Metabolic programming: Implications for feeding infants and children

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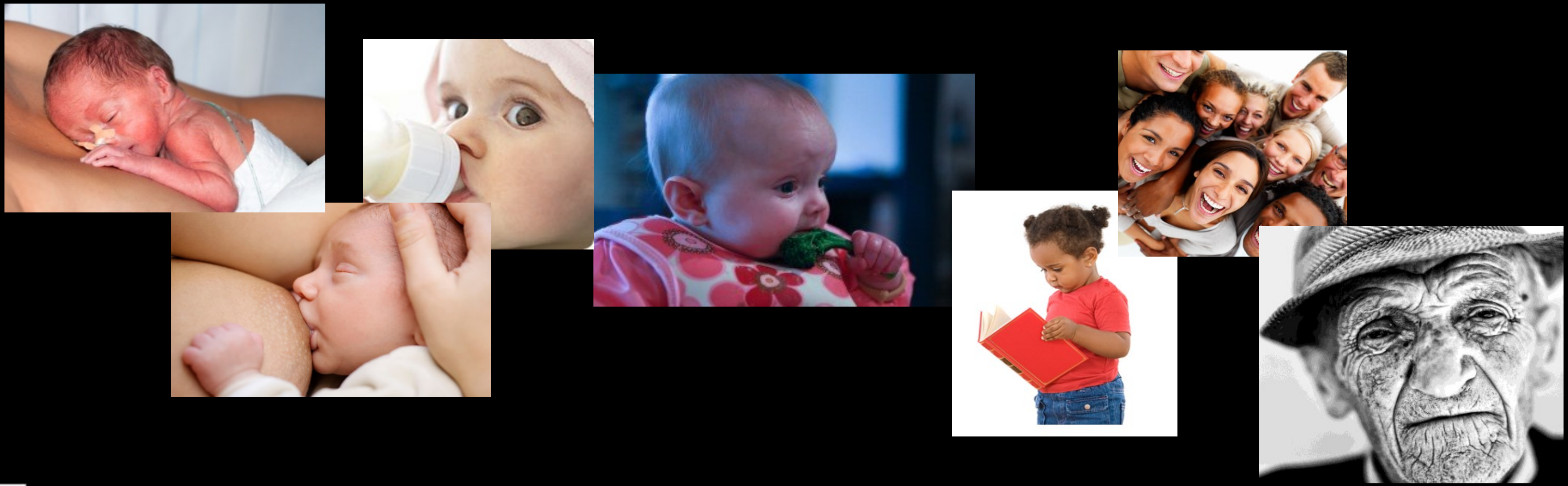


UCL

What is ‘programming’?

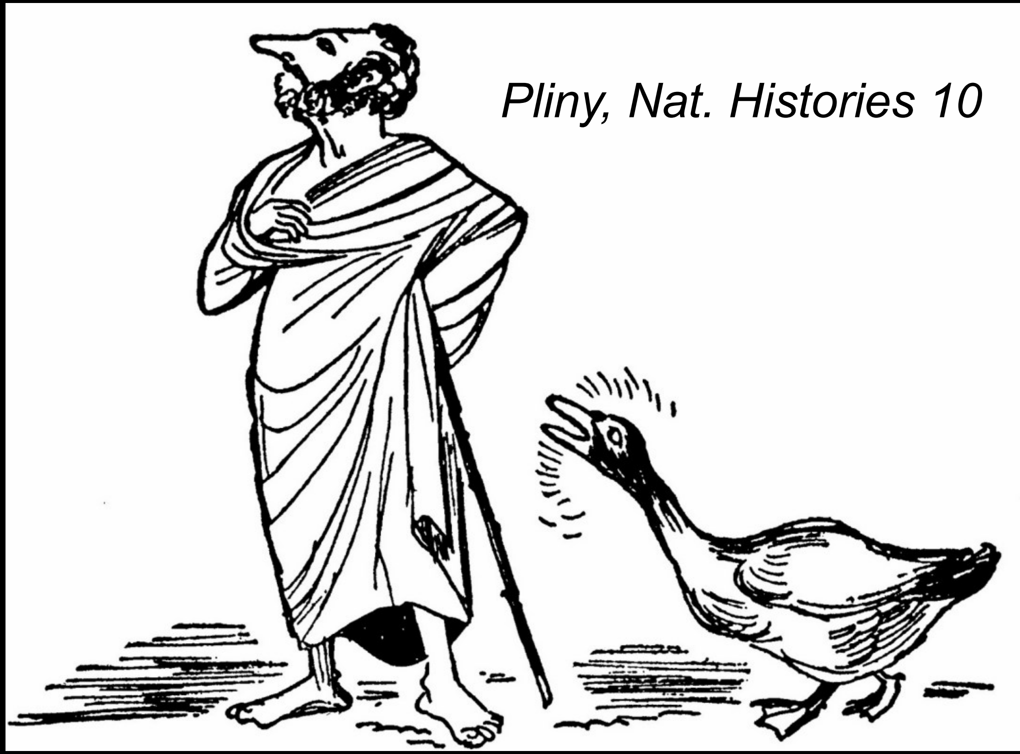
Nutritional programming in humans

Implications for practice

Stimulus at a critical period → **Permanent change in structure or function**

Lucas

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

Noise

Drugs

Stress

Contaminants

Foods / nutrients

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

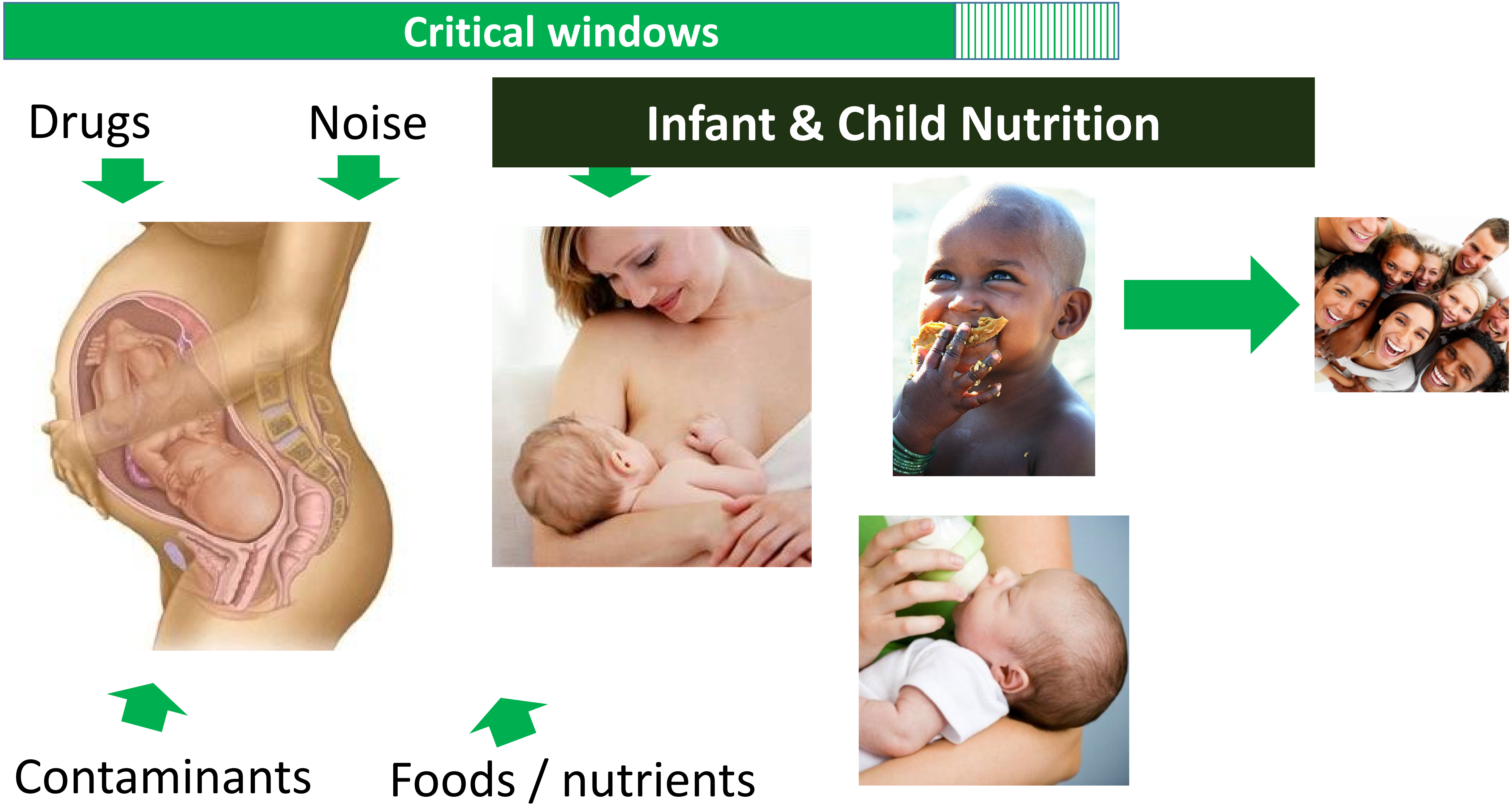
Animal models show nutritional programming of a range of important outcomes

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

‘Metabolic’

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

~~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

	Some BF	More BF
Any BF at 3mo	60.0%	72.7%
EBF at 3mo	6.4%	43.3%
Any BF at 6mo	24.4%	36.1%
EBF at 6mo	0.6%	7.9%
Any BF at 12mo	11.4%	19.7%

Kramer et al

Breastfeeding and metabolic outcomes

	WHO	US	PROBIT RCT 6,11yr	Preterm RCT 15yr
Blood pressure	↓ (1.19 mmHg)	↓ (1.5 mmHg)	no	↓ (3-4mmHg)
Plasma lipids	↓ (0.18mmol/l)	no	no	↓ (14%)
Overweight / obesity	↓ (OR 0.78)	↓ (4%/mo)	no	no

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

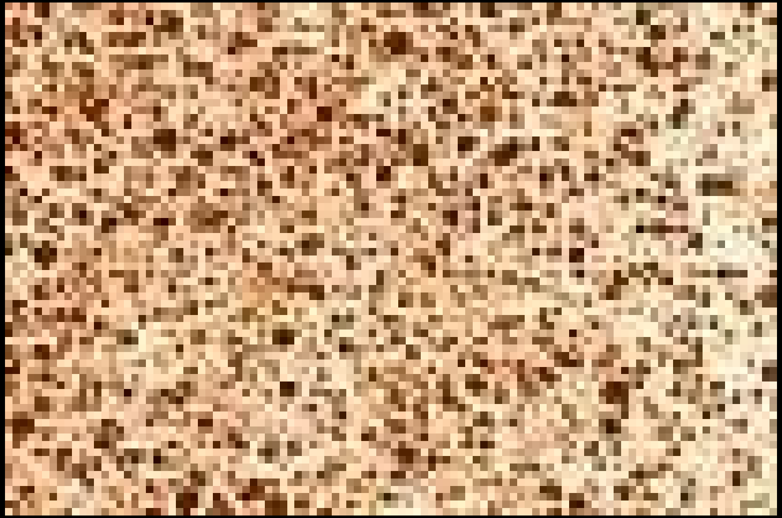
Lowering cholesterol by 10%

↓CVD incidence by 25%

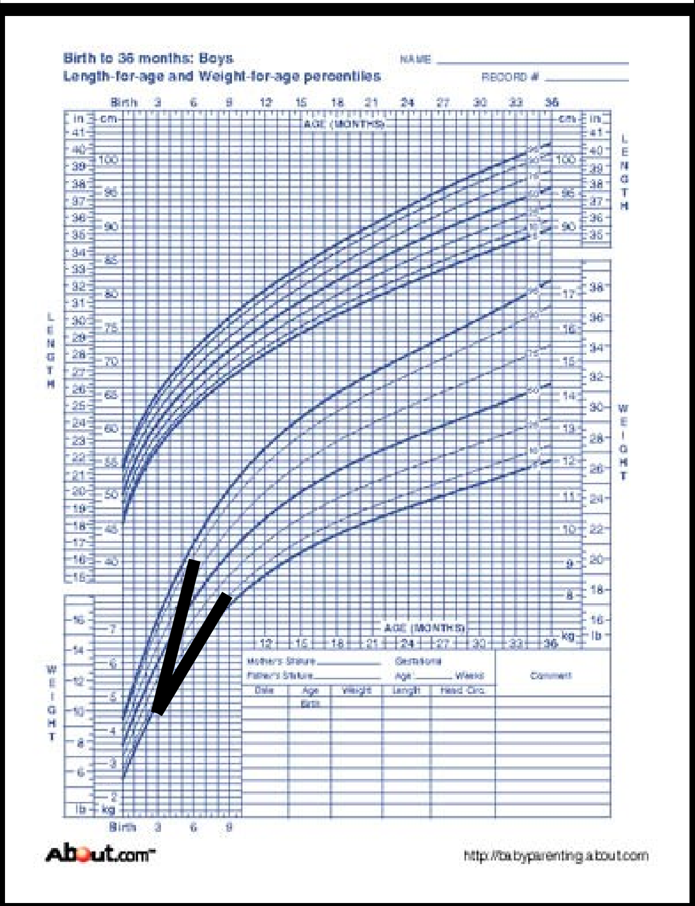
↓CVD mortality by 13-14%

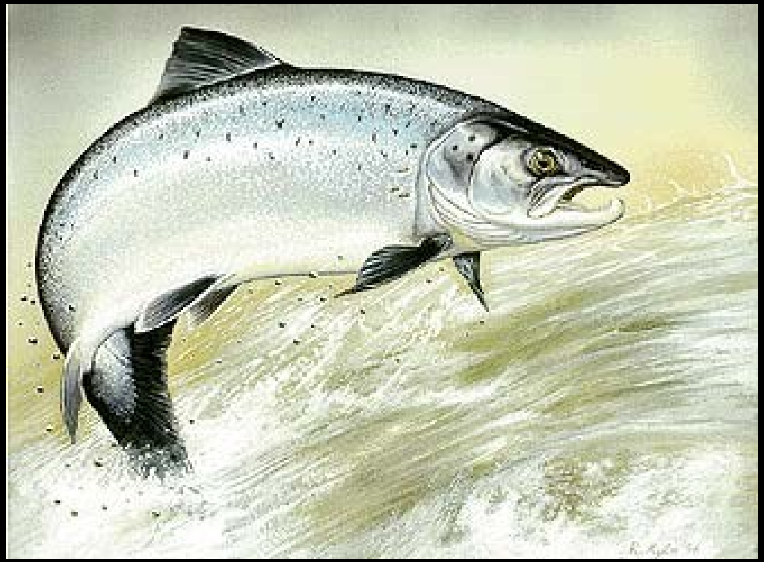
How does breastfeeding reduce the risk of cardiovascular disease and obesity?

Specific factors in breast milk?



Slower early growth?





‘Grow now – pay later’

Metcalfe

TEE 2001;16:254

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

Singhal & Lucas. Lancet 2004;363:1642

Experimental evidence in preterm infants

13-15 yrs

Slower early growth → Improved vascular function (FMD)

↓ Insulin resistance

Experimental evidence in term infants

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

↑BP at 6 yrs

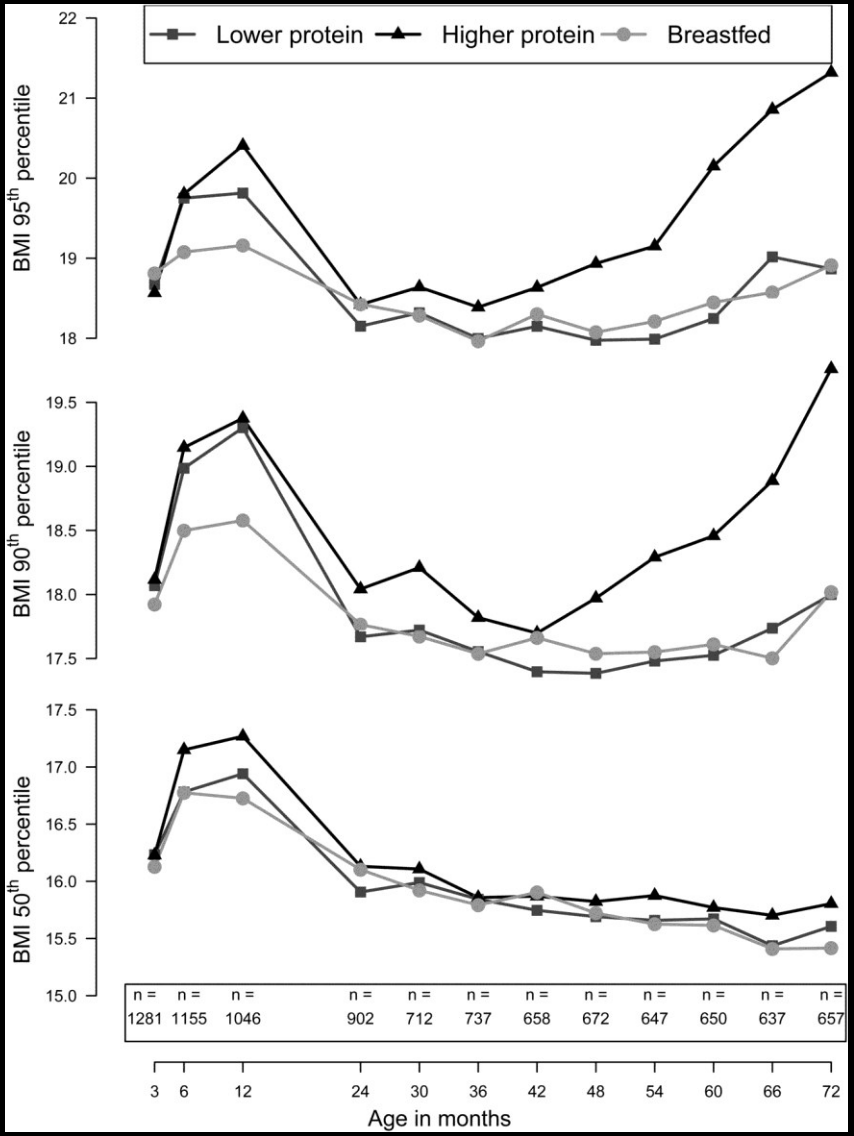
– Fat mass at 5-8 yrs

Effect explained by more rapid early growth

Circulation 2007;115(2):213-20

Association between faster weight gain in infancy and higher fat mass also found in breast-fed reference group

Normal weight term infants



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

Stettler et al. Pediatrics 2002;109:194-199

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

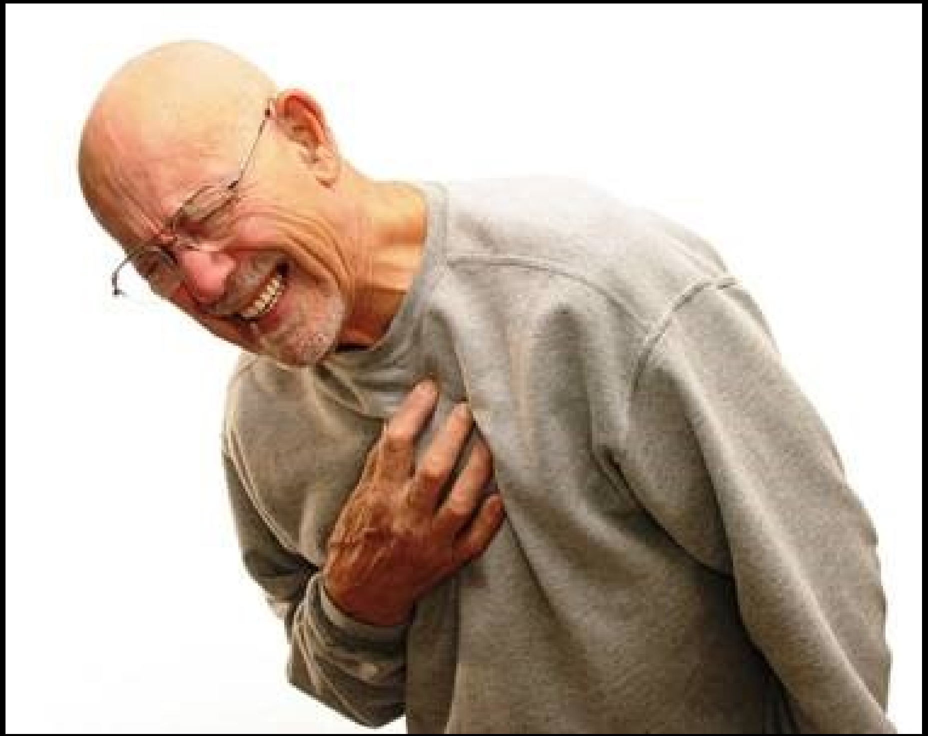
Needs re-appraisal

Modify breast milk substitutes

Lower protein content

Other considerations

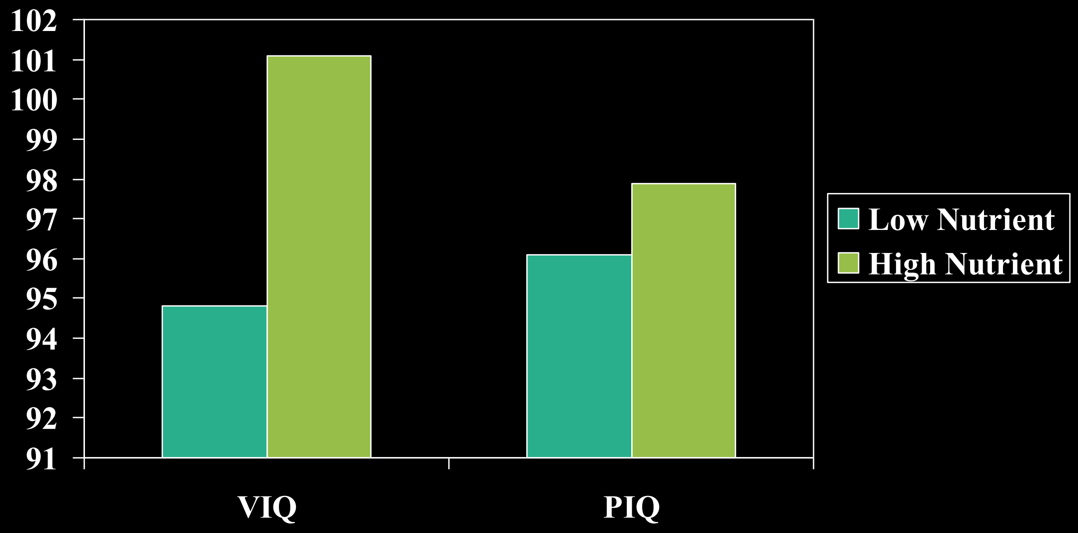


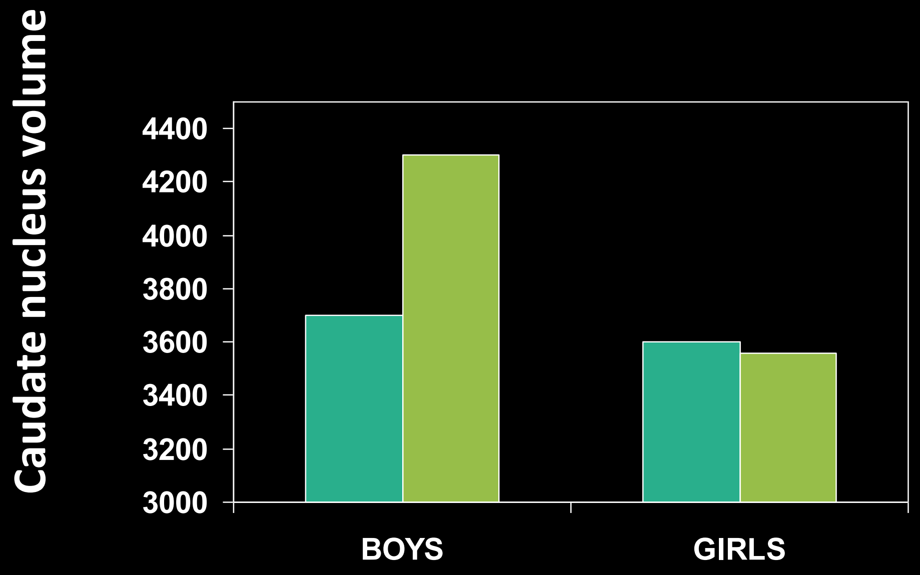


Early nutrition programmes cognitive outcome and brain structure in preterm infants

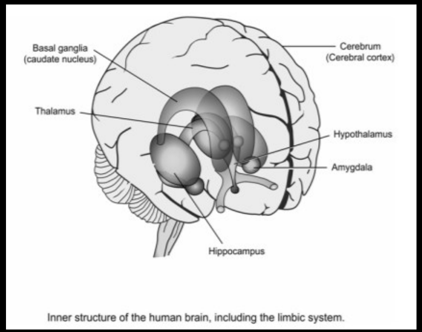
Verbal IQ at 7 and 15 yrs in boys

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





Caudate nucleus volume at 15 yrs

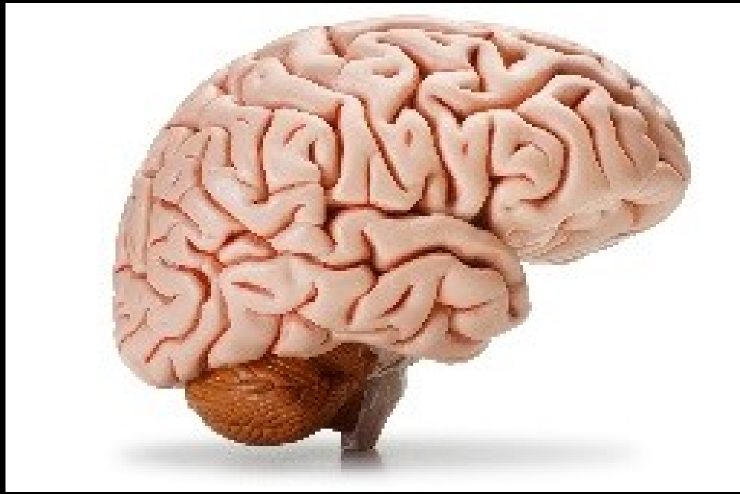


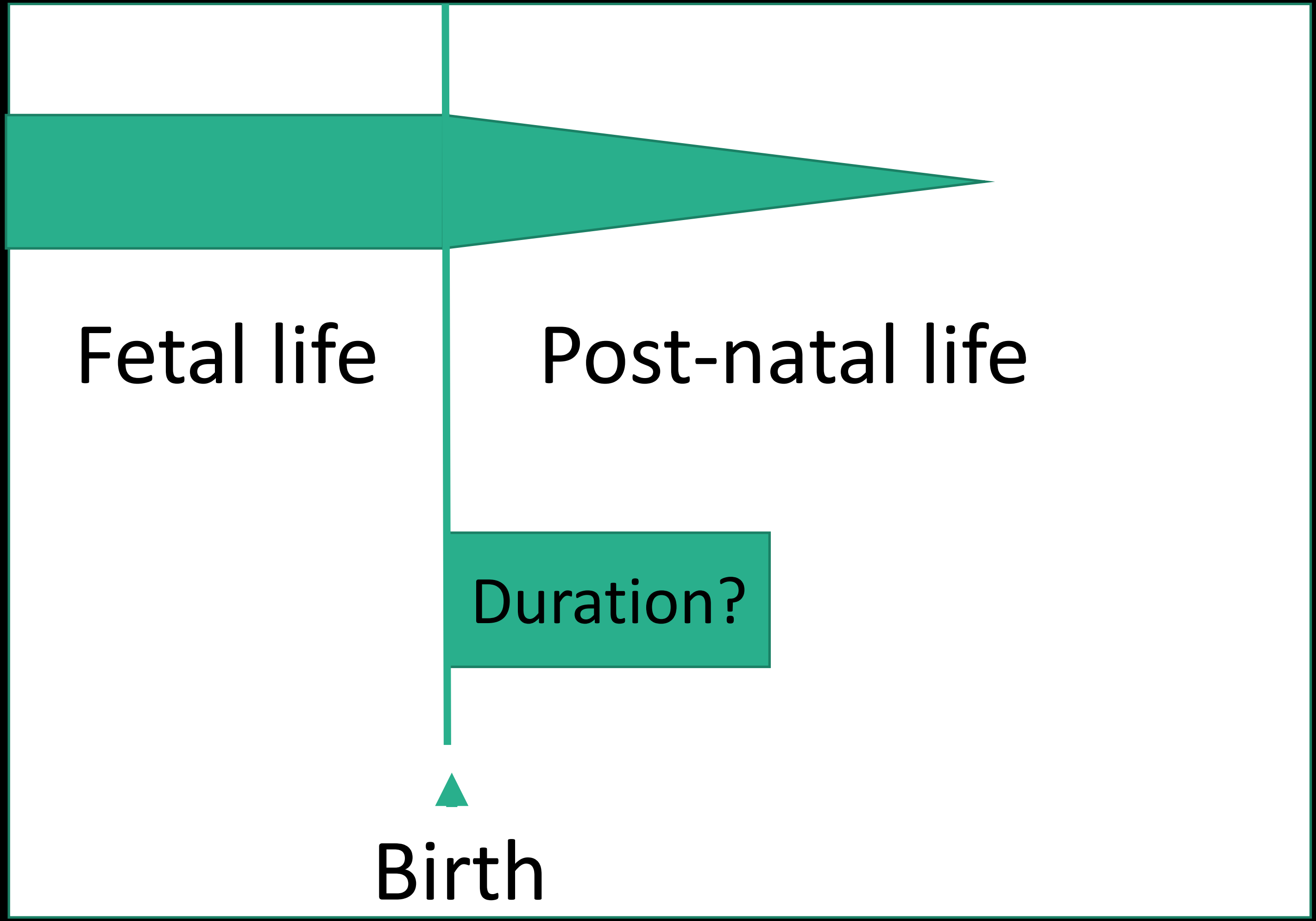
Preterm infants are exquisitely sensitive to effects of early nutrition on the brain

Term infants?

Nutritional interventions - small effects, if any

Different critical windows for different outcomes?





Fetal life
Post-natal life
Duration?
Birth

Promote growth?

√

Survival
Brain development
Bone health

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
Pearce et al. Int J Obesity 2013;37:1295
Huh et al. Pediatr 2011;127:e544
Moss & Yeaton. Mat Child Health J. 2014:18:1224
Jonsdottir et al. Acta Paediatr 2014;103:105

Is high protein intake during CF a risk factor for obesity?

9-12 mo infants from 4 EU countries

PE% 15.0

Michaelsen KF,Nutr.Met & CVD 2012;22:781

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
Thorisdottir. Ann Nutr Metab 2013;63:145

Do critical windows vary in different environments?

In stable environments, critical windows may close earlier?

Wells JC. Evol, Med &Pub Health 2014

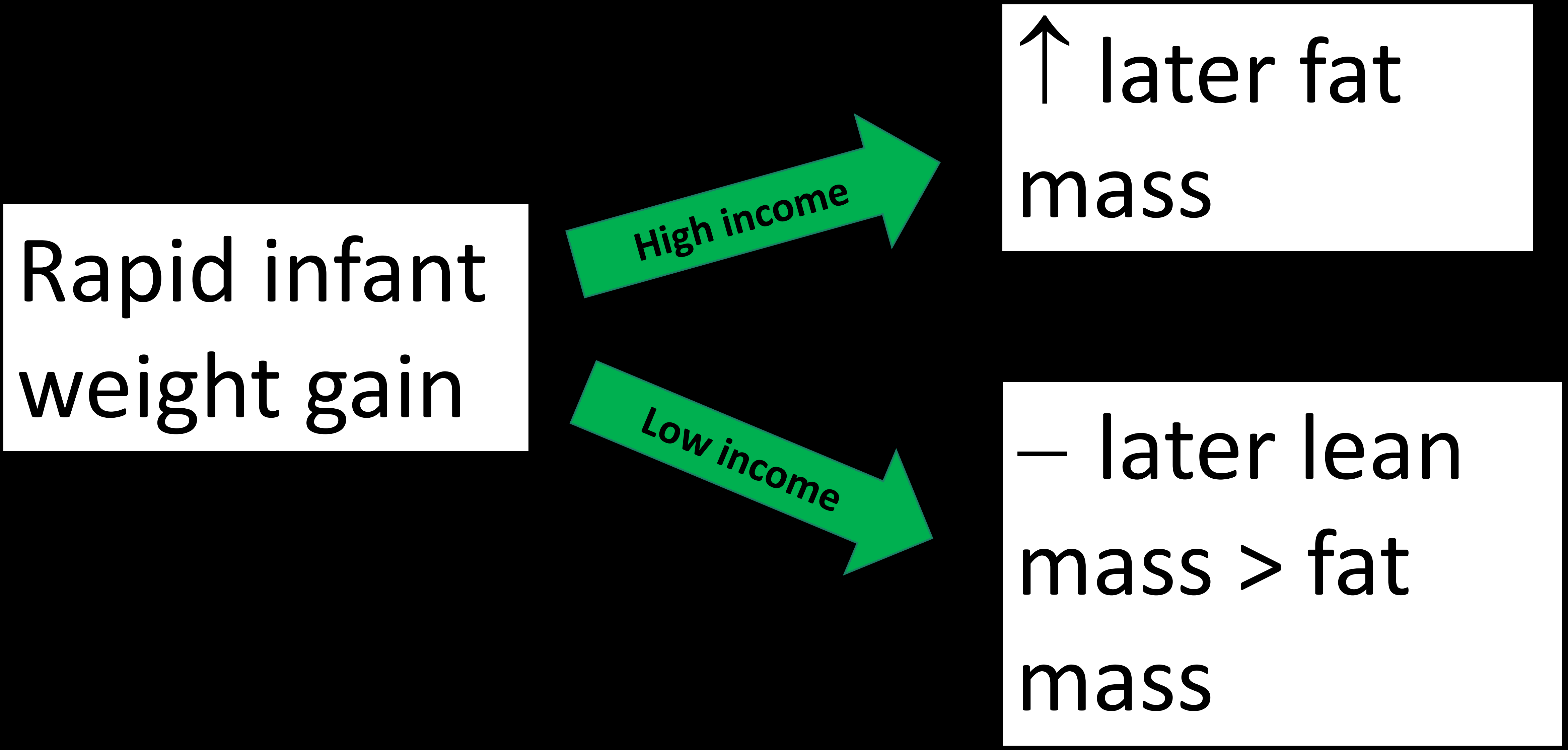
Higher birthweight faster linear growth from 0 to 2 years

High income → ↑ Metabolic risk

Low income →

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

Adair LS, et al. Lancet 2013



Wells et al. Proc Nut Soc 2007;66:423

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

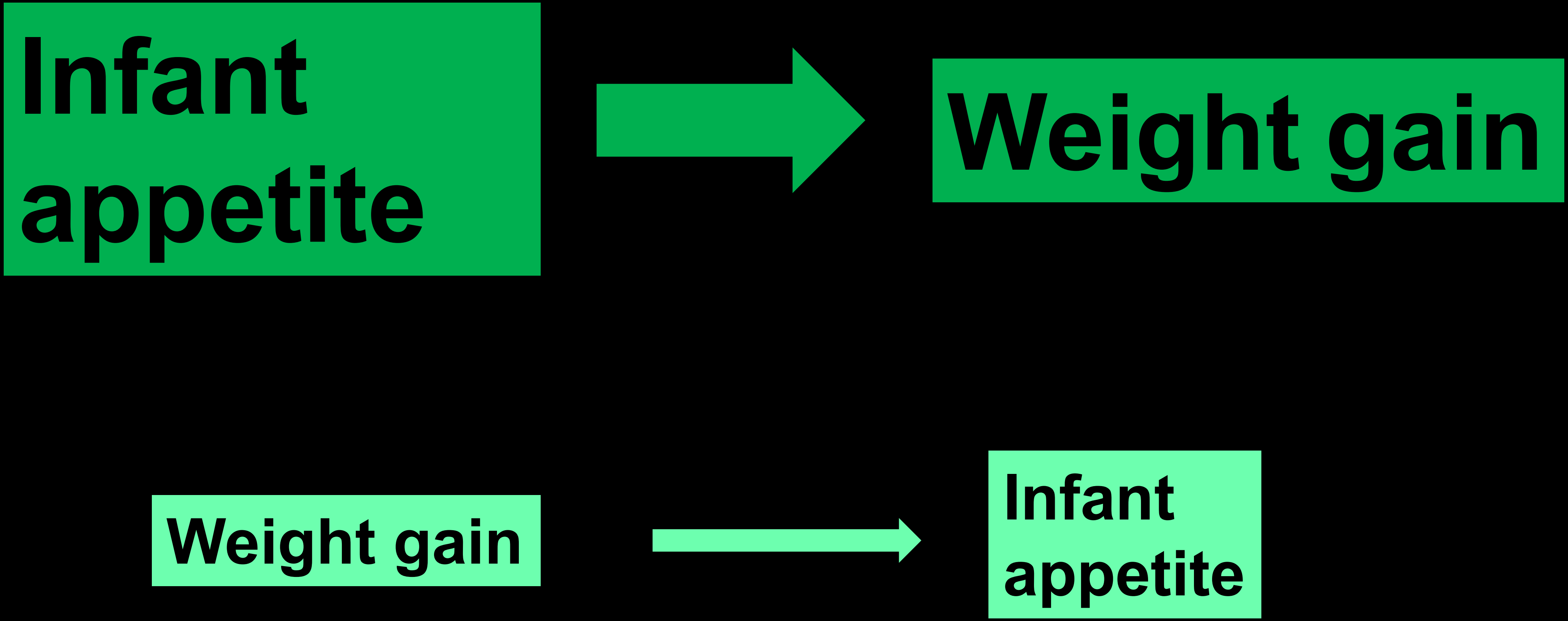
Gemini twin cohort >2400 UK families

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



Van Jaarsveld et al. AJCN 2011;94:1562

Conclusions: What should be advised based on current evidence?

Avoid rapid early weight gain

‘Whole diet’ approach

Breast-feeding – certainly for the first 4 months

Infant formulas – lower protein

Complementary feeding – avoid excessive weight gain

Responsive feeding

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