Continuity and transition of extremely preterm young adults

Neil Marlow

www.epicure.ac.uk
Prematurity is a continuum

<table>
<thead>
<tr>
<th>Gestational Week</th>
<th>PAR due to gestational age</th>
</tr>
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<tbody>
<tr>
<td>24-27</td>
<td>0.5% (0.4-0.6)</td>
</tr>
<tr>
<td>28-32</td>
<td>1.1% (1.0-1.3)</td>
</tr>
<tr>
<td>33-36</td>
<td>2.0% (1.7-2.4)</td>
</tr>
<tr>
<td>Total</td>
<td>10% (0.7-12.9)</td>
</tr>
</tbody>
</table>

Mackay et al. PLOS Medicine 2010

McKay PLOS Medicine 2010
And is continually improving ... cognitive outcomes

Comparison of Bayley MDI scores

Overall mean: 89 (19)

[Mean Bayley-III: 96 (16)]

Mean change in MDI 95-06: 8 points (95%CI 5-10)

Moore T et al BMJ 2012
But ... it is a pervasive disorder
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.
“I can calculate the motion of heavenly bodies, but not the madness of people.”
-- Isaac Newton
The EPI Cure Study

- Births in 1995 in the UK and Ireland
- Gestational age 22-25+6 weeks
- Followed at 2.5y, 6y, 11y, 19y
- Well described population with high rates of morbidity
  - Low IQ
  - Poor school attainment
  - Excess of behavioural problems
  - Compared to classmates collected at 6 years
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 scores at different ages (continuous sample)

<table>
<thead>
<tr>
<th></th>
<th>Extremely preterm</th>
<th></th>
<th>Comparison</th>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>mean (95%CI)</td>
<td>%&lt;70</td>
<td>n</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>mean (95%CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>%&lt;70</td>
</tr>
<tr>
<td>MDI at 2.5y</td>
<td>106</td>
<td><strong>84.5</strong> (82.0, 87.0)</td>
<td>12</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>MPC at 6y</td>
<td>106</td>
<td><strong>87.6</strong> (84.7, 90.5)</td>
<td>8</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>108.6</strong> (105.5, 111.7)</td>
<td>0</td>
</tr>
<tr>
<td>MPC at 11y</td>
<td>106</td>
<td><strong>87.6</strong> (84.7, 90.5)</td>
<td>7</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>105.6</strong> (102.5, 108.7)</td>
<td>0</td>
</tr>
<tr>
<td>FSIQ at 19y</td>
<td>106</td>
<td><strong>87.3</strong> (84.2, 90.4)</td>
<td>15</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>103.4</strong> (100.4, 106.3)</td>
<td>0</td>
</tr>
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</table>

O’Reilly et al PAS 2016
Trajectories

Cognitive scores - all

Mixed model analysis:
EP birth  -25.2 pt
Age  -0.3 pt/y
EP*Age  0.5 pt/y

Cognitive scores completers

Mixed model analysis:
EP birth  -23.9 pt
Age  -0.4 pt/y
EP*Age  0.5 pt/y
Multilevel model

REFERENCE: Female Control High SES

6 year MPC 112.8 (108.4, 117.1)

Mod SES -4.0 (-8.6, 0.5)

low SES -2.6 (-7.7, 2.8)

11 year MPC -2.9 (-5.5, -0.2)

19 year IQ -4.9 (-7.6, -2.2)

Male sex -6.2 (-10.1, -2.3)

EP Birth -21.0 (-25.4, -16.5)

EP Birth 2.8 (-0.4, 6.1)

EP Birth 4.6 (1.3, 7.9)

Effect modifiers

p > .05

p = .04

p < .001

p = .02

p < .0001

O’Reilly et al PAS 2016
Education at 19y

Fig 1. Highest school attainment

Fig 2. Occupational status

Percent attainment

Other  GCSE<-F  GCSE A-C  Vocational  Alevel/BTEC-3

FT Employed  FT Employed  FT Education  Vocational  Disability  Unemployed
Spectrum

Education
Special needs

Cognition
Executive function
Working memory

Socialisation
Peer group
Affect

Behaviour
Inattention
Psychiatric probs
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
Norwegian study
Births 1967-1983 (n=867 692); 19-35y

- Schizophrenia (p=.12)
- Autism Spectrum (p=.002)
- Disorders of psych development, behaviour and emotion (p<.001)

Moster et al NEJM 2008
Socialisation

- Reduced pro-social behaviour
- Peer problems
- Impact ratings higher
- Bullying

Table III. Regressions of prematurity and being bullied at 1 or 2 time points on emotional problem scores in year 6/7 of schooling

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Model 1 (unadjusted), main effects, B (95% CI)</th>
<th>Model 2 (adjusted*), effects, B (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1, main effects, B (95% CI)</td>
<td>Model 2, adjusted*, effects, B (95% CI)</td>
</tr>
<tr>
<td></td>
<td>BLS cohort</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VP/LBW</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Being bullied at 1 time point</td>
<td>0.48 (0.15-0.81)†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.68 (0.32-1.04)†</td>
</tr>
<tr>
<td></td>
<td>Being bullied at 2 time points</td>
<td>1.46 (0.94-1.97)†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>EP</td>
<td></td>
</tr>
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<td>Being bullied at 1 time point</td>
<td>0.91 (0.39-1.42)†</td>
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<tr>
<td></td>
<td></td>
<td>1.37 (0.80-1.95)†</td>
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<tr>
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<td>Being bullied at 2 time points</td>
<td>2.43 (1.68-3.18)†</td>
</tr>
</tbody>
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*Predictors adjusted for each other and for sex, SES, disability, and preexisting emotional problems (BLS: CBCL Internalizing problems; EPICure: SDQ Emotional problems scale).
†P < .01.
‡P < .001.

Wolke J Pediatr 2015
Cleveland Study

Social outcome profile as VLBW young adults

- Substance Use
- Contact with police
- Sexual Activity

Odds Ratio (95% CI)

Tobacco, Alcohol, Recreational, Violation, Conviction, Incarcerated, Intercourse, Live birth

Hack et al. NEJM 2002
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

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## Lung function - Spirometry

<table>
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<tr>
<th></th>
<th>All EP (n=124)</th>
<th>All C (n=64)</th>
<th>EP-C Δ means (95% CI)</th>
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<tr>
<td><strong>Baseline, z scores (mean ± SD)</strong></td>
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<td></td>
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<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>-1.6 ± 1.2</td>
<td>-0.4 ± 0.9</td>
<td>-1.2 (-1.5, -0.9)</td>
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<td>FVC</td>
<td>-0.7 ± 1.0</td>
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<td>FE&lt;sub&gt;25-75&lt;/sub&gt;</td>
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<td><strong>Post-bronchodilator</strong></td>
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<td></td>
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<tr>
<td>Δ FEV&lt;sub&gt;1&lt;/sub&gt; (%)</td>
<td>6.5 ± 5.2</td>
<td>4.0 ± 5.0</td>
<td>2.6 (1.0, 4.1)</td>
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<td>Δ FEV&lt;sub&gt;1&lt;/sub&gt; &gt;12% (%)</td>
<td>12/124 (9.7)</td>
<td>4/64 (6.3)</td>
<td>3.4 (-4.5, 11.4)</td>
</tr>
<tr>
<td>[feNO]</td>
<td>14 ± 11ppb</td>
<td>24 ± 25 ppb</td>
<td>-10 (-17, -4) ppb</td>
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*Beckmann et al PAS 2016*
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Beckmann et al PAS 2016
## Cardiovascular function

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<tr>
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<th>All C (n=64)</th>
<th>Diff in means (95% CI)</th>
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<tbody>
<tr>
<td>Augmentation Index (Aix; %)</td>
<td>6.5</td>
<td>0.4</td>
<td>6.1 (3.4, 8.7)</td>
<td>&lt;0.001</td>
</tr>
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<td>Adjusted Aix</td>
<td>6.6</td>
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<tr>
<td>Adj aortic Pulse Wave Velocity</td>
<td>5.0</td>
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<td>-0.04 (-0.2, 0.1)</td>
<td>0.664</td>
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<tr>
<td>Heart Rate (b.p.m.)</td>
<td>71</td>
<td>67</td>
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<tr>
<td>Cardiac Index (L/min/m²^2)</td>
<td>4.3</td>
<td>4.3</td>
<td>0.02 (-0.2, 0.3)</td>
<td>0.849</td>
</tr>
<tr>
<td>Σ Peripheral Resistance (dyne cm⁻⁵ s)</td>
<td>972</td>
<td>875</td>
<td>97 (27, 166)</td>
<td>0.007</td>
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<tr>
<td>Adjusted TPR</td>
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<td>Central Blood pressure (mmHg)</td>
<td>Systolic</td>
<td></td>
<td>+5 (2.0-7.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diastolic</td>
<td></td>
<td>+3 (.9-5.7)</td>
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* Data adjusted for sex, height and heart rate  
* Data adjusted for sex and MAP  
* Data adjusted for sex

Beckmann et al PAS 2016
## Cardiovascular function

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<td>Adjusted Aix (^b)</td>
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\(^a\) Data adjusted for sex, height and heart rate  \(^b\) Data adjusted for sex and MAP  \(^c\) Data adjusted for sex

Beckmann et al PAS 2016
Implications for adult life

after Fletcher C, Peto R BMJ 1977
Pervasive effects of extremely preterm birth

- Motor disorder
- Cerebral Palsy
- Injuries
- Brain development
- Developmental arrest/Tissue injury
- Antenatal factors
- Lung function
- Vascular function
- Sensory function
- Other organs: e.g. Kidneys

Core Executive Deficits

Low IQ

Behavioural problems
Pervasive effects of extremely preterm birth

- Antenatal factors
  - Core Executive Deficits
  - Motor disorder
  - Cerebral Palsy
  - Injury
  - Brain development
- Developmental arrest
  - Tissue injury
- Adult consequences
  - Mental Health
  - Education
  - Earning
  - Health
  - Ageing
- Vascular function
- Sensory function
- Other organs: e.g. Kidneys
EPI Cure: Acknowledgements

- **EPI Cure Investigators Group**
  - Kate Costeloe
  - Alan Gibson
  - Enid Hennessy
  - Neil Marlow
  - Joan Morris
  - Andrew Wilkinson

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  - Dieter Wolke b,c,e
  - Samantha Johnson c,d,e
  - Janet Stocks, Sooky Lum c,d
  - John Cockcroft c,e, Suellen Walker c,e
  - Elizabeth Draper d, John Hurst e
  - Sebastien Ourselin e, Xavier Golay e

- **Current researchers**
  - Andrei Morgan – epidemiology
  - Katie Gallagher – palliative care
  - Rashmi Gandhi – perinatal infection

- **EPI Cure 30 month study Team a**
  - Nick Wood & 12 Paediatric assessors

- **EPI Cure 6y study Team b**
  - Melanie Bracewell, Kate Bamford & 14 assessors

- **EPI Cure 11 year Study Team c**
  - Sam Johnson, Joe Fawke & 4 assessors

- **EPI Cure2 study team d**
  - Tamanna Moore & 20 assessors
  - Study Manager a-d: Heather Palmer

- **EPI Cure@19 Study Team e**
  - Jo Beckmann,
  - Helen O’Reilly
  - Laura McCormack
  - Kate Bennett
  - Emmi Suonpera, Jade Okell
  - Andrew Melbourne, Isaac Huen

Website: www.epicure.ac.uk