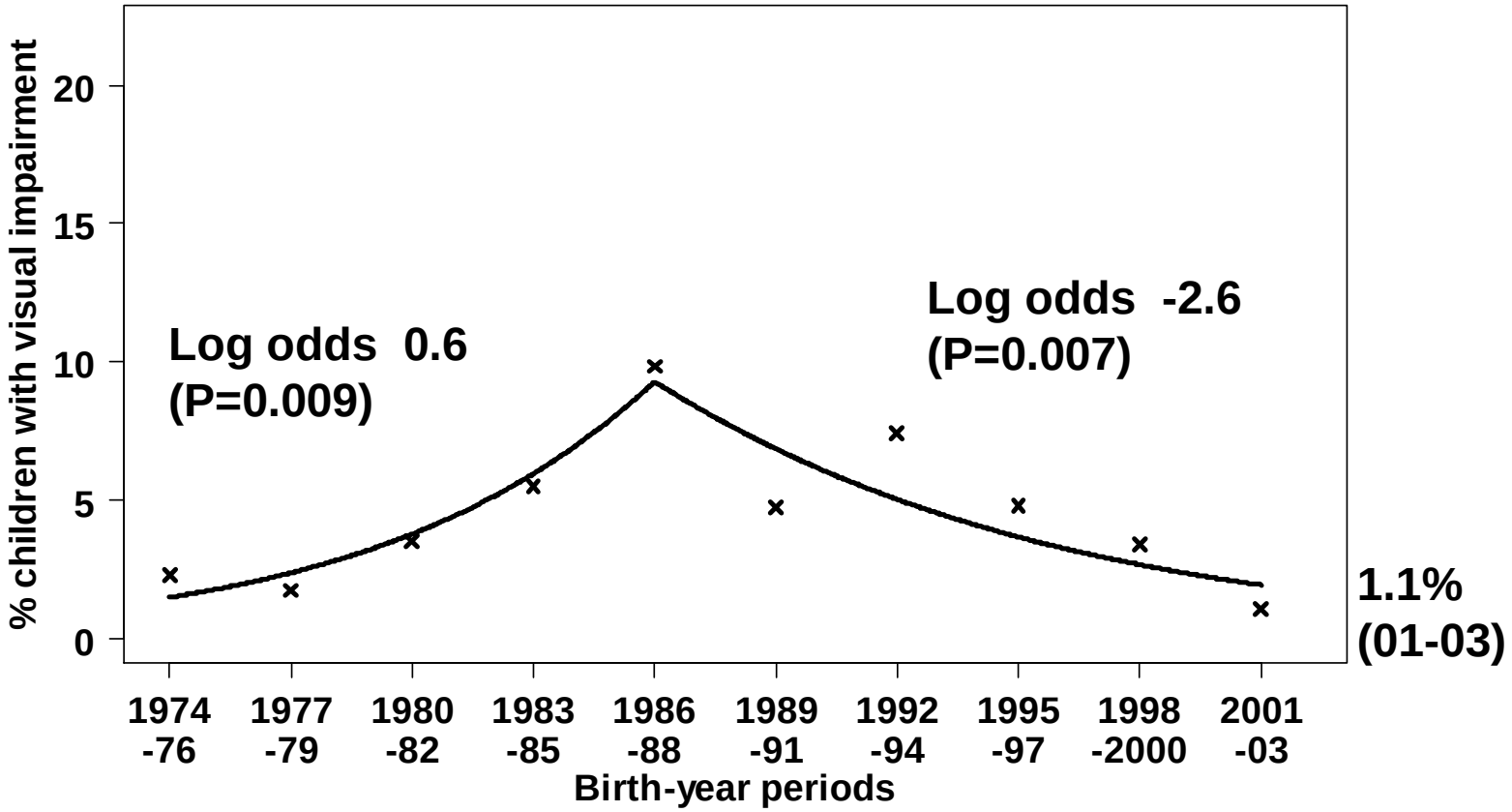
Vision Loss: Legal Blindness,<20/200, or Impairment,<20/60 in the best seeing eye after correction

- Less severe ROP (Chow LC, 2003);more ROP (Slidborg C, 2008)
- Improved functional outcomes (McLoone E, 2006)
- Reduced legal blindness for birth years 2000-02, 500-999g BW, 1% of survivors (Wilson-Costello D, 2007)

Trend in legal blindness (n=30) among 1279 survivors: ≤28w GA and <1250g BW: 1974-2003



Trend in Visual impairment (n=59) among 1279 survivors: ≤28w GA and <1250g BW: 1974-2003



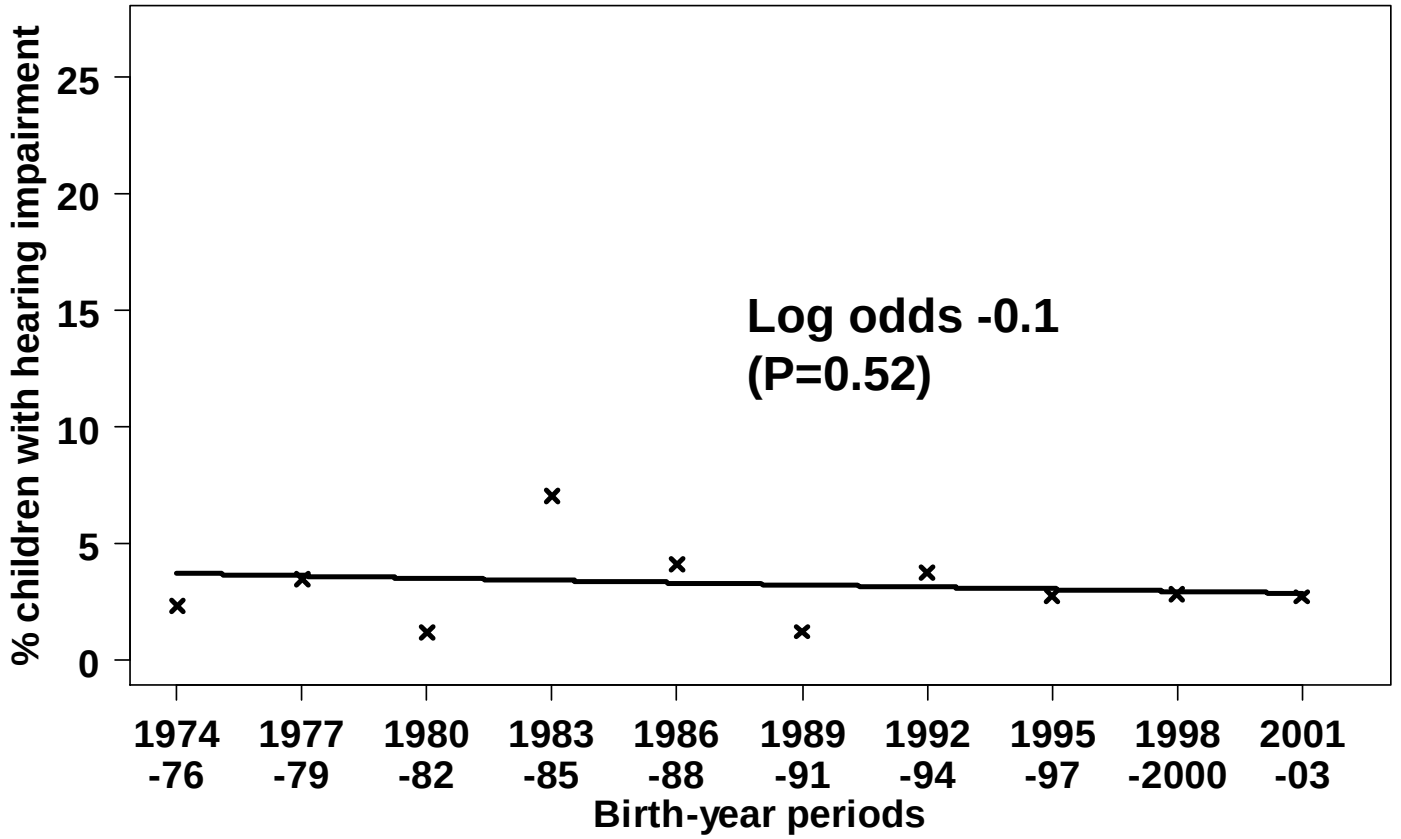
Vision Loss at 2 y after Complex Therapies:

- Complex cardiac surgery at ≤ 6 w of age: 2(1.02%) of 195, 1 ocular albinism, 1 cortical impairment
- Cardiac ECLS at < 5 y: 0(0%) of 16
- Cardiac transplantation at ≤ 5 y: 1(5.9%) of 17, cortical impairment
- Liver transplantation at ≤ 5y: 1 (2.6%) of 39, cortical impairment

Neural Hearing Impairment

- Under 2 y sensorineural hearing loss may be reported in various ways, e.g. as an uncorrected loss in the better ear of >40dbHL within the range of 250-4000Hz, requiring aids, etc. Present lowest reported: -1% of extremely preterm survivors (Wilson-Costello, 2007) ; -2% of BPD survivors (Kobaly K,2008)
- Auditory Neuropathy is becoming more commonly diagnosed as a permanent hearing loss among NICU survivors.

Trend in Hearing Impairment (n=40) among 1279 survivors: ≤ 28w GA and <1250g BW: 1974-2003



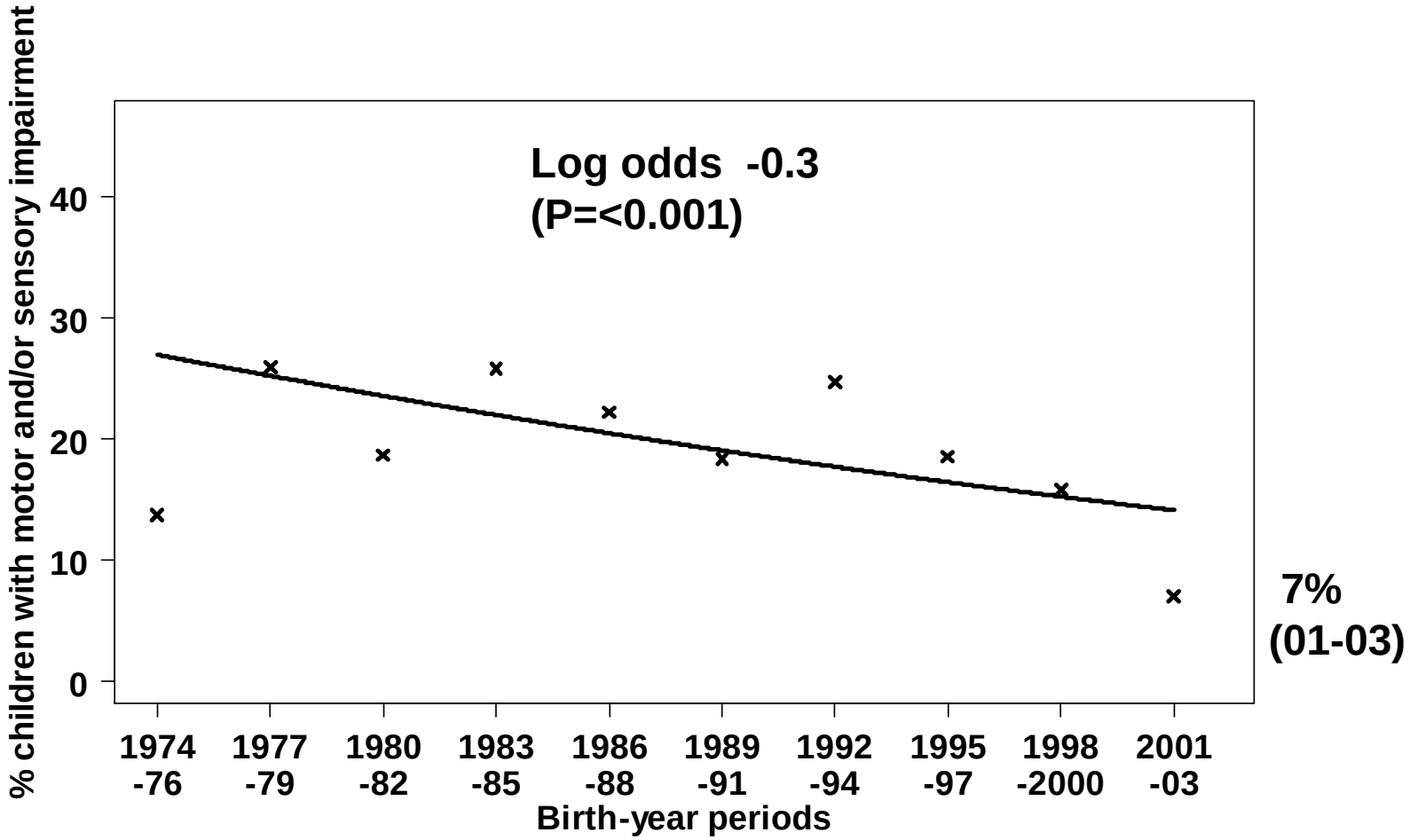
Predictors of Permanent Hearing Loss in 40 of 1279 survivors of ≤28w and<1250g: 1974-2003 Odds Ratios (95% CI)

- Oxygen at 36 w GA 4.6(1.98,10,71)
- Gastrointestinal surgery 4.3(1.96, 9.31)
- PDA ligation 2.1(1.03,4.43)
- SES 0.97(0.94,1.00)
- These 4 predictors give an area under the curve of 0.79

Permanent Hearing Loss at 2 y after Complex Therapies:

- Complex cardiac surgery at ≤ 6 w: 7(3.6%) of 195. NOTE: Norwood-BT (1996-2002),1(3%) of 30; RVPA (2002-2005), 6 (23%) of 26- one with cochlear implant.
- Cardiac ECLS at < 5 y: 0(0%) of 16
- Cardiac transplantation at ≤ 5 y: 0(0%) of 17
- Liver transplantation at ≤ 5 y: 0(0%) of 39

Trend in Motor and/or Sensory Disability (n=237) among 1279 survivors ≤28w GA and <1250g BW: 1974-2003



Neurodevelopmental Standardized Measures

the younger the age tested, the lower the correlation with school age IQ and achievement

Mental and Motor Developmental Levels

-reported as standard scores based on the bell-shaped curve

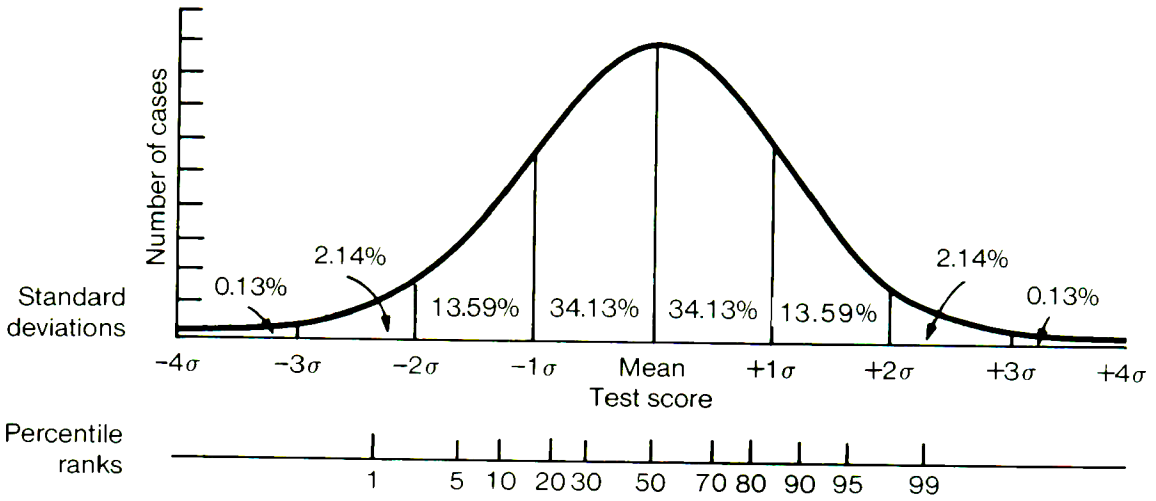
-used as continuous data

mean = 100

standard deviation (SD) = 15

$\bar{X}$ (SD)	Range	% of total population
100(1SD)	85-114	68%
100(2SD)	70-129	95%

Bell-Shaped Curve



Population Curve

mean +1SD = 68%

mean +2SD = 95%

below 2SD(below 70) = 2.27%

Mental Developmental Scores: are not IQ

- Common tests of early childhood development are useful clinically for planning early intervention. Results may be incorrectly interrupted in follow-up research literature as permanent and/or as IQ scores.
- The Bayley Scales of Infant Development versions- I (1969) and II (1993)-Mental Developmental Index (MDI). Concern that the 1993 version resulted in lower MDI scores (Vohr,1999).
- **Key Question!!!** Did the 1993 version result in lower scores for preterm infants?

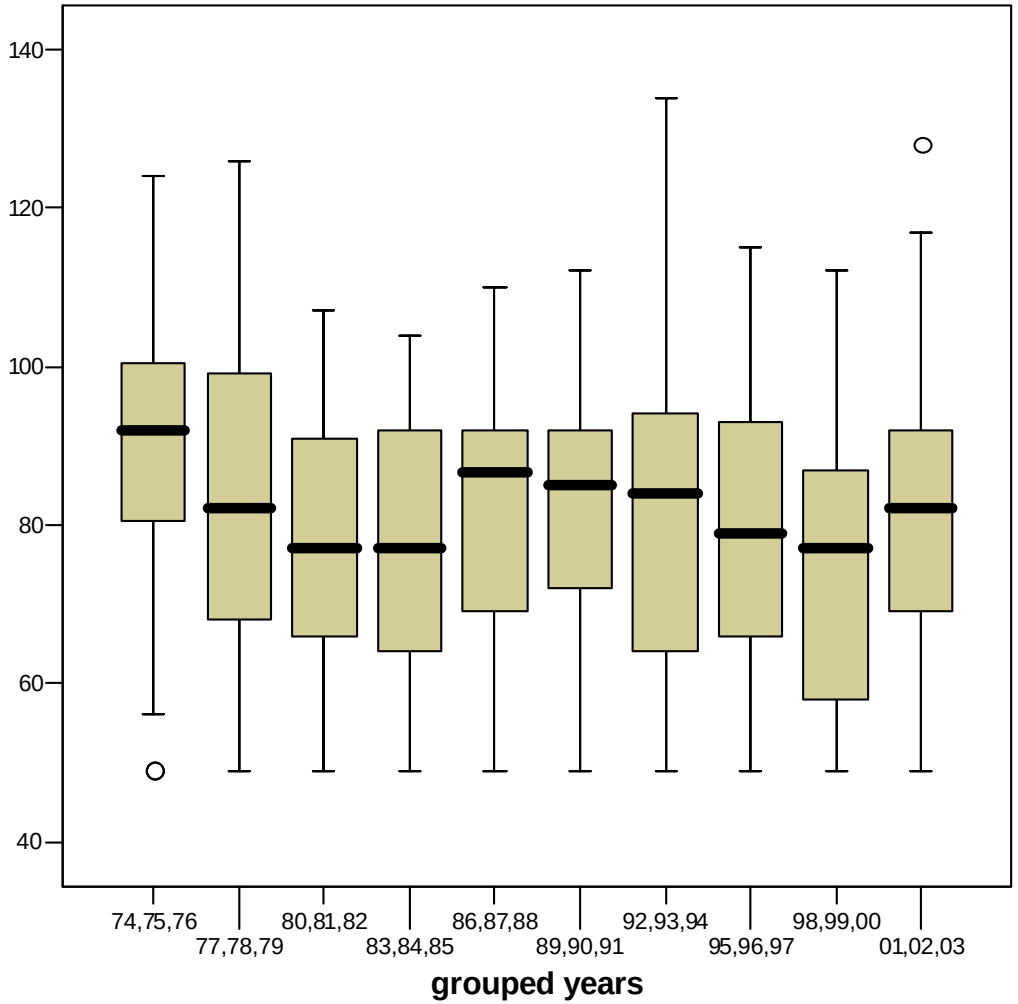
Mental Developmental Scores of 1279 survivors at 18-24 months CA over 10 3 birth-year periods: 1974-2003.

Mental Developmental Index

Mean 80(18)

High 74-76 90(17)

Low 98-00 74(18)

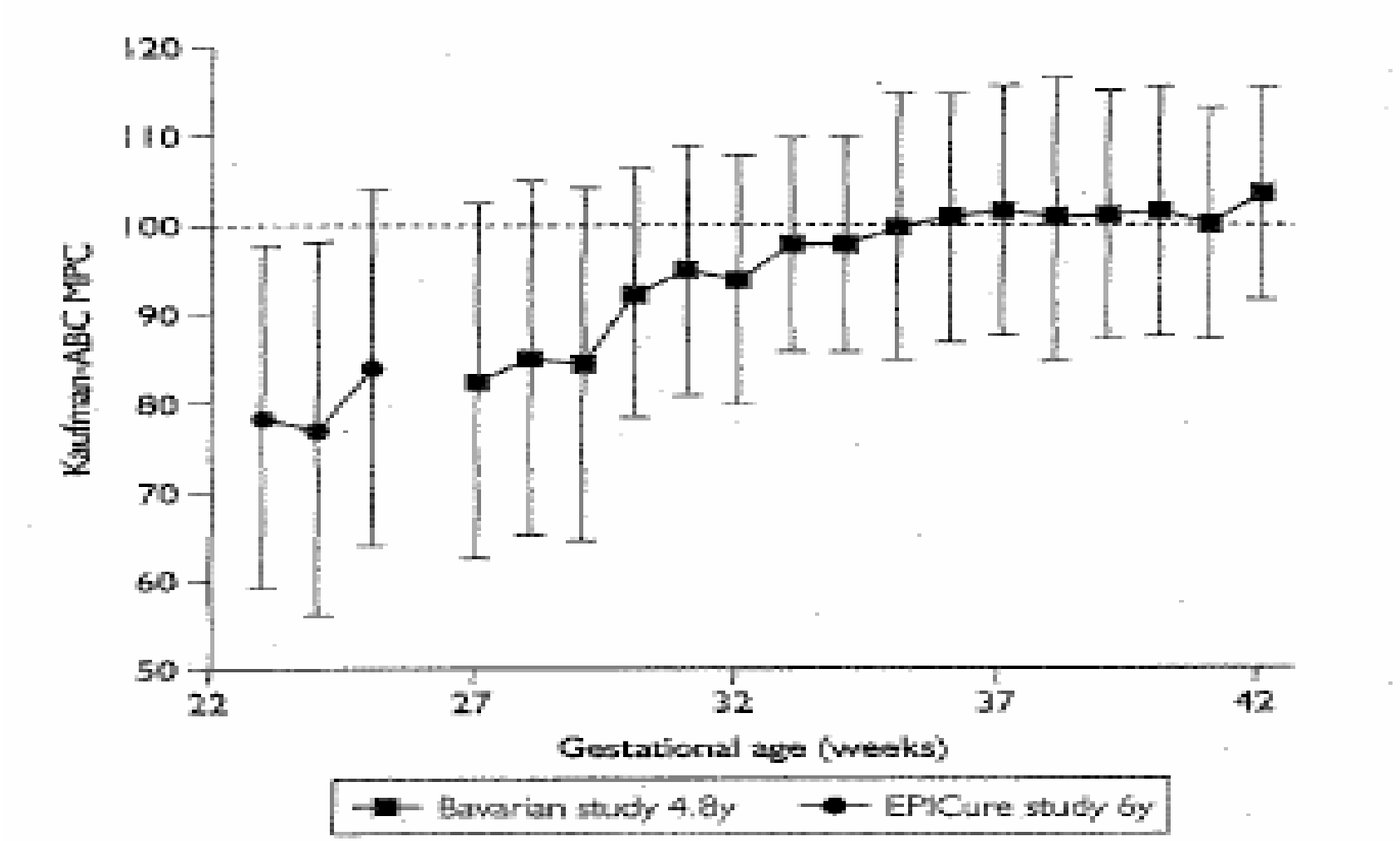


P=ns

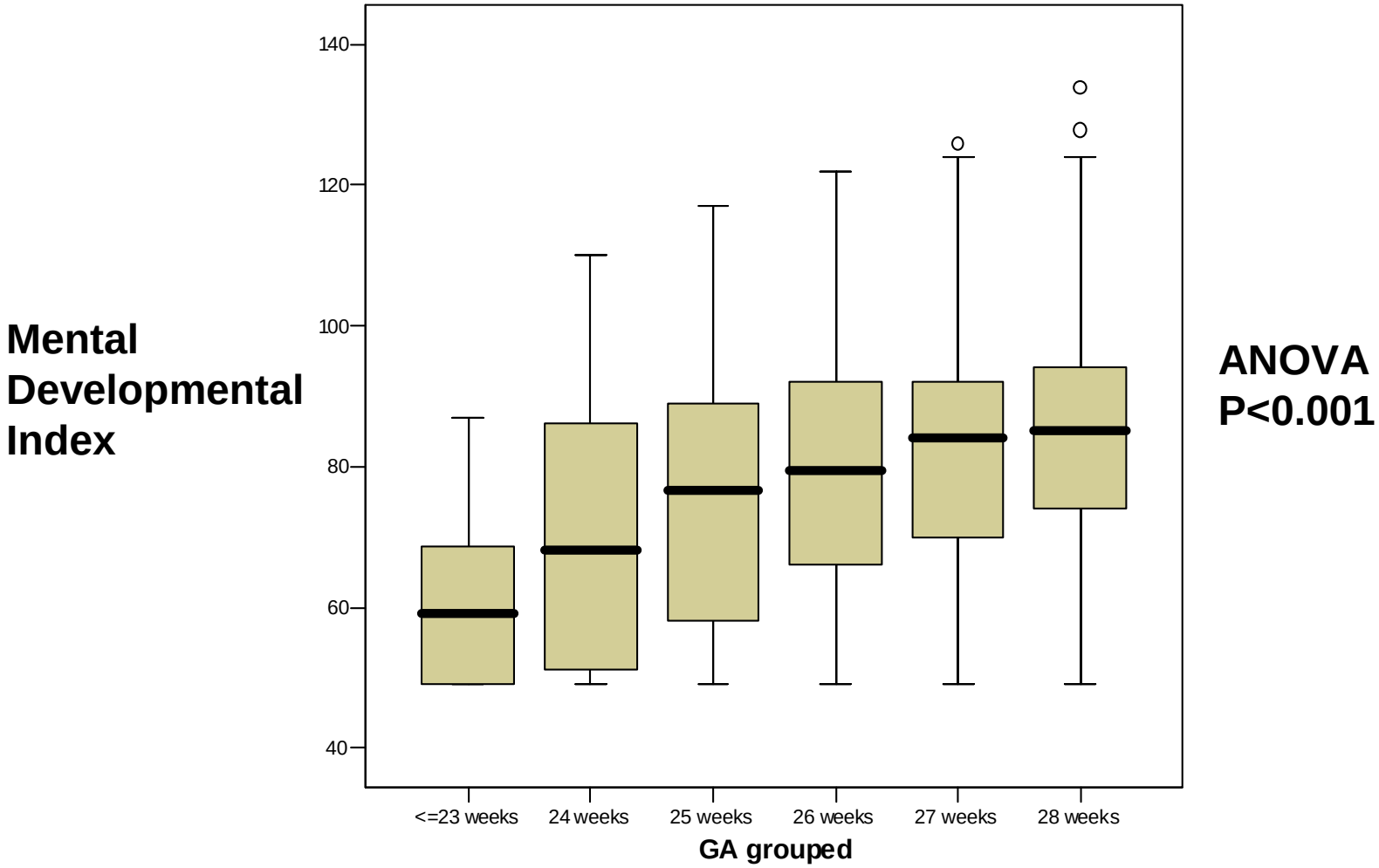
Mental scores related to GA

- Intelligence scores have been reported to increase for each week of GA for very preterm babies (Marlow N,2005)
- It is not known whether the lower scores associated with each lower week are due to prematurity alone, the illness/care of the child, the adaption of the test using inappropriate adjustment for the weeks of prematurity, or...

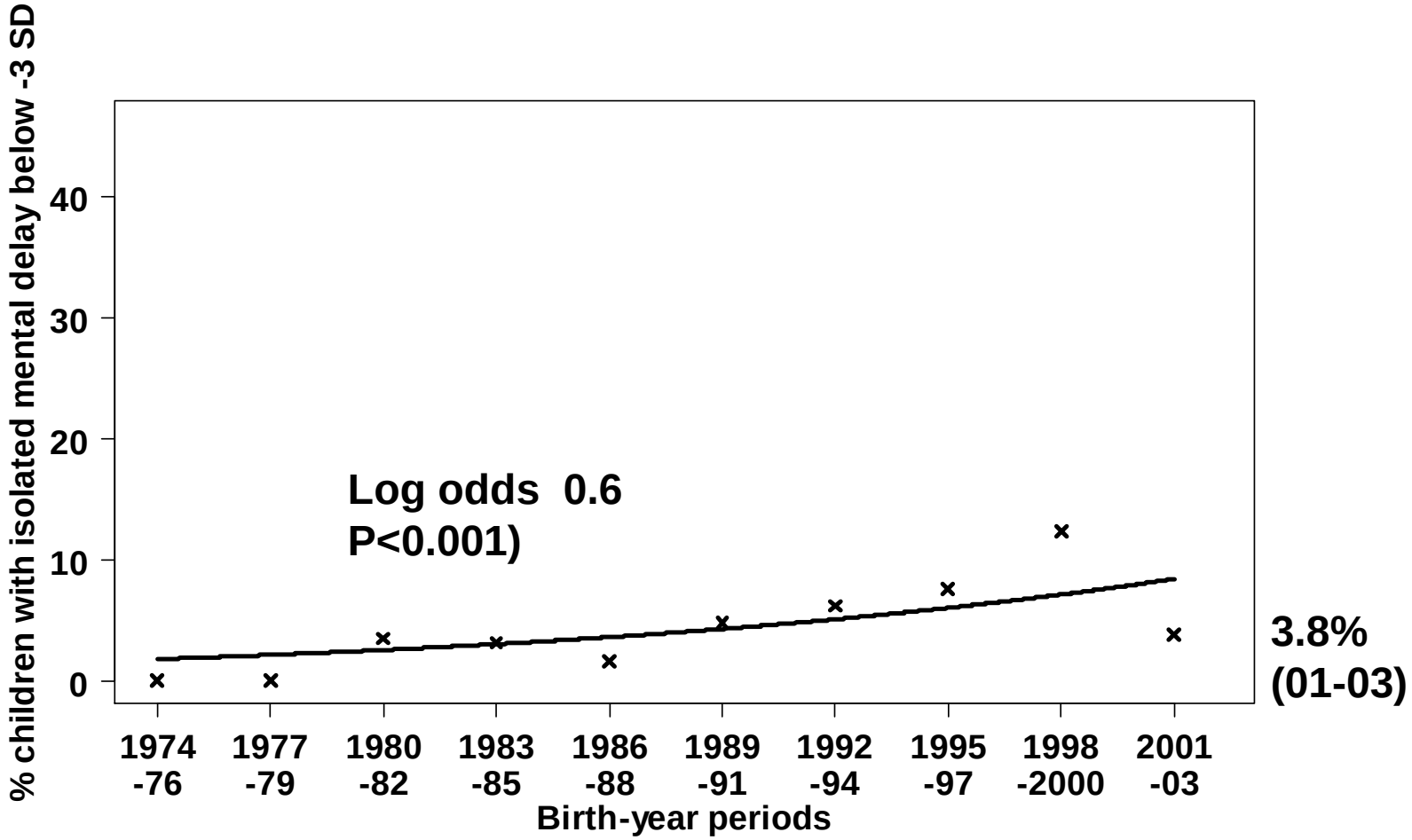
School-age Intelligence Test Scores and GA, Marlow,2005



Mental Developmental Scores and GA: 1279 survivors ≤28 w GA and <1250g BW at 18-24 m CA: 1974-2003



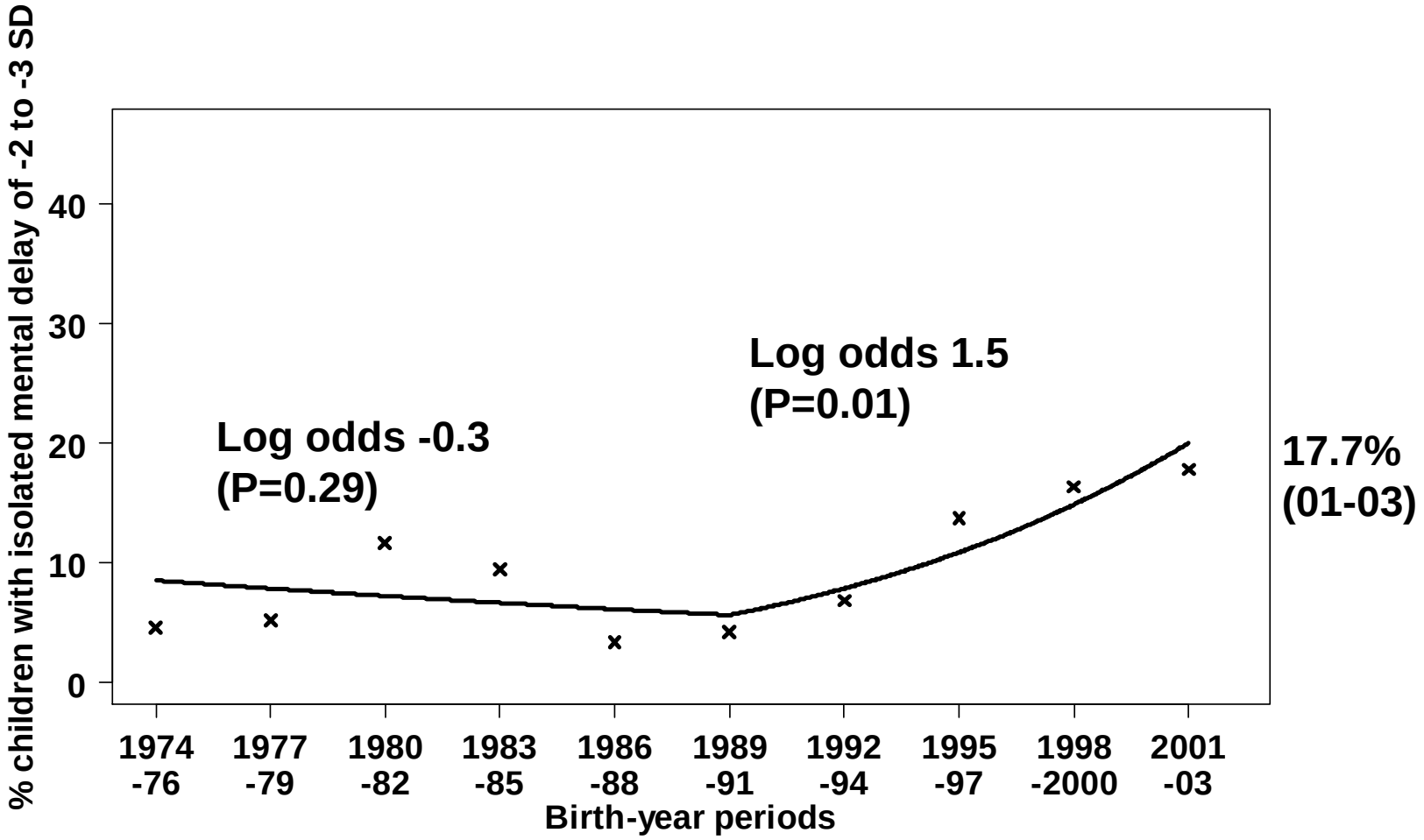
Trend in Isolated Mental Scores (n=67) below -3SD among 1279 survivors: ≤28w GA and <1250g BW:1974-2003



Predictors of Isolated Mental delay (n=67) (below-3SD) among 1043 survivors with out motor/sensory impairment: 1974-2003

- Malformations OR 3.8 (2.3,6.6)
- Lazer/Cryo OR 3.5(1.7,7.4)
- BPD-O2, 36w OR 2.4 (1.4,4.0)
- PDA –ligation OR 1.8 (1.1,3.0)
- SES not <3SD,37(13) vs <3SD,32(15), T=2.7, P=0.007
- Sex, outborn, SGA, multi birth, delivery- ns

Trend in Isolated Mental Scores (n=131) of -2 to >-3 SD among survivors ≤28w GA and <1250g BW: 1974-2003



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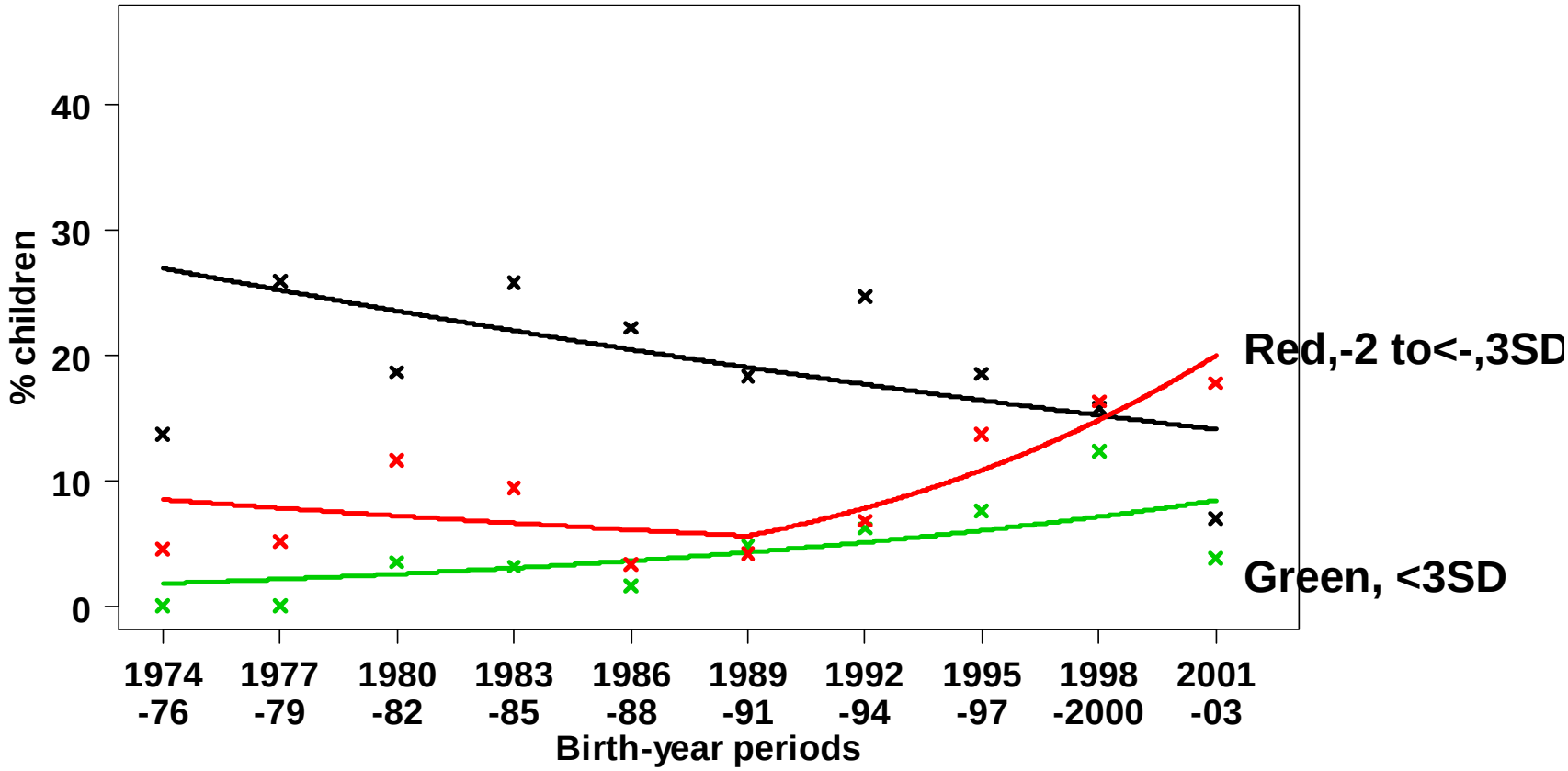
2 y motor and sensory disabilities decrease to 7 %, and isolated mental delay increases to 21.5 %, for 2001-03



Mental Developmental: Predictive Validity for extremely preterm infants

- **MDI under 3 SD** below mean on standardized tests is **<u>good</u>** (Marlow N,2005)
- **MDI under 2 SD** below mean is **<u>low,</u>** especially for those free of motor/sensory impairment (Hack,2005); thus, decision making based on studies of outcomes using MDI scores <70 but >54 as adverse outcome may over estimate the proportion of the mental delay within a cohort.

% Survival and MDI scores for groups: comparison

Group	years	n	2-y survival	MDI
Ext pret	01-03	215	69%	81(17)CA
ASO/TGA	96-04	88	99%	89(17)
Norw-BT	96-02	62	48%	79(18)
No-RVPA	02-05	32	81%	85(18)
TAPVC-s	96-04	32	97%	87(13)
IAA,no chab	96-04	17	100%	83(15)
22q11.2	96-04	16	94%	66(11)
CardiacTx	00-04	30	60%	64(8)
Liver Tx	97-06	54	83%	77(19)

Mental Development: predictive validity of MDI for children after cardiac surgery at ≤ 6 w. Creighton et al, Pediatrics,2007

defect	n	MDI@2y	WPPSI-FS@5y
TGA	20	94(14)	101(16)
Norw-BT	14	82(19)	85(18)
TAPVCs	6	94(10)	99(14)
All	61	85(18)	89(20)

paired-sample correlations tests =0.817, P<.001

Bayley Scales of Infant and Toddler Development III, 2006

Cognitive Composite Score (cog)
Language Composite Score
-Receptive Communication
-Expressive Communication
Motor Composite Score
-Fine Motor
-Gross Motor
Adaptive-Behavior Score

Bayley III: Cognitive Score- unlike MDI

- For 18-24m old preterm children with previously low and borderline MDI scores, cognitive scores may be higher than we expected. Reasons:
- -begin at CA
- -not structured in item sets allowing the child to attempt more difficult tasks
- -different normative procedure
- -exclusion of language tasks.
- **Key Questions!!!** How will we adapt clinical care and research because of these higher mental scores for preterm infants? How will results relate to IQ? Will scores also increase for other at risk children?

Preterm Comparison: IQ scores with Bayley II-MDI(n=46), Bayley III-cog(n=29)

MDI(03)	78(16)	cog(04)	89(15)	<.001
IQ	83(14)		79(15)	ns

- NOTE: For 18 m scores between 2003 and 2004, the clinical difference of 11 points is >7.5 points, thus > 0.5 SD and of clinical significance.

Early cardiac surgery comparison: mean BayleyII-MDI(n=247), BayleyIII-cog(n=63)

- 83(14)(≤2003) 97(16)(2004)
- Difference is 14 points, almost 1 SD.
- Is this difference due to improved outcomes reflecting improved care?
- How will this effect research results and clinical care?

Post-intensive care Interventions

- Research is needed to decrease the **Vulnerable Child Syndrome** which results from low expectations of abilities and over-protection.
- **Early intervention and early education programs should be strongly encouraged.** Spittle AJ, Orton J, Doyle LW, Boyd R. Early developmental intervention programs post hospital discharge to prevent motor and cognitive impairments in preterm infants (Review). The Cochrane Library, 2007: Issue (3), John Wiley & Sons, Ltd.

Summary : Outcomes of children after life-saving care.

- Survivors free of major disabilities are increasing
- Cerebral palsy and vision loss are decreasing among extremely preterm children and are not common after other life-saving care.
- Permanent hearing loss may be related to respiratory failure and its care. More than expected has been found in HLHS survivors since 2002.
- Adverse mental developmental outcomes remain a concern for most groups.

Implications: Outcomes of children after life-saving care

- Intellectual impairment is a common adverse outcome and should be confirmed using adaptive measures.
- For research purposes, consideration should be given to reporting IQ scores and not developmental outcomes.
- We must investigate the causes of the intellectual impairment for each child. Shevell M Neurology 2003;60:367-80.
- Modifiable acute care factors should be identified and changes made to improve outcomes.

Pre-School Measures

gold standard tests – Wechsler Scales

- Wechsler Preschool and Primary Scales of Intelligence – 3rd edition (WPPSI-III)
  - (2-6 to 3-11 – abbreviated form), (4 – 7.3)
  - Provides scores for Verbal, Performance, and Full-scale IQ, Processing Speed, General Language
- Early Intervention and Early Education Programs are critical. Please refer!

Impact on Children and Families- quoting- G Remple, Qualitative Health Research, 2007

- “Extraordinary parenting in a context of uncertainty (about ongoing health and development) was evident as parents safeguard the precarious survival of their children (with HLHS) and themselves as care-providing parents.”
- “…..practice must reflect an in-depth understanding of the needs of these parents so that benefits of technological advances are fully realized for the child, parents, and family.”

To be the best I can be