Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

Trinity Research in Childhood Centre (TRiCC) Annual Lecture 2019

Professor Neil Marlow

"Young adult preterm: fit for the future?"

#TRiCClecture19 @TCD_TRICC

In Collaboration with
Children's Research Network

Children's Research Network

An Roinn Leanaí agus Gnóthaí Óige
Department of Children and Youth Affairs

WHAT WORKS
SHARING KNOWLEDGE

Young adult preterms: Fit for the Future?

Neil Marlow

UCL EGA Institute for Women's Health

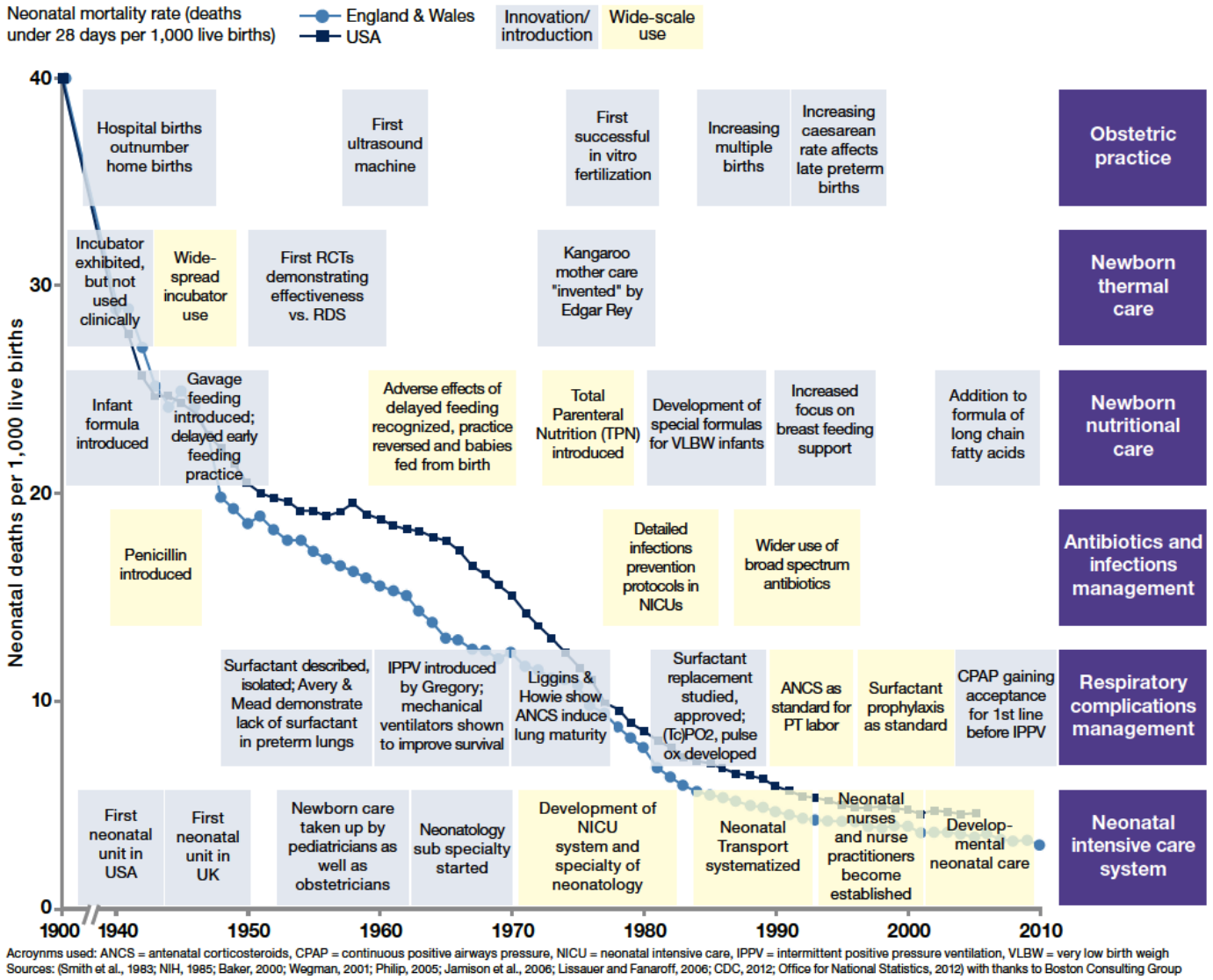
Declaration

- Neil Marlow declares the following potential COI
  - Consultancy fees from Novartis and Shire/Takeda
  - Executive Board member EFCNI (unpaid)

Objectives

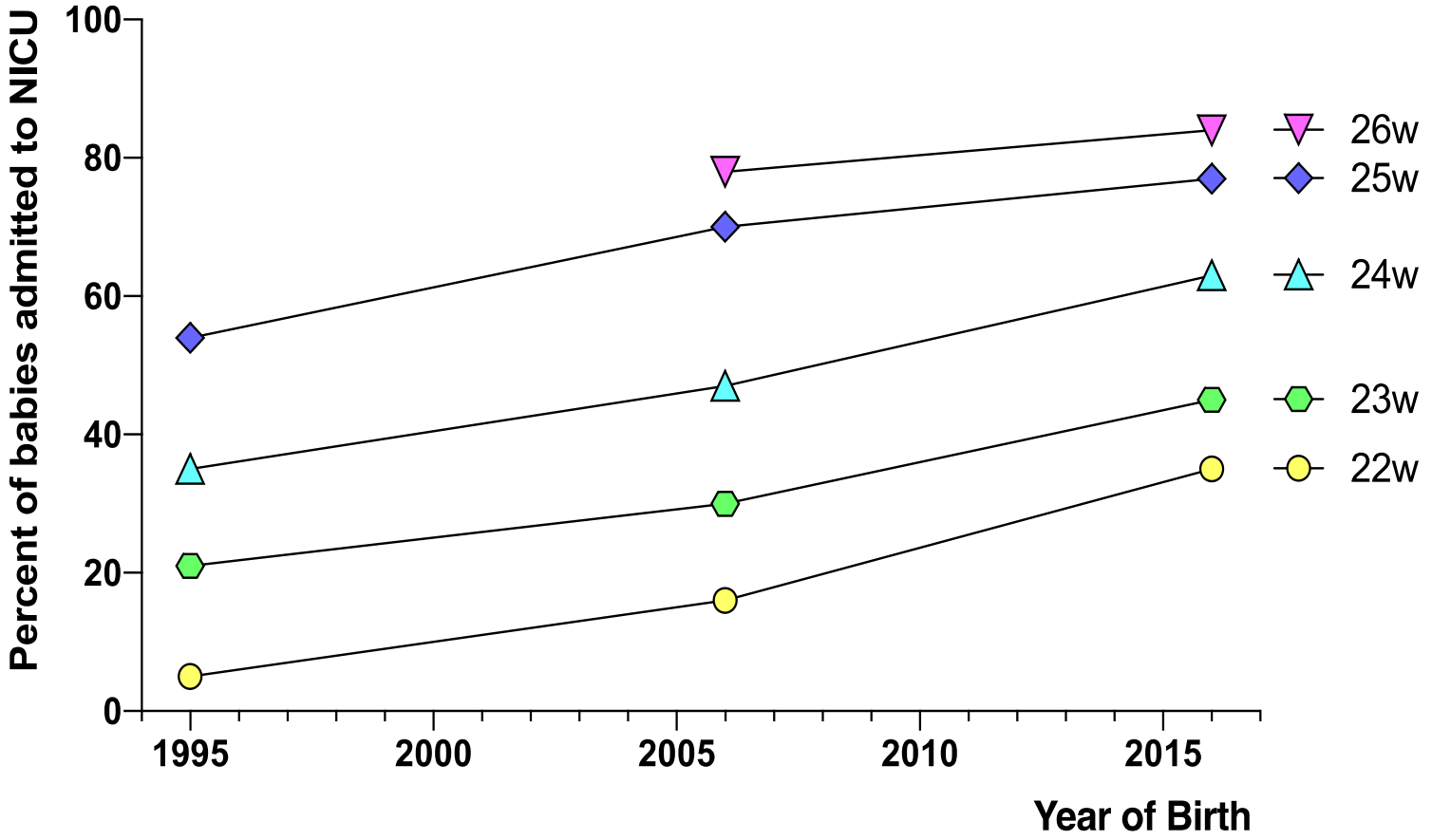
1. To explore the range of outcomes in early adult life following EP birth
2. To understand the relative roles of tissue injury and developmental problems in generating poor outcomes
3. To evaluate the effectiveness of early interventions
4. To discuss potential therapeutic strategies

- Saving lives
- Marginal gains
- Marginal harms
- Thinking outside the neonatal period



Born too soon. WHO 2012

Survival



Survival to discharge for infants born 22–26 weeks of gestation and admitted to neonatal units in England in 1995 (EPICure)[10], 2006 (EPICure 2)[2] and 2016 (MBRRACE-UK).[3]

THE TIMES
Wednesday October 23 2019

News

Survival rate doubles for premature babies

Kaya Burgess

The number of extremely premature babies who survive has doubled over the past decade, prompting new guidance allowing doctors to try to save babies born as early as 22 weeks into a pregnancy.

The threshold recommended by the British Association of Perinatal Medicine (BAPM) was previously 23 weeks, but experts said that intensive care had improved significantly.

In 2008 only two out of ten babies born alive at 23 weeks went on to survive. Today it is four out of ten.

Guidance previously recommended that doctors should not attempt resuscitation and "active care" for babies born before 23 weeks, as their chances of survival were too slim and those who lived were likely to suffer severe complications. It was recommended that these babies be offered palliative care to ensure their comfort.

The BAPM cited figures showing that doctors now offered intensive care to 23 per cent of babies who survived at 22 weeks. It has updated its guidance but said that each case should be assessed for chances of survival, quality of life and the wishes of parents.

Four out of ten babies born alive at 23 weeks go on to survive
ALAMY

The survival rate of babies born at 22 weeks is still very low. About 60 per cent have died before labour begins and of foetuses still alive when labour starts, only 63 per cent survive the birth. Only 5 per cent of babies born at 22 weeks survive to their first birthday and a third will have disabilities including blindness, deafness, severe learning difficulties or movement problems.

About 60,000 babies are born prematurely in the UK each year, of which 3,148 are considered "extremely premature" — born before 27 weeks.

Dominic Wilson, professor of medical ethics at Oxford University, said that such "complex ethical decisions" could not be reduced to simple rules.

The legal abortion limit is set at 24 weeks, allowing for the termination of foetuses at 23 and 22 weeks. Professor Wilson said that the BAPM's guidance was "focused on the care of extremely premature babies [and] does not deal at all with questions of termination". ■

At 22 weeks a baby in the foetal position is the size of a bell pepper

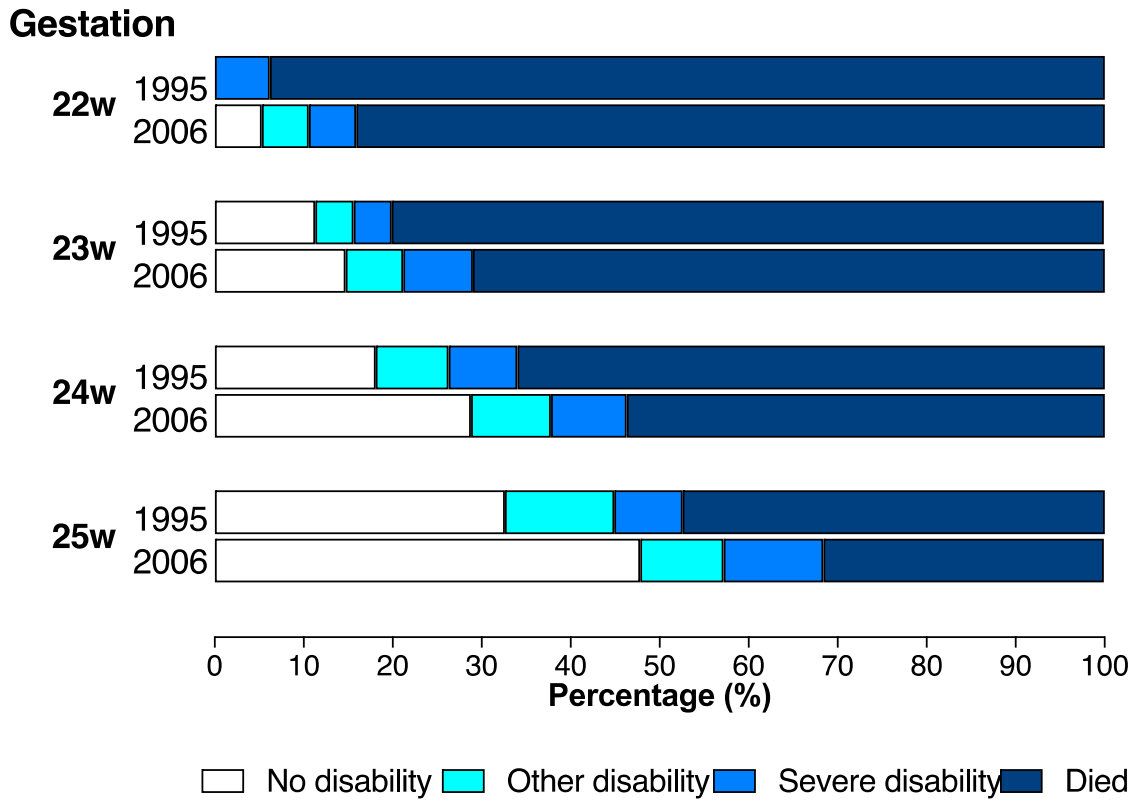
18 weeks
Left of nine-month pregnancy

- Height **28cm outstretched**
- Weight **Less than 1lb**

Source: What to Expect

Impairment

- Disability
  - 1995-2006
  - 15% improvement in survival
  - 13% in survival with no impairment
  - No change in disability
- 2019 ?

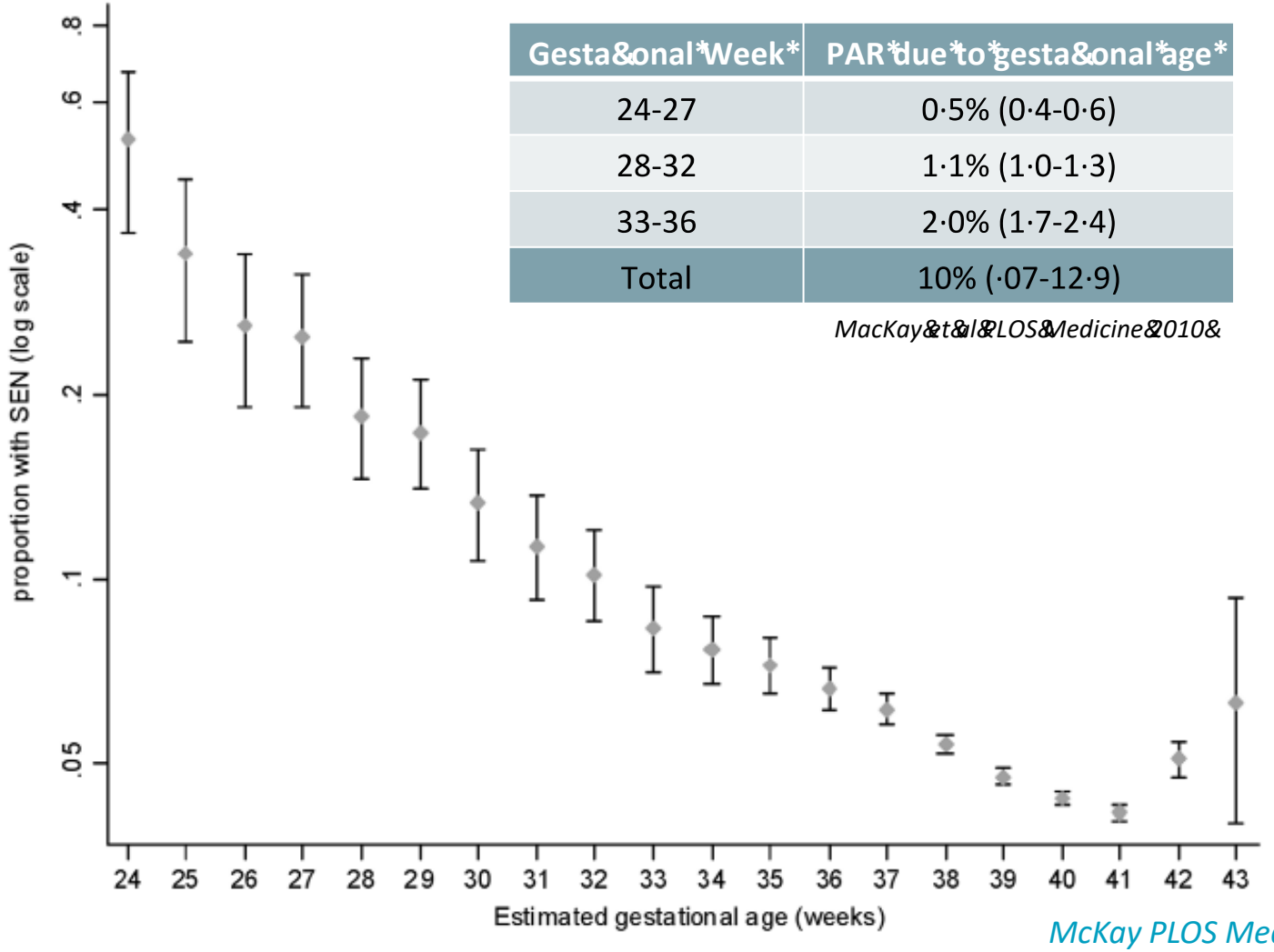


Moore T et al BMJ 2012

Prematurity is a continuum

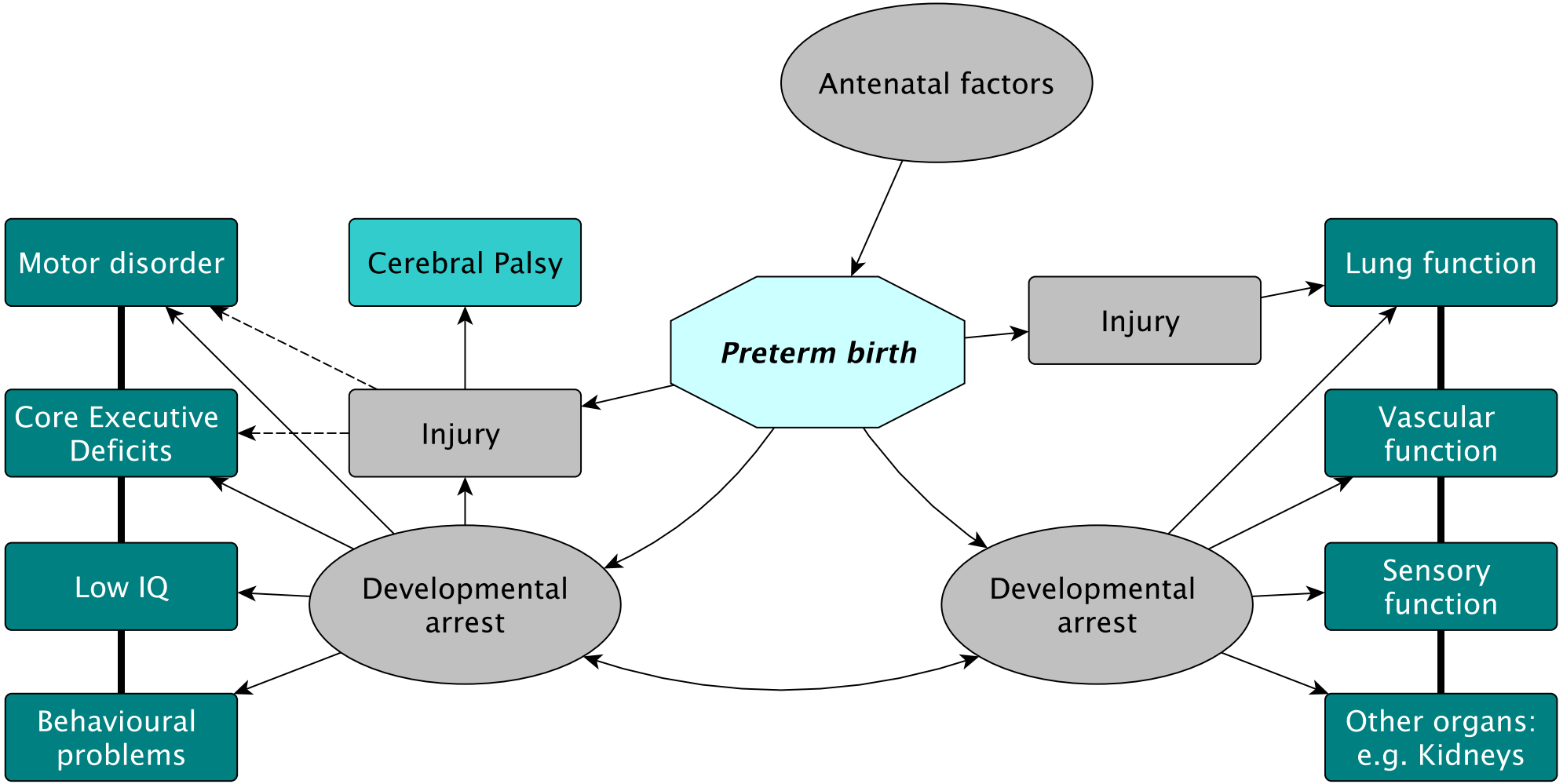
Gestational Week	PAR due to gestational age
24-27	0·5% (0·4-0·6)
28-32	1·1% (1·0-1·3)
33-36	2·0% (1·7-2·4)
Total	10% (·07-12·9)

MacKay et al PLOS Medicine 2010



McKay PLOS Medicine 2010

Prematurity is a pervasive disorder



Transition to young adult life

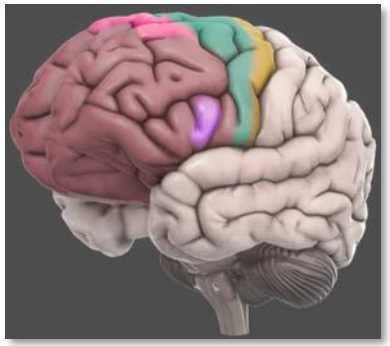
Review

- Cognitive and consequent attainment
- Social and mental health outcomes
- Lung and cardiovascular function

Spectrum of neurocognitive findings

Education
Special needs

Cognition
Executive function
Working memory



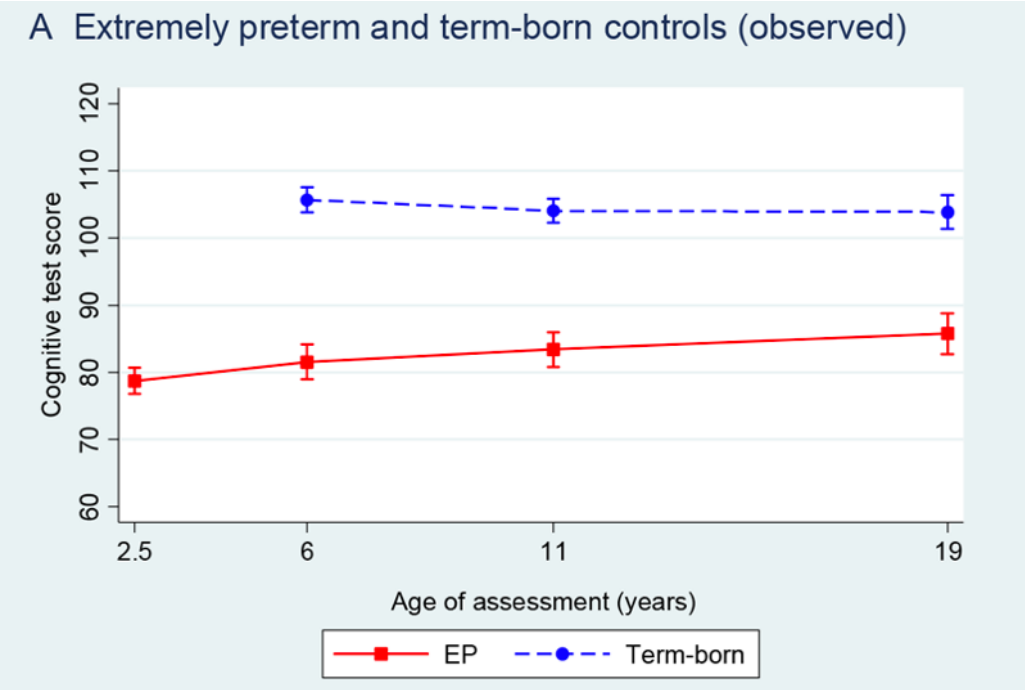
Socialisation
Peer group
Affect

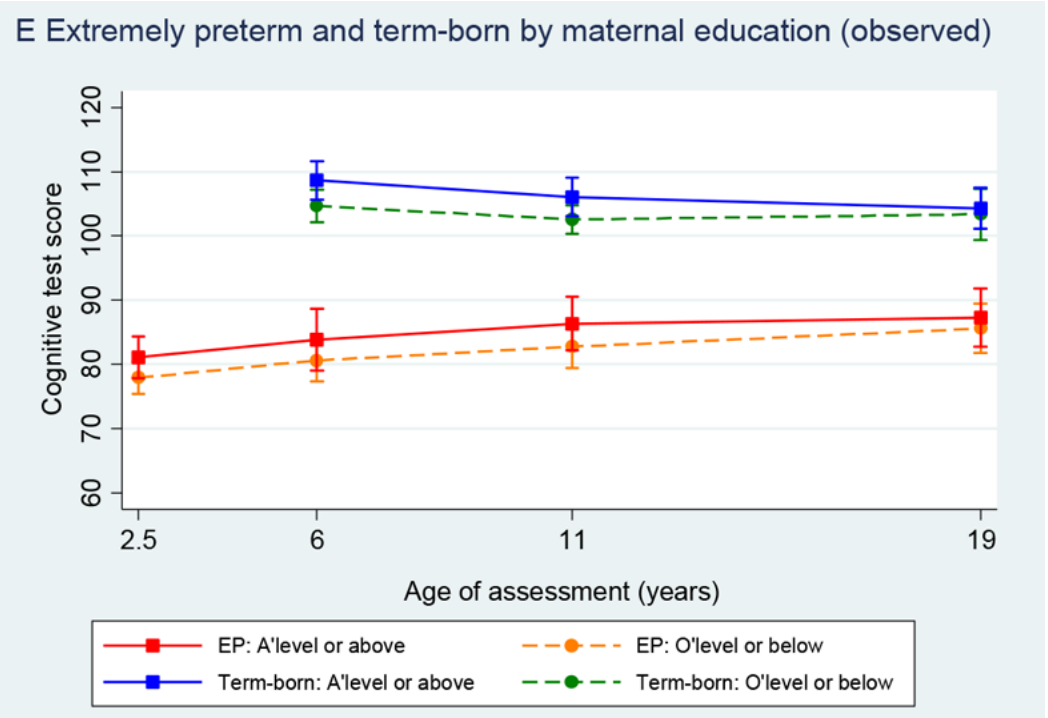
Behaviour
Inattention
Psychiatric probs

Cognitive outcomes following EP birth

- Commonest domain of impairment
- Translates into
  - Poor educational attainment
  - Behavioural phenotype
- Stability over childhood poorly defined
  - Bavarian Longitudinal Study *(Breeman et al Pediatrics 2015; 136:415)*
  - VP/VLBW scores more stable over time
  - Prediction from 20m for VPT/VLBW (r >0.50)

Cognitive trajectories

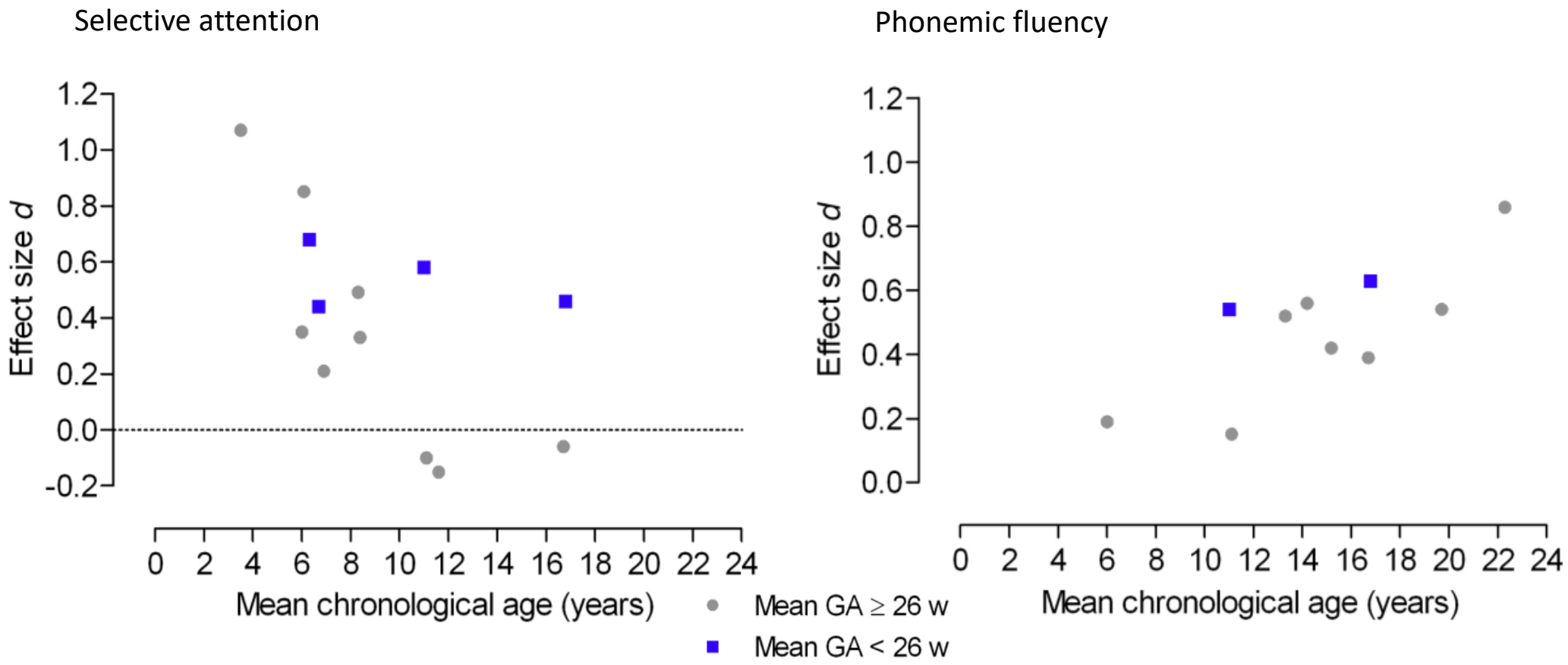




Linsell Arch Dis Child 2018

Preterm birth: development of executive function

Effect size *d*: Difference preterm-term in SD



Mulder, Marlow, Pitchford Dev Neuropsychol 2009

Key executive processes differentiating preterms

- Most δδ accounted for by
  Verbal processing speed
  Working memory
- Including:
  - Overall FSIQ differences
  - Differences on behavioural measures (SDQ, Connors rating)
  - Academic attainment

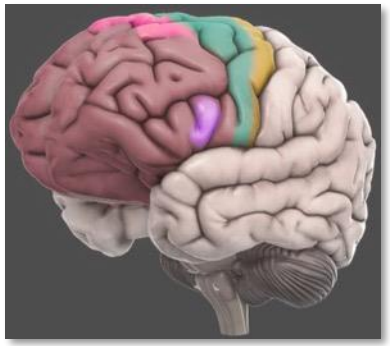
	Predictor	AUC	(95% CI)	*p*
Maths rating	Verbal speed	**.83**	.73 - .93	<.001
	Working memory	**.79**	.68 - .90	<.001
English rating	Verbal speed	**.73**	.61 - .85	.002
	Working memory	**.73**	.61 - .85	.002
Teacher rating	Verbal speed	**.74**	.61 - .86	.002
	Working memory	**.81**	.70 - .92	<.001
SEN provision	Verbal speed	**.74**	.62 - .86	.001
	Working memory	**.75**	.63 - .88	.001

Mulder, Pitchford, Marlow BJ Educ Pscychol 2011, JINS 2011, ADC 2010

Spectrum

Education
Special needs

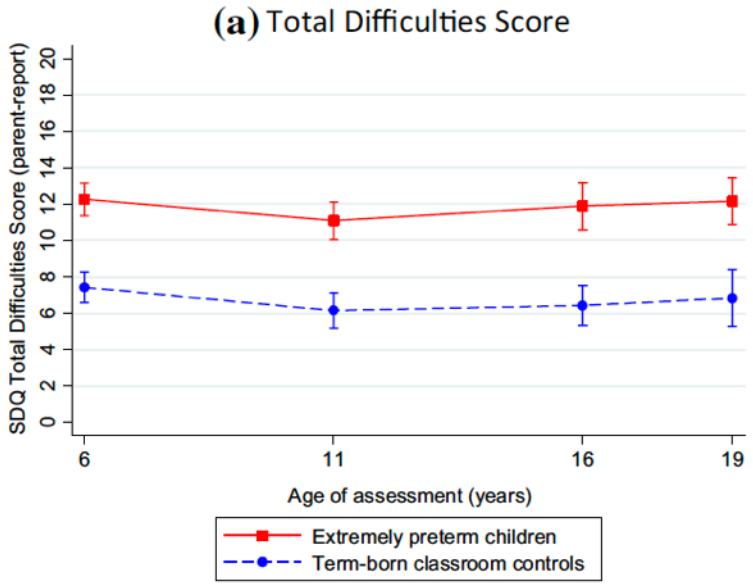
Cognition
Executive function
Working memory

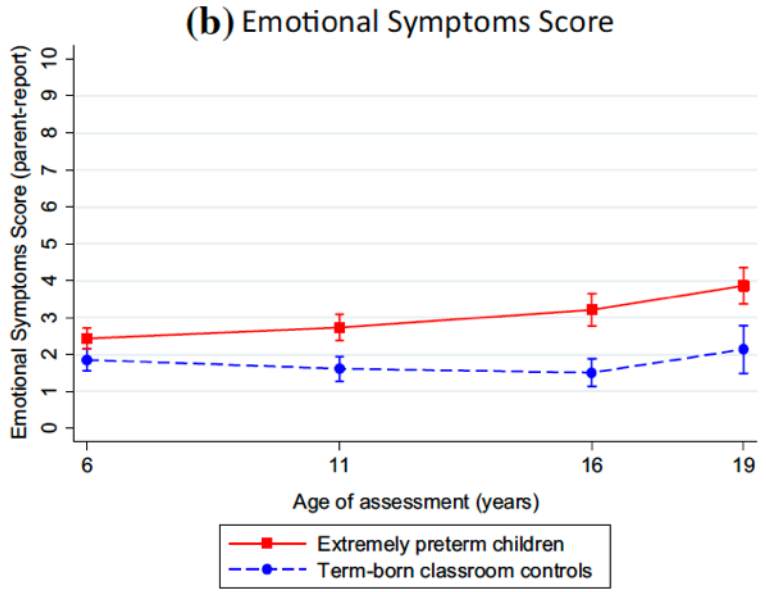


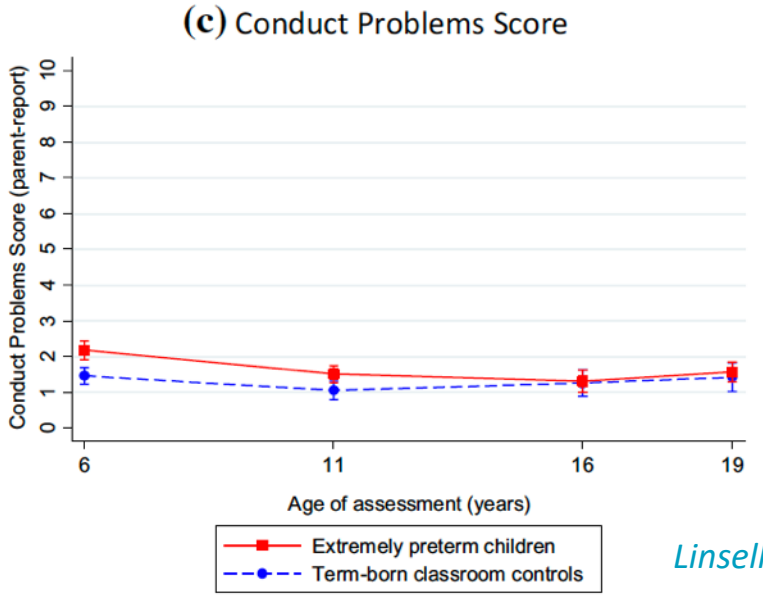
Socialisation
Peer group
Affect

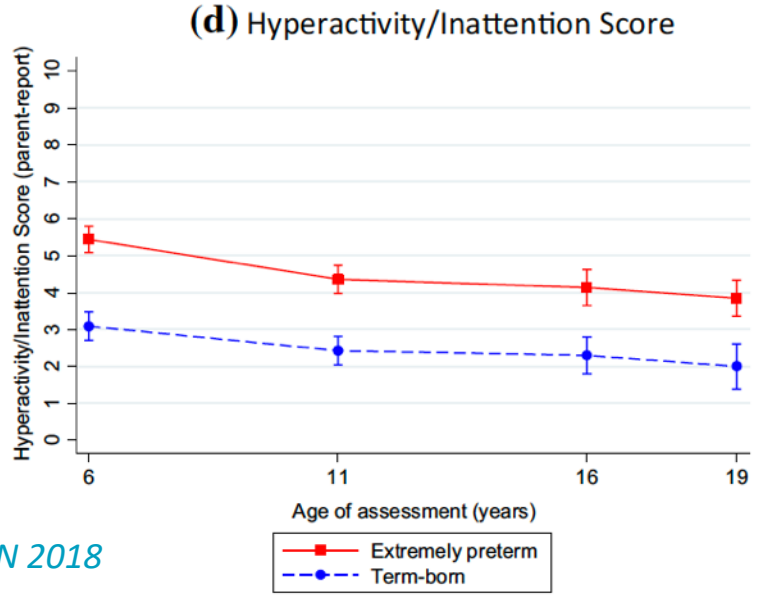
Behaviour
Inattention
Psychiatric probs

Behaviour



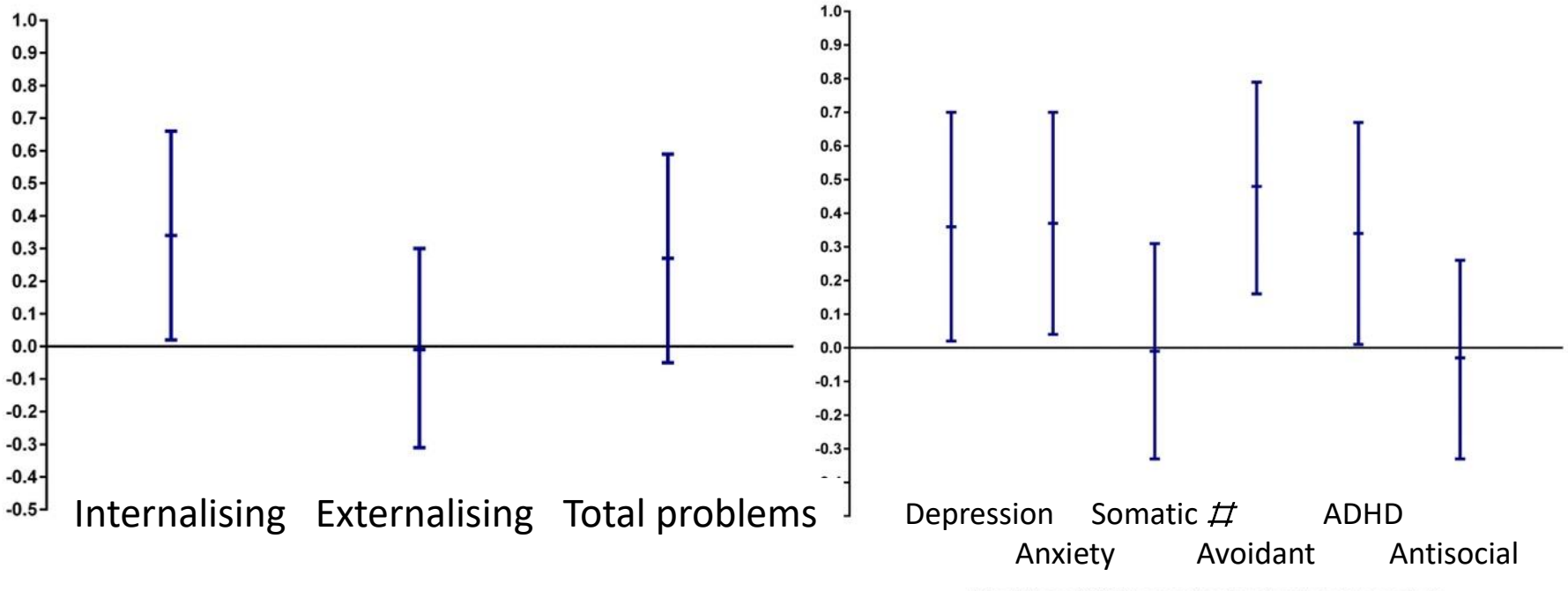






Linsell DMCN 2018

DSM4 Outcomes



Mean difference in symptom 'z' scores from controls (95%CI)

O'Reilly et al PAS 2016

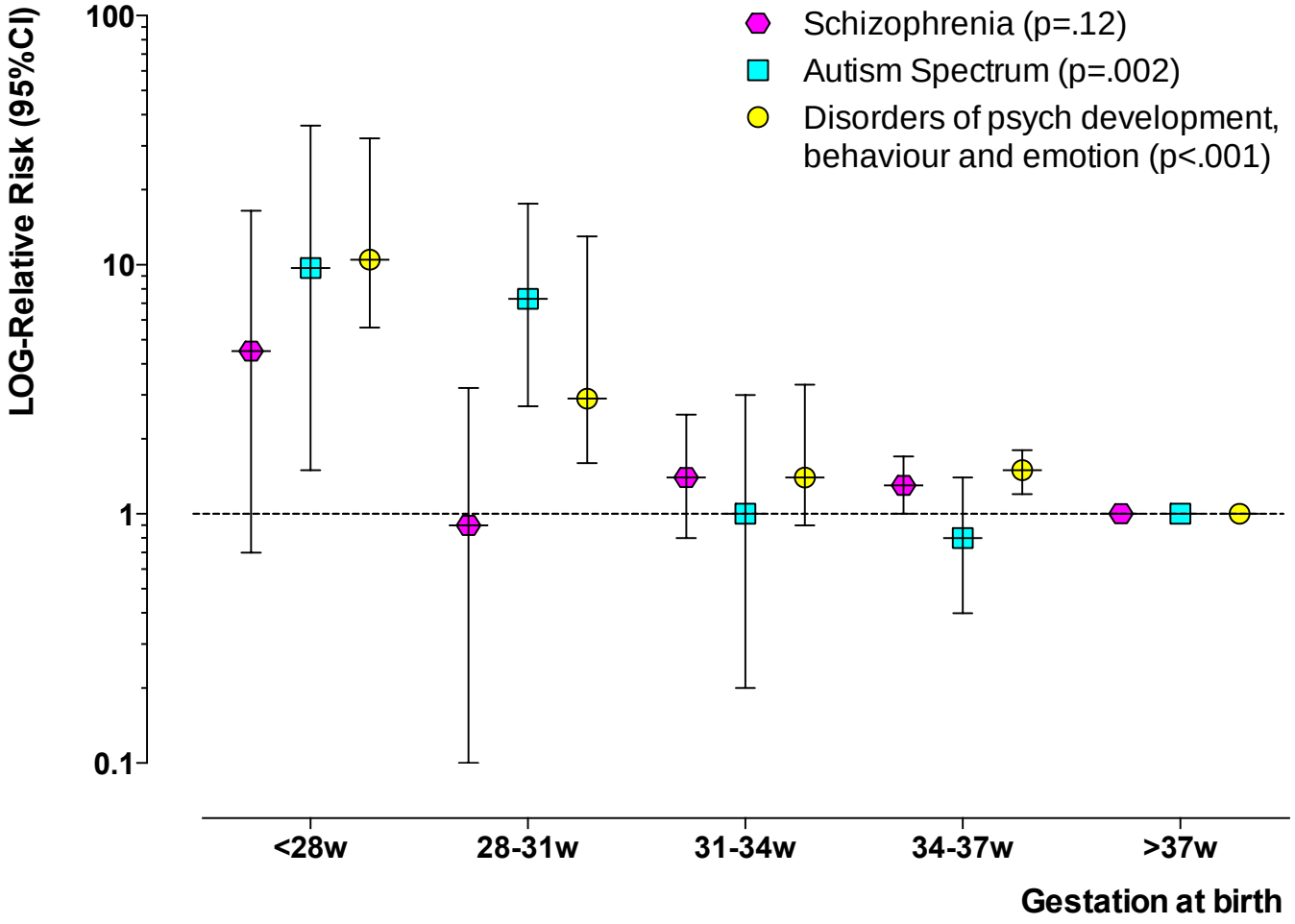
Database association studies

- Extremely preterm adults at risk of:
  - Increased ASD[1] RR: 9.5 (1.5, 36.2)
  - Other behaviour/emotional disorders[1] RR: 10.5 (5.6, 19.9)
  - ADHD[2] aRR: 5.0 (2.1, 11.8)
  - Non-affective psychosis, depressive disorder, bipolar disorder[3] (<32w)
  - Psychotrophic meds[4]
    - Antipsychotics, antidepressants, anxiolytics
- All have "dose-dependent effect" of gestation

1. *Moster et al NEJM 2008*
2. *Halmoy et al Biol Psychiatr 2012*
3. *Nosarti et al Arch Gen Psychiatr 2012*
4. *Crump et al Int J Epidemiol 2010*

Norwegian study

Births 1967-1983 (n=867 692); 19-35y



Moster et al NEJM 2008

Babies born very prematurely 'more likely to be unemployed and single as adults'

The prematurely-born babies were also found to be more likely to suffer from chronic health problems as adults

Independent 24 May 2016

Education and occupation at 19y

Fig 1. Highest school attainment

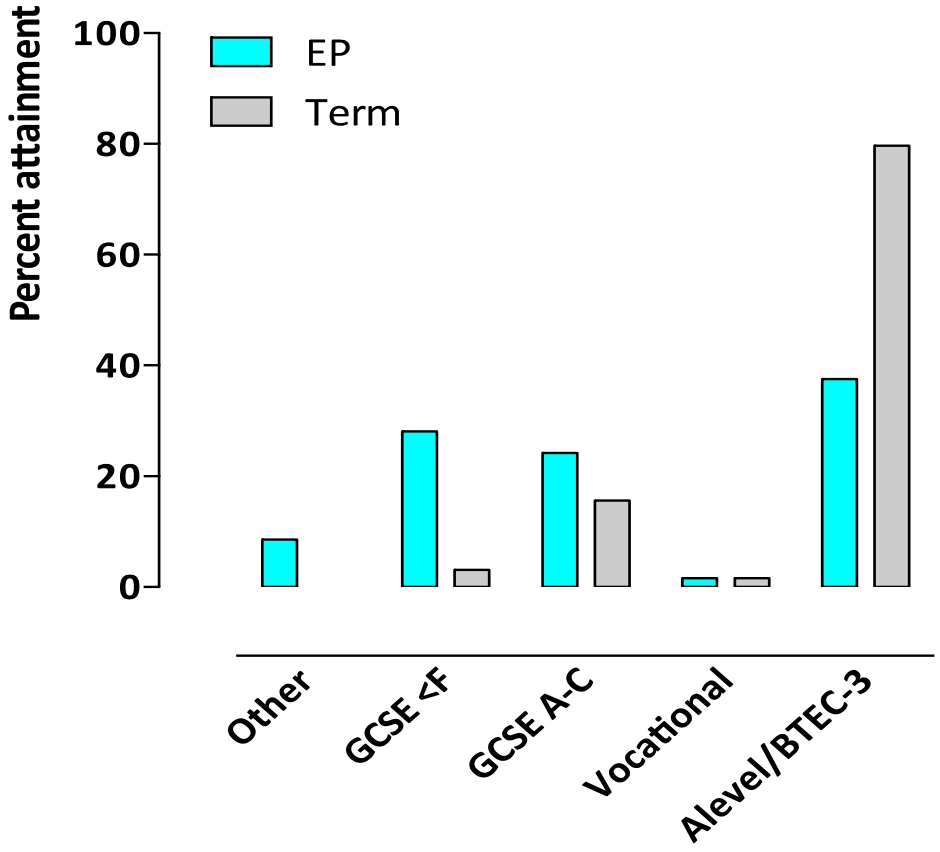
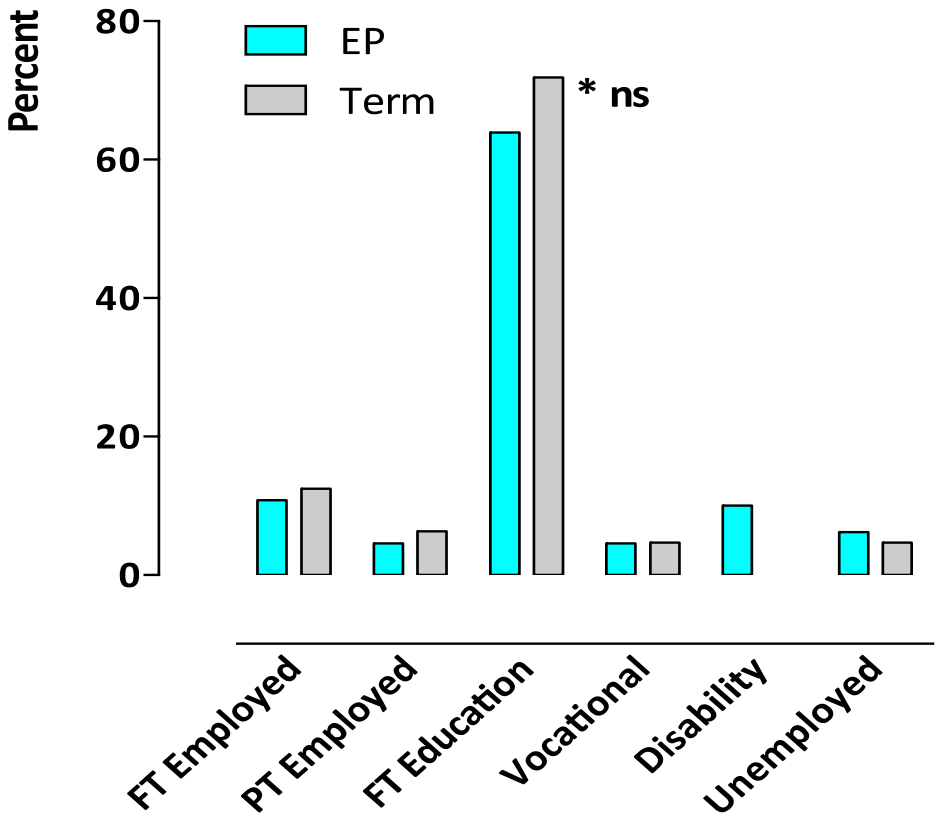
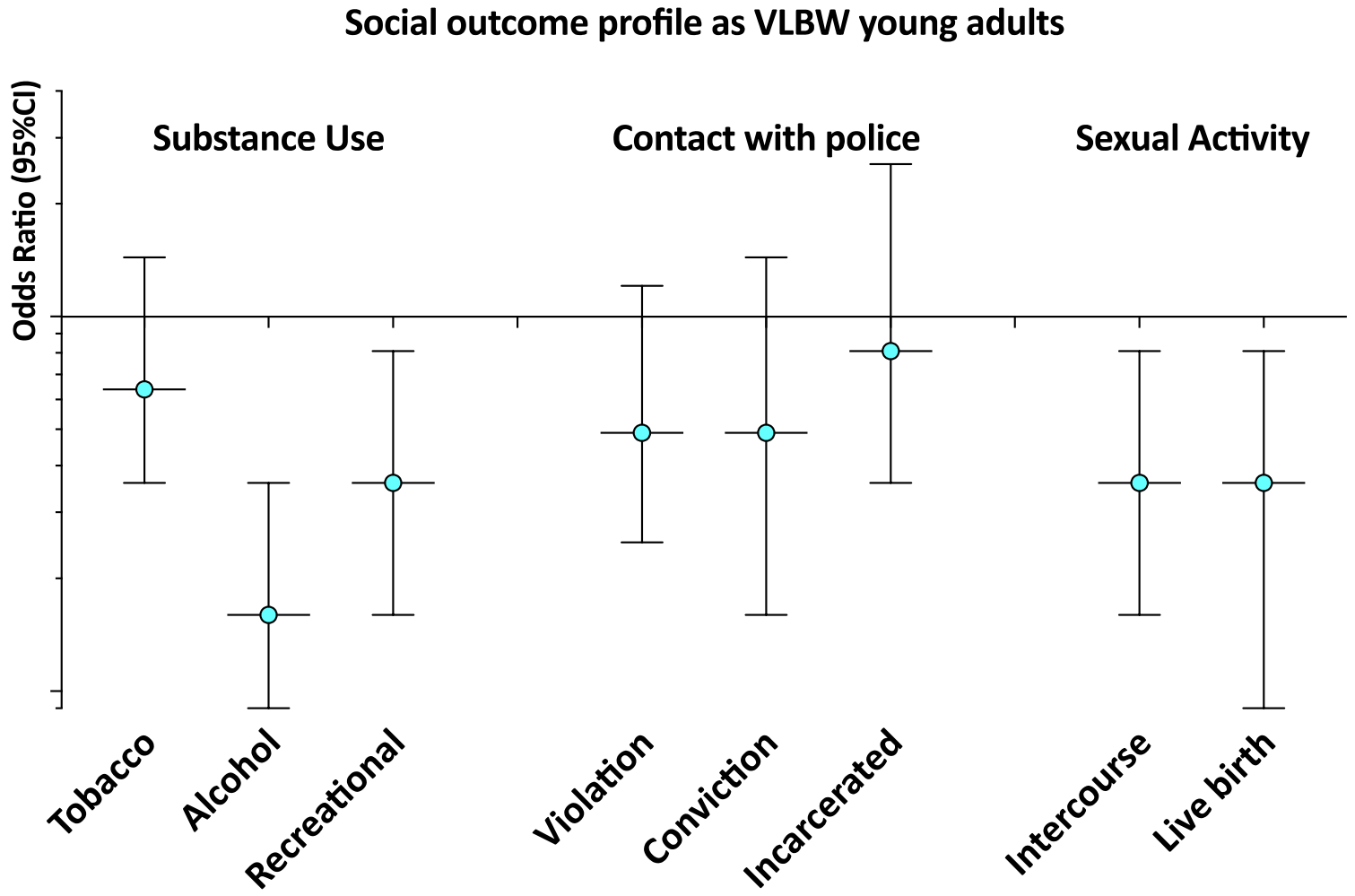


Fig 2. Occupational status

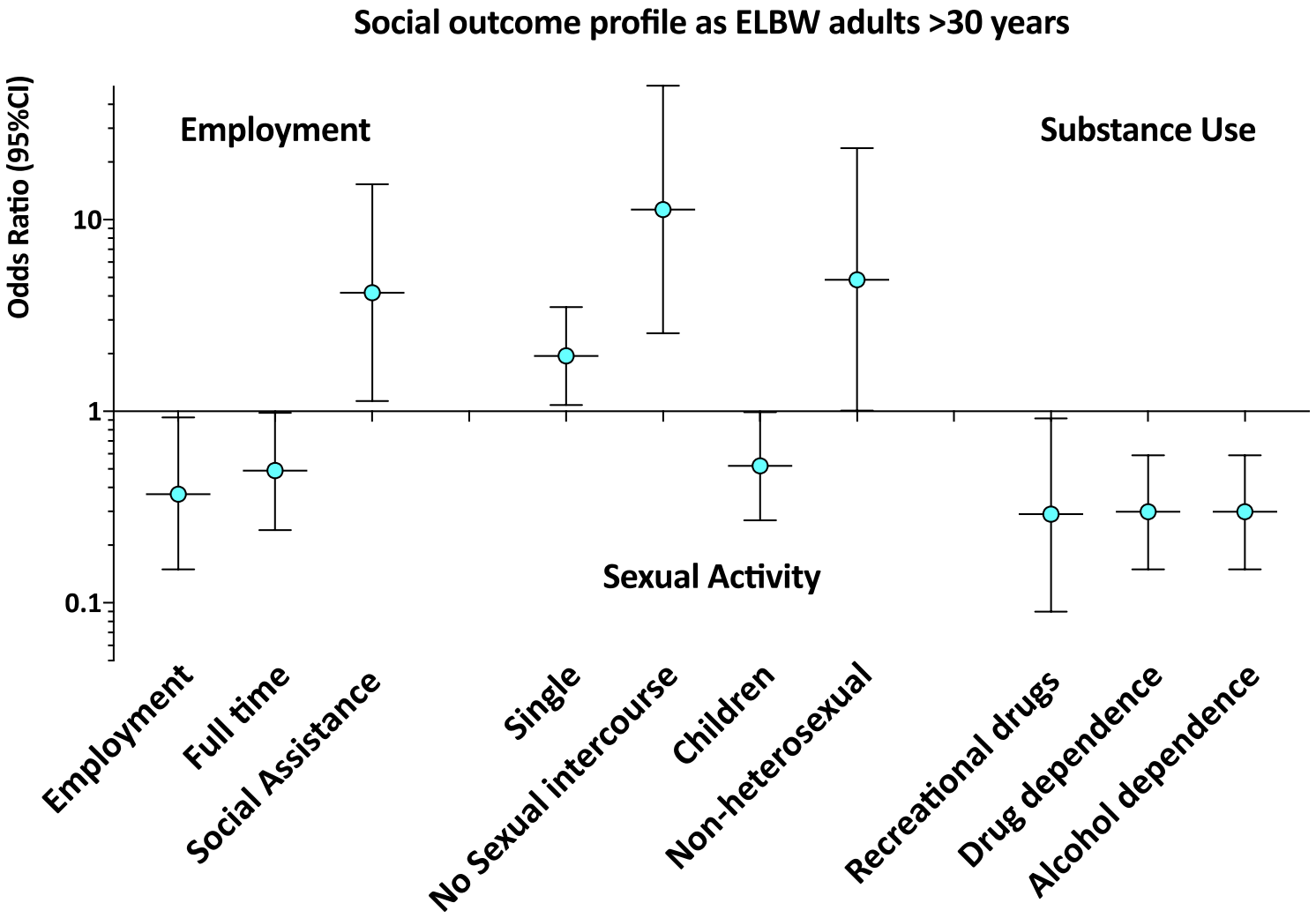


Cleveland Study



Hack et al NEJM 2002

Hamilton Study



Income C$20,000 less
More chronic health problems
Less self esteem

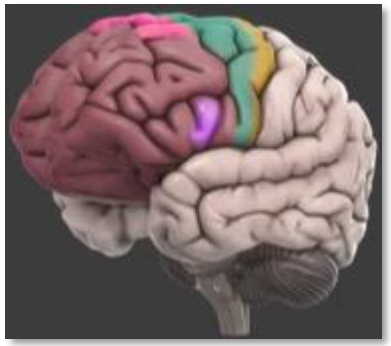
Differences dependent on presence of NS impairment

Saigal et al JAMA Peds 2016

Spectrum of outcomes

Education
Special needs

Cognition
Executive function
Working memory

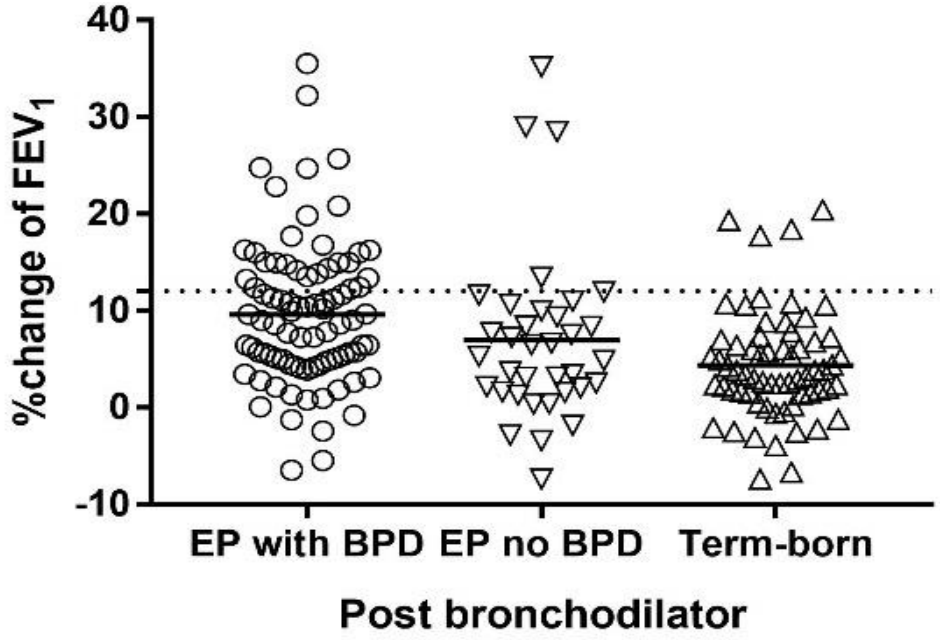


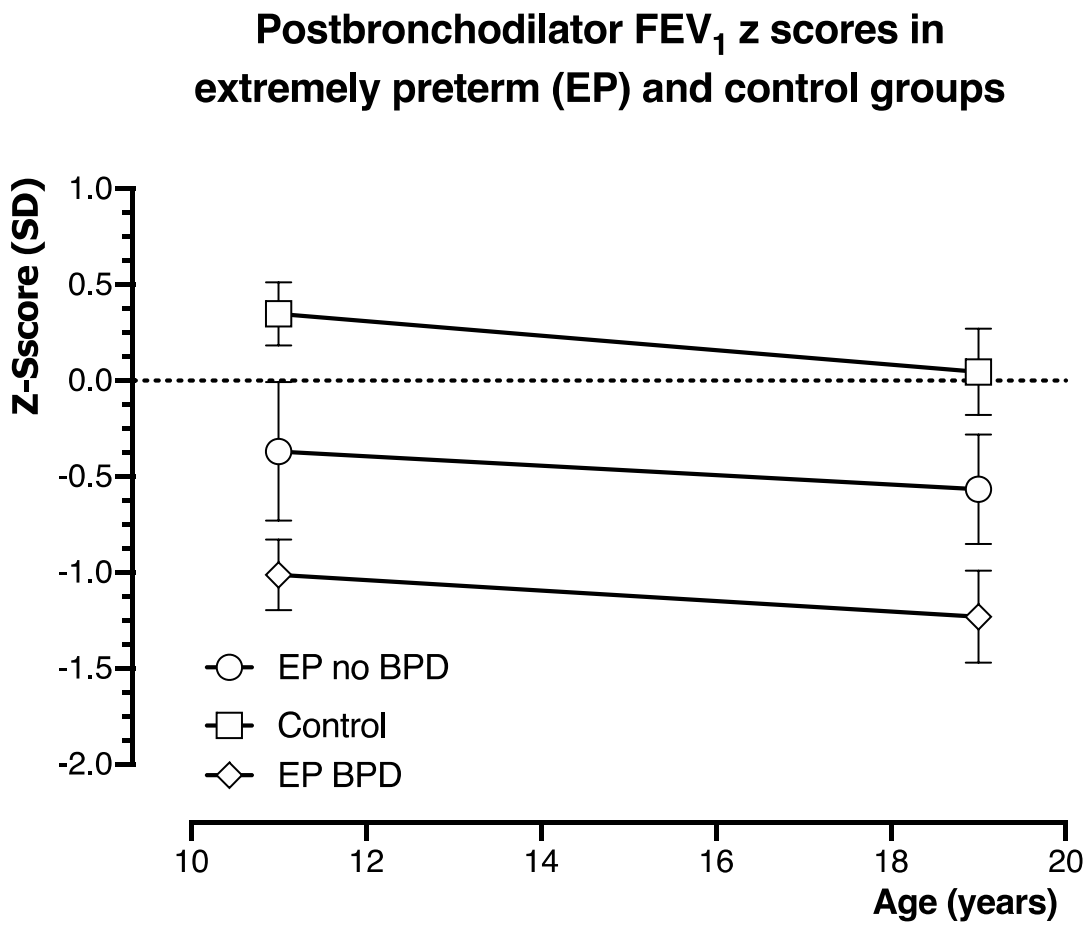
Socialisation
Peer group
Affect

Behaviour
Inattention
Psychiatric probs

?

Lung function - Spirometry

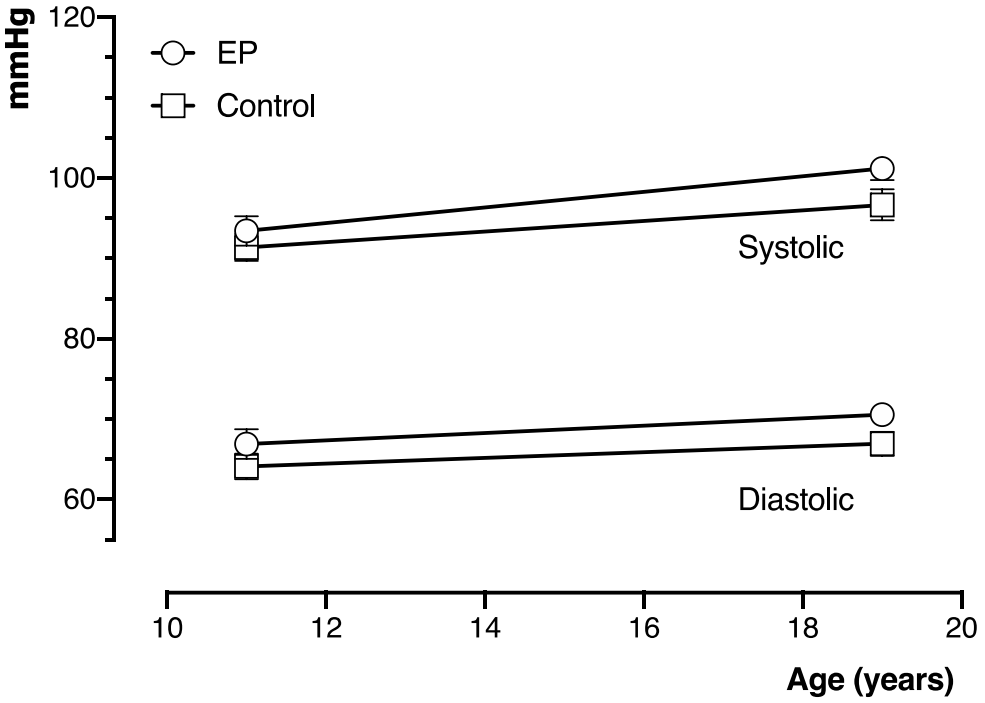




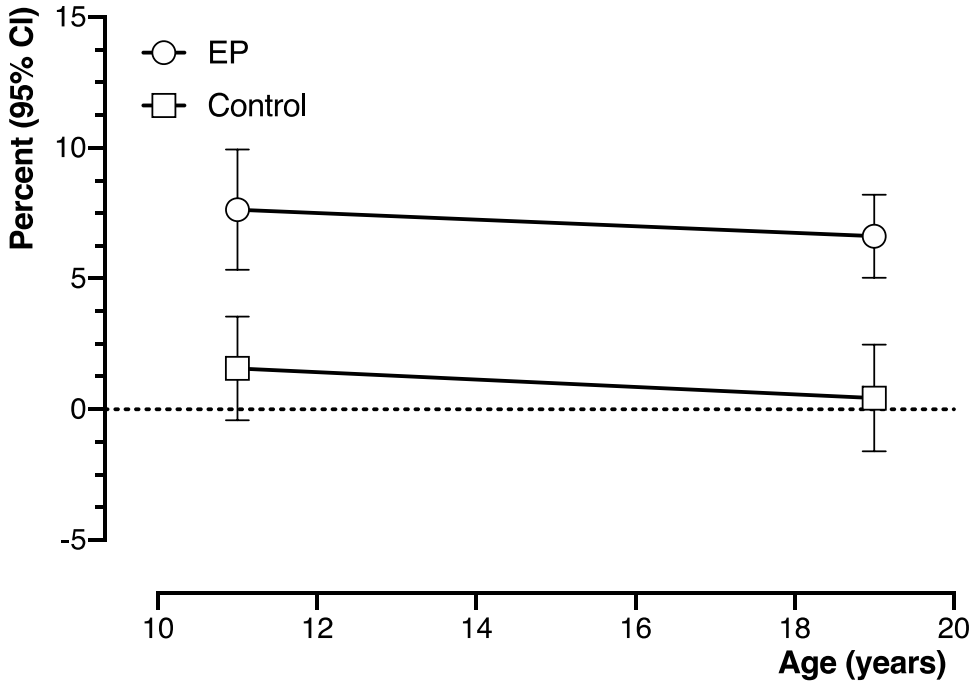
Beckmann et al PAS 2016

Cardiovascular function

Central blood pressure values in extremely preterm (EP) and control groups

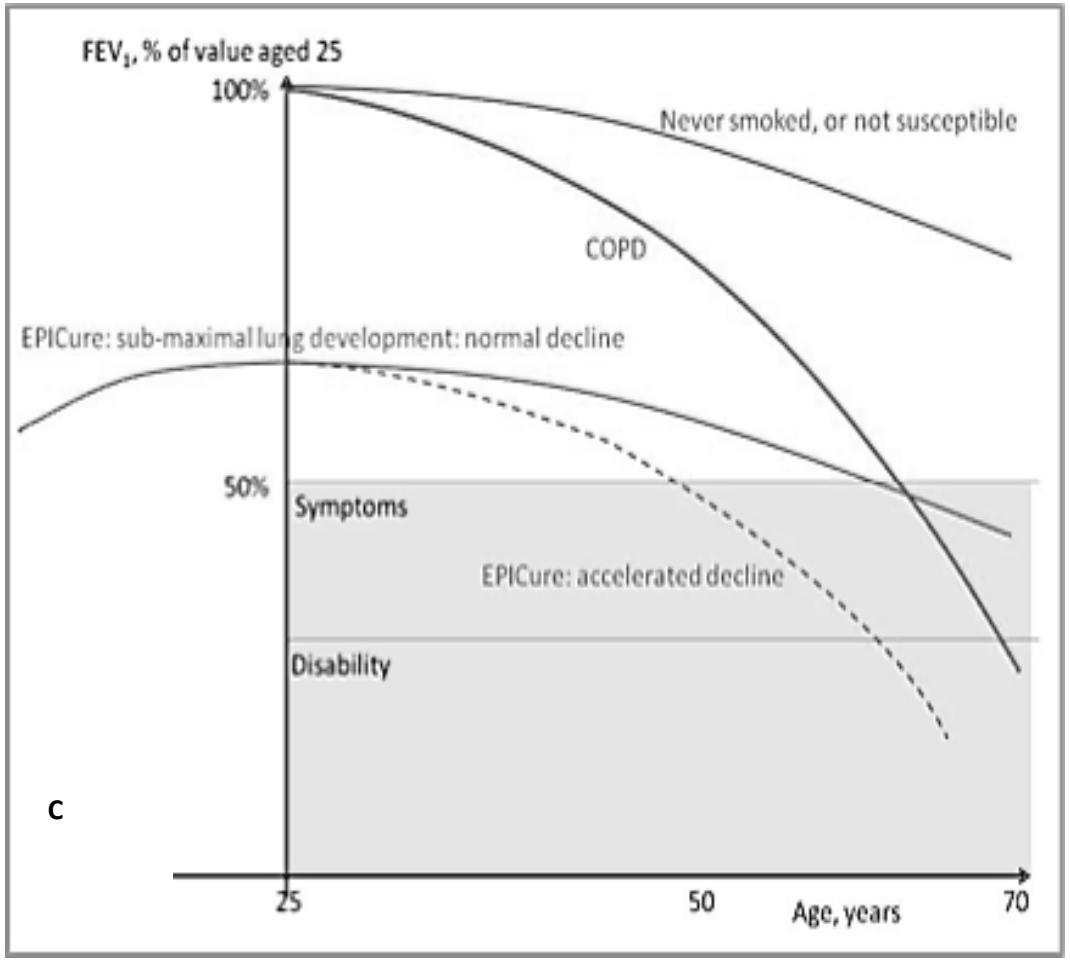


Augmentation index in extremely preterm (EP) and control groups



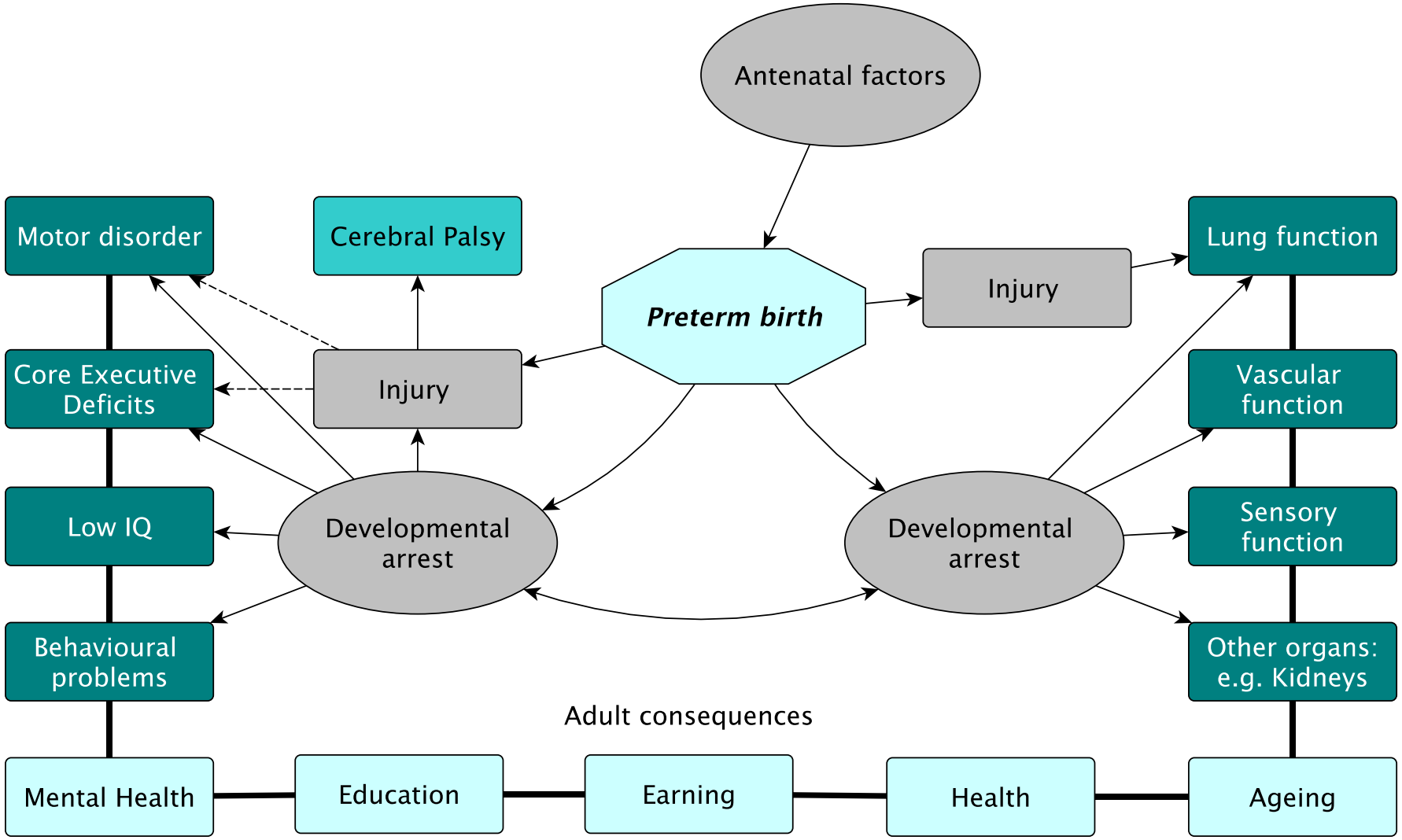
Beckmann et al PAS 2016

Implications for adult life



after Fletcher C, Peto R BMJ 1977

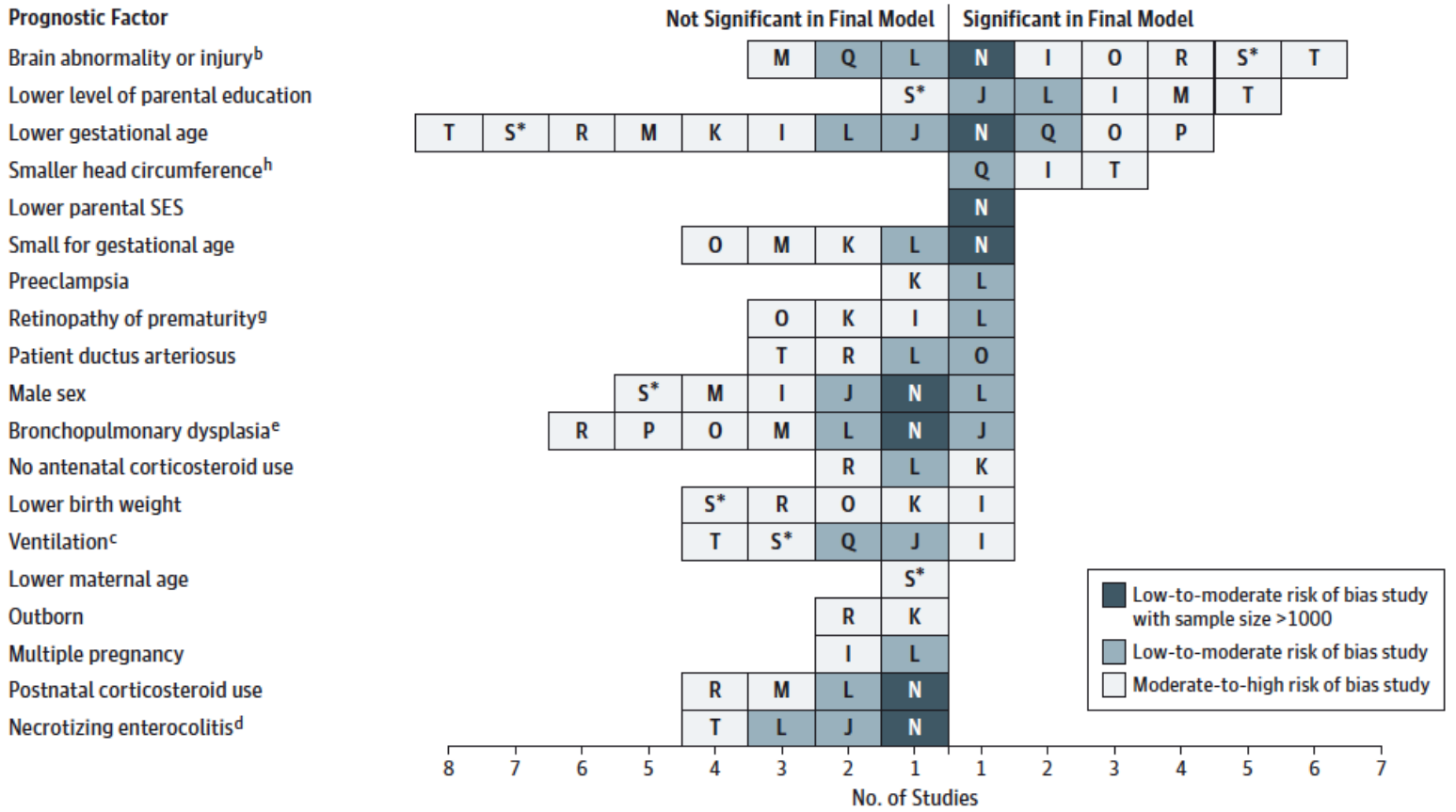
Pervasive effects of extremely preterm birth



Risk factors for preterm cognitive impairment

- Parental education
- Lower SES
- SGA
- Small OFC

- **Brain injury**



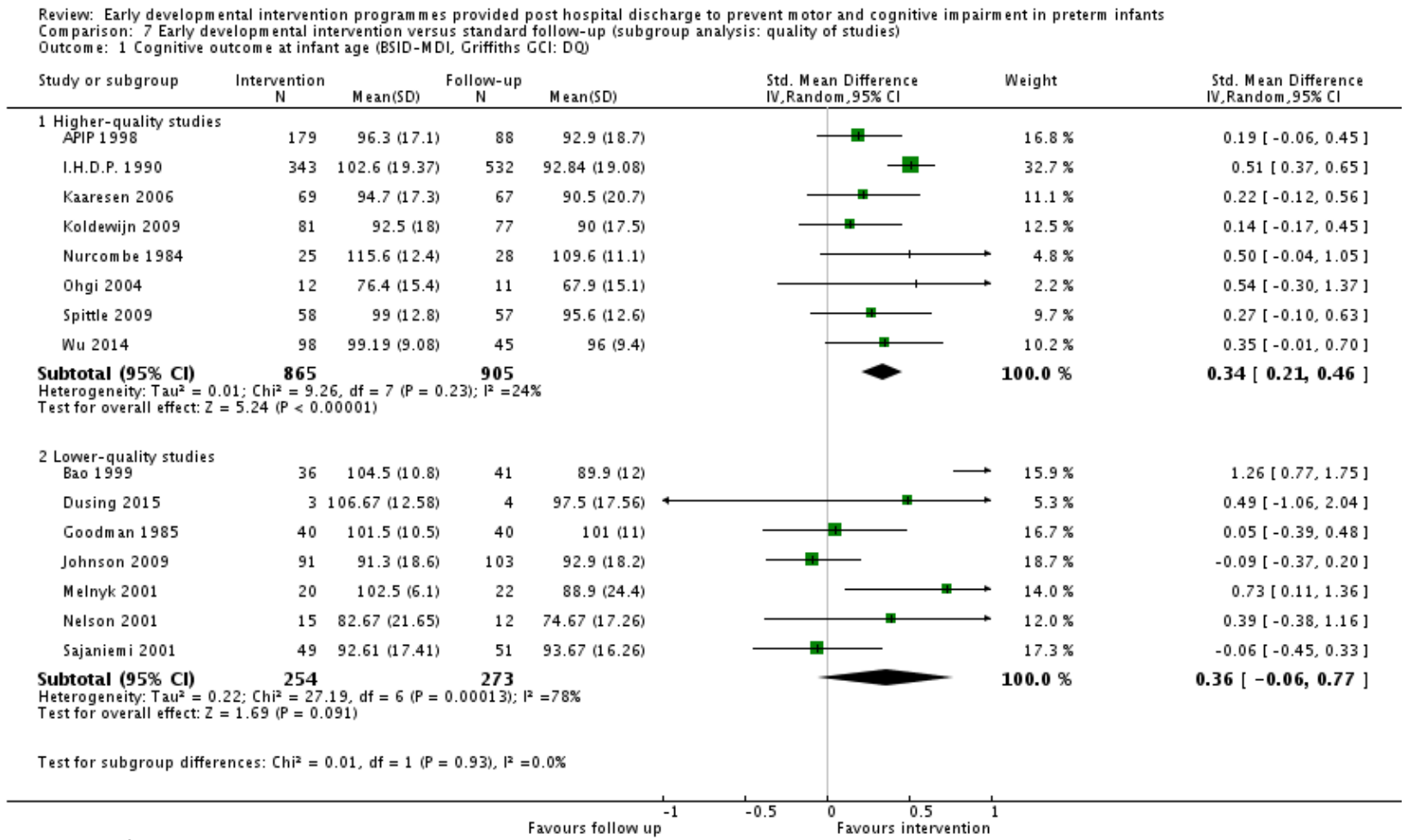
Linsell et al JAMA Pediatr doi:10.1001/jamapediatrics.2015.2175

Doing something about it …

- Effective early intervention?

Early developmental intervention programmes provided post hospital discharge to prevent motor and cognitive impairment in preterm infants

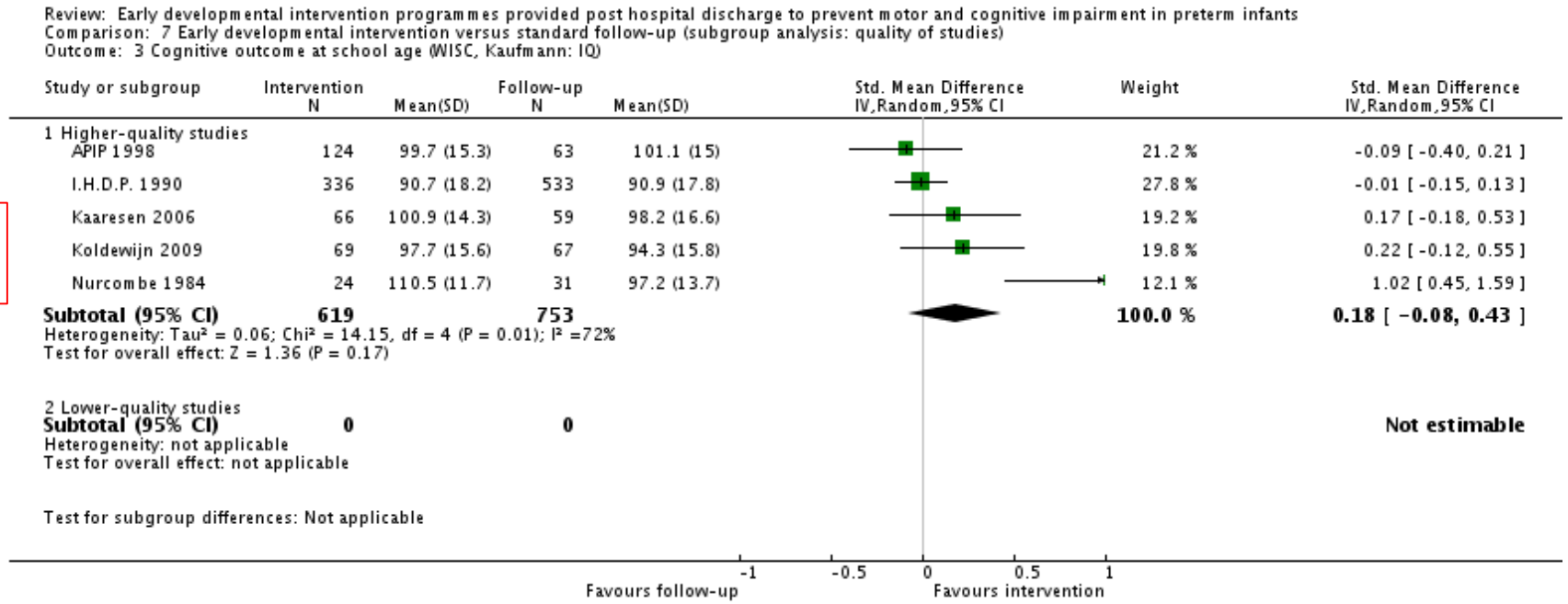
INFANT outcomes



Cochrane Database of Systematic Reviews
24 NOV 2015 DOI: 10.1002/14651858.CD005495.pub4
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005495.pub4/full#CD005495-fig-00701

Early developmental intervention programmes provided post hospital discharge to prevent motor and cognitive impairment in preterm infants

School Age



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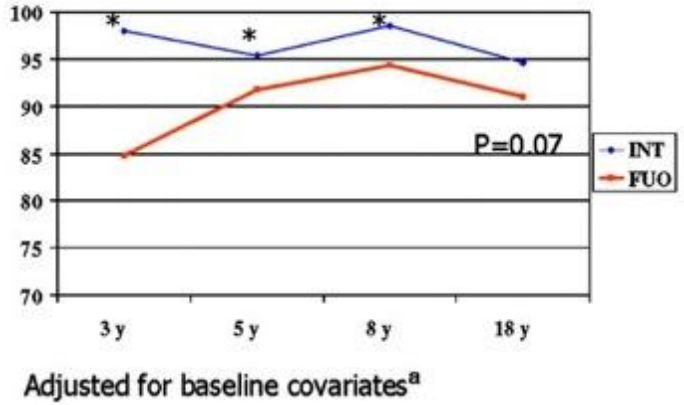
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005495.pub4/full#CD005495-fig-00703

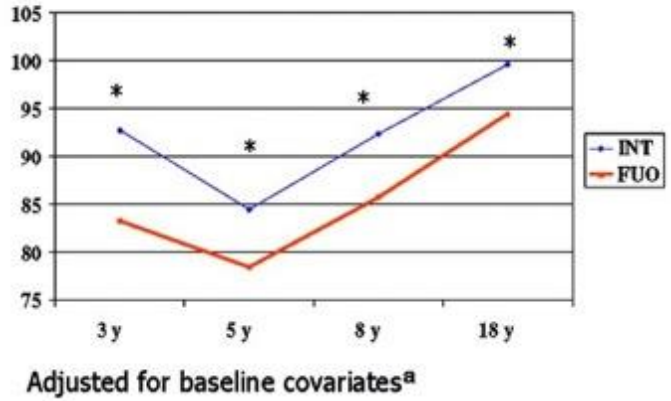
Infant Health and Development Program

1250-2500g
or <37w

Heavier BW group – IQ



PPVT



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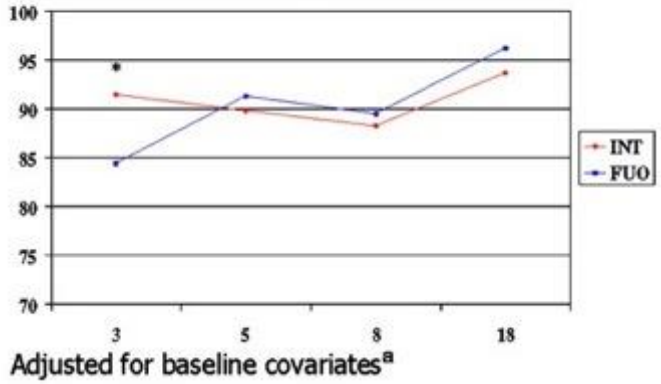
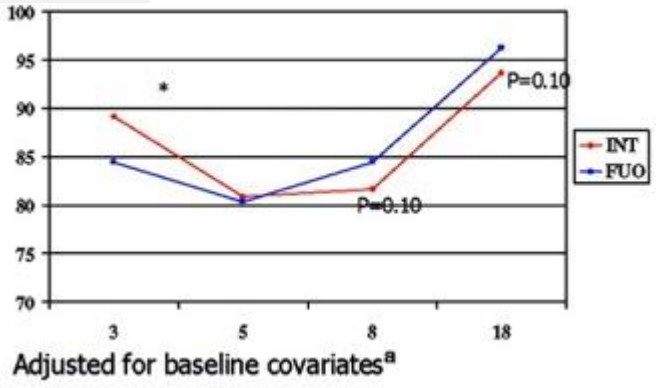
Lower BW group – IQ



PPVT



McCormick Pediatrics 2006

Doing something about it …

- Effective early intervention?
  - Too early?
- Working memory training?
- Processing speed?
- Inattention?
- Educational support?
  - Too late?

Cognitive outcomes

- Measurement challenging
- Development not cognition
- IQ is a global summary score
- IQ comprises a series of processes
  - Basic functions – processing speed
  - Executive functions – higher order
- Functions differentiate over time
- Intervene when differentiating?

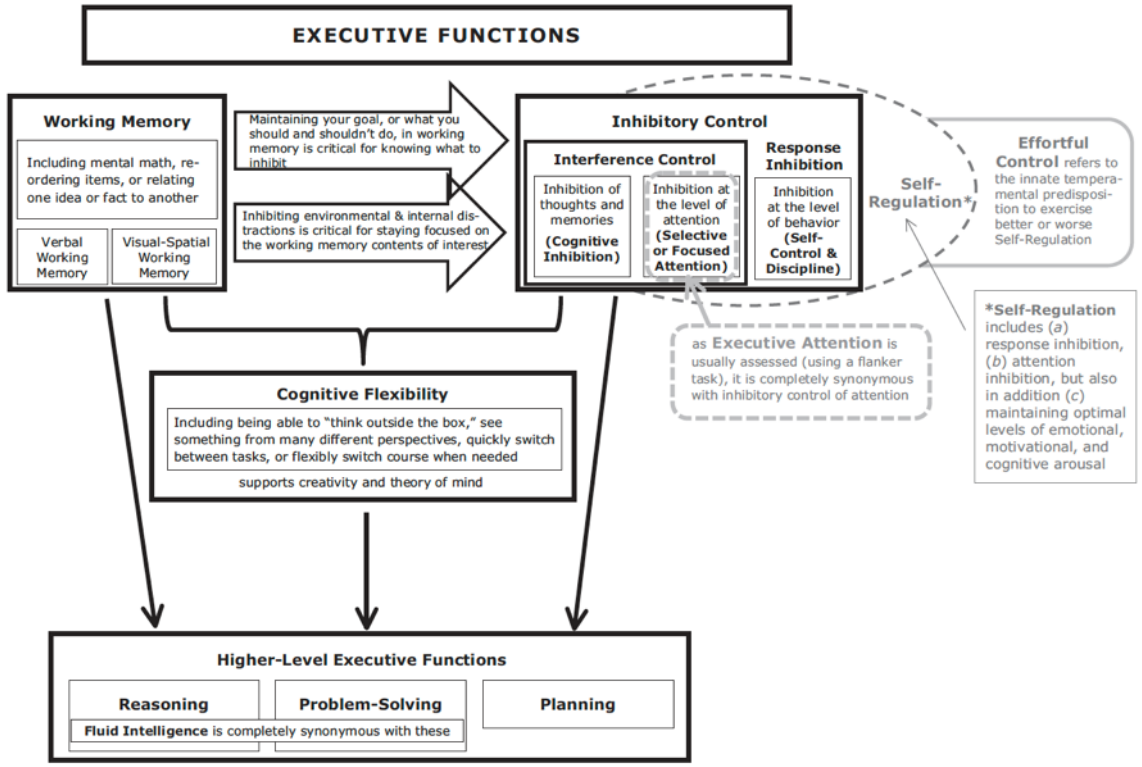


Figure 4

Executive functions and related terms.

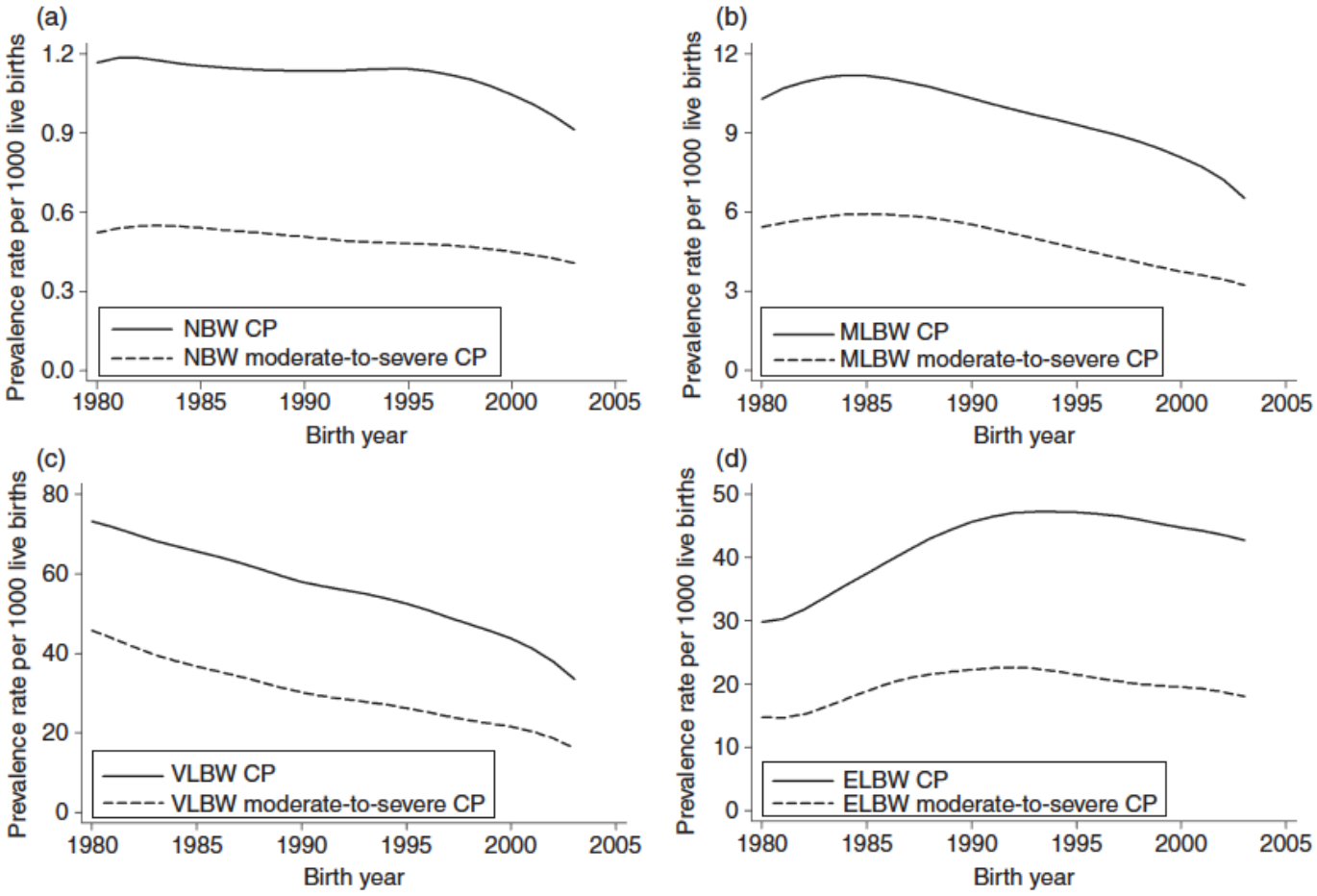
Diamond Ann Rev Psychol 2013

The fate of British Cycling changed one day in 2003

- ..the performance of British riders had been so underwhelming that one of the top bike manufacturers in Europe refused to sell bikes to the team because they were afraid that it would hurt sales if other professionals saw the Brits using their gear. *James Clear*
- Dave Brailsford –

  "*the aggregation of marginal gains*"

Cerebral Palsy rates



Sellier et al Dev Med Child Neurol. 2016

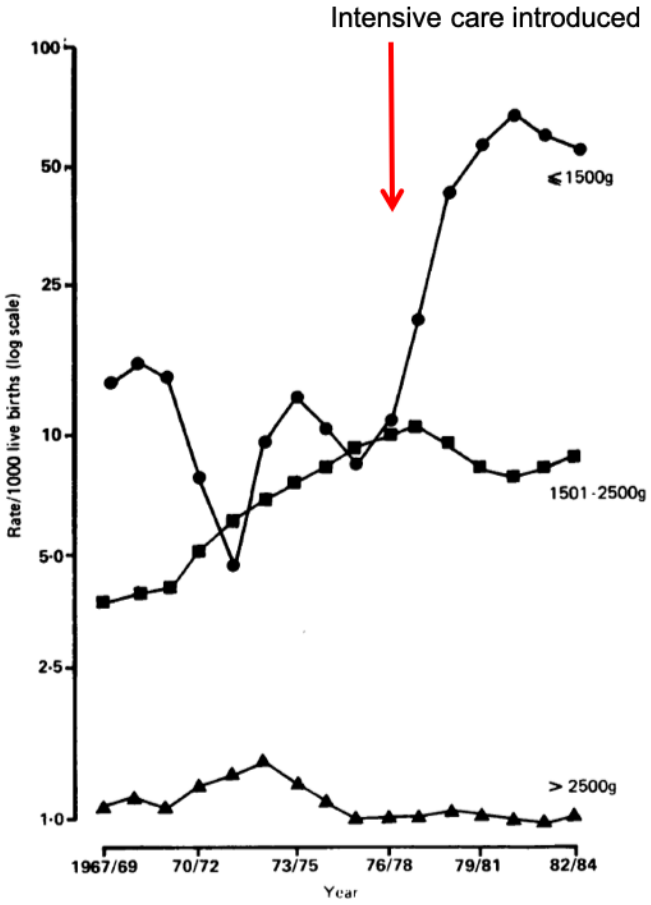


Figure 1 ***Birthweight specific trends in cerebral palsy.***

Pharoah et al Arch Dis Child. 1990

Potentially better practices

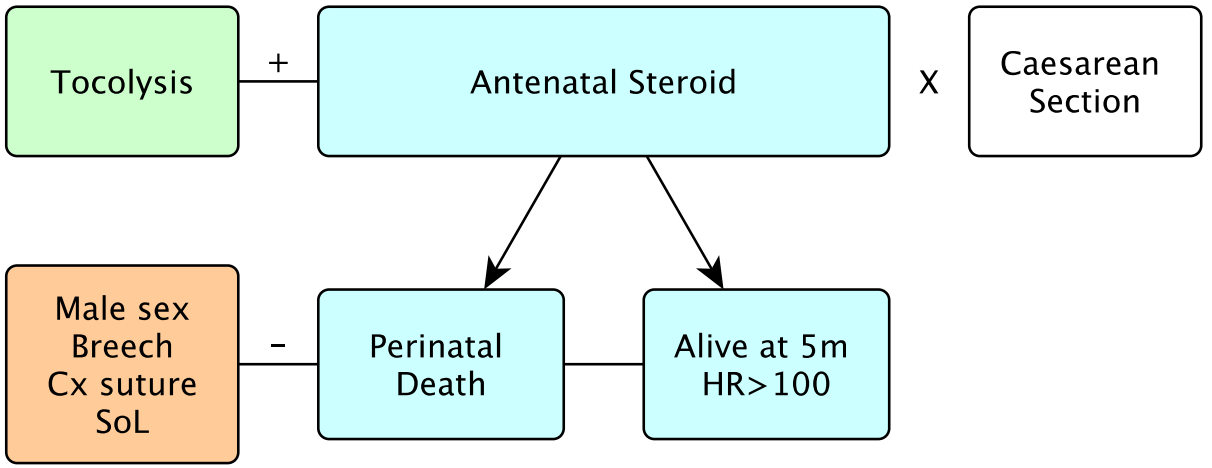
VON Qi initiative e.g.:

- Neurodevelopment – 16 practice changes
- BPD – 13 PBP identified
- Sepsis bundle reduced infection rates
  - Antibiotic stewardship
- Staffing – reduced staffing turnover
- Neonatal abstinence
- ALL need local leadership for QI team

Can we improve outcomes further?

- Antenatal Steroid

- No RCT data
- Key positive influence in many studies (confounded)



Morgan et al BMC Pregnancy & Childbirth 2016

Can we improve outcomes further?

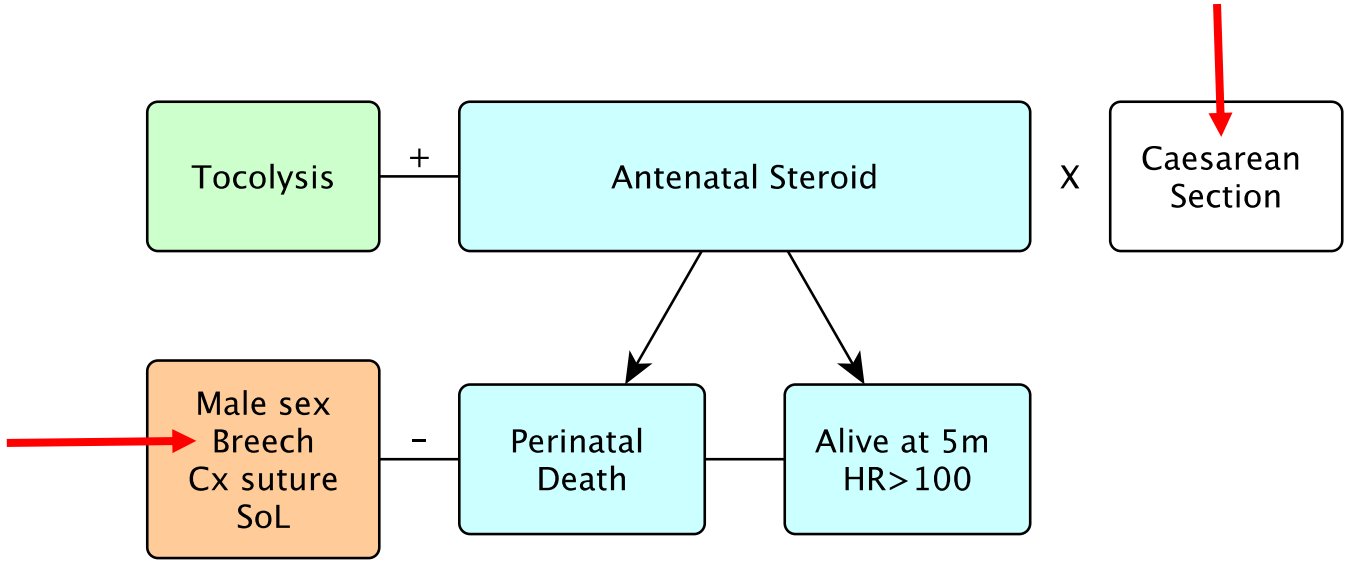
- Antenatal Steroid
- Magnesium Sulphate

- No RCT data <24 weeks
- Accuracy of dating?
- Should this stop its use?
- PReCePT Study

Can we improve outcomes further?

- Antenatal Steroid
- Magnesium Sulphate
- Delivery Route

- No RCT data



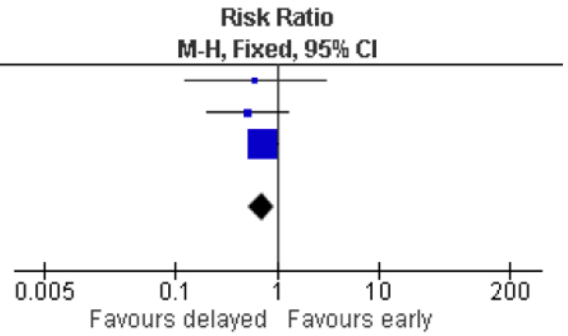
Morgan et al BMC Pregnancy & Childbirth 2016

Can we improve outcomes further?

- Antenatal Steroid
- Magnesium Sulphate
- Delivery Route
- Physiological cord clamping

Study or Subgroup	Delayed Events	Delayed Total	Early Events	Early Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Backes 2016	2	18	4	22	4.4%	0.61 [0.13, 2.96]
Duley 2016	6	46	10	39	13.1%	0.51 [0.20, 1.27]
WTM APTS 2017	50	436	68	435	82.5%	0.73 [0.52, 1.03]
Total (95% CI)		**500**		**496**	**100.0%**	**0.70 [0.51, 0.95]**
Total events	58		82			

Heterogeneity: Chi² = 0.57, df = 2 (P = 0.75); I² = 0%
Test for overall effect: Z = 2.25 (P = 0.02)



Tarnow Mordi et al AmJOG 2017

Can we improve outcomes further?

- Antenatal Steroid
- Magnesium Sulphate
- Delivery Route
- Physiological cord clamping
- Senior person at delivery
  - Obstetric
  - Neonatal

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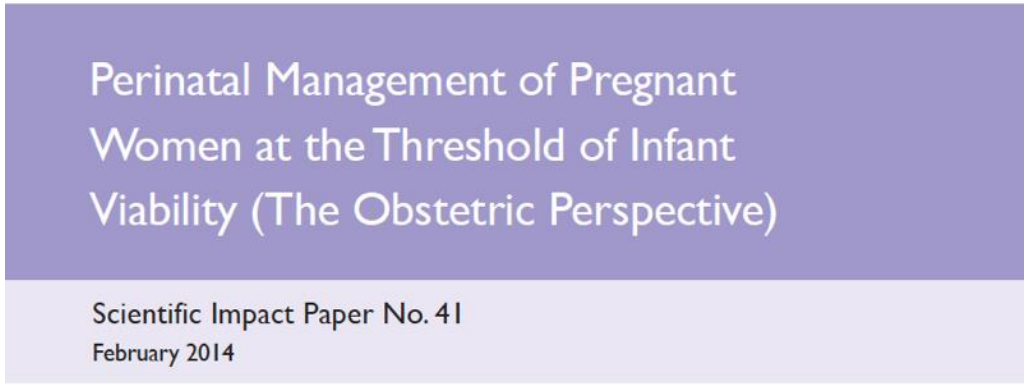

Can we improve outcomes further?

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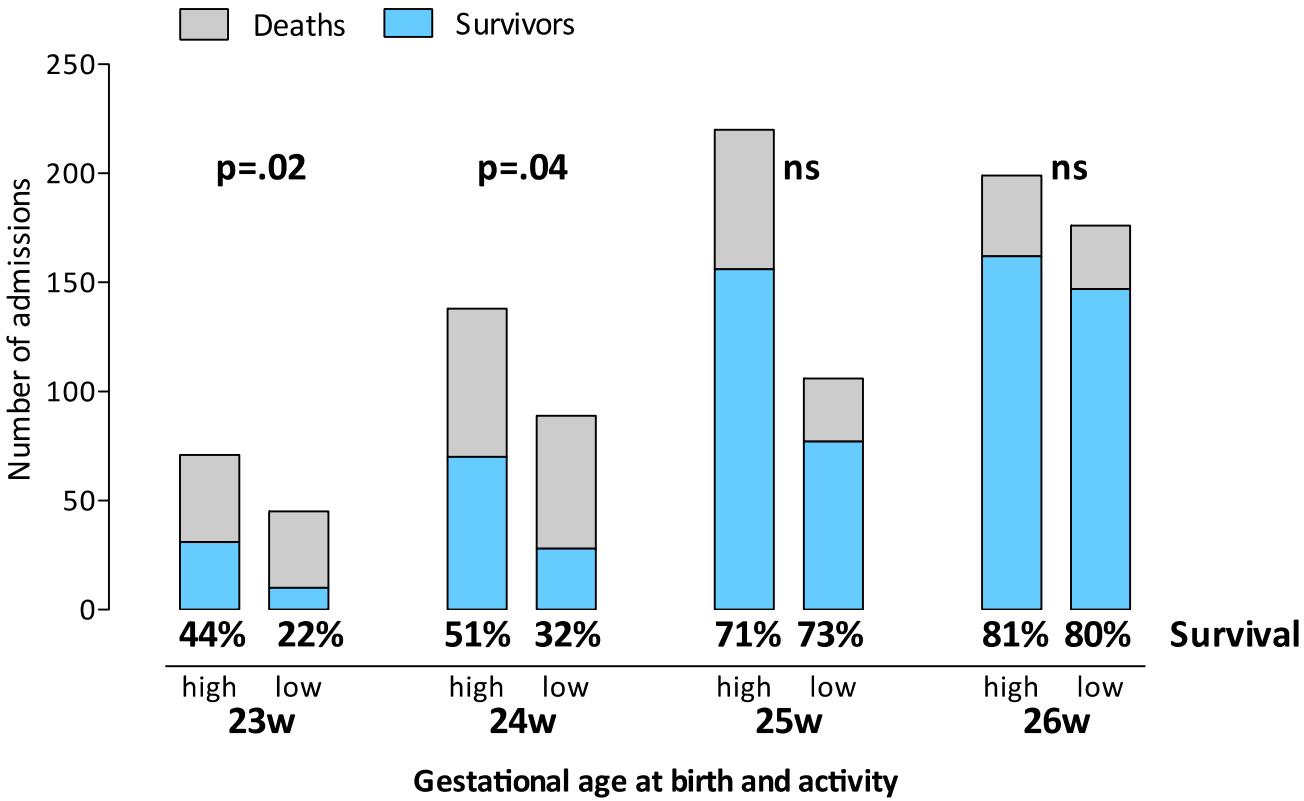
- Care in the right place



Marlow et al ADC F&N 2014

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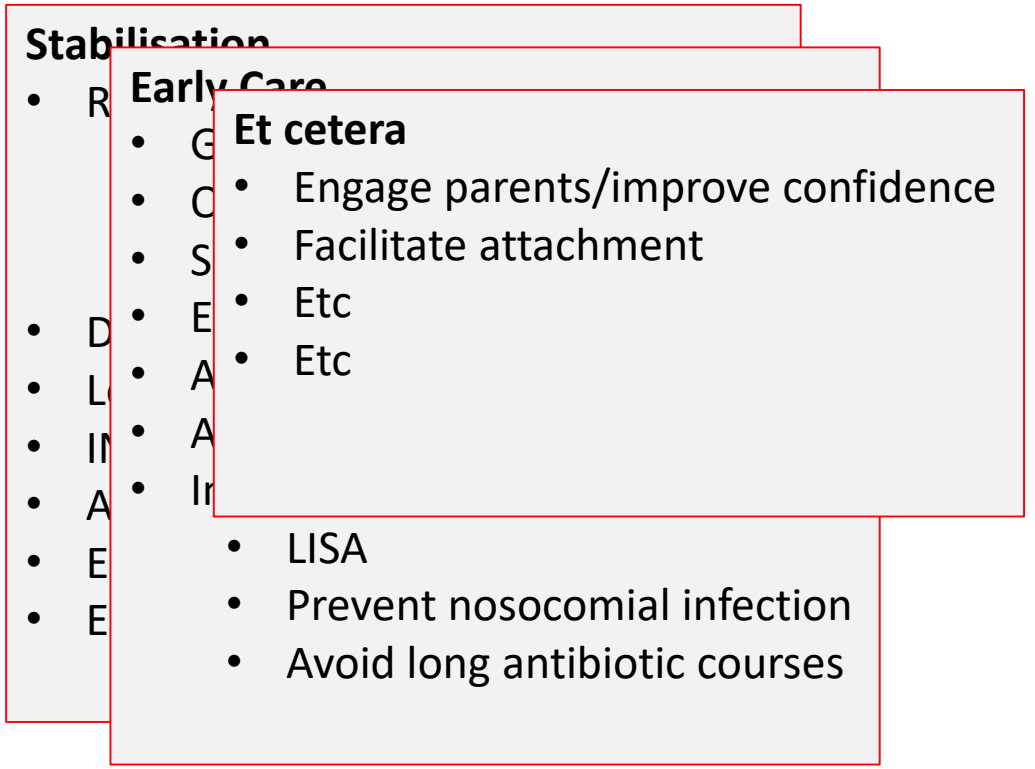

Summary

1. Prematurity produces a range of adverse outcomes through into early adult life
2. The origin of long term outcomes is a subtle mix between sociodemographics, specific developmental changes and tissue injuries
3. Current developmental and neonatal interventions are of uncertain efficacy in changing these long term outcomes
4. Potential therapeutic strategies include marginal improvements in a range of neonatal care issues and developing better informed post discharge interventions