

# Short and Long-Term Consequences of Prematurity: the Importance of Follow-Up

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# DISCLOSURE

*I have no financial relationships to  
disclose, or conflicts of interest to resolve*

# Global Burden of Prematurity

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Preterm is defined as babies born alive before 37 weeks of pregnancy are completed. Sub-categories of preterm birth based on gestational age are:

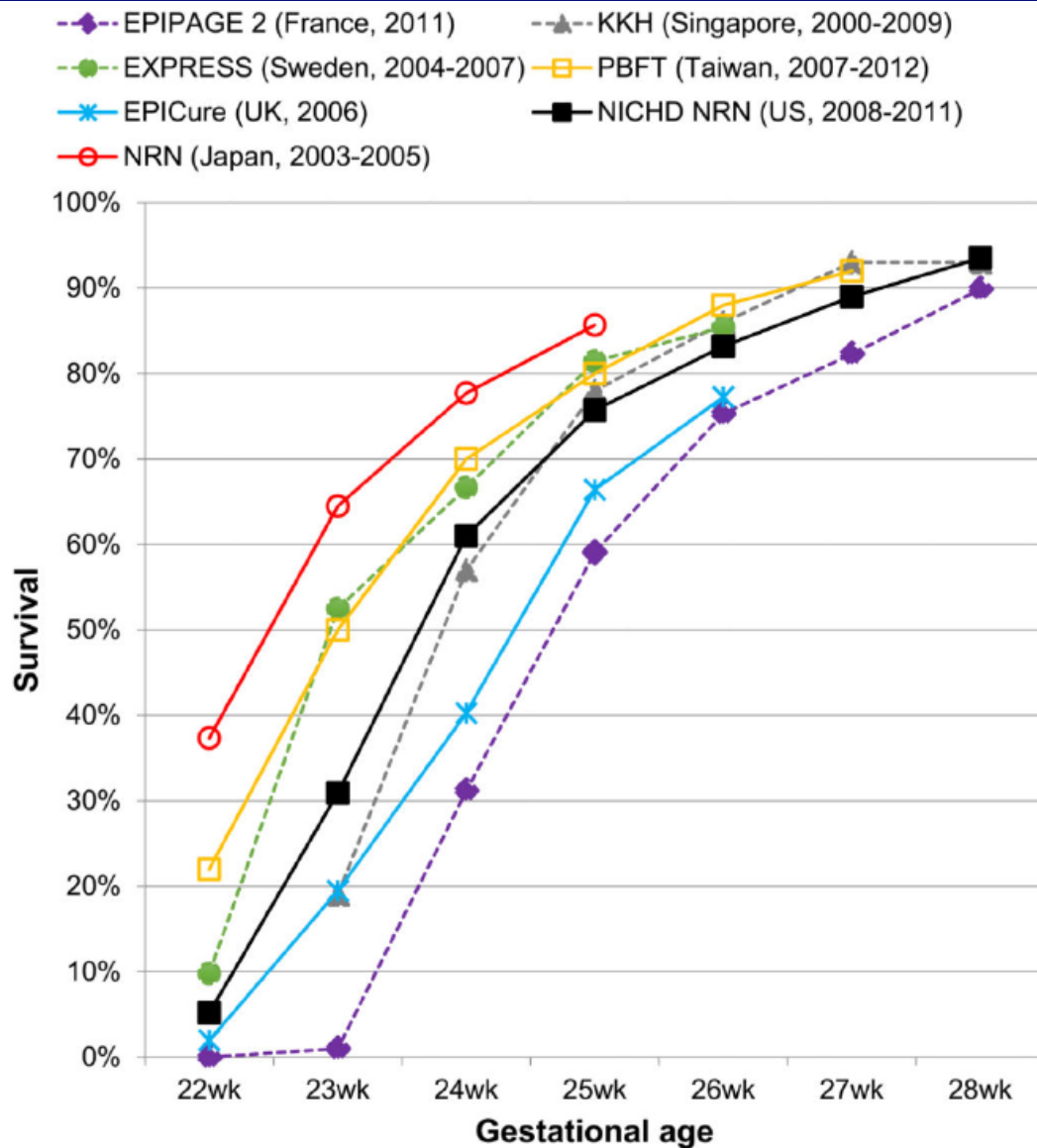
- extremely preterm (less than 28 weeks)
  - very preterm (28 to 32 weeks)
  - moderate to late preterm (32 to 37 weeks).
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- **Every year, an estimated 15 million babies are born preterm (<37 completed wks ), and this number is rising. Liu'16**
  - **Preterm birth complications are the leading cause of death among children <5 years- approx 1 million deaths in 2015.**
  - **Across 184 countries, the rate of preterm birth ranges from 5% in N Europe to 18% in sub-Saharan Africa and Asia.**

# Objectives

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- **To present the survival and short and long-term outcomes of extremely premature (EPT) and very premature infants (VPT).**
- **To review the continuity and change over time, and the impact of biological and environmental factors on recovery.**
- **To highlight the importance of follow-up and surveillance, and to emphasize the need for early intervention and support services for high-risk infants.**

# Gestational age specific survival for extremely preterm infants



# Who should be followed?

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- VLBW ?
- ELBW ?
- 'Micropreemies'?
- Late preterm infants?
- Other high-risk conditions eg HIE, seizures?

*Around the world, including in developing countries, NICUs are flourishing and survival of premature infants is improving.*

# ETHICAL VIEWPOINT

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- 'Neonatal intensive' care should not cease at discharge from the NICU.....it is unethical to provide NIC without consideration of outcomes.
- Follow-up is mandatory to provide clinical and support services to optimize the outcome of both the child and the family and to implement intervention strategies.
- *The best interest of the parents and children are paramount.*

# Duration of follow-up of premature infants

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- **Short-term:** first two years of life are very important
- **Long term:**
  - **Preschool**
  - **School age**
  - **Adolescence**
  - **Young adulthood**
- **Middle-age?**
- **Old-age?**

*Do our responsibilities lie from cradle to death?*



# Advantages of long-term outcome studies

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## Allow more accurate measures of:

- Intellectual abilities and academic achievements.
- *Multidimensional* outcome – “the new morbidity.”
- May not be relevant to neonatal intensive care as is currently practised, but still provides valuable information for future planning and utilization of health care resources.
- Long-term studies should be performed in academic institutions for research purposes.

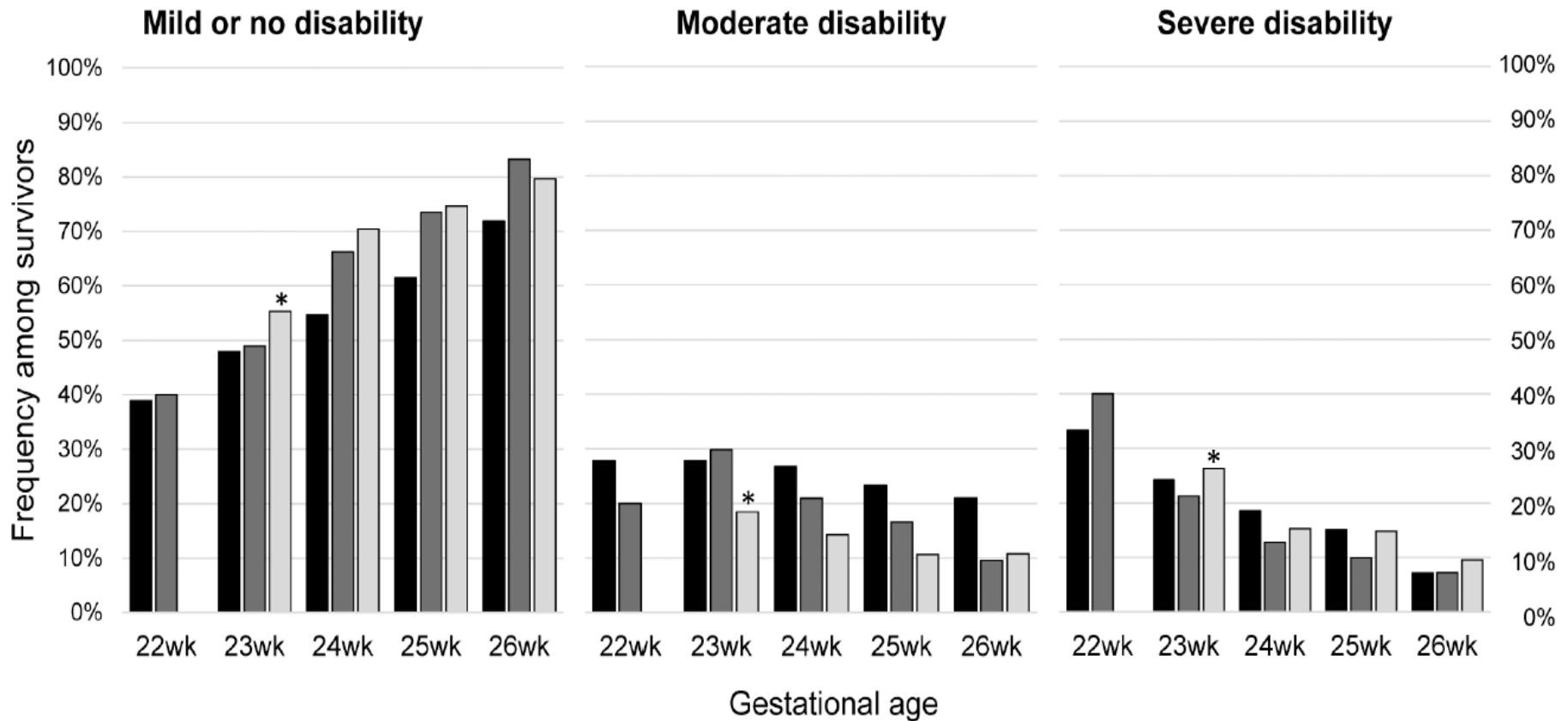
*A Journey of Premature Infants  
from Infancy to Adulthood*

# Outcomes during infancy

- Outcomes include survival and neurodevelopmental impairments (NDI)
- Striking improvement in survival from the mid-1990s: 24 wks GA = 16-70%; 26 wks GA = 53-88% **Saigal & Doyle'08**
- Centres that offer NIC selectively have a lower survival rate, but also lower prevalence of disabling CP (Netherlands vs US) **Lorenz'01**

# The spectrum of disability among surviving extremely preterm infants

■ NICHD NRN (United States)   ■ EXPRESS (Sweden)   ■ EPICure (United Kingdom)



\* Estimates reported for infants  $\leq$  23 wk gestational age

# Neurodevelopmental Impairments

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- Neurodevelopmental impairments (NDI): 21-35% for  $\leq 26$  wks GA, and around 15% for 28-32 wks GA.
- In the NICHD Network for 2006-2011 births, overall *survival without severe impairments* Rysavy '15 at 18mths were: 22 wks =3%; 23wks =18%; 24 wks = 48%; 25 wks =61%.
- Neuroimaging studies show decrease in white matter volume. Inder '05

# Cerebral Palsy

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- CP is the most common impairment in VPT. CP rates have fallen / remained stable / increased – around 10% now.
- Prevalence of CP is inversely related to GA: occurs in 14% at 22-25 wks and 8-9% at 32 wks. It is considered a marker of quality of care.
- The prevalence of CP has decreased slightly in Swedish studies with lower rates of severe and higher rates of mild impairments. PT infants *without* CP can have higher rates of gross and fine motor difficulties and DCD. Marlow '07

# Moderate and Late Preterm Infants

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*Moderate PT (32-33 wks GA) and Late Preterm (34-37wks GA) make up the largest subgroup of PTs contributing to 80% of PT births in the US.*

- **MPT and LPT infants have higher mortality than FT and are at increased risk of neurological impairments, developmental disabilities, lower IQ, <sup>Cheong '17</sup> school failure (up to 33%), <sup>Huddy '01</sup> autism, behavioral and psychiatric problems at school age. <sup>Talge '10</sup>**
- **As the absolute number of such births is higher, it has a major impact on educational and health-care resources.**
- **MLPT is associated with smaller brain size, poorer myelination and more immature gyri than FT. <sup>Walsh, 2014</sup>**

# School-age outcomes

- Mean IQs of ELBW infants shown to be 12-17 points lower than term peers; **Saigal '91** smaller difference in Australian children **Anderson & Doyle' 04**
- A difference of 10 points has been found in sibling-control studies. **Kilbride '04**
- The magnitude of difference in IQ places the preterm infant at a distinct disadvantage in the classroom **Aylward '02, Anderson '03, Saigal '91, 2000, Hack '05**



# Cognition and Learning Disabilities

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- VLBW children have cognitive deficits, academic underachievement, grade failure and higher need for educational assistance that are more severe in the smallest and more immature infants.
- PT children have been reported to have deficits in Executive Function (refers to high level mental processes that regulate behavior and cognition) that play an important role in school achievement. **Marlow'07**
- LD can be present even in infants without NDI.

# School-age outcomes (cont'd)

- Even normal survivors have high prevalence/ low severity dysfunctions eg: low IQ, learning and attentional deficits, and behavioural and emotional problems (estimated in 50-75% of ELBW infants, with an **inverse BW / GA gradient**) **Aylward '02, '05**
- The likelihood of an infant <750g having a lower IQ than controls is 10-fold higher , while for 750g-1499g more than 2-fold higher than infants born at term. **Taylor 2000**

# Other morbidities in mid-childhood

- Significantly higher prevalence of remedial assistance / grade repetition. Saigal '91, '03, Marlow '05, Doyle '05
- VLBW infants have 2.6 to 4 times higher rates of dysfunction such as ADHD, inattention, hyperactivity and emotional problems in early childhood that affect academic functioning. Trevaud '13, Hille '01, Anderson '3
- Poorer general health and greater utilization of health care resources in early childhood VLBW infants have about 2-3 times the rate of respiratory illnesses. Farooqi '06, Hack '05

# Outcomes during adolescence

- Persistence of school difficulties and continued greater requirements of remedial assistance.
- Difference in mean IQ between ELBW and controls remained at 13 points; inverse BW / GA gradient.
- Even neurologically intact teens with normal IQs performed less well on achievement measures.
- Other deficits: visual-motor function, perceptual planning, math, and Executive Functioning.

Botting '98, Saigal 2000, Anderson '04, Bhutta '02

# Behaviour

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- VPT adolescents and YA have a higher incidence of shyness, social maladaptation, and are unassertive, anxious and withdrawn.
- They have higher rates of anxiety and depression at teenage that persist to adulthood.
- These problems have been identified even in infants without NDI.
- VPT have lower delinquency and risk-taking behaviours.

# Young Adulthood: Summary McMaster Study

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- Contrary to our hypothesis, at young adulthood, ELBW YAs in Ontario, Canada, were functioning at about the same level as the NBW participants in their **educational attainments, employment status, independent living, marital status/cohabiting, and becoming parents.** Saigal '06
- There are, however, some 'qualitative' differences in the markers achieved by ELBW YA, compared to NBW YA

# Young Adulthood: Risk-taking Behaviours

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- VLBW YAs have a lower prevalence than NBW of **alcohol consumption, smoking, marijuana use, contact with police, convictions / incarcerations** (*but not of unprotected sex!*).
- However, whether these behaviours are due to increased parental monitoring, lack of opportunities (particularly for those with disabilities) or development lags, is unclear.

# Adulthood mid-30s: Summary McMaster Studies

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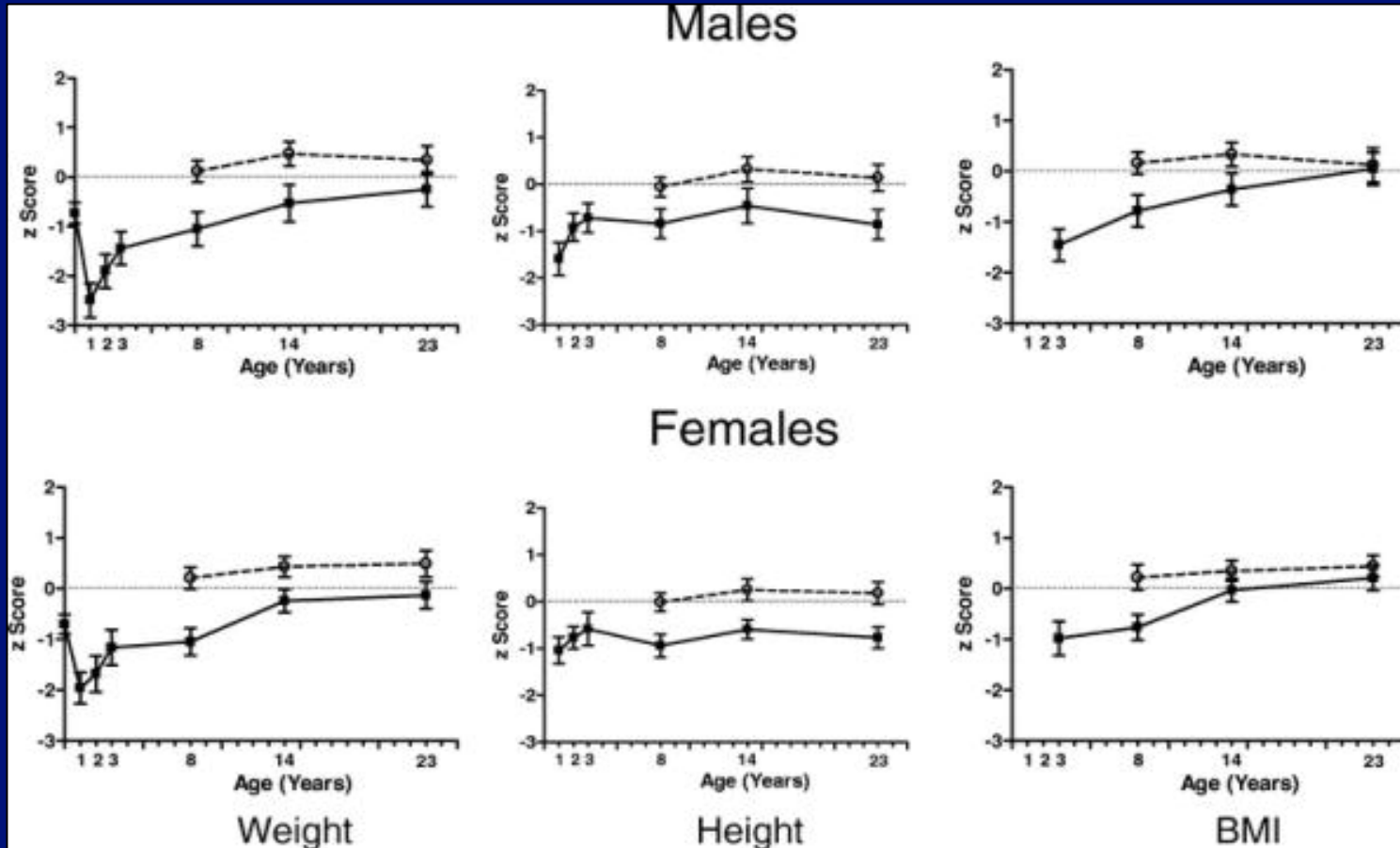
- Overall, ELBW had similar levels of education to FT.
- ELBW had lower rates of employment / personal income.
- Fewer ELBW were married or cohabiting.
- ELBW had higher rates of psychiatric problems particularly depression and anxiety disorders.
- ELBW had lower reproductive rates.
- ELBW had a lower incidence of risk-taking behaviours.

Saigal et al, JAMA Pediatric 2016;170:678-86



# Growth: Birth to young adulthood

## Mean height, weight, BMI z-scores and 95% CI



ELBW = black small square  
NBW = white circle

Adapted from: Saigal et al, Ped Res, 2006

# Anthropometric Measurements at 29-36 years of age

	ELBW		NBW		p
	Mean	SD	Mean	SD	
Height (m)	1.64	0.10	1.71	0.11	<0.001
Weight (kg)	71.9	16.54	77.5	18.28	0.03
BMI (kg/m <sup>2</sup> )	26.9	6.41	26.5	5.08	0.61

# Blood Pressure of ELBW and NBW

McMaster Studies, Morrison, Saigal et al, '16

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	ELBW n = 94 M (SD)	NBW n = 88 M (SD)
Systolic BP mm Hg	113.8 (11.93)	108.9 (10.59) *
Diastolic BP mm Hg	73.7 (10.00)	70.5 (8.27) **

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\*P .004; \*\*P .02; No differences in BP between AGA and SGA

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*Births <32 wks GA is associated with a nearly 2-fold increased risk of CV disease, adjusted HR (95% CI) =1.89 (1.01-3.54) Ueda et al, European L Epidemiol, 2014.*

*A 5mm increase in systolic BP is associated with a 34% increase in mortality due to stroke. Lewington, Lancet, '02.*

# Cardio-Metabolic Health

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*Adults born with ELBW compared to NBW have:*

- **Increased body fat** ( $p=.04$ ), **reduced lean mass** for Ht ( $p=.02$ ) by DXA, but **similar waist circ and BMI**.
- A **4-fold** increased risk of developing **dysglycemia** (95%CI 1.53-10.66) by oral GTT.
- **Body fatness** was the strongest predictor of **dysglycemia** –they had higher BMI and waist circ.

**Morrison, saigal et al. Pediatrics 2016;138:e20160515**

# Future concerns at adulthood and beyond

Kajantie et al. J. Endocrinol Metab. 2015; 100:244-50

Morrison et al, Ped 2016; Swamy et al. JAMA. 2008; 299, 1429-36

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- **ELBW will likely continue to be disadvantaged in job opportunities, income and social functioning.**
- **Mounting evidence of an increase in the prevalence of CVS and metabolic sequelae – Insulin resistance, possibility of Type 2 Diabetes, and hypertension.**
- **ELBW display lower probability of reproducing (HR 0.81M, 0.78F); increased infertility, SB /prematurity rates.**
- **A higher prevalence of anxiety disorders, depression and psychiatric hospitalizations, particularly in females.**

***“Had follow-up studies not been performed to adulthood, we might never have known the extent of recovery and adaptation to life reported in recent studies.”***

**The outcomes of premature infants have to be looked from a lifetime perspective. Outcomes are age-related and the focus is different at the earlier ages relative to adulthood.**

*It is important to remember that the effects of extreme prematurity are not uniformly deleterious and are observed in a small subgroup.*

*Most preterm young adults seem to enjoy a healthy and fulfilling lifestyle.*

# Early Human Development and Brain Plasticity

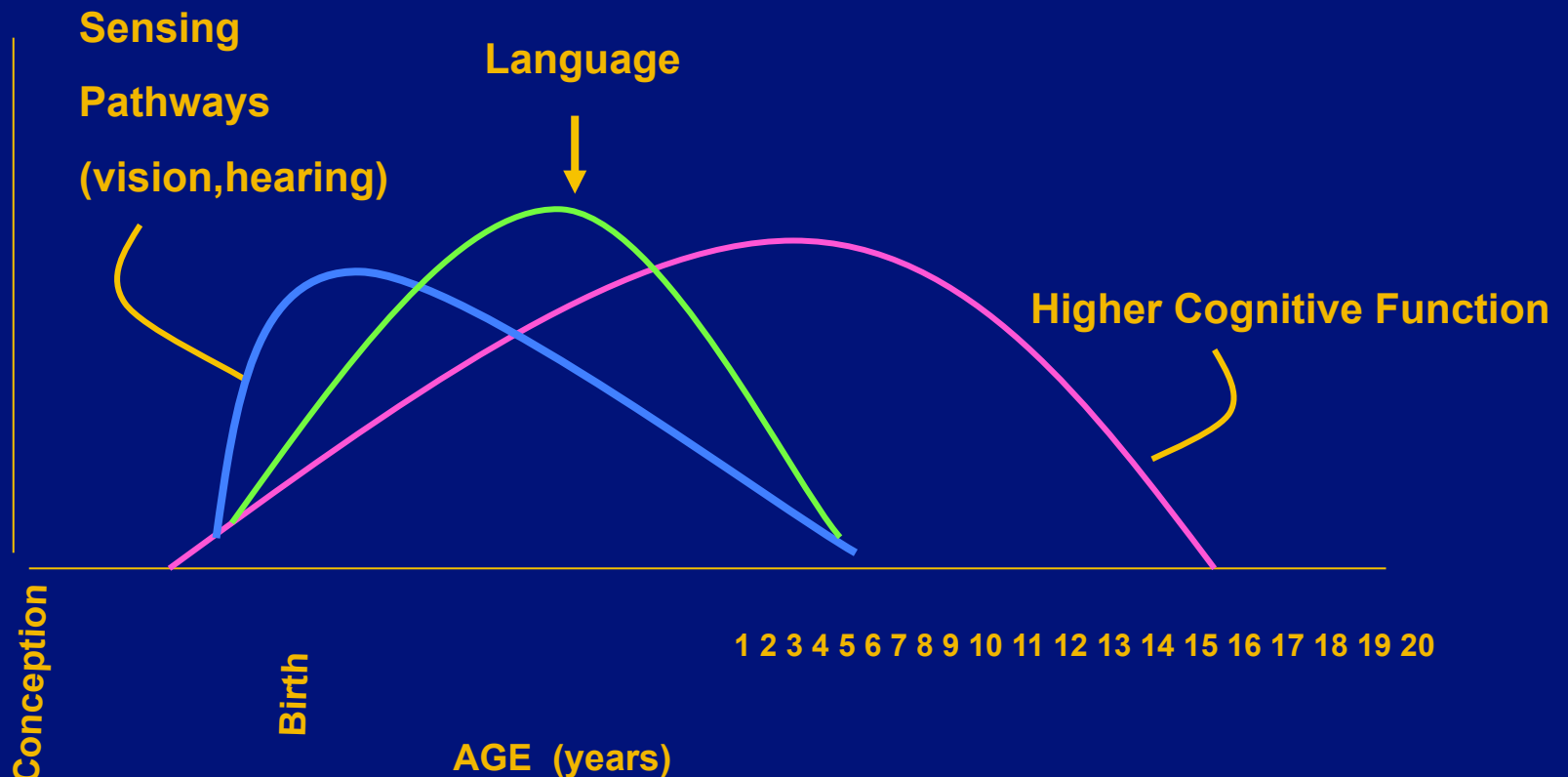


# Early Human Development

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- **Period of great opportunity and also great vulnerability.**
- **The first 3 years comprise a long period of immaturity and dependence and also dramatic physical and mental developments.**
- **These developments are building blocks for adult cognitive and emotional functioning.**

# Human Brain Development - Synapse Formation



# Cerebral-Cortex Development in Preterm Infants

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- Growth in cortical connections and complexity occurs after 25 weeks.
- At 38-42 wks cerebral cortex of preterm infants had less cortical surface area and was less complex than their siblings **O'Connell '04** and NBW infants **Ajayi-obe et al 2000**
- Damage acquired in critical periods of brain development are permanent.

# Continuity and change over time

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- Prevalent belief that early adverse life experiences lead to *permanent irreversible damage* shown to be incorrect. **Bowlby '51**
- Even markedly adverse experiences in infancy carried fewer risks if subsequent rearing environment was a good one. **Rutter '87**
- Certain 'protective processes' (mentor, teacher etc) can change life's trajectories from risk to adaptation. **Werner & Smith '92**

# Plasticity of the developing brain

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- Human brain development is relatively slow permitting adaptation and plasticity to “override” the adverse neonatal events.
- Plasticity critically depends on the environment in which the child is raised.
- Transactional Model proposed by Sameroff & Chandler in the 1960s: dynamic interplay between the child’s biology and the child’s environment.

# Limitation of plasticity

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It is possible that the ‘plasticity’ is only sufficient to give an appearance of being *“apparently normal”*, as these children never reach the same potential as those who are born at term.

# Background for Intervention: Preterm

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- **Premature children are vulnerable to deficits in almost every area of development.**
- **Vulnerability increases if reared in an environment of minimal stimulation.**
- **Lower socioeconomic environment poses a double hazard.**
- **Common belief, that early stimulation offers an effective means of developmental intervention.**

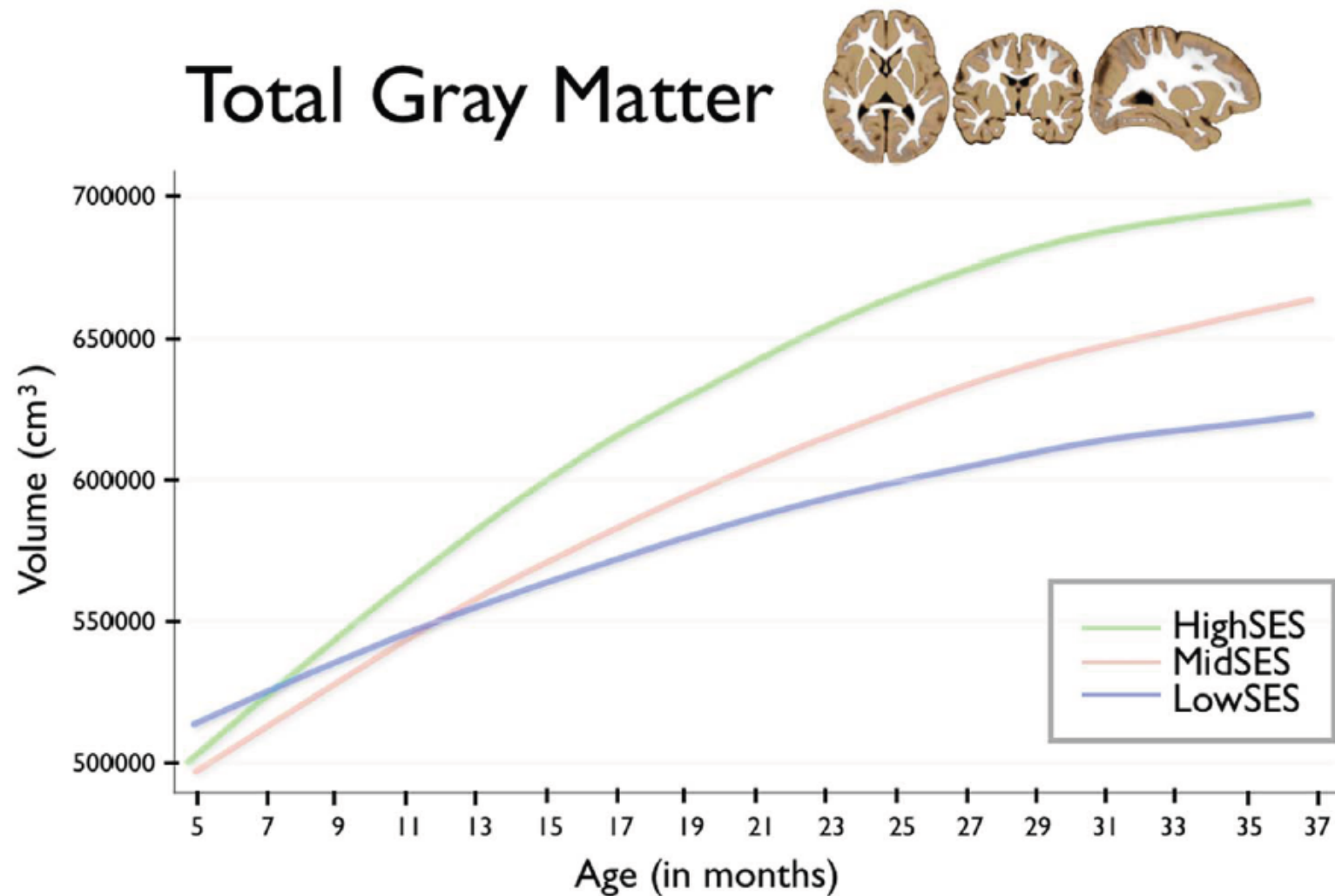
# Impact of Poverty in Childhood

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- **Impact of poverty above and beyond other socio-demographics (education, occupation, race, single parent).**
- **Poverty during early childhood (1-5 yrs) was more detrimental than if it occurred later ( 6-10; 11-15 yrs), in terms of it's association with high school graduation and post-secondary education.**



# Family Poverty Affects the Rate of Human Infant Brain Growth. *JL Hanson et al. PlosOne 2013*



How Good is the Evidence that  
Intervention Works?

# Who does intervention work for?

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## Intervention works in selected samples:

- More mature premature babies >2000g.
- Little or no effect seen in the smaller, most vulnerable and those with CP, ie. *not often effective for those that need it the most.*
- *Infants from socioeconomically disadvantaged families are likely to benefit most from most interventions, particularly maternal educations.*

# Intervention in NICU



McMaster Children's Hospital  
Hamilton, Ontario





Ruben, Museodel Prado, Madrid

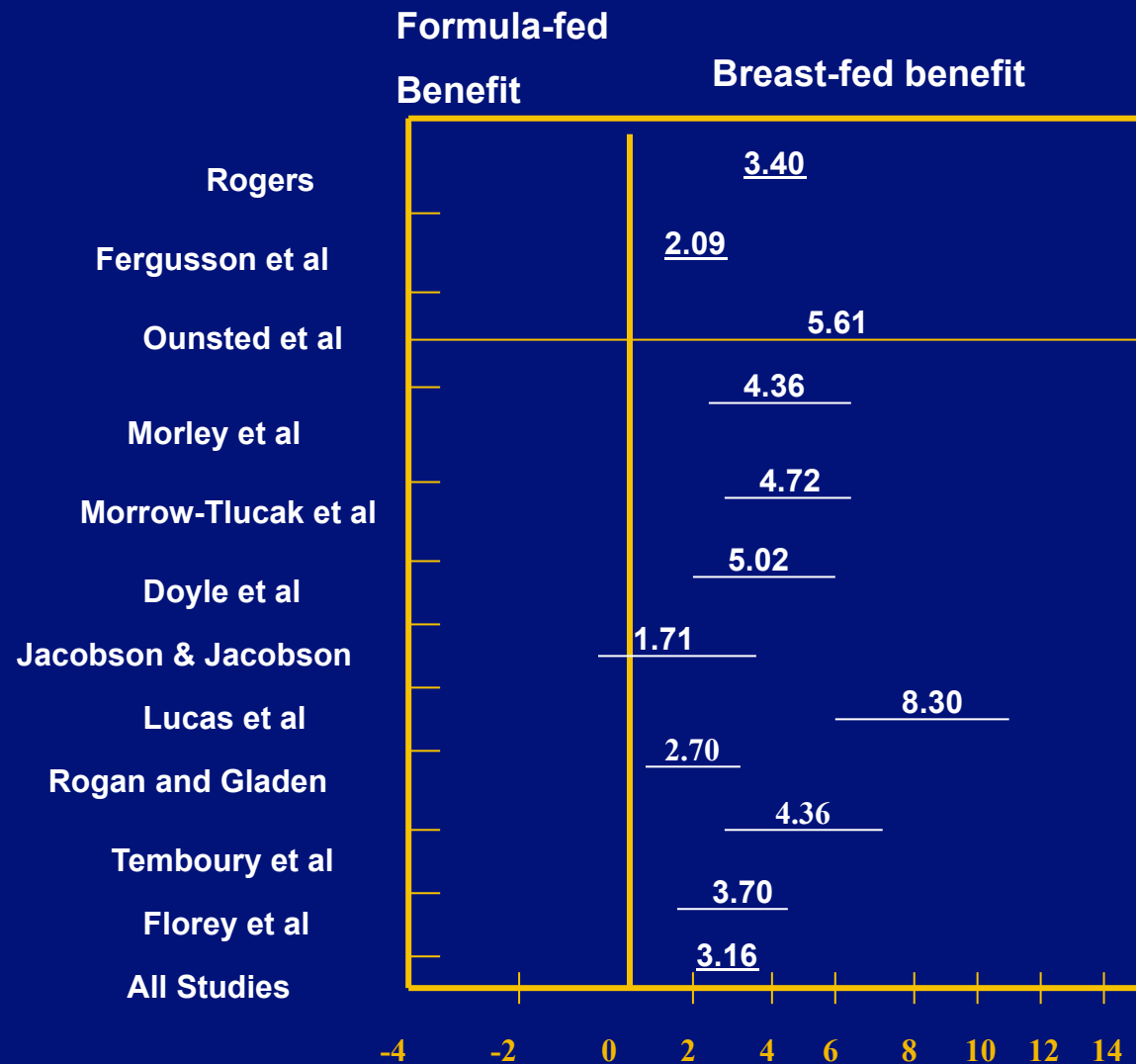
# Breast-feeding and brain function

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**BF appears to have a broad range of enhanced brain functions:**

- **Rapid maturation of visual function/acuity**
- **Acquired motor skills at an earlier age**
- **Fewer emotional or behavioural problems**
- **Fewer minor neurological problems**
- **↑scores on Bayley Scales of Infant Development in the early years – not long lasting.**

# Effect of breast-feeding versus formula-feeding on cognition: Meta-analysis



# Summary of Breast feeding

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- **Small, but statistically significant advantages for breast-fed children from 2 to 5 years.**
- **Advantages more consistent for cognitive skills.**
- **Consistent dose response shown.**
- **Covariables such as maternal education and birth order advantage needs to be considered.**
- **Although effect size is small, BF offers the potential for enhancing the child's development.**





***What are the latest conclusions  
on KMC?***

***Is it beneficial?***

# Benefits of KMC

- Among all interventions, Kangaroo Care (KC) showed the most frequent positive impact across outcomes. **Puthussery'18 meta-review**
- Most of the evaluated studies determined that weight gain was greater among the kangarooing premature infants even in low-resource settings. **Everekilian 2017**
- Compared with conventional neonatal care, KMC was found to reduce mortality at discharge or at 40 to 41 weeks.'
- Researchers noted no differences in neurodevelopmental and neurosensory outcomes at 12 months' corrected age.

# Current recommendations for KMC

- **Cochrane Review:** demonstrated benefits in many aspects of the studied outcomes and supports the use of KMC in LBW infants as an alternative to conventional NIC in **low-resource settings** Conde-Agudelo, Diaz-Rossello, 2016
- WHO is currently initiating a trial of *immediate* kangaroo mother care (KMC) multi-country trial (compared with the current recommendations of initiating KMC when baby is stable) in Ghana, India, Malawi, Nigeria and the United Republic of Tanzania.



**PLUS**



**Kangaroo care promotes successful breast feeding, and together, both offer the potential for enhancing the child's development at no risk and little cost.**