MRC Epidemiology Unit

UNIVERSITY OF CAMBRIDGE

Life-course Epidemiology

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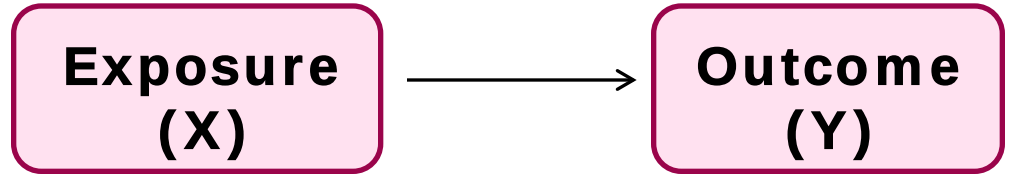
CDS April 2019

Wellcome Trust – MRC IMS Institute of Metabolic Science

Cambridge Institute of Public Health

Aetiological Epidemiology: Does **X** cause **Y**?

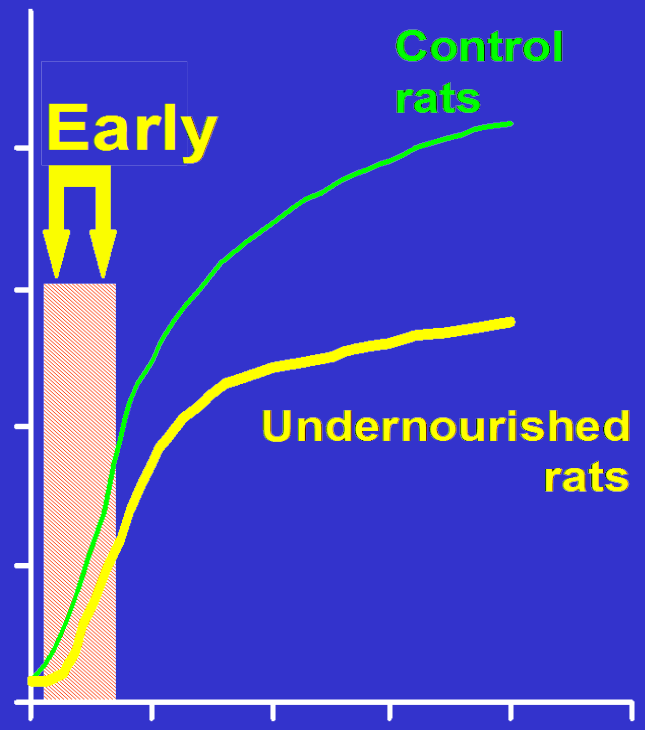


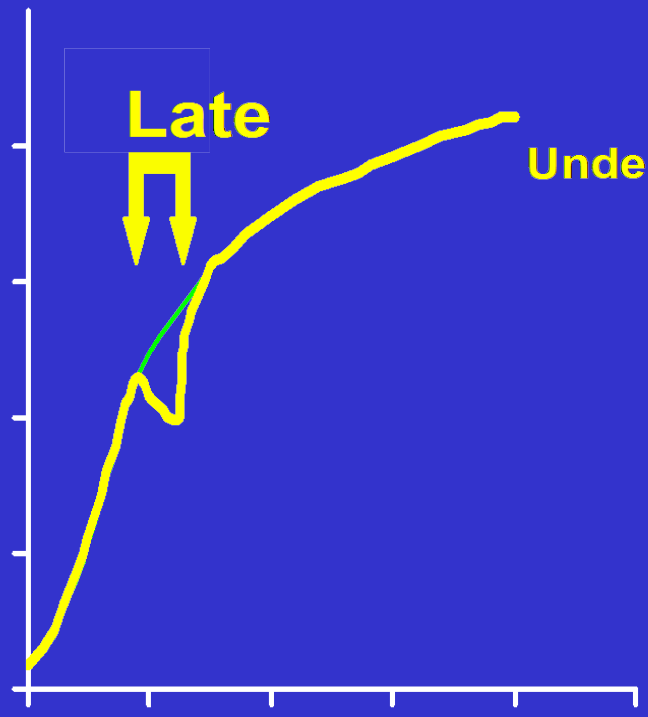
Life-course Epidemiology

Only / Particularly if the exposure occurs during a specific period of the life-course

Critical Windows in Early Life:
Impact of Early *vs* Late Undernutrition on Growth

McCance & Widdowson 1962





"Programmes"
"Plastic"

"Transient"
"Elastic"

A life-course perspective

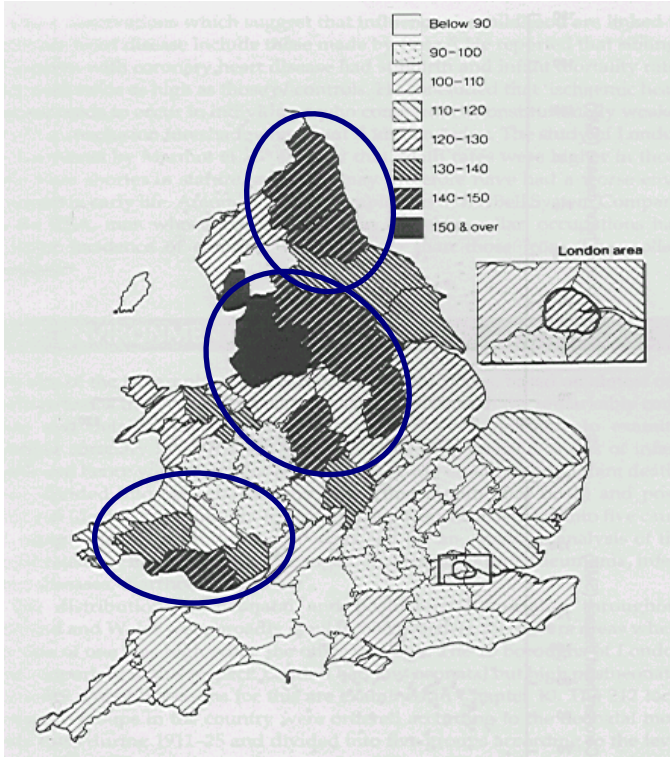
British 1946 Birth Cohort Study

The MRC **N**ational **S**urvey of **H**ealth and **D**evelopment (NSHD)

Maternity survey of all 13,687 births in England, Scotland and Wales in 1 week

National Survey 65 YEARS 1946 - 2011

The Barker Hypothesis



Infant Mortality rate

1901-1910

Mortality ratio for coronary heart disease

1968-1978

Birth weight and CVD mortality

Hertfordshire Study

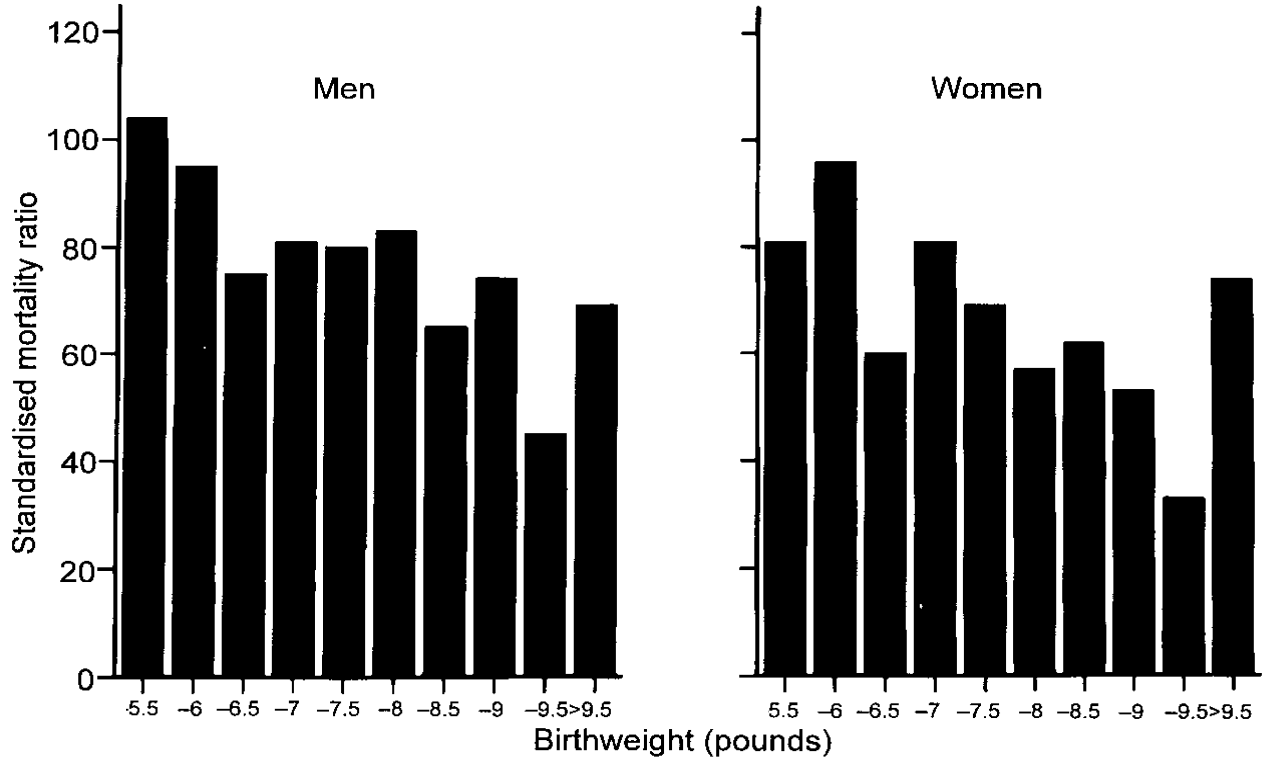
A ‘historical’ cohort study:

10,141 men, born 1911-30

(→ † 2,990)

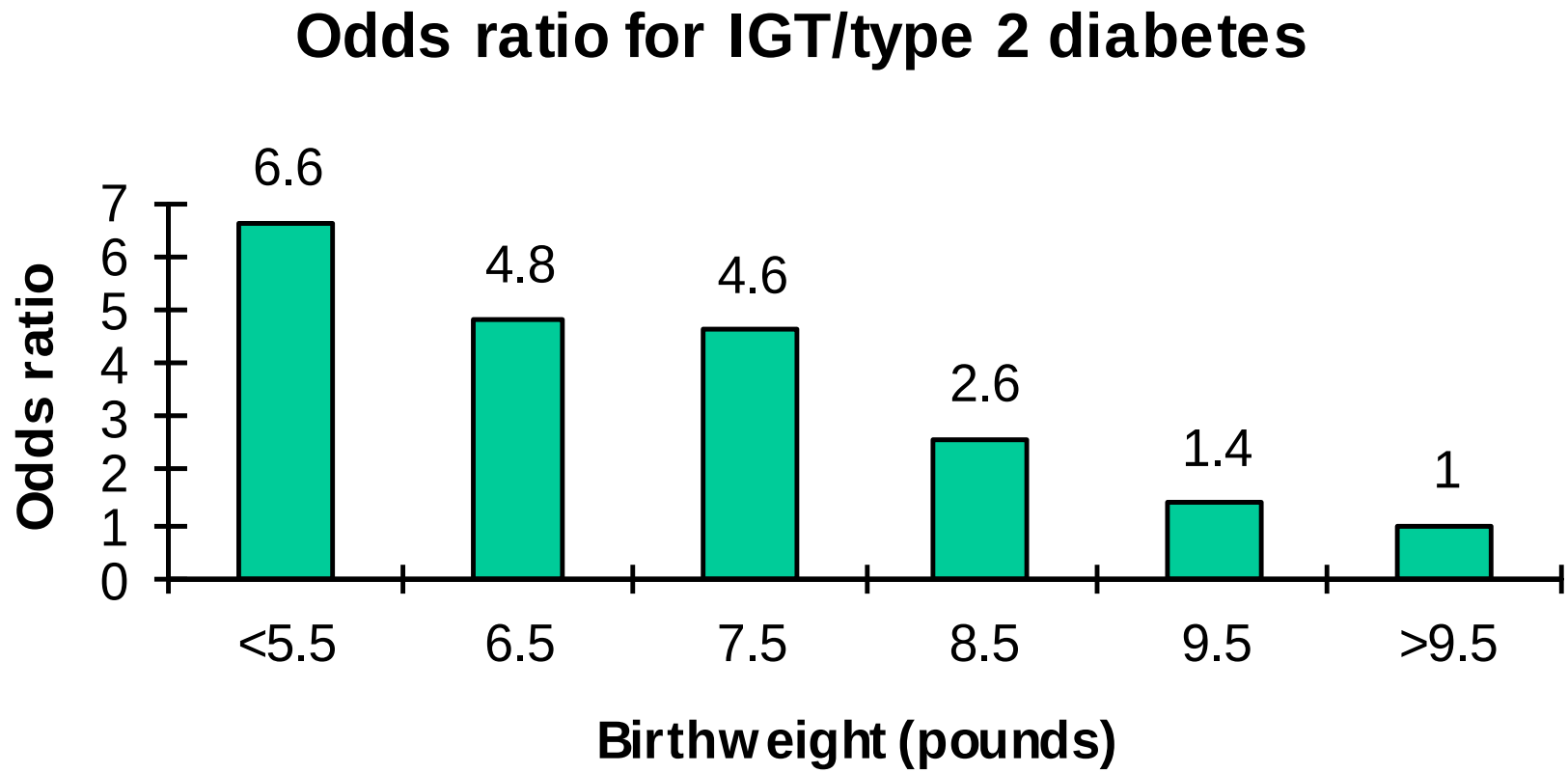
5,585 women, born 1923-30

(→ † 875)



Widely replicated in Europe, USA, India etc.

Birth Weight and Adulthood Disease
A ‘continuous’ association



Nick Hales et al. *BMJ* 1991

Low Birth Weight and Adult Disease

“Fetal origins of adult disease”

- Coronary Heart Disease
- Type 2 Diabetes
- Cerebral-Vascular Disease
- Hypertension
- Insulin Resistance
- “Metabolic Syndrome”

Hales & Barker, *Brit Med Bulletin* 2001

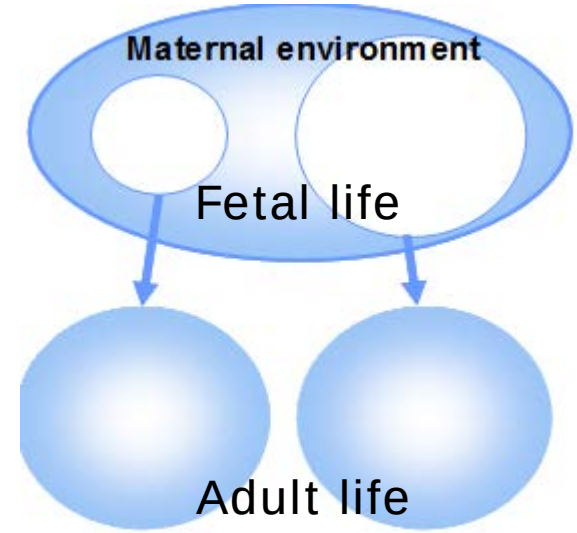
Twins studies: "Co-twin control model"

'Cohort' analysis:

Hypertension risk is higher by:

OR = 1.42 (95% CI: 1.25-1.61)

for each 500-g lower mean birth weight



Association with intra-pair difference in BW:

DZ twins: OR = 1.34 (95% CI: 1.07-1.69)

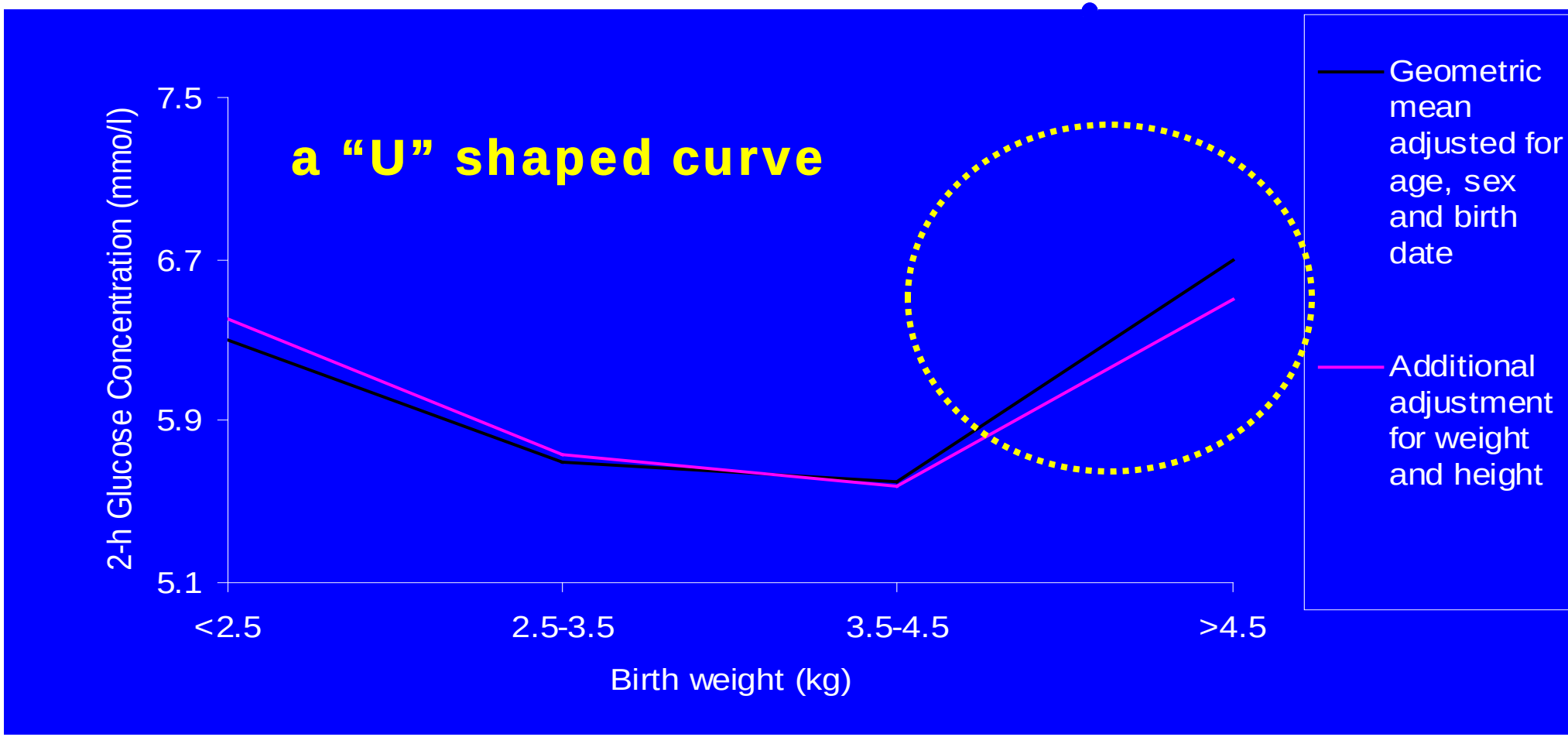
MZ twins: OR = 1.74 (95% CI: 1.13-2.70)

"Association is independent of shared maternal environment & genetic factors"

16,265 Swedish twins

Bergvall et al. *Circulation* 2007

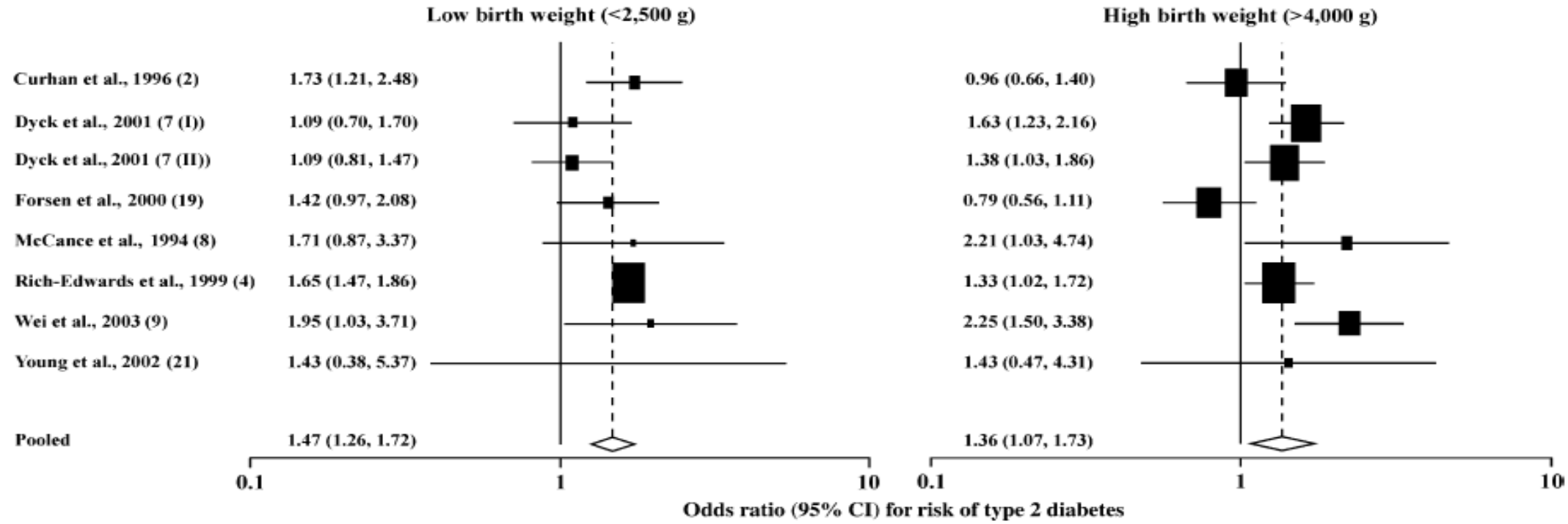
Glucose Tolerance vs. Birth Weight in Pima Indians



MRC | Medical Research Council

McCance et al., *BMJ* 1994

Meta-analysis of BW → T2DM



14 studies (132,180 individuals)

Harder et al. *Am J Epidemiol*. 2007

Both at risk for later obesity and T2DM?

Maternal GDM / Obesity

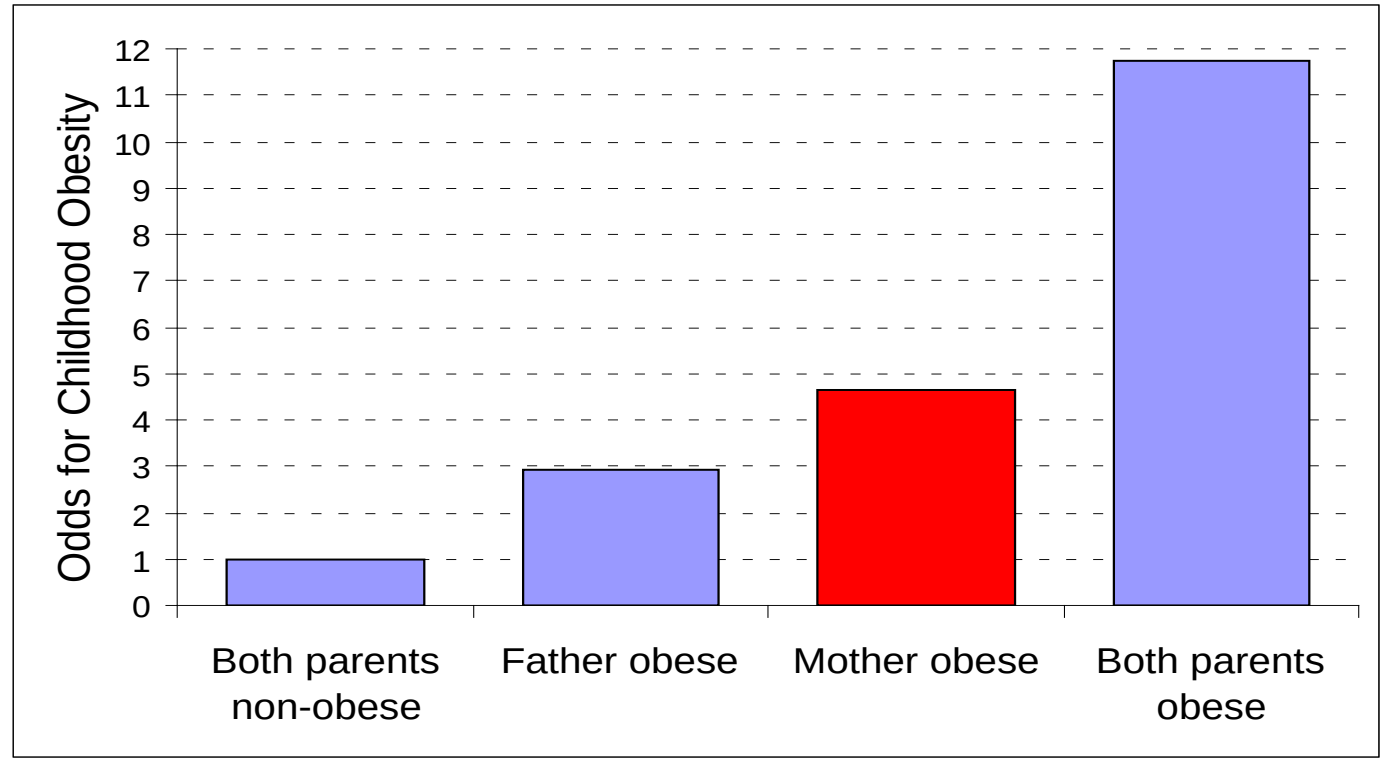
↑ maternal glucose
↑ fetal glucose
↑ fetal insulin
↑ growth and adiposity

Placental Insufficiency

↓ fetal glucose
↓ fetal insulin
↓ growth and adiposity

The Obese Mother & Child

Obesity at age 7y - in 8,234 ALSPAC children



Reilly et al. *BMJ* 2005

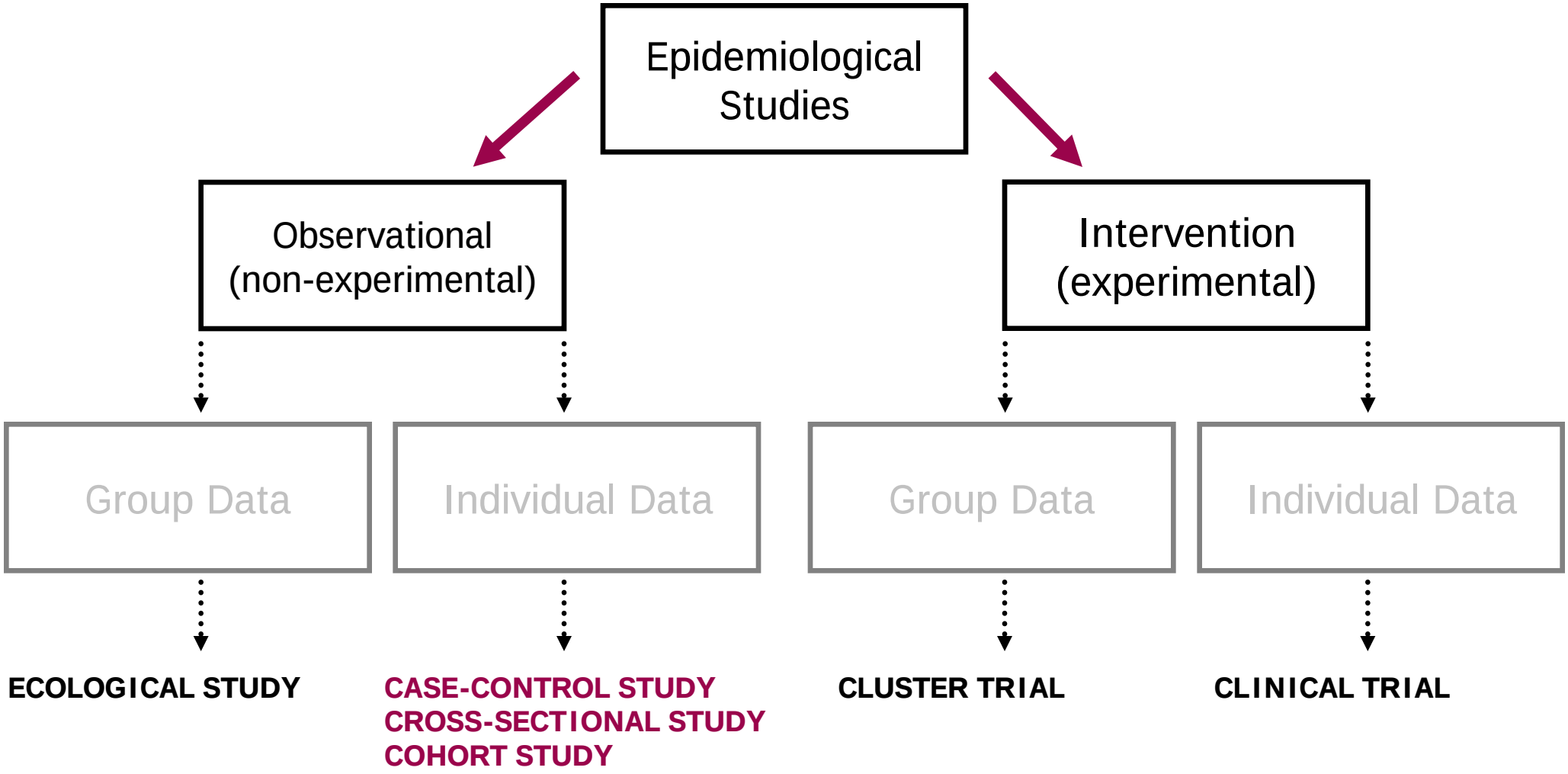
The Obese Mother & Child

Antenatal

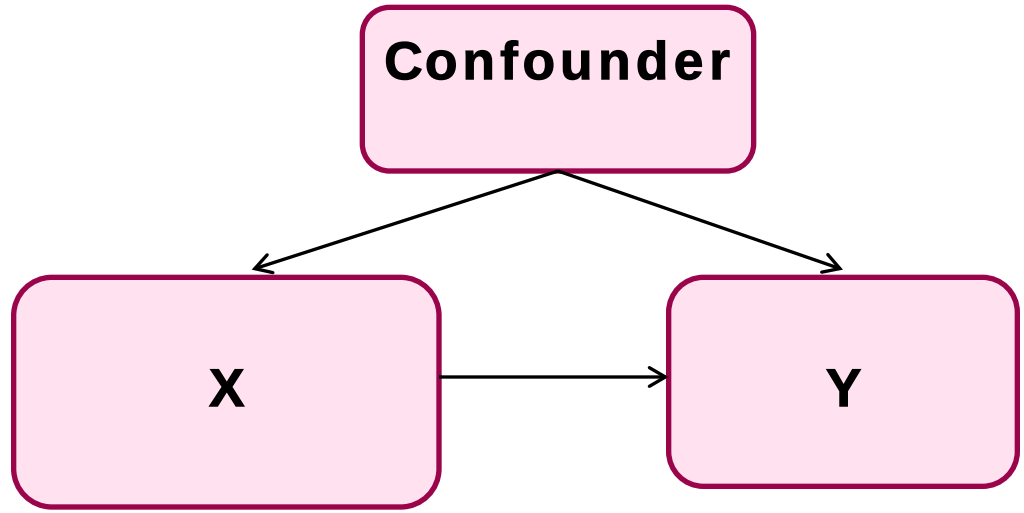
Postnatal environment

Genetic

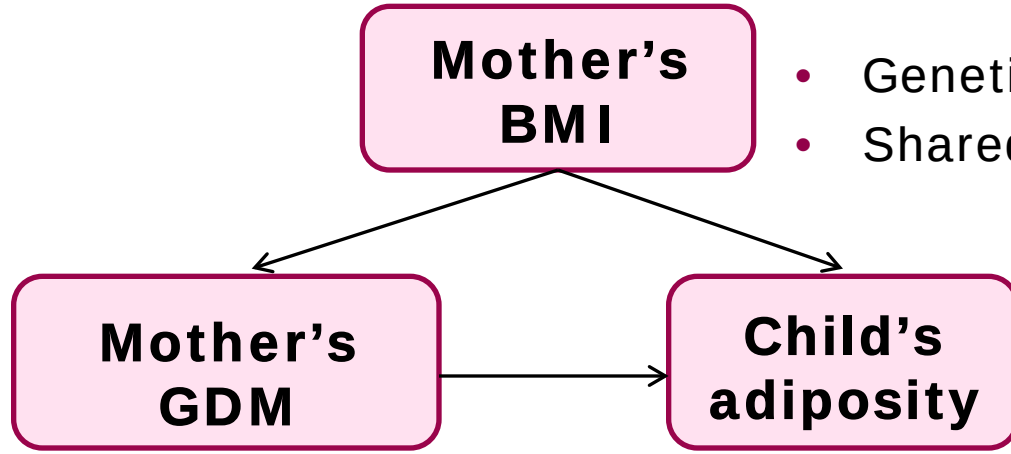
Study Design Overview



Observed Associations – Possible explanations?



Observed Associations with GDM → Child adiposity

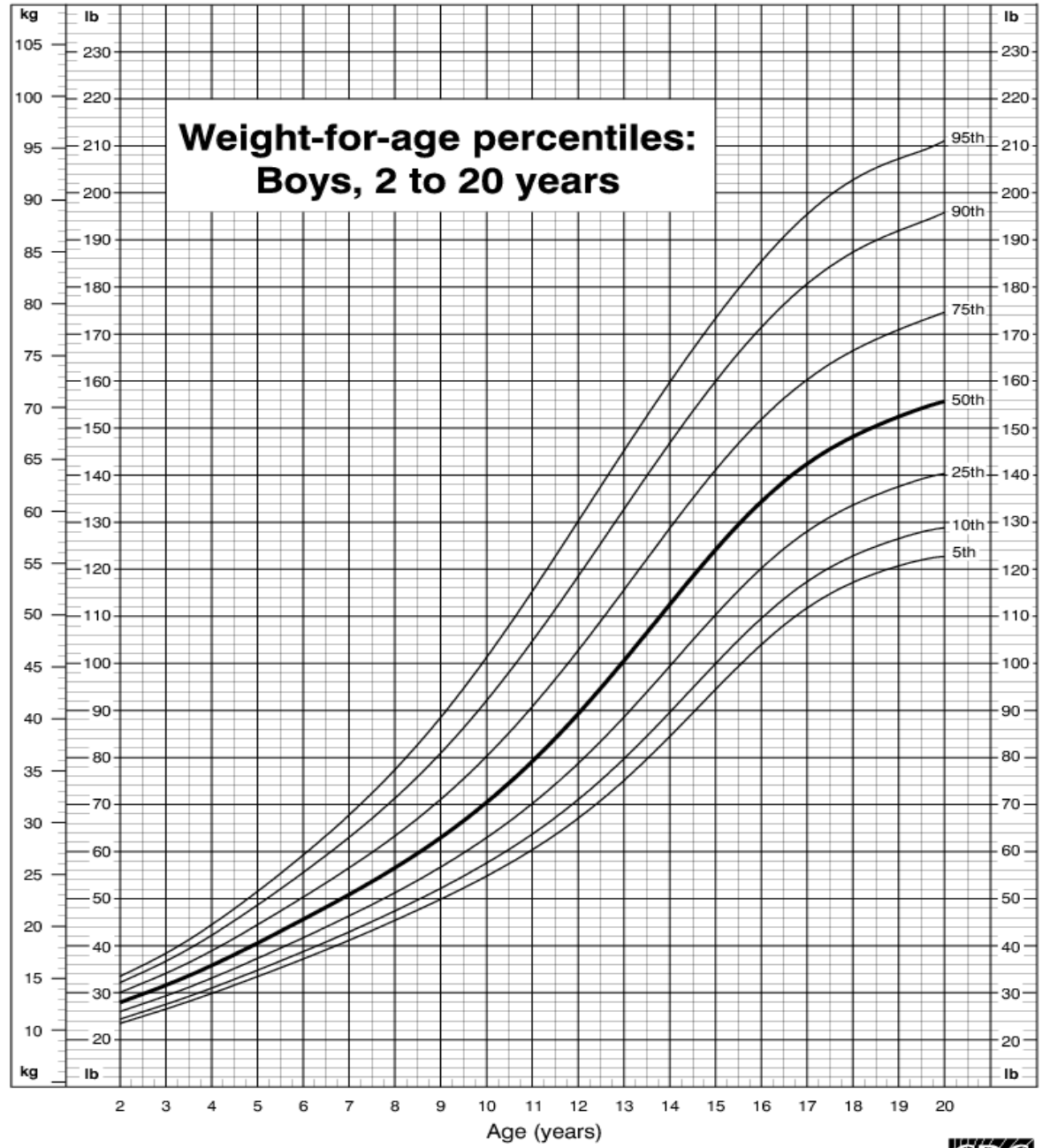


- Genetics
- Shared postnatal environment

	GDM (14.1%)	Non-GDM	OR adjusted for mother's BMI
Child Obese or OW	39.5%	28.6%	**1.21** (1.00-1.46)
Child Obese	19.1%	9.9%	**1.58** (1.24-2.01)

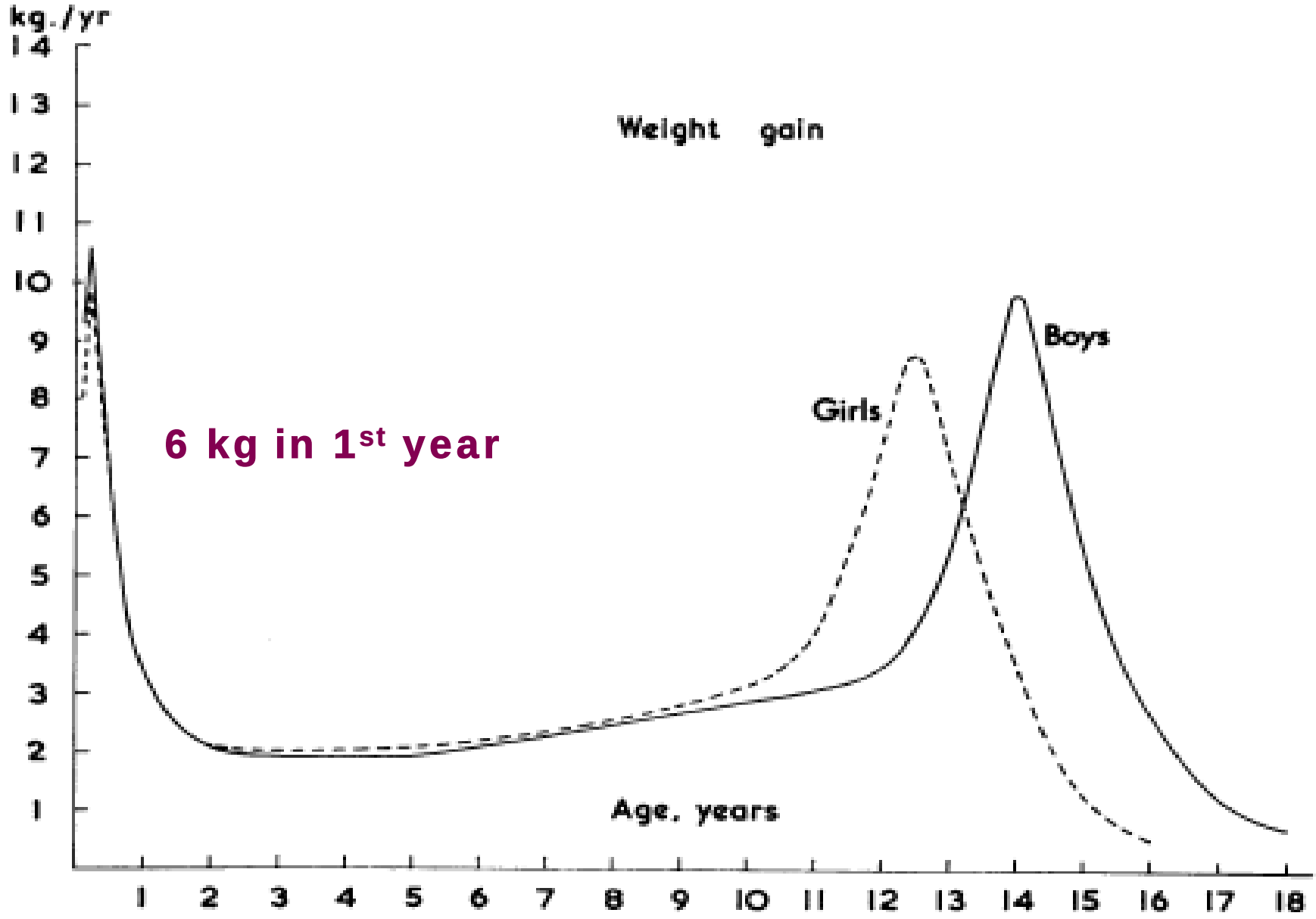
HAPO Follow-up Study (4832 children)
Lowe WL et al. *JAMA*. Sept 2018

CDC Growth Charts: United States

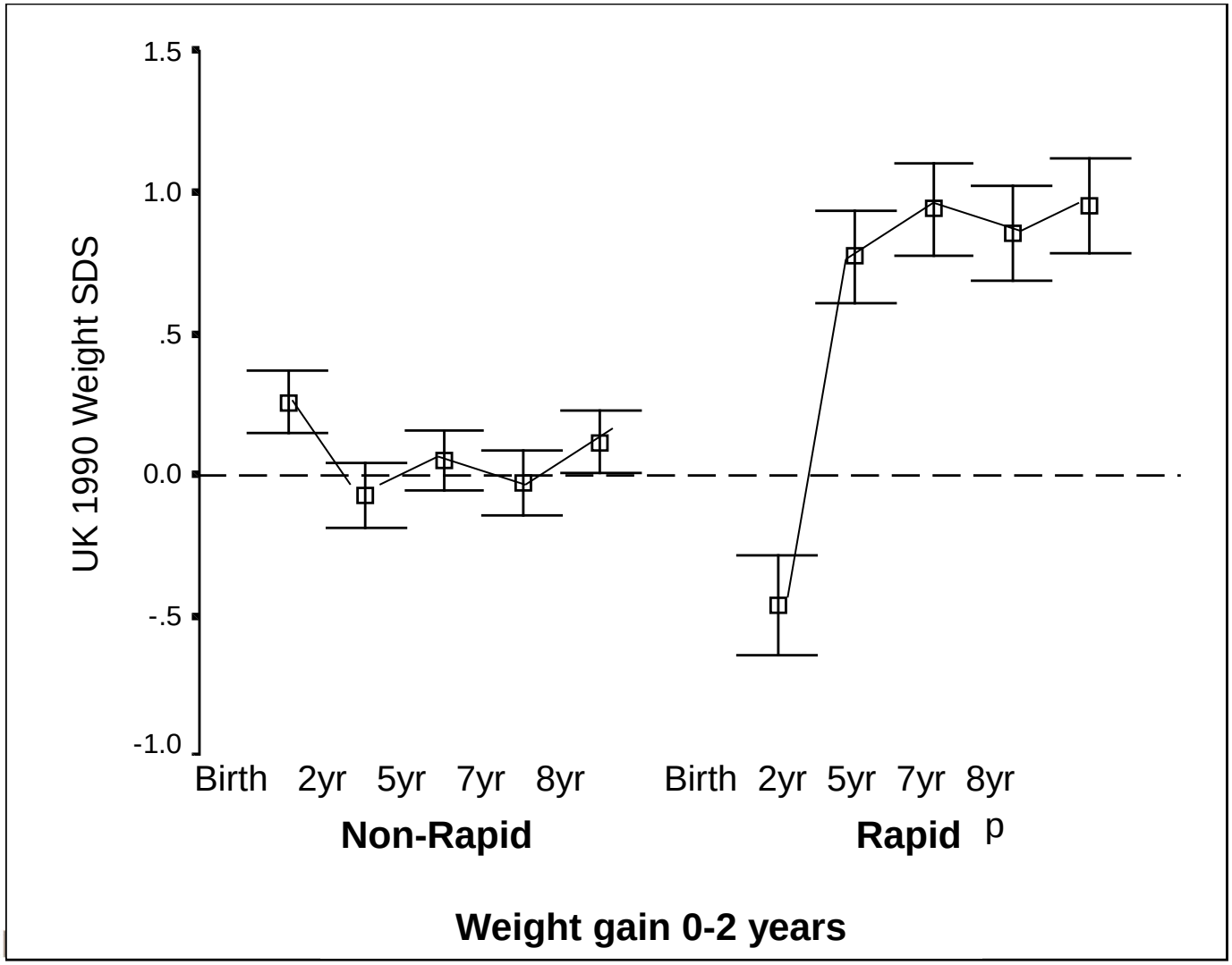


Published May 30, 2000.
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).

SAFER • HEALTHIER • PEOPLE™


kg./yr
14
13
12
11
10
9
8
7
6
5
4
3
2
1
Weight gain
Boys
Girls
6 kg in 1st year
Age, years
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18

Persisting effects of early postnatal rapid weight gain

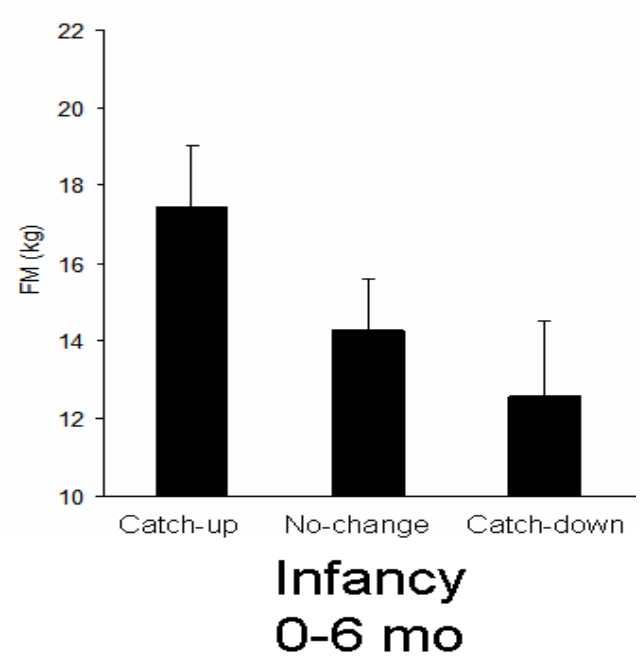


Ong et al. *BMJ* 2000

plus updated ALSPAC data at age 8y

Rapid Infancy Weight Gain and Subsequent Obesity

Fat mass
at 17 years



Ekelund et al, *AJCN* 2006

Systematic Reviews:

Monteiro & Victora (Obes Rev 2005)	13 studies
Baird et al. (BMJ 2005)	10 studies
Ong & Loos (Acta Paediatrica 2006)	21 studies
Woo-Baidal et al. (Am J Prev Med 2016)	***+ve in 45/46 studies***

Health

Too many babies overfed, experts fear

By Michelle Roberts
Health editor, BBC News online

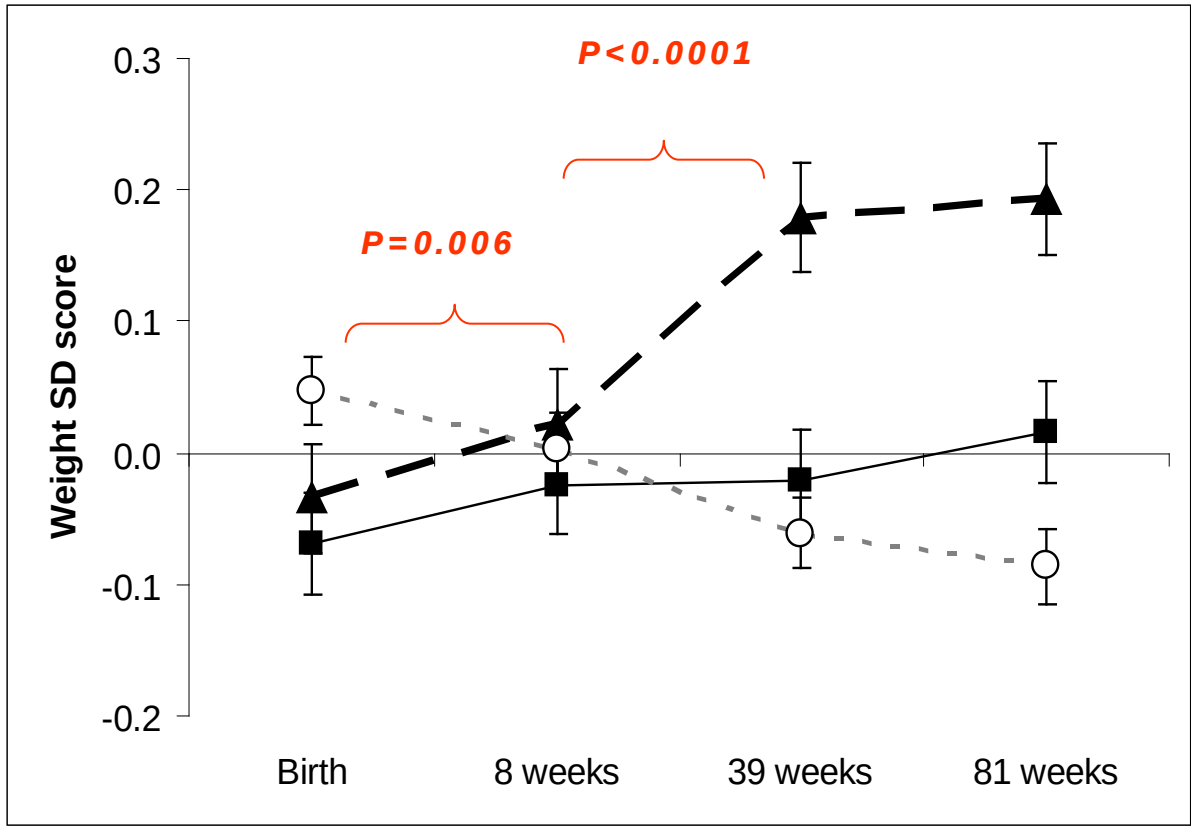
18 July 2018 Share

It's time to tackle over-eating from birth to make sure children get the best start in life, according to Public Health England.

It comes as government advisers publish **new guidance** - the first in more than 20 years - on feeding babies.

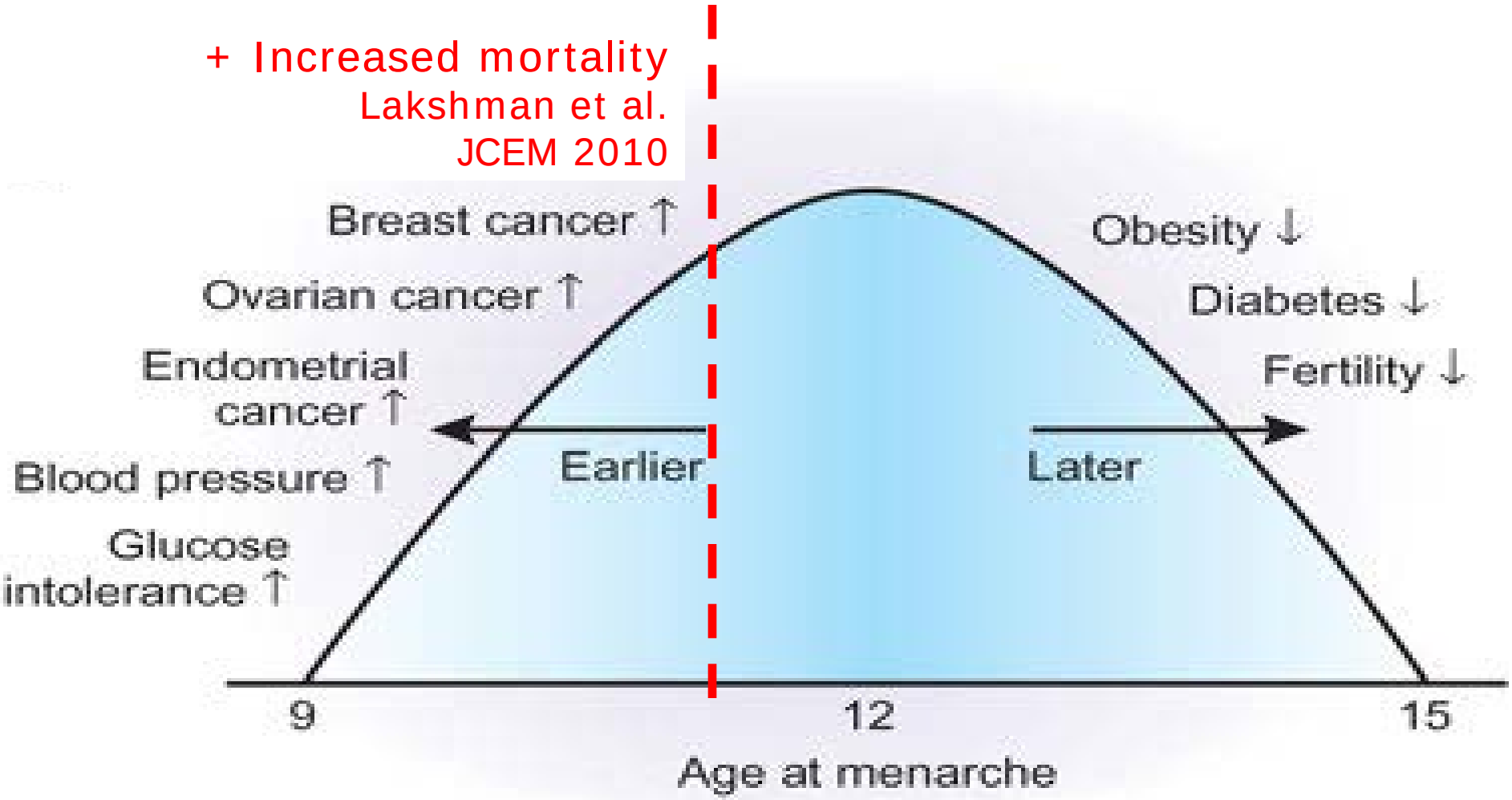
75% of infants (age 4-18 mo) have intakes that exceed the EAR for energy.

Early menarche in girls related to faster infancy growth



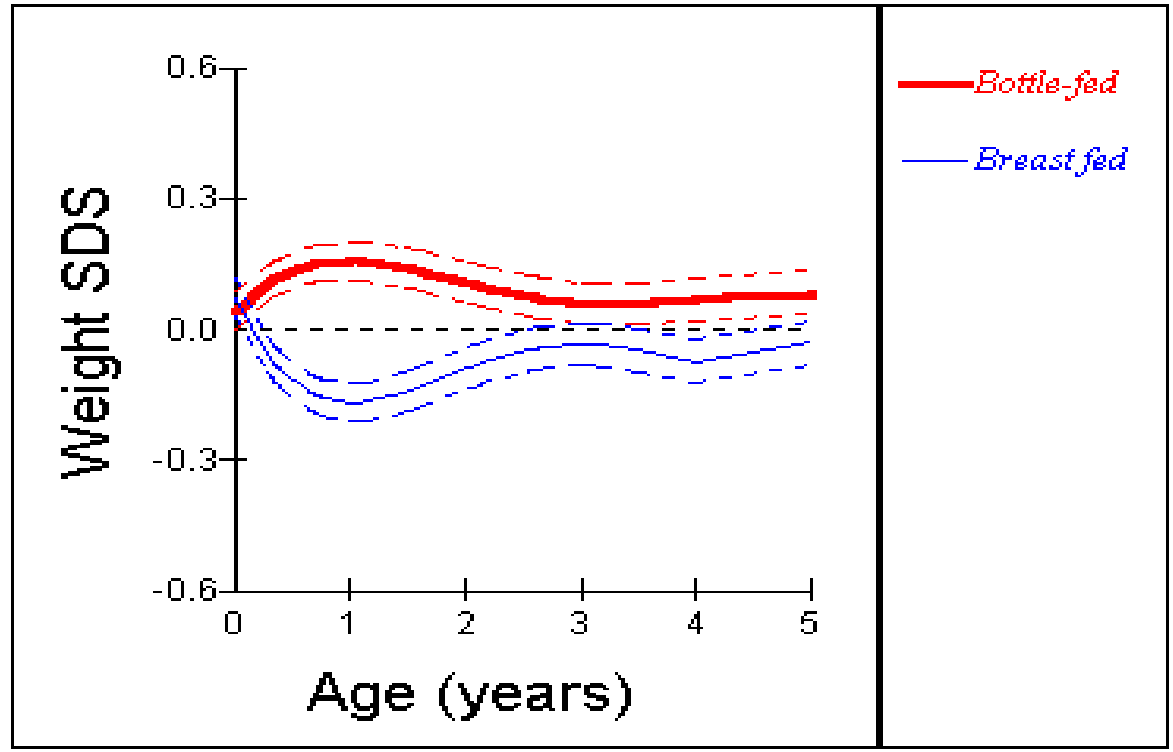
Ong et al. *JCEM 2009*

Long-term consequences of pubertal timing



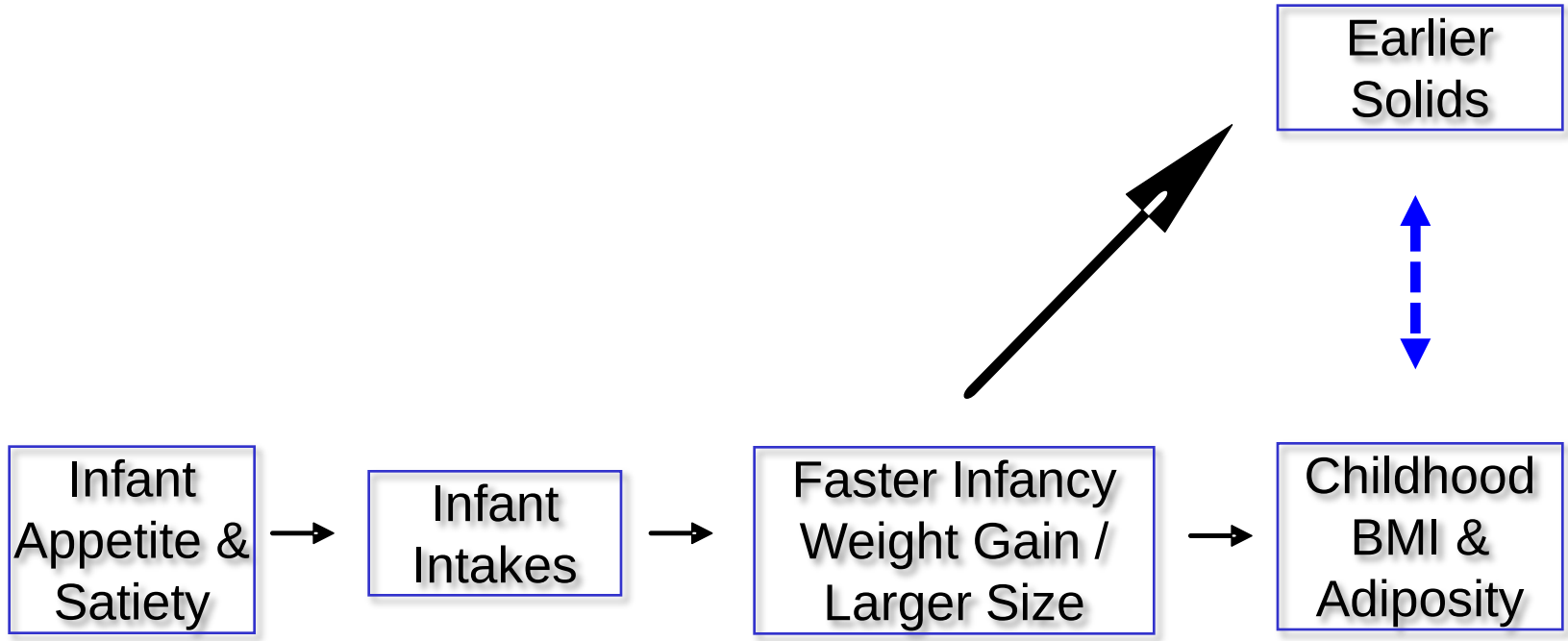
Hartge P. *Nat Genet* 2009

Breastfed infants grow more slowly than formula-fed



Ong et al, *Pediatric Research* 2002

Rapid weight gain PRECEDES earlier **Age at Solids**



Cambridge Baby Growth Study

Brennan Vail et al, *J Peds* 2015

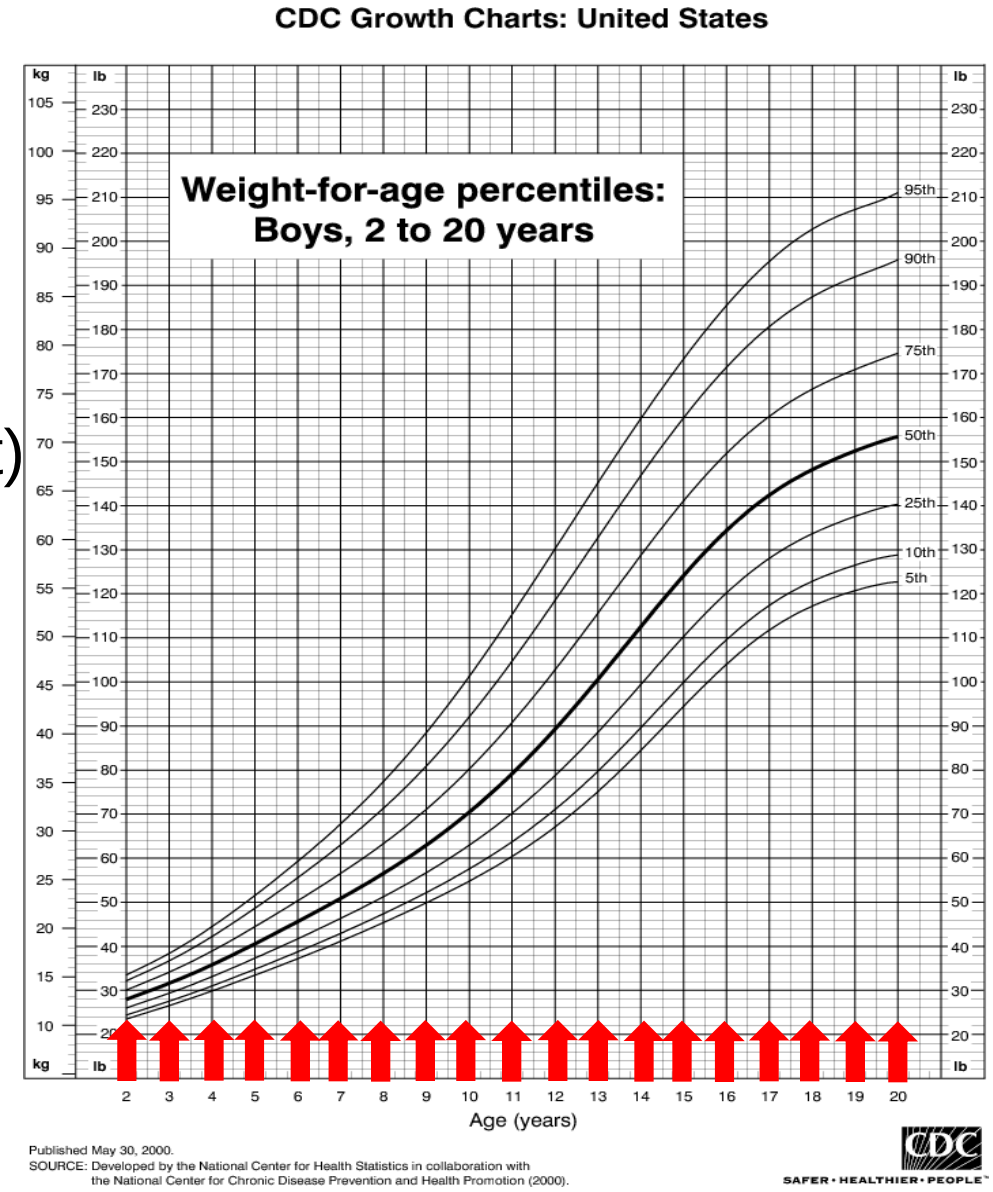
Observed Associations – aren't they all causal?

X causes Y? or…

- **Chance** (*False Positive*)
- **Reverse Causality**
- **Confounding** (by a 3rd factor)
- **Confounding** (time-dependent)

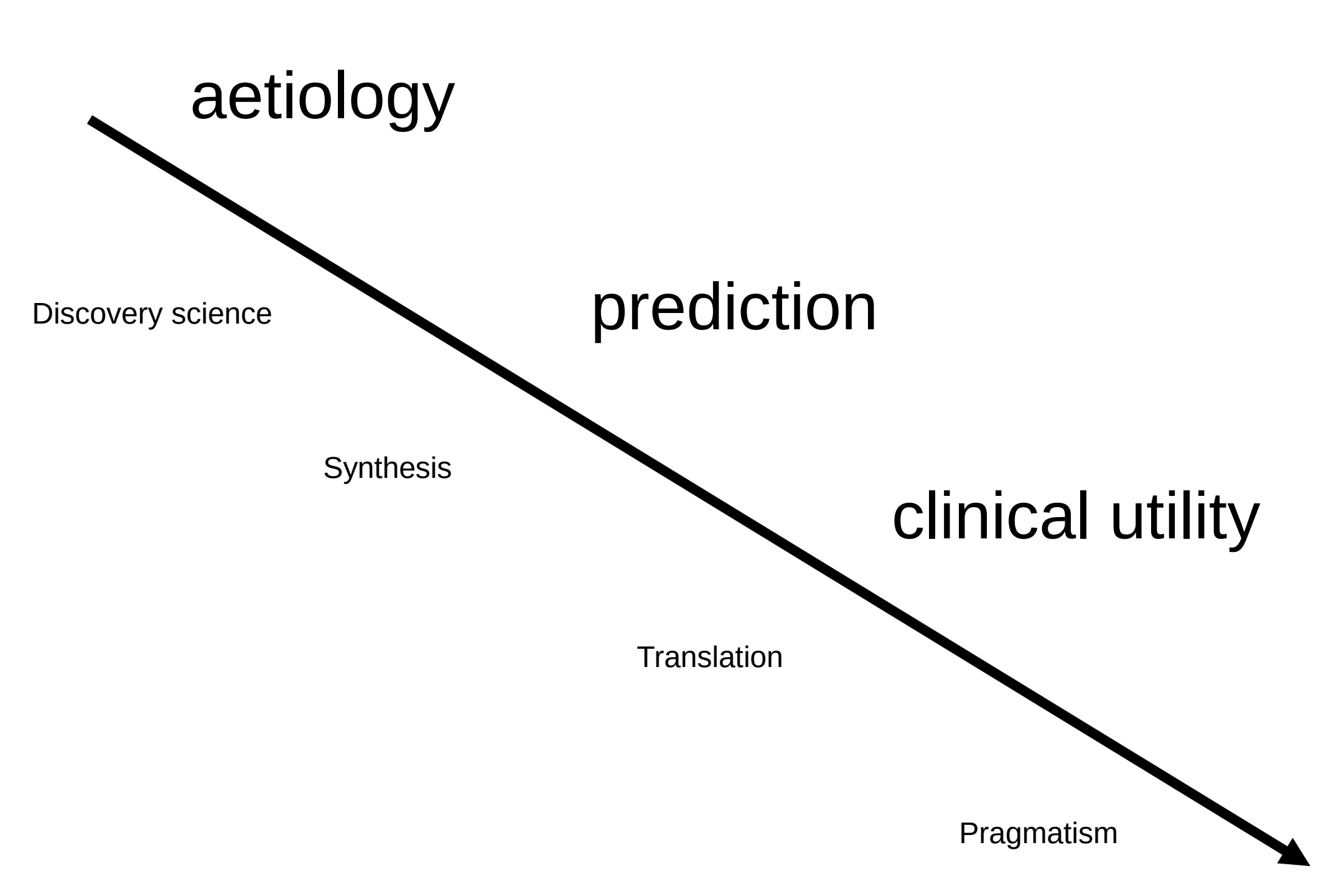
Growth modelling:

- Conditional models (2-stage)
- Life-course (co-enter all data)
- Change models (B *minus* A)
- Mixed models

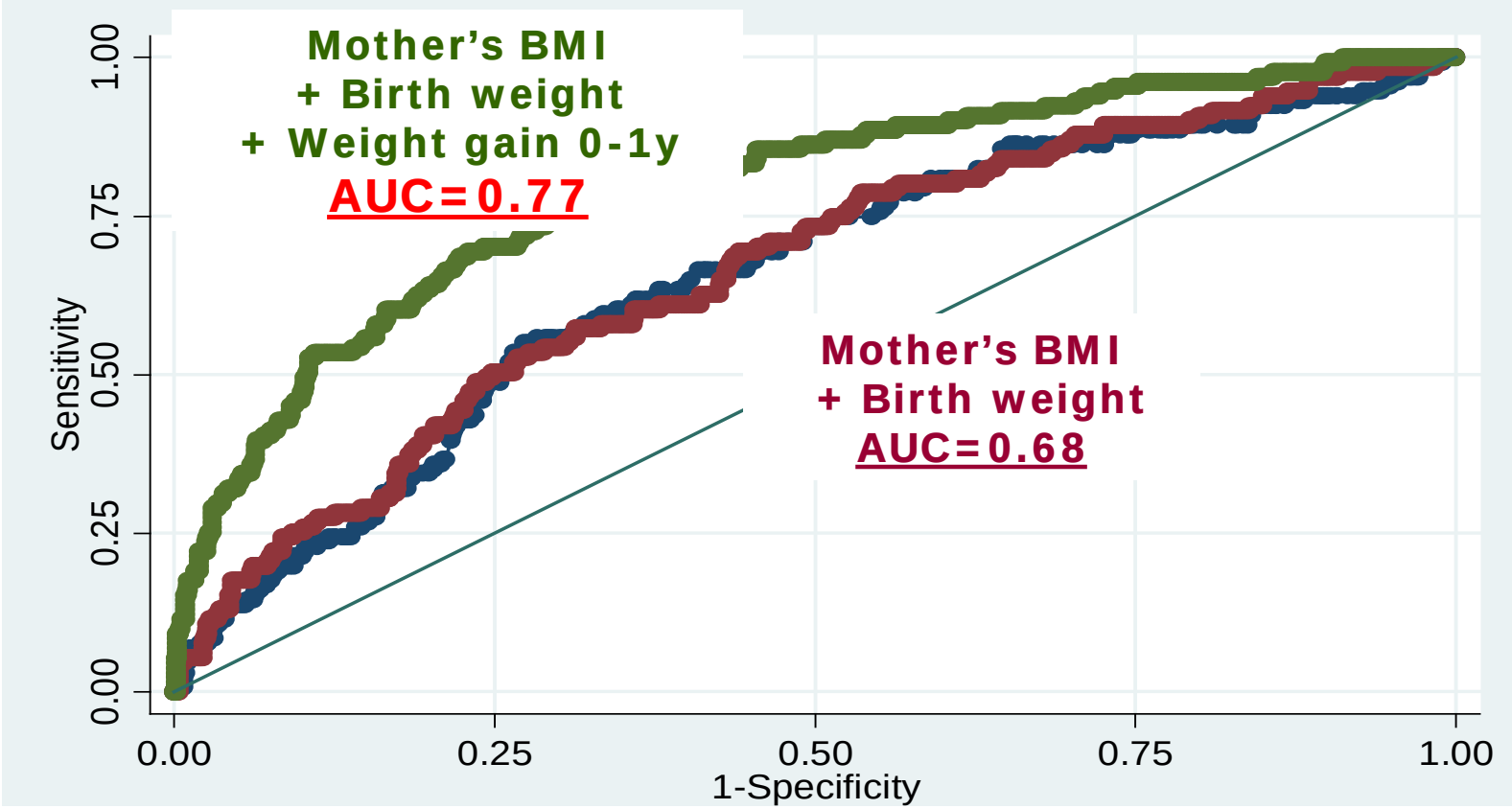


The search for the secrets of the universe paled into insignificance once Professor Smith learned he had won the national lottery.

What's the point of Lifecourse Epidemiology?


aetiology
Discovery science
prediction
Synthesis
clinical utility
Translation
Pragmatism

Prediction of childhood obesity: by mother's BMI, birth weight and infant weight gain 0-1y



METRIC collaboration: Area under the ROC curve

The power of early intervention?

- Evidence for ‘critical windows’ in development from animal models

Source: https://pixabay.com/en/marked-queen-honey-bee-hive-1640094/

Source: https://commons.wikimedia.org/wiki/File:Agouti_Mice.jpg

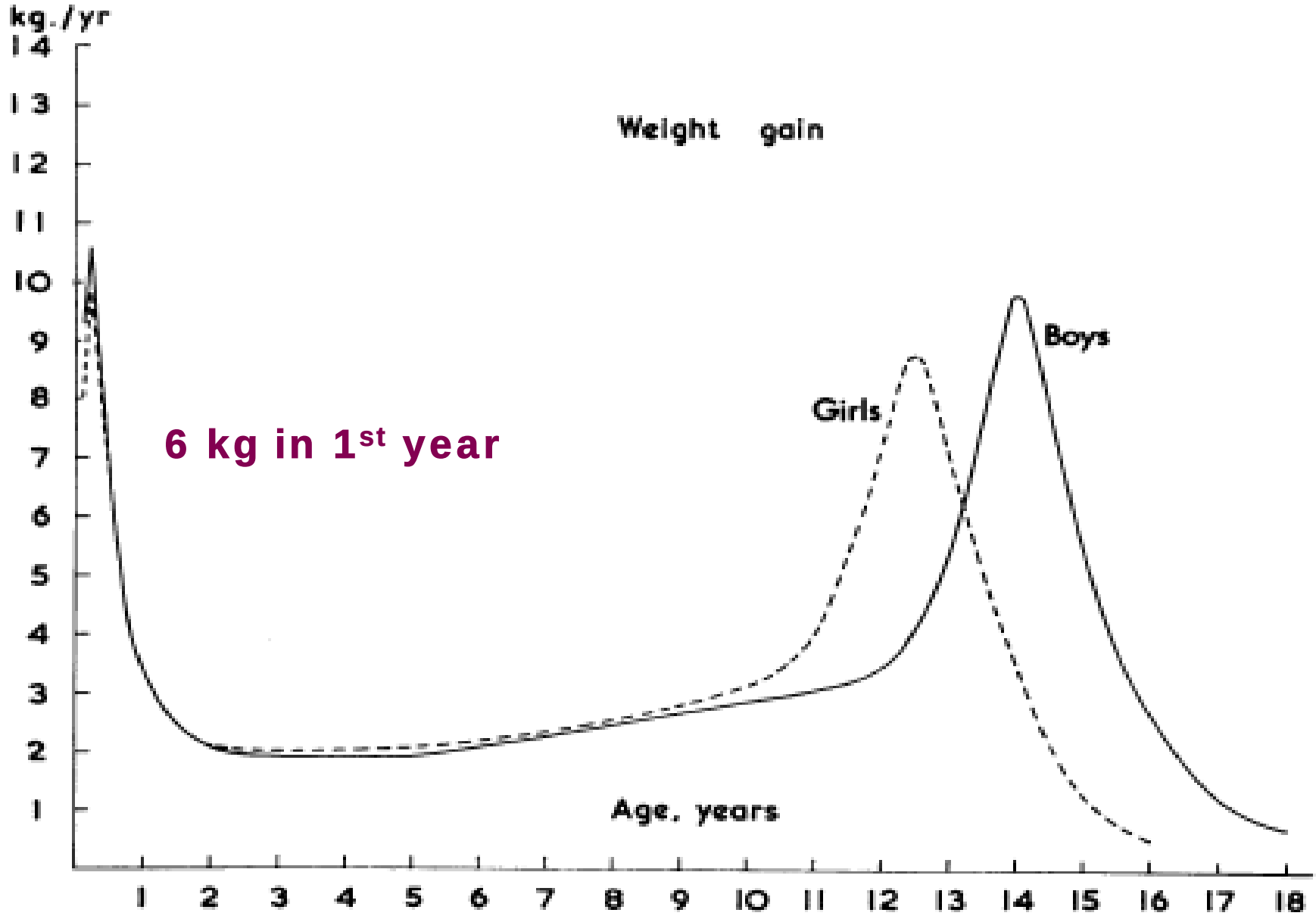
Risks associated with maternal obesity: for both Mother and Baby

Mother	Baby
Gestational diabetes mellitus **x3**	Preterm birth (<32w) **x1.5**
Pre-eclampsia and hypertension **x3-10**	High infant BW **x2.3**
Mode of birth:	Miscarriage **x1.3**
Caesarean birth **x2**	Stillbirth **x1.6-2.0**
Induction of labour **x1.9**	Congenital anomalies:
Failure to progress **x2.3**	Neural tube defect **x1.87**
Postpartum haemorrhage **x1.2**	CVS **x1.3**
Surgical site infection **x2**	Cleft palate **x1.2**
Depression/Anxiety **x1.4**	Limb anomaly **x1.3**
	Anorectal anomalies **x1.6**
	Not breast-feeding **x1.2-3.6**

Also **infant mortality** **x1.4** (*BMJ 2014*)

A review of reviews

Marchi J et al, *Obesity Reviews* 2015


kg./yr
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1
Weight gain
Boys
Girls
6 kg in 1st year
Age, years
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18

Summary: Life-course Epidemiology

i. **Aims to identify age-specific risk factors** (and therefore age-specific interventions)

ii. **Complexities in study design & Statistical analysis** (longitudinal analyses)

iii. **Confounding & mediation are difficult issues**

iv. **Heterogeneity between different era's** (relevance of historical studies?)

v. **Potential for large impact & long-lasting interventions** ("Re-programming")