Metabolic programming: Implications for feeding infants and children

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What is ‘programming’?

Nutritional programming in humans

Implications for practice
Stimulus at a critical period  \rightarrow  Permanent change in structure or function
The general concept has been recognised for centuries

Pliny, Nat. Histories 10
Programming stimuli can be

- **endogenous**
  
  eg. hormones

- **environmental**
  
  eg. temperature, light, drugs, contaminants, nutrients
Critical window

Post-natal effects can be produced following ‘normal’ pregnancy.
Both under and over-nutrition can programme later outcome

Programmed effects may not appear until later in life

Programmed effects can differ by gender
Animal models show nutritional programming of a range of important outcomes

- blood pressure
- cholesterol metabolism
- glucose tolerance
- obesity
- behaviour and learning
- longevity

‘Metabolic’ outcomes

Other outcomes
Nutritional programming in humans
Critical windows

Drugs

Noise

Infant & Child Nutrition

Contaminants

Foods / nutrients
Observational studies

Compare outcomes in subjects according to early diet or growth

X Causality
Experimental studies – randomised trials

Demonstrate causal relationship between intervention and outcome

THE GOLD STANDARD
RCT not always ethical or feasible

Breast-feeding versus formula-feeding
Cohort attrition / Loss to follow-up

- selection bias
- loss of power

Attrition in long-term nutrition research studies: a commentary by the ESPGHAN Early Nutrition Research Working Group. JPGN; in press
Programming of CVD risk and obesity in humans
Two systematic reviews / meta analyses

Evidence on the long-term effects of breastfeeding: Systematic reviews and meta-analyses (Horta et al. 2007)
WHO Library Cataloguing-in-Publication Data
ISBN 978 92 4 159523 0

Breastfeeding and Maternal and Infant Health Outcomes in Developed Countries
(Ip et al. 2007)
Evidence Report/Technology Assessment Number 153
USA: Agency for Healthcare Research and Quality 2007
Experimental study 1

Randomised trial in 926 preterm infants 1982-1985

Banked donor breast milk v preterm formula

..... as sole diet or supplement to maternal breast milk

Lucas et al
Experimental study 2

PROBIT study
Cluster randomised trial of a breastfeeding promotion intervention
\( n=17,046 \) mother-infant pairs from 31 centres

<table>
<thead>
<tr>
<th></th>
<th>Some BF</th>
<th>More BF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any BF at 3mo</td>
<td>60.0%</td>
<td>72.7%</td>
</tr>
<tr>
<td>EBF at 3mo</td>
<td>6.4%</td>
<td>43.3%</td>
</tr>
<tr>
<td>Any BF at 6mo</td>
<td>24.4%</td>
<td>36.1%</td>
</tr>
<tr>
<td>EBF at 6mo</td>
<td>0.6%</td>
<td>7.9%</td>
</tr>
<tr>
<td>Any BF at 12mo</td>
<td>11.4%</td>
<td>19.7%</td>
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</tbody>
</table>

Kramer et al
Breastfeeding and metabolic outcomes

<table>
<thead>
<tr>
<th></th>
<th>WHO</th>
<th>US</th>
<th>PROBIT RCT 6,11yr</th>
<th>Preterm RCT 15yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure</td>
<td>↓ (1.19 mmHg)</td>
<td>↓ (1.5 mmHg)</td>
<td>no</td>
<td>↓ (3-4 mmHg)</td>
</tr>
<tr>
<td>Plasma lipids</td>
<td>↓ (0.18 mmol/l)</td>
<td>no</td>
<td>no</td>
<td>↓ (14%)</td>
</tr>
<tr>
<td>Overweight / obesity</td>
<td>↓ (OR 0.78)</td>
<td>↓ (4%/mo)</td>
<td>no</td>
<td>no</td>
</tr>
</tbody>
</table>
Are the effect sizes clinically relevant?

2mm Hg reduction in BP reduces
• hypertension 16%
• coronary artery disease 6%
• stroke 15%
prevents 67,000 coronaries and 34,000 strokes/yr in USA alone

Lowering cholesterol by 10%
↓ CVD incidence by 25%
↓ CVD mortality by 13-14%
How does breastfeeding reduce the risk of cardiovascular disease and obesity?

Specific factors in breast milk?

Slower early growth?
Growth acceleration hypothesis

An adverse long-term effect of faster growth is CVD

- Consistent with ‘fetal origins’ hypothesis
- Early post-natal period likely to be very important
- Explains the effect of infant nutrition

Experimental evidence in preterm infants

- Slower early growth
- Improved vascular function (FMD)
- ↓ Insulin resistance

13-15 yrs
Experimental evidence in term infants

**Term SGA infants**
RCT nutrient-enriched v standard formula
Promoted early growth

- ↑BP at 6 yrs
- Fat mass at 5-8 yrs

Effect explained by more rapid early growth
Association between faster weight gain in infancy and higher fat mass also found in breast-fed reference group.
Infant randomised to higher protein formulas had significantly higher BMI at 6 yrs

RR of obesity 2.43

Koletzko et al. AJCN 2009;89;1836
Weber et al. AJCN 2014;99:104
Epidemiological studies

Rapid infant growth associated with
• Increased obesity risk
• Greater insulin resistance
• Greater risk of CVD

20% of the risk of overweight explained by high infant weight gain 0-4 mo

Implications for practice
Effect of infant feeding on later metabolic risk probably relates to early growth pattern

Avoid fast infant weight gain
Cultural bias favours faster infant growth
Needs re-appraisal

Modify breast milk substitutes
Lower protein content
Other considerations
Early nutrition programmes cognitive outcome and brain structure in preterm infants

Verbal IQ at 7 and 15 yrs in boys

*Lucas et al. BMJ. 1998;317:1481-7*

Caudate nucleus volume at 15 yrs
Preterm infants are exquisitely sensitive to effects of early nutrition on the brain.
Term infants?

Nutritional interventions - small effects, if any
Different critical windows for different outcomes?
Duration?

Fetal life

Post-natal life

Duration?

Birth
Survival
Brain development
Bone health

Promote growth?

√

CVD risk factors

X
CVD risk factors

Promote growth?

√

?

X

CVD risk factors

Obesity
Does the critical window for metabolic programming extend to the complementary feeding period?
No clear association between the age of introduction of solid foods and obesity

Some evidence that introduction at or before 4 months may increase the risk of overweight

Moorcroft et al. MCN 2011;7:3
Huh et al. Pediatr 2011;127:e544
Moss & Yeaton. Mat Child Health J. 2014:18:1224
Is high protein intake during CF a risk factor for obesity?

9-12 mo infants from 4 EU countries

PE% 15.0

Average Protein Intake (grams/d): FITS 2008 Compared to Estimated Requirements

Butte et al. Am Diet Assn 2010
Are all proteins equivalent?

Gunther et al. AJCN 2007;86:1765
Do critical windows vary in different environments?
In stable environments, critical windows may close earlier?

Wells JC. Evol, Med &Pub Health 2014
Higher birthweight faster linear growth from 0 to 2 years

↑ Metabolic risk

- Large gains in human capital
- Little association with adult CVD

Rapid infant weight gain

High income

Later fat mass

Low income

Later lean mass > fat mass

Identifying and targeting ‘high risk’ groups
Genes Environment Programming

Implications for infant and child nutrition?
Target for interventions to avoid rapid weight gain and overfeeding
Appetite

Gemini twin cohort >2400 UK families

Genetic v environmental effects

Appetite traits are highly heritable:

- Slowness of eating: 84%
- Satiety responsiveness: 72%
- Food responsiveness: 59%
- Enjoyment of food: 53%

Llewellyn et al. AJCN 2010;91:1172
Conclusions: What should be advised based on current evidence?
Breast-feeding – certainly for the first 4 months

Infant formulas – lower protein

Complementary feeding – avoid excessive weight gain

Responsive feeding

Avoid rapid early weight gain

‘Whole diet’ approach
Good nutrition important for optimal brain outcomes

Promote growth

Human milk + fortifiers

Preterm formula
Further improvements in breast milk substitutes

Programming effects of specific nutrients eg. different protein sources during CF
Refine recommendations and interventions for different groups / individuals

- infants of obese mothers
- environmental factors
- appetite traits
- genotypes
- epigenetics
Thank you